PAEDIATRIC PROTOCOLS

For Malaysian Hospitals

4th Edition

Hussain Imam Hj Muhammad Ismail
Hishamshah Mohd Ibrahim
Ng Hoong Phak
Terrence Thomas

Kementerian Kesihatan Malaysia

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printed by the

Malaysian Paediatric Association

for

Kementerian Kesihatan Malaysia

1. First and foremost, I would like to thank the Editorial Board and it is my pleasure to write the foreword for the Paediatric Protocols for Malaysia Hospital 4th Edition.

2. Since independence, the Malaysian health system has achieved remarkable outcomes in improving the health status of the population.
Life expectancy at birth has increased by more than 10 years, driven by rapid declines in infant, child, and maternal mortality. However, over the past 15 years, the declines in maternal and child mortality rates have plateaued, with no further notable improvement.

3. Over the years, we have seen the introduction of new technologies in health system. Healthcare workers must keep up with current therapeutics developments and ensure that they provide safe, appropriate and effective treatment to their patients. Clearly, then, the development and maintenance of effective therapeutic skills is essential especially to those working in acute settings.

4. This pocket book is mainly aimed at doctors, clinical officers, nurses and other healthcare workers who are responsible for the care of sick newborns and young children. These protocols are meant to serve as s guide for clinical practice, based on the best available evidence at the time of development. Every healthcare worker is responsible for the management of their patient based on the clinical features presented by the patient and the management options available locally. We hope this handy pocket sized booklet will also be useful to students in medical schools and other training institutions.

Datuk Dr Noor Hisham bin Abdullah
Director-General of Health, Malaysia

FOREWORD TO THE FOURTH EDITION

It has been 13 years since we produced the first edition of a national protocol book for Paediatrics. This effort was of course inspired by the Sarawak Paediatric Protocols initiated by Dr Tan Poh Tin. The 3rd edition in 2012 has proven to be very popular and is now the standard reference for House officers and Medical Officers in Paediatrics.

In producing a fourth edition we have retained the layout of the current version, updating the contents and colour scheme. Again it is targeted at young doctors in the service many of whom seem to have had a suboptimal exposure to paediatrics in their undergraduate years. It is hoped that the protocol book will help them fill in the gaps as they prepare to serve in district hospitals and health clinics. The use of the book has extended way beyond its initial targeted audience.

We want to thank the Ministry of Health of Malaysia which has once again agreed to support the printing of the book for distribution to MOH facilities. We will continue to make the full PDF version available for download on the MPA website. We hope that in time the protocol will be available as an iOS and android app.

As previously this new edition is only possible because of the willingness of busy clinicians to chip in and update the content for purely altruistic reasons and we hope this spirit will persist in our fraternity. We want to thank all the contributors and reviewers for this edition. Prof Frank Shann has gracefully agreed for the latest edition of his drug dosages handbook to be incorporated into the new edition. The Director General of Health has also kindly provided a foreword to this edition.

We wish to thank all who have made this new edition possible and hope this combined effort will help in improving the wellbeing of the children entrusted to our care.

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DISCLAIMER

These protocols serve as a guideline for the management of some common childhood illnesses in Malaysia. The guideline is not a substitute for clinical judgement.

Variation from the guideline, taking into account individual circumstances may be appropriate, depending on locally available resources and expertise, or with new evidence based research findings.

TABLE OF CONTENTS

Chapter 1: Normal Values in Children

VITAL SIGNS

Normal Ranges forRespiratory Rate (RR) and Heart rate (HR)				
Age	Guide weight (kg)		RR at Rest Breaths per minute 5th to 95th Centile	HR Beats per minute 5th to 95th Centile
	Boys	Girls		
Birth	3.5	3.5	25 - 50	120 - 170
1 month	4.5	4.5		
3 months	6.5	6	25 - 45	115 - 160
6 months	8	7	20 - 40	110 – 160
12 months	9.5	9		
18 months	11	10	20 - 35	100 - 155
2 years	12	12	20 - 30	100 - 150
3 years	14	14		90 - 140
4 years	16	16		80 - 135
5 years	18	18		
6 years	21	20		80 - 130
7 years	23	22		
8 years	25	25	15 - 25	70 - 120
9 years	28	28		
10 years	31	32		
11 years	35	35		
12 years	43	43	12 - 24	65 - 115
14 years	50	50		60 - 110
Adult	70	70		

Blood Pressure (BP) Levels in **Girls** for Age and Height Percentile							
Age (Yr)	BP Percentile	SBP (mmHg)			DBP (mmHg)		
		Height Percentile or cm			Height Percentile or cm		
	Height Percentile	5%	50%	95%	5%	50%	95%
1	Height (cm)	75.4	80.8	86.1	75.4	80.8	86.1
	50%	84	86	88	41	43	46
	90%	98	100	102	54	56	58
	95%	101	103	105	59	60	62
2	Height (cm)	84.9	91.1	97.4	84.9	91.1	97.4
	50%	87	89	91	45	48	51
	90%	101	103	106	58	60	62
	95%	104	106	109	62	64	66
3	Height (cm)	91	97.6	104.6	91	97.6	104.6
	50%	88	90	93	48	50	53
	90%	102	104	107	60	62	65
	95%	106	108	110	64	66	69
4	Height (cm)	97.2	104.5	112.2	97.2	104.5	112.2
	50%	89	92	94	50	53	55
	90%	103	106	108	62	65	67
	95%	107	109	112	66	69	71
5	Height (cm)	103.6	111.5	120	103.6	111.5	120
	50%	90	93	96	52	55	57
	90%	104	107	110	64	67	70
	95%	108	110	113	68	71	73
6	Height (cm)	110	118.4	127.7	110	118.4	127.7
	50%	92	94	97	54	56	59
	90%	105	108	111	67	69	71
	95%	109	111	114	70	72	74
7	Height (cm)	115.9	124.9	134.7	115.9	124.9	134.7
	50%	92	95	99	55	57	60
	90%	106	109	112	68	70	72
	95%	109	112	115	72	73	75

Blood Pressure (BP) Levels in **Girls** for Age and Height Percentile (cont.)							
Age (Yr)	BP Percentile	SBP (mmHg)			DBP (mmHg)		
		Height Percentile or cm			Height Percentile or cm		
	Height Percentile	5%	50%	95%	5%	50%	95%
8	Height (cm)	121	130.6	140.9	121	130.6	140.9
	50%	93	97	100	56	59	61
	90%	107	110	113	69	72	73
	95%	110	113	117	72	74	75
9	Height (cm)	125.3	135.6	146.6	125.3	135.6	146.6
	50%	95	98	101	57	60	61
	90%	108	111	114	71	73	73
	95%	112	114	118	74	75	75
10	Height (cm)	129.7	141	152.8	129.7	141	152.8
	50%	96	99	103	58	60	62
	90%	109	112	116	72	73	73
	95%	113	116	120	75	76	76
11	Height (cm)	135.6	147.8	160	135.6	147.8	160
	50%	98	102	106	60	61	64
	90%	111	114	120	74	74	75
	95%	115	118	124	76	77	77
12	Height (cm)	142.8	154.8	166.4	142.8	154.8	166.4
	50%	102	105	108	61	62	65
	90%	114	118	122	75	75	76
	95%	118	122	126	78	78	79
13	Height (cm)	148.1	159.2	170.2	148.1	159.2	170.2
	50%	104	107	109	62	64	66
	90%	116	121	123	75	76	76
	95%	121	124	127	79	79	81

These normative blood pressures figures were extracted from the guidelines "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents." Published in PEDIATRICS August 2017.

Blood Pressure (BP) Levels in **Boys** for Age and Height Percentile							
Age (Yr)	BP Percentile	SBP (mmHg)			DBP (mmHg)		
		Height Percentile or cm			Height Percentile or cm		
	Height Percentile	5%	50%	95%	5%	50%	95%
1	Height (cm)	77.2	82.4	87.9	77.2	82.4	87.9
	50%	85	86	88	40	41	42
	90%	98	100	101	52	53	54
	95%	102	103	105	54	55	57
2	Height (cm)	86.1	92.1	98.5	86.1	92.1	98.5
	50%	87	89	91	43	44	46
	90%	100	102	104	55	56	58
	95%	104	106	108	57	59	61
3	Height (cm)	92.5	99	105.8	92.5	99	105.8
	50%	88	90	92	45	47	49
	90%	101	103	105	58	59	61
	95%	106	107	109	60	62	64
4	Height (cm)	98.5	105.9	113.2	98.5	105.9	113.2
	50%	90	92	94	48	50	52
	90%	102	105	107	60	62	64
	95%	107	108	110	63	66	68
5	Height (cm)	104.4	112.4	120.3	104.4	112.4	120.3
	50%	91	94	96	51	53	55
	90%	103	106	108	63	65	67
	95%	107	109	112	66	69	71
6	Height (cm)	110.3	118.9	127.5	110.3	118.9	127.5
	50%	93	95	98	54	56	58
	90%	105	107	110	66	68	69
	95%	108	111	114	69	71	73
7	Height (cm)	116.1	125.1	134.5	116.1	125.1	134.5
	50%	94	97	99	56	58	59
	90%	106	109	111	68	70	71
	95%	110	112	116	71	73	74

Blood Pressure (BP) Levels in **Boys** for Age and Height Percentile (cont.)							
Age (Yr)	BP Percentile	SBP (mmHg)			DBP (mmHg)		
		Height Percentile or cm			Height Percentile or cm		
	Height Percentile	5%	50%	95%	5%	50%	95%
8	Height (cm)	121.4	131	141	121.4	131	141
	50%	95	98	100	57	59	60
	90%	107	110	112	69	71	73
	95%	111	114	117	72	74	75
9	Height (cm)	126	136.3	147.1	126	136.3	147.1
	50%	96	99	101	57	60	62
	90%	107	110	114	70	73	74
	95%	112	115	119	74	76	77
10	Height (cm)	130.2	141.3	152.7	130.2	141.3	152.7
	50%	97	100	103	59	62	63
	90%	108	112	116	72	74	76
	95%	112	116	121	76	77	78
11	Height (cm)	134.7	146.4	158.6	134.7	146.4	158.6
	50%	99	102	106	61	63	63
	90%	110	114	118	74	75	76
	95%	114	118	124	77	78	78
12	Height (cm)	140.3	152.7	165.5	140.3	152.7	165.5
	50%	101	104	109	61	62	63
	90%	113	117	122	75	75	76
	95%	116	121	128	78	78	79
13	Height (cm)	147	160.3	173.4	147	160.3	173.4
	50%	103	108	112	61	62	65
	90%	115	121	126	74	75	77
	95%	119	125	131	78	78	81

These normative blood pressures figures were extracted from the guidelines "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents." Published in PEDIATRICS August 2017.

Age	5th centile Blood Pressure
< 1 year	65 - 75
1-2 years	70 - 75
2-5 years	70 - 80
5-12 years	80 - 90
>12 years	90 - 105
The calculation for expected systolic blood pressure is: **65 + (2 x age in years) mmHg for 5th centile**	
Reference: Advanced Paediatric Life Support: The Practical Approach To Emergencies, 6th Edition 2016	

ANTHROPOMETRIC MEASUREMENTS

Age	Weight	Height	Head size
Birth	3.5 kg	50 cm	35 cm
6 months	7 kg	68 cm	42 cm
1 year	10 kg	75 cm	47 cm
2 years	12 kg	85 cm	49 cm
3 years	14 kg	95 cm	49.5 cm
4 years		100 cm	50 cm
5-12 years		5 cm/year	0.33 cm/year

Points to Note

Weight

- In the first 7 - 10 days of life, babies lose 10 - 15% of their birth weight.
- In the first 3 months of life, the rate of weight gain is 25 gm/day
- Babies *regain* their birth weight by the 2nd week, *double* this by 5 months age, and *triple* the birth weight by 1 year of age
- Weight estimation for children (in Kg):

  Infants: (Age in months X 0.5) + 4
  Children 1 – 10 years: (Age in yrs + 4) X 2

Head circumference

- Rate of growth in preterm infants is 1 cm/week, but reduces with age. Head growth follows that of term infants when chronological age reaches term
- Head circumference increases by 12 cm in the 1st year of life (6 cm in first 3 months, then 3 cm in second 3 months, and 3 cm in last 6 months)

Other normal values are found in the relevant chapters of the book.

References:

1. Advanced Paediatric Life Support: The Practical Approach Textbook, 5th Edition 2011
2. Nelson Textbook of Pediatrics, 18th Edition.

HAEMATOLOGICAL PARAMETERS

Age	Hb	PCV	Retics	MCV *fl*	MCH *pg*	TWBC	Neutrophil	Lymphocyte
	g/dL	%	%	Lowest	Lowest	*x1000*	Mean	Mean
Cord Blood	13-7-20.1	45-65	5.0	110	-	9-30	61	31
2 weeks	13.0-20.0	42-66	1.0	-	29	5-21	40	63
3 months	9.5-14.5	31-41	1.0	-	27	6-18	30	48
6 mths - 6 yrs	10.5-14.0	33-42	1.0	70-74	25-31	6-15	45	38
7 - 12 years	11.0-16.0	34-40	1.0	76-80	26-32	4.5-13.5	55	38
Adult male	14.0-18.0	42-52	1.6	80	27-32	5-10	55	35
Adult female	12.0-16.0	37-47	1.6	80	26-34	5-10	55	35

Differential counts	
< 7 days age	neutrophils > lymphocytes
1 wk - 4 years	lymphocytes > neutrophils
4 - 7 years	neutrophils = lymphocytes
> 7 years	neutrophils > lymphocytes

Points to note

- **Differential WBC:** eosinophils: 2-3%; monocytes: 6-9 %
- **Platelets counts** are lower in first months of age; but normal range by 6 months
- **Erythrocyte sedimentation rate (ESR)** is < 16 mm/hr in children, provided PCV is at least 35%.

NATIONAL IMMUNISATION SCHEDULE FOR MALAYSIA (MINISTRY OF HEALTH, MALAYSIA)

	Age in months										Age in years		
Vaccine	birth	1	2	3	5	6	9	12	18	21	7 yrs	13 yrs	15 yrs
BCG	1			if no scar									
Hepatitis B	1	2				3							
DTaP			1	2	3				4		DT (B)		T (B)
IPV			1	2	3				4				
Hib			1	2	3				4				
Measles						Sabah							
MMR							1	2			MR*		
JE (Sarawak)							1			2			
HPV												2 doses	

Legend: B, Booster doses; BCG, Bacille Calmette-Guerin; DTaP, Diphhteria, Tetanus, acellular Pertussis; DT, Diphtheria, Tetanus; T, Tetanus; IPV, Inactivated Polio Vaccine; Hib, Haemophilus influenzae type B; MMR, Measles, Mumps, Rubella; JE, Japanese Encephalitis; HPV, Human Papilloma Virus;
* Until the present cohort (9 and 12 months MMR) reaches 7 years

General Notes

- Vaccines (inactivated or live) **can be given simultaneously** (does not impair antibody response or increase adverse effect). Administer at different sites unless using combined preparations.
- Sites of administration
  - Oral – rotavirus, live typhoid vaccines
  - Intradermal (ID) - BCG. Left deltoid area (proximal to insertion deltoid muscle)
  - Deep SC, IM injections. (ALL vaccines *except* the above)
    - Anterolateral aspect of thigh – preferred site in children
    - Upper arm – preferred site in adults
    - Upper outer quadrant of buttock - associated with lower antibody level production

Immunisation : *General* contraindications

- **Absolute contraindication** for **any vaccine**: severe anaphylaxis reactions to previous dose of the vaccine or to a component of the vaccine.
- Postponement during **acute febrile illness**: Minor infection without fever or systemic upset is NOT a contraindication.
- **Live vaccines: Absolute contraindications**
  - *Immunosuppressed children* - malignancy; irradiation, leukaemia, lymphoma, post-transplant, primary immunodeficiency syndromes (but NOT asymptomatic HIV): **need to defer (see below)**
  - Pregnancy (live vaccine - theoretical risk to foetus) UNLESS there is significant exposure to serious conditions like polio or yellow fever in which case the importance of vaccination outweighs the risk to the foetus.
  - Live vaccines may be given together. If not administering simultaneously then an interval ≥ 4 weeks is required.
  - Tuberculin skin test (Mantoux test) and MMR: after a Mantoux test, MMR should be delayed until the skin test has been read. There should be ≥ 4 weeks interval for Mantoux test after MMR given.
- **Killed vaccines are safe.** Absolute contraindications: SEVERE local induration (involving > 2/3 of the limbs) or severe generalised reactions in previous dose.

The following are *not* contraindications to vaccination

- Mild illness without fever e.g. mild diarrhoea, cough, runny nose
- Asthma, eczema, hay fever, impetigo, heat rash (avoid injection in affected area)
- Treatment with antibiotics, locally acting steroids or inhaled steroids
- Child's mother is pregnant
- Breastfed child (does not affect polio uptake)
- Neonatal jaundice
- Underweight or malnourished
- Over the recommended age
- Past history of pertussis, measles or rubella (unless confirmed medically)
- Stable neurological conditions: cerebral palsy, mental retardation, febrile convulsions, stable epilepsy
- Family history of convulsions
- History of heart disease, acquired or congenital
- Prematurity (immunise according to schedule irrespective of gestational age)

IMMUNISATION: SPECIAL CIRCUMSTANCES

Immunisation of the Immunocompromised child:

Includes malignancy; leukaemia, lymphoma, post-transplant, congenital immunodeficiency syndromes (but NOT asymptomatic HIV), immunosuppressive therapy:

- BCG is contraindicated
- Non-live vaccines can be given but may need to be repeated depending on underlying condition and individual vaccine due to suboptimal response
- For oncology patients on chemotherapy
  - Avoid live vaccines for two weeks before, during and for 6 months after completion of chemotherapy
  - Safe to give influenza and pneumococcal vaccines, if indicated
- For post- Haematopoeitic Stem Cell Transplant (HSCT) and Solid Organ Transplant (SOT) :
  - Non-live vaccines can be given 6 months after HSCT or SOT
  - Live vaccines to be given at least 2 years after HSCT and no graft versus host disease and not on immunosuppressive therapy (and acceptable CD4 count and IgM levels)
  - Live vaccines contraindicated in SOT as most likely on immunosuppressive therapy
- Patients on Corticosteroid Therapy
  - On high-dose steroids i e. Prednisolone >or equal to 2 mg/kg/day for >14 delay live vaccines for at least 1 month after cessation of steroids
  - On low-dose systemic steroids of 1mg/ kg/day < 2 weeks or EOD for > 2 weeks, can administer live vaccines
  - Any dose for 28 days or longer delay live vaccines for at least 1 month after cessation of steroids
- Interval between administration of Immunoglobulins or blood products and measles- or varicella-containing vaccine
  - 3 months: following IM Hepatitis B prophylaxis (HBIG)
  - 8 months: following Normal Human Immunoglobulin (NHIG) at dose of 400 mg/kg IV
  - 10 months: following NHIG at dose of 800-1000 mg/kg IV
  - 11 months: following NHIG at dose of 1600-2000 mg/kg IV (e.g. Kawasaki disease)
  - 6 months: following Packed RBCs 10 mL/kg transfusion
  - 6 months: following Whole blood 10 mL/kg transfusion
  - 7 months: following Plasma/platelets transfusion

Note: If measles- or varicella-containing vaccine is given <2 weeks before administration of Immunoglobulins or blood products, then repeat immunisation.

Immunisation of children with HIV infection

(Please refer to Paediatric HIV section)

Measures to protect inpatients exposed to another inpatient with measles

- Protect all **immunocompromised children** with Immunoglobulin (NHIG) 0.25-0.5 mls/kg. (Measles may be fatal in children in remission from leukaemia)
- Check status of measles immunisation in the other children. Give measles-specific Immunoglobulin, if none available to give IVIG to **unimmunised children** within 24 hrs of exposure. Immunisation within 72 hours aborts clinical measles in 75% of contacts.
- Discharge the inpatient child with uncomplicated measles.
- Do not forget to notify the Health Office.

Close contacts of immunodeficient children and adults

- Must be immunized, particularly against measles, polio (use IPV), varicella.

Children with Asplenia (Elective or emergency splenectomy; asplenic syndromes; sickle cell anaemia) are susceptible to encapsulated bacteria and malaria.

- Pneumococcal, Meningococcal A, C, Y & W-135, Haemophilus influenza b vaccines should be given.
- For elective splenectomy (and also chemotherapy or radiotherapy): give the vaccines preferably 2 or more weeks before the procedure. However, they can be given even after the procedure.
- Penicillin prophylaxis should continue ideally for life. If not until 16 years old for children or 5 years post splenectomy in adults.

In patients with past history or family history of febrile seizures, neurological or developmental abnormalities that would predispose to febrile seizures:

- Febrile seizures may occur 5 - 10 days after measles (or MMR) vaccination or within the first 72 hours following pertussis immunisation.
- Routine administration of paracetamol following immunisation is not recommended.

Maternal Chicken Pox during perinatal period
(Please refer to Perinatally acquired varicella section)

In contacts of a patient with invasive Haemophilus influenzae B disease

- Chemoprophylaxis for all household with at least 1 contact < 4 years who is unimmunised or incompletely immunised mmunise all household, nursery or kindergarden contacts < 4 years of age.
- Chemoprophylaxis for preschool and child care facility should be at the discretion of local health department
- Chemoprophylaxis: Rifampicin at 20 mg/kg once daily (Maximum 600 mg) for 4 days (except pregnant women - give one IM dose of ceftriaxone)
- Index case should be immunised irrespective of age.

Babies born to mothers who are Hbe Ag OR Hbs Ag positive should be given Hepatitis B immunoglobulin (200 IU) and vaccinated with the Hepatitis B vaccine within 12 hours and not later than 48 hours.
Given in different syringes and at different sites

Premature infants may be immunised at the same chronological age as term infants. (Please refer **Chapter 11: The Premature Infant** for more discussion)

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
BCG	To be given at birth and to be repeated at 3 months of age if no scar is present	Not to be given to symptomatic HIV infected children. Can be given to newborns of HIV infected mother as the infant is usually asymptomatic at birth.	BCG adenitis may occur.	Intradermal. Local reaction: a papule at vaccination site may occur in 2 - 6 weeks. This grows and flattens with scaling and crusting. Occasionally a discharging ulcer may occur. This heals leaving a scar of at least 4 mm in successful vaccination.
Hepatitis B	All infants, including those born to HBsAg positive mothers All health care personnel.	Severe hypersensitivity to aluminium. The vaccine is also not indicated for HBV carrier or immuned patient (i.e. HBsAg or Ab positive)	Local reactions. Fever and flu-like symptoms in first 48 hours. Rarely, erythema multiforme or urticaria.	Intramuscular. Give with Hep B immunoglobulin for infants of HBsAg positive mothers.
Diphtheria, Tetanus (DT)	All infants should receive 5 doses including booster doses at 18 months and Standard 1	Severe hypersensitivity to aluminium and thiomersal	Swelling, redness and pain A small painless nodule may develop at injection site – harmless. Transient fever, headaches, malaise, rarely anaphylaxis. Neurological reactions rare.	Intramuscular

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Pertussis	All infants should receive 4 doses including booster at 18 months It is recommended that booster doses be given at Std 1 and at Form 3 due to increased cases of Pertussis amongst adolescents in recent years	Anaphylaxis to previous dose; encephalopathy develops within 7 days of vaccination Precautions: severe reaction to previous dose (systemic or local) and progressive neurological diseases.	Local reaction. Severe if involve 2/3 limbs Severe systemic reaction: Anaphylaxis (2 per 100 000 doses), encephalopathy (0 – 10.5 per million doses), high fever (fever>40.5), fits within 72 hours, persistent inconsolable crying (0.1 to 6%), hyporesponsive state. Acellular Pertussis vaccine associated with less side effects	Intramuscular. Static neurological diseases, developmental delay, personal or family history of fits are NOT contraindications.
Inactivated Polio Vaccine (IPV)	All infants to be given 4 doses including booster at 18 months.	Allergies to neomycin, polymyxin and streptomycin Previous severe anaphylactic reaction	Local reactions.	Intramuscular.
Haemophilus Influenzae type B (Hib)	All infants should receive 4 doses including booster at 18 months. Patients with splenic dysfunction, and post splenectomy.	Confirmed anaphylaxis to previous Hib and allergies to neomycin, polymyxin and streptomycin	Local swelling, redness and pain soon after vaccination and last up to 24 hours in 10% of vaccinees Malaise, headaches, fever, irritability, inconsolable crying. Very rarely seizures.	Intramuscular

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Measles, Mumps, Rubella (MMR)	All infants and 9 and 12 months. Booster at 7 years Measles vaccine at 6 month for Sabah, Orang Asli population	Avoid in patients with hypersensitivity to neomycin and polymyxin or severe reaction to hen's eggs Pregnancy. Children with Immunodeficiency.	Transient rash in 5%. May have fever between D5-D12 post vaccination. URTI symptoms. Febrile convulsions (D6-D14) in 1:1000 – 9000 doses of vaccine. (Natural infection 1:200) Encephalopathy within 30 days in 1:1,000,000 doses. (Natural infection 1:1000 - 5000)	Intramuscular. Can be given irrespective of previous history of measles, mumps or rubella infection. Long term prospective studies have found no association between measles or MMR vaccine and inflammatory bowel diseases, autism or SSPE.
Mumps			Rarely transient rash, pruritis and purpura. Parotitis in 1% of vaccinees, > 3 weeks after vaccination. Orchitis and retro bulbar neuritis very rare. Meningoencephalitis is mild and rare. (1:800,000 doses). (natural infection 1:400).	Intramuscular

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Rubella			Rash, fever, lymphadenopathy, thrombocytopenia, transient peripheral neuritis. Arthritis and arthralgia occurs in up to 3% of children and 20% of adults.	Given as MMR
Japanese Encephalitis (JE)	Given in Sarawak at 9 and 21 months.	Immunodeficiency and malignancy, diabetes , acute exacerbation of cardiac, hepatic and renal conditions	Local redness, swelling, pain, fever, chills, headache, lassitude..	Inactivated vaccine. Subcutaneous. Protective efficacy > 95%.
Human Papilloma Virus (HPV)	Indicated for females aged 9-45 years.	Not recommended in pregnant patients.	Headache, myalgia, injection site reactions, fatigue, nausea, vomiting, diarrhoea, abdominal pain, pruritus, rash, urticaria, myalgia, arthralgia, fever.	2 vaccines available: Cervarix (GSK): bivalent. Gardasil (MSD): quadrivalent. - 3 dose schedule IM (0, 1-2month, 6 month). Recombinant vaccine. Protective efficacy almost 100% in preventing vaccine type cervical cancer in first 5 years.

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Pneumo-coccal (conjugate) vaccine: PCV 13/ PCV 7	Dosage: Infants 2-6 mth age. 3-dose primary series at least 1 mth apart from 6 wks of age. Booster: 1 dose between 12-15 mths of age. Unvaccinated: infants 7-11 mths 2 doses 1 month apart, followed by a 3rd dose at 12- 15 months; children 12-23 months 2 doses at least 2 months apart; healthy children 2 - 5 years: Single dose Unvaccinated high risk children 2-5 yrs age may be given 2 doses (6-8 wks apart)	Children who have severe allergic reaction to previous pneumococcal vaccine Healthy children under 6 weeks and more than 59 months of age	Decreased appetite, irritability, drowsiness, restless sleep, fever, inj site erythema, induration or pain, rash.	*Listed in Blue Book* Immunogenic in children < 2 years Inactivated vaccine. Intramuscular High risk children: immunosuppression (includ-ing asymptomatic HIV), asplenia, nephrotic syndrome and chronic lung or heart disease.

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Pneumococcal (polysaccharide vaccine)	Recommended for children at high risk. > 2 years old. Single dose. Booster at 3-5 years only for high risk patients.	Age < 2 years old. Revaccination within 3 years has high risk of adverse reaction; Avoid during chemotherapy or radiotherapy and less than 10 days prior to commencement of such therapy – antibody response is poor. Pregnancy.	Hypersensitivity reactions.	Listed in Blue Book. Intramuscular, Subcutaneous Immunogenic in children ≥2 yrs. Against 23 serotypes. High risk: immunosuppression, asymptomatic HIV, asplenia, nephrotic syndrome, chronic lung disease. If these children are <2 yrs old, they should first receive pneumococcal conjugate vaccine; when > 2 yrs, then the polysaccharide vaccine is used.
Rotavirus	First dose given to infants ≥ 6 wks old. *Rotateq* (3 doses) Subsequent doses given at 4-10 wks interval. 3rd dose given ≤ 32 weeks age. *Rotarix* (2 doses). 2nd dose to be given by 24 weeks age. Interval between doses should be > 4 wks.	Prior hypersensitivity to any vaccine component. Uncorrected congenital GIT malformation, e.g. Meckel's diverticulum Severe combined immunodeficiency disease (reported prolonged shedding of vaccine virus reported in infants who had live Rotavirus vaccine)	Loss of appetite, irritability, fever, fatigue, diarrhoea, vomiting, flatulence, abdominal pain, regurgitation of food.	Oral live-attenuated vaccine. Protective efficacy 88-91% for any rotavirus gastroenteritis episode; 63-79% for all causes of gastroenteritis.

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Varicella Zoster	*12 mths to 12 yrs:* 2 doses at least ≥ 4 wks apart. Non immune susceptible health care workers who regularly come in contact with VZV infection Asymptomatic/mildly symptomatic children with HIV (with CD4% > 15%); 2 doses at 3 mths interval. Children in remission from leukemia for ≥1 yr, have >700/ml circulating lymphocytes may receive vaccine under paediatrician supervision (2doses).	Pregnant patients. Patients receiving high dose systemic immunosuppression therapy. Patients with malignancy especially haematological malignancies or blood dyscrasias. Hypersensitivity to neomycin.	Occasionally, papulovesicular eruptions, injection site reactions, headache, fever, paresthesia, fatigue	Live attenuated vaccine. Subcutaneous. 70 – 90% effectiveness.
Hepatitis A	For children >1 yr. 2 doses., given 6-12 months apart.	Severe hypersensitivity to aluminium hydroxide, phenoxyethanol, neomycin	Local reactions. Flu-like symptoms lasting 2 days in 10% of recipients	Intramuscular. Inactivated vaccine. Protective efficacy 94%.

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Cholera	Children 2-6 yrs: 3 doses at 1-6 wk interval. Children > 6 yrs: 2 doses at 1-6 wks interval. Booster dose >2 yrs.		Gastroenteritis	Oral inactivated vaccine. Protective efficacy 80-90% after 6 mths waning to 60% after 3 yrs.
Influenza	Single dose. Min age 6 mths. Unprimed individuals require 2nd dose 4 - 6 wks after 1st dose. Recommended for children with: chronic decompensated respiratory or cardiac disorders, e.g. cyanotic heart diseases chronic lung disease, HIV infection. In advanced disease, vaccination may not induce protective antibody levels.	Hypersensitivity to egg or chicken protein, neomycin, formaldehyde. Febrile illness, acute infection.	Transient swelling, redness, pain and induration locally. Myalgia, malaise and fever for 1 – 2 days starting within a few hours post vaccination. Very rarely, neurological (Guillain-Barre), glomerulonephritis, ITP or anaphylactic reaction occurs.	Intramuscular. Inactivated vaccine. Protective efficacy 70-90% Require yearly revaccination for continuing protection.

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Rabies	Pre-exposure: 3 doses at Day 0, 7, 28. Booster every 2-3 yrs. Post-exposure treatment: Fully immunised: 2 doses at Day 0, Day 3. Rabies Immune Globulin (RIG) unnecessary. Unimmunised: 5 doses at Day 0, 3, 7, 14 and 28. RIG (20 IU/kg given half around the wound and the rest IM.		Headache, dizziness, malaise, abdominal pain, nausea, myalgia. Injection site reactions such as itching, swelling, pain.	Inactivated vaccine. (Available in Malaysia as Purified Vero Cell Rabies Vaccine (PVRV). Intramuscular.
Meningococcus A, C, Y & W-135	Single dose. Immunity up to 3 yrs.		Local reactions. Irritability, fever and rigors for 1-2 days. Very rarely, anaphylaxis.	Intramuscular.
Typhoid (Typhim Vi)	Single dose. Seroconversion in 85-95% of recipients; confers 60-80% protection beginning 2 wks after vaccination. Boosters every 3 yrs.	Children < 2yrs. (Immunogenicity < 2 yrs of age has not been established)	Local reactions. Myalgia, malaise, nausea, headaches and fever in 3% of recipients.	Intramuscular. Polysaccharide vaccine
Typhoid (Ty21a vaccine)	Three doses two days apart. Effective 7 days after last dose. Booster every 3 years.	Infant <6 mth. Congenital or acquired immunodeficiency. Acute febrile illness & acute intestinal infection.	Very rarely: mild GIT disturbances or a transitory exanthema.	Oral. Live attenuated vaccine.

IMMUNISATION FOR CHILDREN WHO HAVE DELAYED FIRST VISIT TO THE CLINIC (NOT GIVEN IMMUNISATION)

Immunisation should be started on the first visit for children who have delayed visit to the clinic for immunisation.
Below is the suggested schedule according to age for these children:

Immunisation Visits	Age			
	< 2 Months	2 – 8 months	9 – 12 months	> 1 year and < 7 years
1st visit	BCG Hepatitis B (1st dose)	BCG Hepatitis B (1st dose) DTaP-IPV// Hib (1st dose)	BCG Hepatitis B (1st dose) DTaP-IPV// Hib (1st dose) MMR	BCG Hepatitis B (1st dose) DTaP-IPV// Hib (1st dose) MMR
2nd visit (1 mth later)	follow Immunisation Schedule	Hepatitis B (2nd dose) DTaP-IPV// Hib (2nd dose)	Hepatitis B (2nd dose) DTaP-IPV// Hib (2nd dose)	Hepatitis B (2nd dose) DTaP-IPV// Hib (2nd dose) MMR (2nd dose)
3rd visit (1 mth later)	follow Immunisation Schedule	DTaP-IPV//	DTaP-IPV// Hib (3rd dose) Hepatitis B (3rd Dose)	DTaP-IPV// Hib (3rd dose) Hepatitis B (3rd Dose)
4th visit (2 mths later)	follow Immunisation Schedule	Hepatitis B (3rd dose)	Hepatitis B (3rd dose) MMR (2nd dose)	Hepatitis B (3rd dose)
18 months of age or 6 months after completed DTaP-IPV// Hib 3rd dose	follow Immunisation Schedule	follow Immunisation Schedule	DTaP-IPV// Hib (booster)	DTaP-IPV// Hib (booster)
For the subsequent dose please refer Immunisation Schedule				

SUGGESTED IMMUNISATION SCHEDULE FOR VACCINES NOT LISTED IN NATIONAL IMMUNISATION PROGRAM

Vaccines listed below are available in private hospitals or clinics

Pneumococcal (conjugate vaccine)	• Recommended to complete 3 doses within the first year of life starting at 6 weeks of age. • Consult your doctor for the individual recommended schedule according to the age of child receiving the first dose.
Meningococcal	• Recommended for children travelling to high risk area. • Single dose provides immunity up to 3 years
Rotavirus	• Recommended first dose to be given after 6 weeks of age. • Consult your doctor for the subsequent doses and intervals according to the manufacturer recommendation.
Varicella / chicken pox	• For children 12 months and above: 2 doses more than 4 weeks apart
Hepatitis A	• For children above 1 year : 2 doses given 6-12 months apart.

Chapter 3: Paediatric Fluid and Electrolyte Guidelines

Well children with Normal hydration

- Children who are well rarely require intravenous fluids (IV). Whenever possible, use an enteral (oral) route for fluids.
- These guidelines apply to children who are unable to tolerate enteral fluids.
- The safe use of IV fluid therapy in children requires accurate prescribing of fluids and careful monitoring because incorrectly prescribed or administered fluids are hazardous.
- If IV fluid therapy is required then **maintenance fluid requirements should be calculated using the Holliday and Segar formula based on weight.**
- However this should be only be used as a starting point and the individual's response to fluid therapy should be monitored closely by clinical observation, fluid balance, weight and a minimum daily electrolyte profile.

Prescribing Intravenous fluids

Fluids are given intravenously for the following reasons:

- Circulatory support in resuscitating vascular collapse.
- Replacement of previous fluid and electrolyte deficit.
- Maintenance of daily fluid requirement.
- Replacement of ongoing losses.
- Severe dehydration with failed nasogastric tube fluid replacement (e.g. on-going profuse losses, diarrhoea or abdominal pain).
- Certain co-morbidities, particularly GIT conditions (e.g. short gut or previous gut surgery)

For Resuscitation	• Bolus • 0.9% Sodium Chloride • Alternatively and ONLY under direction of Specialist: other crystalloids, e.g. balanced salt solutions, or colloids may be used
For Replacement	• Dehydration or ongoing losses • 0.9% Sodium Chloride or Ringer's /Hartmann 's solution
For Maintenance	• 0.9% Sodium Chloride + 5% Glucose +/- Potassium Chloride 20mmol/L • Alternatively and ONLY under direction of Specialist: 0.45% Sodium Chloride + 5% Glucose +/- Potassium Chloride 20mmol/L or balanced solution

- A Balanced solution is made to a physiological pH and isotonic salt concentration.
- If electrolytes are outside the normal range, discuss with a specialist as necessary.

Electrolyte Composition (mmol/l), Osmolarity and Tonicity of commonly used intravenous solution (Crystalloid)							
Electrolyte	Plasma	0.9% NaCL	0.45%NaCL + Dextrose 5%	Ringer's Lactate/ Hartmann's	Stero-fundin	Plasmalyte 148	0.9%NaCl + Dextrose 5%
Sodium	140	154	77	131	140	140	154
Potassium	5	0	0	5	4	5	0
Chloride	100	154	77	111	127	98	154
Calcium	22	0	0	2	25	0	0
Magnesium	1	0	0	1	1	15	0
Bicarbonate	24	0	0	0	0	0	0
Lactate	1	0	0	29	0	0	0
Acetate	0	0	0	0	24	27	0
Gluconate	0	0	0	0	0	23	0
Maleate	0	0	0	0	5	0	0
Glucose g/L		0	50	0	0	0	50
Osmolarity (mosm/L)	275-295	308	406	273	309	294	560
Tonicity	Isotonic		Hypotonic	Isotonic	Isotonic	Isotonic	Isotonic

Electrolyte Composition (mmol/l), Osmolarity and Tonicity of commonly used intravenous solution (Colloid)			
Electrolyte	Albumin 5%	Gelofusine	Voluven
Sodium	140	150	154
Potassium	0	5	0
Chloride	128	100	154
Calcium	0	0	0
Magnesium	0	0	0
Bicarbonate	0	0	0
Lactate	0	0	0
Acetate	0	0	0
Gluconate	0	0	0
Maleate	0	0	0
Octanoate	64	0	50

Resuscitation

Fluids appropriate for bolus administration are:	
Crystalloids	0.9% Normal Saline Ringer's Lactate @ Hartmann's solution Sterofundin, Plasmalytes
Colloids	Gelafundin 4.5% albumin solution
Blood products	Whole blood, blood components
*Do not use starch based solution i.e. voluven as resuscitation fluid.	

- Fluid deficit sufficient enough to cause **impaired tissue oxygenation (clinical shock)** should be **corrected with a fluid bolus of 10-20mls/kg**.
- **Always reassess circulation** - give repeat boluses as necessary.
- **Look for the cause of circulatory collapse** - blood loss, sepsis, etc. This helps decide on the appropriate alternative resuscitation fluid.
- **Fluid boluses of 10mls/kg in selected situations** - e.g. diabetic ketoacidosis, intracranial pathology or trauma.
- If **associated cardiac conditions**, then use aliquots of **5-10mls/kg**
- **Avoid low sodium-containing (hypotonic) solutions** for resuscitation as this may cause hyponatremia.
- **Measure blood glucose:** treat **hypoglycaemia** with **2mls/kg of 10% Dextrose solution.**
- **Measure Na, K and glucose** at the beginning and at least 24 hourly from then on (more frequent testing is indicated for ill patients or patients with co-morbidities). Rapid results of electrolytes can be obtained from blood gases measurements.
- **Consider septic work-up or surgical consult** in severely unwell patients with abdominal symptoms (i.e. gastroenteritis).

Maintenance

- Maintenance fluid is the volume of daily fluid intake. It includes insensible losses (from breathing, perspiration, and in the stool), and allows for excretion of the daily production of excess solute load (urea, creatinine, electrolytes) in the urine.
- 0.45% Sodium chloride +/- glucose 5% may be used as maintenance fluid and is restricted to specialised areas (high dependency, renal, liver and intensive care unit) to replace ongoing loses of hypotonic fluids.
- Most children will tolerate standard fluid requirements. However some acutely ill children with inappropriately increased anti-diuretic hormone secretion (SIADH) may benefit from their maintenance fluid requirement being restricted to two-thirds of the normal recommended volume.
- **Children at high risk of hyponatremia should be given isotonic solutions (0.9% saline ± glucose)** with careful monitoring to avoid **iatrogenic hyponatremia.** These include children with:
  - Peri-or post-operative
  - Require replacement of ongoing losses
  - A plasma Na^+ at lower range of normal (definitely if < 135mmol/L)
  - Intravascular volume depletion, Hypotension
  - Central nervous system (CNS) infection
  - Head injury
  - Bronchiolitis
  - Sepsis
  - Excessive gastric or diarrhoeal losses
  - Salt-wasting syndromes
  - Chronic conditions such as diabetes, cystic fibrosis and pituitary deficits.

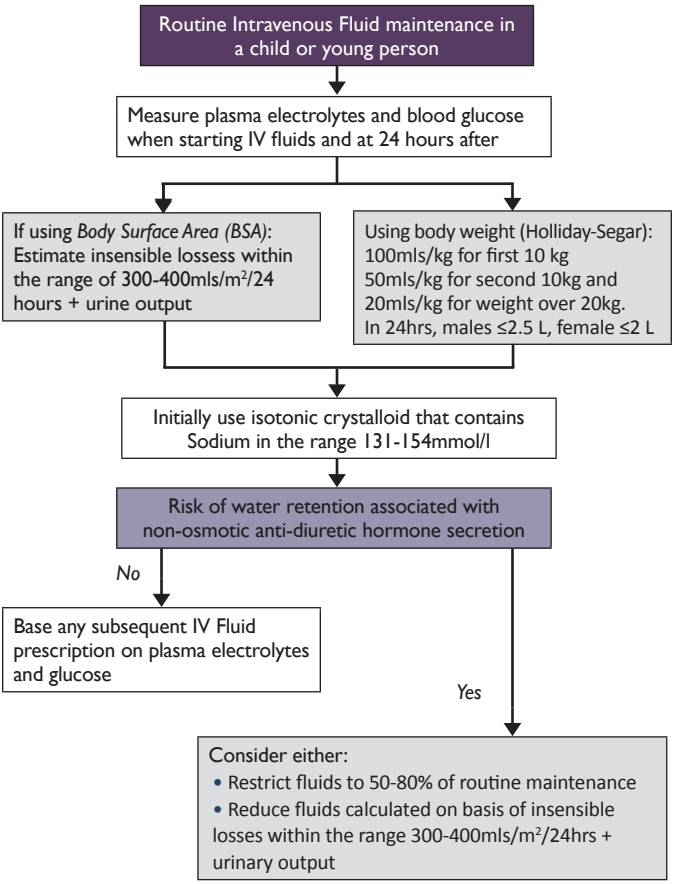
Calculation of Maintanence Fluid Requirements

The following calculations approximate **the maintenance fluid requirement of well children according to weight in kg** (Holliday-Segar calculator).

Weight	Total fluids	Infusion rate
First 10 Kgs	100 ml/kg	4 mls/kg/hour
Subsequent 10 Kgs	50 ml/kg	2 mls/kg/hour
All additional Kg	20 ml/kg	1 ml/kg/hour

Example: A Child of 29 kg will require:		
100mls/kg for first 10kg of weight	10 x 100	= 1000 mls
50mls/kg for second 10kg of weight	10 x 50	= 500 mls
20mls/kg for all additional weight	9 x 20	= 180 mls
	Total	= 1680 mls
	Rate	= 1680/24 = 70mls/hour

Flow Chart for Maintenance Intravenous Fluid Prescription



Deficit

• A child's water deficit in mls can be calculated following an estimation of the degree of dehydration expressed as % of body weight.

Example: A 10kg child who is 5% dehydration has a water deficit of 500mls.		
Maintenance		
100mls/kg for first 10 kg	= 10 × 100	= 1000mls
Infusion rate/hour	= 1000mls/24 hr	= 42mls/hr
Deficit (give over 24hours)		
5% dehydration (5% of body water): 5/100 × 10kg × 1000mls		= 500mls
Infusion rate/hour (given over 24 hrs)	= 500mls/24 hr	= 21mls/hr

- The deficit is replaced over a time period that varies according to the child's condition. Precise calculations (e.g. 4.5%) are not necessary. The rate of rehydration should be adjusted with ongoing clinical assessment.
- Use an isotonic solution for replacement of the deficit, e.g. 0.9% saline.
- Reassess clinical status and weight at 4-6hours, and if satisfactory continue. If child is losing weight, increase the fluid and if weight gain is excessive decrease the fluid rate.
- Replacement may be rapid in most cases of gastroenteritis (best achieved by oral or nasogastric fluids), but should be slower in diabetic ketoacidosis and meningitis, and much slower in hypernatremic states (aim to rehydrate over 48-72 hours, the serum Na should not fall by >0.5mmol/l/hr).

Ongoing losses (e.g. from drains, ileostomy, profuse diarrhoea)

- These are best measured and replaced. Any fluid losses > 0.5ml/kg/hr needs to be replaced.
- Calculation may be based on each previous hour, or each 4 hour period depending on the situation. For example; a 200mls loss over the previous 4 hours will be replaced with a rate of 50mls/hr for the next 4 hours).
- Ongoing losses can be replaced with 0.9% Normal Saline or Hartmann's solution. Fluid loss with high protein content leading to low serum albumin (e.g. burns) can be replaced with 5% Human Albumin.

SODIUM DISORDERS

- The daily sodium requirement is 2-3mmol/kg/day.
- **Normal serum sodium is between 135-145mmol/l.**

Hypernatremia

- **Hypernatremia is defined as serum Na^+ > 150mmol/l,** *moderate* hypernatremia = serum Na^+ is 150-160mmol/l, and *severe* hypernatremia = serum Na^+ > 160mmol/l.
- It can be due to:
  - water loss in excess of sodium (e.g. diarrhoea)
  - water deficit (e.g. diabetes insipidus)
  - sodium gain (e.g. large amount of $NaHCO_3$ infusion or salt poisoning).

Clinical signs of Hypernatremic dehydration
Irritability
Skin feels "doughy"
Ataxia, tremor, hyperreflexia
Seizure
Reduced awareness, coma

- Children **may appear sicker than expected for degree of dehydration.**
- **Shock occurs late because intravascular volume is relatively preserved.**
- Signs of hypernatremic dehydration tend to be predominantly that of intracellular dehydration and neurological dysfunction.
- In hypernatremia due to **central diabetes insipidus**, consult Endocrinology.

Management

For hypernatremic dehydration with Na^+> 150mmol/l:

- **If the patient is in shock, give volume resuscitation with 0.9% Normal saline as required with bolus/es.**
- **Avoid rapid correction** as may cause cerebral oedema, convulsion and death.
- Aim to correct deficit over 48-72 hours and fall of serum $Na^+ \leq 0.5$mmol/l/hr.
- Give 0.9% Sodium Chloride to ensure the drop in sodium is not too rapid.
- Remember to give maintenance fluids and replace ongoing losses
- **Repeat blood urea and electrolytes** every 6 hours until stable.
- If hypernatraemia worsens or is unchanged after replacing deficit, review fluid type and consider changing to a hypotonic solution (e.g. 0.45% Sodium Chloride with dextrose).
- If no evidence of dehydration and an isotonic fluid is being used, consider changing to a hypotonic fluid (e.g. 0.45% Sodium Chloride with dextrose).
- If the fluid status is uncertain, measure urine sodium and osmolality.
- When correcting hypernatraemia, ensure that the rate of fall of plasma sodium < 12 mmol/litre in a 24-hour period (0.5mmol/l/hour).
- Measure plasma electrolytes every 4–6 hrs for the first 24 hrs, and the frequency of further electrolyte measurements depends on response.

Special considerations

- Use a slower rate in chronic Hypernatraemia (present for > 5 days).
- Measure **Calcium and glucose** as hypernatremia can be associated with hypocalcaemia and hyperglycemia, and need to be corrected concurrently.

Hyponatremia

- **Hyponatremia is defined when serum Na^+ < 135mmol/l.**
- **Hyponatremic encephalopathy is a medical emergency** that requires rapid recognition and treatment to prevent poor outcome.
- **Symptoms** associated with acute hyponatraemia during IV fluid therapy: Headache, nausea, vomiting, confusion, disorientation, irritability, lethargy, reduced consciousness, convulsions, coma, apnoea.

Calculating sodium correction in acute hyponatremia	
mmol of sodium required	= (135-present Na level)× 0.6 × weight(kg)
The calculated requirements can then be given from the following available solutions dependent on the availability and hydration status:	
0.9% sodium chloride contains **154 mmol/l of Sodium**	
3% sodium chloride contains **513mmol/l of Sodium**	

- In acute symptomatic hyponatraemia in term neonates and children, review the fluid status, seek immediate expert advice (for example, from the paediatric intensive care team) and consider taking action as follows:
  - A 2 ml/kg bolus (max 100 ml) of 3% Sodium Chloride over 10–15 mins.
  - A further 2 ml/kg bolus (max 100 ml) of 3% Sodium Chloride over the next 10–15 mins if symptoms are still present after the initial bolus.
  - If symptoms are still present after the 2nd bolus, check plasma sodium level and consider a third 2ml/kg bolus (max 100 ml) of 3% Sodium Chloride over 10–15 mins.
  - Measure the plasma sodium concentration at least hourly.
  - As symptoms resolve, decrease the frequency of plasma sodium measurements based on the response to treatment.
  - Do not manage acute hyponatraemic encephalopathy using fluid restriction alone.
  - After hyponatraemia symptoms have resolved, ensure that the rate of increase of plasma sodium does not exceed 12 mmol/l in a 24-hr period.
- Children with **asymptomatic hyponatremia** do not require 3% sodium chloride treatment and if dehydrated may be managed with oral fluids or intravenous rehydration with 0.9% sodium chloride.
- Children who are hyponatremic and have a normal or raised volume status should be managed with fluid restriction.
- For Hyponatremia secondary to **diabetic ketoacidosis**; refer DKA protocol.

POTASSIUM DISORDERS

- The daily potassium requirement is 1-2mmol/kg/day.
- **Normal values of potassium are:**
  - **Birth - 2 weeks: 3.7 - 6.0mmol/l**
  - **2 weeks – 3 months: 3.7 - 5.7mmol/l**
  - **3 months and above: 3.5 - 5.0mmol/l**

Hypokalemia

- **Hypokalemia is defined as serum K^+ < 3.4 mmol/l**
  (Treat if < 3.0mmol/l or Clinically Symptomatic and < 3.4 mmol/l)
- Causes are:
  - Sepsis
  - Gastrointestinal losses
    - diarrhoea, vomiting
  - Iatrogenic- e.g. diuretic therapy, salbutamol, amphotericin B.
  - Diabetic ketoacidosis
  - Renal tubular acidosis
- Hypokalaemia is often seen with chloride depletion and metabolic alkalosis
- **Refractory hypokalaemia** may occur with hypomagnesaemia.

ECG changes of Hypokalemia
These occur when K^+ < 2.5mmol/l
Prominent U wave
ST segment depression
Flat, low or diphasic T waves
Prolonged PR interval (severe hypoK^+)
Sinoatrial block (severe hypoK^+)

Treatment

- Identify and treat the underlying condition.
- **Unless symptomatic, a potassium level of 3.0 and 3.4 mmol/l is generally not supplemented** but rather monitored.
- The treatment of hypokalaemia will need to be individualized for each patient.

Oral Supplementation

- Oral Potassium Chloride (KCL), to a maximum of 2 mmol/kg/day in divided doses is common but more may be required in practice.

Intravenous Supplementation (1gram KCL = 13.3 mmol KCL)

- **Potassium chloride is always given by IV infusion, *NEVER* by bolus injection.**
- **Maximum *concentration* via a peripheral vein is 40 mmol/l** (concentrations of up to 60 mmol/l can be used after discussion with senior medical staff).
- **Maximum *infusion rate* is 0.2mmol/kg/hour** (in non-intensive care setting).

Intravenous Correction (1gram KCL = 13.3 mmol KCL)

- K^+ < 2.5 mmol/L may be associated with significant cardiovascular compromise. In the emergency situation, an IV infusion KCL may be given
  - Dose: initially 0.4 mmol/kg/hr into a central vein, until K^+ level is restored.
  - Ideally this should occur in an intensive care setting.

POTASSIUM DISORDERS

- The daily potassium requirement is 1-2mmol/kg/day.
- **Normal values of potassium are:**
  - **Birth - 2 weeks: 3.7 - 6.0mmol/l**
  - **2 weeks – 3 months: 3.7 - 5.7mmol/l**
  - **3 months and above: 3.5 - 5.0mmol/l**

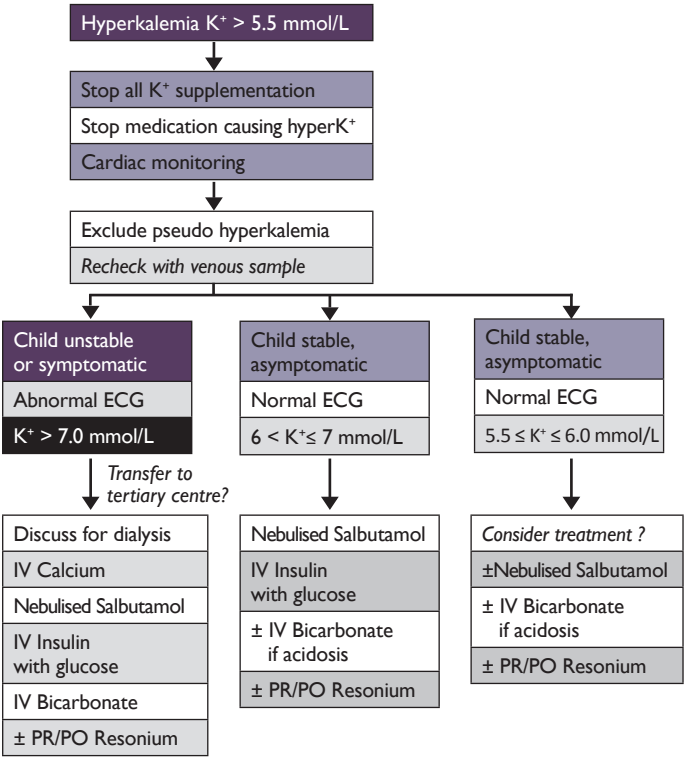
Hyperkalemia

- Causes are:
  - Dehydration
  - Acute renal failure
  - Diabetic ketoacidosis
  - Adrenal insufficiency
  - Tumour lysis syndrome
  - Drugs e.g. oral potassium supplement, K^+ sparing diuretics, ACE inhibitors.

ECG changes in Hyperkalemia
Tall, tented T waves
Prolonged PR interval
Prolonged QRS complex
Loss of P wave, wide biphasic QRS

Treatment: *Follow Algorithm on next page*

HYPERKALEMIA TREATMENT ALGORITHM



Drug doses:

- IV Calcium 0.1 mmol/kg.
- Nebulised Salbutamol:
  Age ≤2.5 yrs: 2.5 mg; Age 2.5-7.5 yrs: 5 mg; >7.5 yrs: 10 mg
- IV Insulin with Glucose:
  Start with IV Glucose 10% 5ml/kg/hr (or 20% at 2.5 ml/kg/hr).
  Once Blood sugar level >10mmol/l and the K^+ level is not falling, add IV Insulin 0.05 units/kg/hr and titrate according to glucose level.
- IV Sodium Bicarbonate: 1-2 mmol/kg.
- PO or Rectal Resonium : 1Gm/kg.

Age	Gross Motor	Fine Motor	Speech/Language	Self-care, Social Behaviour & Play
6 wks	*Pulled to sit:* Head lag and rounded back. *Ventral Suspension:* Head held up momentarily in same plane as body. *Prone:* Pelvis high but knees no longer under abdomen. Chin raised intermittently off couch. Head turned to one side.	Fixates on objects. In supine, follows object from side to midline (90°) Defensive blink by 6-8 weeks	Quietens to sound at 4 weeks. Vocalises when talked to at 8 weeks.	Social smile.
3 mths	*Pulled to sit:* Only slight head lag. Head occasionally bobs forward. *Ventral Suspension:* Head held up above plane of body. *Prone:* Pelvis flat. Lifts head up 45° - 90°, weight supported on forearms	Hand regard. Follows dangling toy from side to side (180°) Hands loosely open. Holds rattle placed in hand momentarily.	Squeals of pleasure. Says 'aah' or 'naah' when spoken to. Turns head to sound at the same level.	Sustained social contact. Responds with pleasure to friendly handling.

Age	Gross Motor	Fine Motor	Speech/Language	Self-care, Social Behaviour & Play
6 mths	*Pulled to sit:* Lifts head off couch. Sits with support. Bears full weight on legs. *Prone:* Supports weight on hands with chest and upper part of abdomen off couch. Rolls over from prone to supine at 5-6 mths, supine to prone at 6-7 mths.	Palmar grasp of cube. Drops one cube when another is given at 6 mths, retains one cube at hand when another is offered at 7 mths. Transfers object from one hand to another at 7 mths. Eyes move together (any squint is abnormal). Follows activities across room with alertness.	Smiles and vocalises at mirror image. Monosyllabic babble. Polysyllabic sounds formed-ba,da,ka at 7 mths. Turns head towards a sound above the level (7 to 9 months).	Mouthing. Place hand on bottle and pats it. Grasps feet. Stretches arms out to be carried. Shows delighted response to rough and tumble play. Still friendly with strangers, becomes more reserved after 7 mths.
9 mths	Sits steadily. Leans forward to pick toy without losing balance. Pulls self to stand. Stands holding on to furniture. Progresses on the floor by rolling, wriggling on abdomen or crawling.	Pokes at small object & begins to point at distant object with index finger. Inferior pincer grasp. Release toy by dropping or pressing against firm surface. Looks in correct direction for fallen toys. Grasp string to pull toy (causal understanding).	Babbles loudly in long repetitive syllables. Responds to name. Understands 'No' and 'Bye- bye' Imitates playful sounds e.g. cough, 'brrr' Localises sound above and below the ear level.	Mouthing. Holds and bites small piece of food. Stranger anxiety. Plays Peek-a-boo, imitates hand clapping. Waves bye-bye. Understands 'object permanence'

Age	Gross Motor	Fine Motor	Speech/Language	Self-care, Social Behaviour & Play
12 mths	Gets from lying to sitting to crawling to standing. Walks on hands and feet like a bear. Walks with one hand held. Stands alone. May walk alone.	Neat pincer grasp. Bangs 2 cubes. Points with index finger at object of interest.	Knows and responds to name. Babbles in conversational cadences. Understands simple instructions. 1 - 3 words with meaning. Locates sounds in all directions.	Drinks from cup with assistance, helps with dressing. Gives toys on request. Finds toys hidden from view. Demonstrates affection to family. Enjoys joint interactive play with adults. Plays "Pat-a-Cake"
15 mths	Creeps up stairs. Walks alone with broad based gait.	Tower of 2 cubes. Hold 2 cubes in one hand. To and fro scribble with palmar grasp.	Jargon. 2-6 intelligible words. Obeys simple commands. Points to familiar persons, toys when requested.	Holds and drinks from cup, attempts to hold spoon. Functional play e.g. pushing toy car. Repeated casting.
18 mths	Walks well, runs rather stiffly though seldom falls. Carry large doll or teddy while walking. Walks up and downstairs with help. Squats to pick up toy.	Tower of 3 cubes. Enjoys putting small objects in and out of containers. Scribbles spontaneously. Enjoys picture books, turns few pages at a time. Hand preference.	Jargon. 6-20 intelligible words. Points to 2 - 3 body parts.	Imitates housework. Uses spoon well. Assists with dressing. Mouthing stops. Casting less often. Plays contently alone but likes to be near familiar adult.

Age	Gross Motor	Fine Motor	Speech/Language	Self-care, Social Behaviour & Play
2 years	Runs safely, avoiding obstacles. Goes up and down stairs alone, 2 feet per step. Able to walk backward pulling toy handle. Walks into large ball while trying to kick it.	Tower of 6 - 7 cubes. Imitates train of cubes, without adding chimney. Circular scribbles. Imitates vertical line. Enjoys picture books and turns pages singly.	Uses 50 or more words. Uses 2 - 3 word phrases. Points to 6 body parts. Names familiar objects and pictures. Follows a series of 2 simple but related commands. Joins in nursery rhymes and sings.	Puts on shoes, socks, pants. Dry by day. Parallel play. Watches others play and plays near them, but not with them. Pretend play. Tantrums when frustrated but attention is usually easily distracted.
2.5 years	Jump with 2 feet together from a low step. Stand on tiptoe if shown. Kicks large ball gently.	Tower of 7- 8 cubes. Imitates train, adding chimney. Recognizes minute details in picture books. Imitates and	Speaks in phrases. Frequently asks questions (What, Who). Uses pronouns (I, me, you) correctly. Knows full name. Can select pictures of action e.g. which one is eating.	May be dry by night, variable. Eats skilfully More sustained role play e.g. putting dolls to bed, feeding them. Tantrums when thwarted and is less distracted.

Age	Gross Motor	Fine Motor	Speech/Language	Self-care, Social Behaviour & Play
3 years	Goes up stairs one foot per step and down stairs 2 feet per step. Walk on tiptoe. Stands on 1 foot momentarily. Rides tricycle. Kicks ball forcibly, throw a ball overhand.	Tower of 9 - 10 cubes. Imitates bridge with 3 cubes. Copies  Imitates  Draw a man on request (3 - 10y). Cuts with scissors	Gives full name, gender, sometimes age. Uses personal pronouns and most prepositions correctly. Ask many questions (What, where, who) Identify objects by function e.g. which one we drink from. Counts by rote up to 10 or more but does not appreciate quantity beyond 2 or 3. Names 2 colours.	Eats independently, washes hands. May be dry by night. Joins in active make believe play with other children. Understands sharing toys.
4 years	Walks or runs up and down stairs one foot per step. Stand, walk and run on tiptoe. Stands on one foot for 3-5 seconds and hops on one foot.	Builds 3 steps with 6 cubes after demonstration. Holds pencil with good control. Copies cross. Draws a person with head, legs and trunks. Matches 4 primary colours.	Speech grammatically correct and completely intelligible Names 4 colours. Gives full name, address and age. Listens to and tells long stories. Counts by rote up to 20 and begins to count by word and touch up to 4 or 5.	Brushes teeth, dresses independently except for laces, ties and back buttons. Imaginative dressing up and make believe play. Understands need for turn taking in play. Appreciates past, present and future time.

Age	Gross Motor	Fine Motor	Speech/Language	Self-care, Social Behaviour & Play
5 years	Walks on narrow line. Skips on alternate feet. Balance on one foot for 8-10 seconds. Dances to music.	Copies square at 5 years and a triangle at 5 ½ years. Colours neatly, staying within outlines. Draws a man with head, trunk, legs, arms and features. Can cut a strip of paper neatly.	Names birthday and home address. Defines nouns by use. Uses "first, then, last" (time and sequence concepts). Enjoys jokes and riddles. Tells time.	Dresses and undresses alone. Engages in elaborate make believe group play. Chooses own friends. Cooperative with companions and understands need for rules and fair play.

Chapter 5: Developmental Assessment

Development is defined as the progressive and orderly acquisition of skills and abilities as a child grows.
It is influenced by genetic, neurological, physical, environmental and emotional factors.

Global developmental delay (GDD)

- Defined as delay in 2 ≥ developmental domains of gross/fine motor, speech/language, cognition, social/personal and activities of daily living, affecting children under the age of 5 years.
- GDD is considered significant when there is a deficit in performance of at least 2 SD below the age appropriate mean on accepted standardised assessment tests.
- Intellectual disability (ID) is the term used after 5 years when cognitive and adaptive functions can be reliably tested.

Key Developmental Warning Signs	
1	Discrepant head size or crossing centile lines (too large or too small).
2	Persistence of primitive reflexes > 6 months of age
3	No response to environment or parent by 12 months
4	Not walking by 18 months
5	No clear spoken words by 18 months
6	No two word sentences by 2 years
7	Problems with social interaction at 3 years
8	Congenital anomalies, odd facies
9	Any delay or failure to reach normal milestones
Note: Parental concerns must always be taken seriously	

Important points to note when assessing a child with developmental delay

- Child must be co-operative, not tired, fretful, hungry or sick. Children may behave differently in an unfamiliar environment.
- Allowance must be made for prematurity up to two years.
- Note parental account of what child can or cannot do and concerns on gait, speech etc.
- Ensure child's hearing and vision are normal.
- Normal speech and language development is essential for normal social, intellectual and emotional development.

History

- Significant family history, consanguinity
- Antenatal: maternal illness, ingestion of drugs, alcohol, smoking.
- Birth: prematurity, perinatal asphyxia
- Postnatal: severe neonatal jaundice, hypoglycaemia or seizures
- Serious childhood infections, hospital admissions or trauma
- Home environment, stimulation (environmental deprivation)

Physical examination

- Head circumference, growth, dysmorphic features, neurocutaneous markers
- Neurological abnormalities
- Full developmental assessment
- Observation of behaviour, social interaction and play

Clinical pointers to consider referral to a Paediatric Neurologist/ Developmental Paediatrician

Features in the history

- Regression or possible regression including significant change in behaviour
- Possible or definite seizures
- Movement disorder: continuous or paroxysmal
- Muscle pain/fatigue
- New onset sensory impairment, e.g. significant decline in visual acuity
- Cognitive decline/behavioural change in a child with epilepsy or autism spectrum disorder

Examination findings

- Neurological signs: dystonia, ataxia, chorea, focal signs, cranial neuropathy, peripheral neuropathy, arthrogryposis/joint contractures
- Cerebral Palsy picture without a clear cause/history
- Ocular signs: cataract, nystagmus, eye movement disorder, abnormal fundi

Investigations

Should be individualised based on clinical assessment. Abnormal neurology, microcephaly, dysmorphism, and abnormal prenatal or perinatal history are linked with higher yield.

- Visual & hearing assessment must be done.
- Genetic tests
  - Molecular karyotyping
  - Specific tests: Fragile X (FMR1), Prader Willi or Angelman syndrome
  - Recent guidelines promote use of array-based comparative genomic hybridisation (aCGH) (only available in genetic clinics).
- Second-line genetic tests
  To refer to clinical geneticist when syndromic features are present.
- Metabolic & Biochemical
  - Blood
    - Urea & electrolytes, Creatine Kinase, Thyroid Function Test, Full Blood Count
    - Amino Acid, Homocysteine, Acylcarnitine Profile
  - Urine
    - Organic Acid, Oligosaccharides, Creatine/GAA, Purine and pyramidines
- MRI brain
  Higher yield when associated with microcephaly, non-familial macrocephaly, rapid change in head circumference, focal neurological signs or epilepsy.
- EEG if history of seizures

Consider
Hypothyroidism
Chromosomal anomaly
Cerebral palsy
Congenital intrauterine infection
Congenital brain malformations
Inborn errors of metabolism
Autism spectrum disorder
Attention deficit hyperactivity disorder
Prior brain injury, brain infections
Neurocutaneous disorders
Duchenne's muscular dystrophy

ASSESSMENT OF CHILDREN WITH SPEECH DELAY OR SUSPECTED HEARING IMPAIRMENT

History

- Congenital infection
- Perinatal medications
- Severe neonatal jaundice
- Family history of deafness or speech delay
- Chronic ear infections
- Quality, quantity of speech

Physical examination

- Examine ears
- Dysmorphic features
- Distraction Test
- Assess expressive and receptive speech
- Neurological / developmental assessment

Warning Signs for Hearing Impairment	
1	Child appears not to hear
2	Child makes no attempt to listen.
3	Does not respond to name, "No" or clue words e.g. "Shoe", by 1 yr age
4	Any speech/language milestone delay

Consider
Congenital sensorineural deafness
Familial, genetic deafness
Congenital rubella infection
Congenital Cytomegelovirus infection
Oro-motor dysfunction

Management

- Formal hearing assessment
- Speech-language assessment and intervention

Hearing Tests at different ages		
Age	Test	Comments
Newborn screening	Automated Otoacoustic Emission (OAE) test	Determines cochlear function. Negative test in conductive hearing loss, middle ear infections, or in moderate to severe sensorineural hearing loss.
Any age	Brainstem Auditory Evoked Responses (BAER)	Measures brainstem responses to sound. Negative test in sensorineural hearing loss
7-9 months	Infant Distraction Test (IDT)	Determines response to sound whilst presented during a visual distraction.
Infants	Behavioural Observation Assessment (BOA) test	Audiologist identifies bodily reactions to sound, i.e. cessation of activity, body movement, eye widening and opening suckling rate.
> 2.5 years	Conditioned Play Audiometry	Earphones placed on child and various games are done when test tone is heard.
Older Children	Pure Tone Audiometry	Patient presses a response button or raises a hand when the test tone is heard

ASSESSMENT OF CHILDREN WITH SUSPECTED VISUAL IMPAIRMENT

Children at risk

- Prematurity
- Intrauterine Infection (TORCHES)
- Family history of cataract, squint or retinoblastoma
- Previous history of meningitis or asphyxia
- Syndromic children

Warning Signs for Visual Impairment	
1	Does not fix on mother's face by 6 wks
2	Wandering or roving eyes after 6 wks
3	Abnormal head postures
4	Leukocoria (white eye reflex)
5	Holds objects very close to eye.
6	Squint after 6 months of age.

ASSESSMENT OF CHILDREN WITH SUSPECTED LEARNING DIFFICULTIES

It is sometimes a challenge to identify the primary cause of the learning difficulty as many of them share common symptoms.

A. Detailed history

- Antenatal, perinatal and postnatal complications
- Relevant maternal history including substance abuse
- Family history of development delay, learning difficulties, mental illness
- Detailed history of developmental milestones
- When learning problems were first noted (preschool achievement, etc.)
- Past and current academic performance
- Details on area of difficulties (e.g. reading, writing, arithmetic difficulties) and areas of strength (e.g. visual memory)
- Adaptive functioning
- Behaviour
- Home environment, social background and stimulation. Include exposure to learning.

B. School performance

- Review concerns with patient, parents and teachers (Include teachers report).
- Common symptoms include apathy towards school, avoidance or poor performance and disruptive or negative behaviour in certain classes/subjects
- Review report card, school workbooks and examination papers.

C. Basic Cognitive (intellectual functioning) screening tool in Paediatric Clinic

- Ask child to talk about a recent event: birthday, visit to grandparents etc. (note whether language is fluent, coherent, organized).
- Ask parents whether child has difficulty retaining instructions in classroom or at home (short term memory).
- Observe handwriting and use of pencil to copy symbols/words (fine motor/visual perceptual disorder, easy distractibility)
- Ask the child to perform a 3-step command (sequencing ability, to understand information in an orderly and meaningful manner)
- Ask the child to say 4 words, remember them and repeat them when asked in 5-10 minutes (memory, attention).
- Ask the child to repeat 3, then 4 digits forward then repeat them backward (concentration).

D. Physical Examination

- Anthropometric measurement
- General alertness and response to surrounding
- Dysmorphism, neurocutaneous stigmata
- Complete CNS examination including eye hand coordination to look for motor coordination difficulties
- Complete developmental assessment.
- Draw a man or anything child likes (for an estimate on cognitive level)* *See Scoring Next Pages: in the Goodenough Draw A Person Test*

Block and Pencil test (From *Parry TS: Modern Medicine, 1998*)		
Age	Block Test	Pencil Test
3 - 3.5 yrs	Build a bridge 	Draw a circle 
3.5 - 4 yrs		Draw a cross 
3 - 4.5 yrs	Build a gate 	Draw a square 
5 - 6 yrs	Build steps 	Draw a triangle 
This test screens cognitive and perceptual development for age. Block test: build the structure without child observing then ask the child to copy the structure. Pencil test: Draw the object without child observing then ask the child to copy it.		

E. Differential Diagnosis

- Autism Spectrum Disorder (ASD)
- Attention Deficit Hyperactivity Disorder (ADHD)
- Specific learning disorder like Dyslexia, Dyscalculia, Dysgraphia
- Intellectual Disability
- Developmental Coordination Disorder
- Limited environmental stimulation
- Genetic disorders e.g. Fragile X
- Endocrine disorders e.g. Hypothyroidism
- Neurological disorders e.g. Tourette's, Neurofibromatosis, Epilepsy, Neurodegenerative disorders
- Other causes: Anaemia, Toxins (foetal alcohol syndrome, prenatal cocaine exposure, lead poisoning)
- Auditory or visual impairment

F. Management

- Depends on the primary cause
- Dyslexia screening test if available
- DSM-5 for ASD or ADHD (Refer Clinical Practise Guidelines)
- Refer occupational therapist for school readiness/ preparedness (pencil grip, handwriting, attention span) or motor coordination difficulties
- Refer speech therapist (if indicated)
- Hearing and visual assessment
- School placement and extra support.
  - Discuss with parents & child and set realistic goals
  - Placement in mainstream/inclusive/ integrated class
  - One-to-one learning may be beneficial
  - Extra training at government/private/NGO intervention centres depending on availability and feasibility
- Registration as *Child with Special Need*s as per clinical indication and after discussion with parents

G. Investigations

Consider the following if clinically indicated:

- Genetic tests
- IEM screening
- TSH/ Creatine Kinase
- MRI brain/EEG

When is IQ Testing Indicated?

- When diagnosis is unclear and there is a need to determine appropriate school placement.
- If unsure of diagnosis, refer patient to a Developmental Paediatrician, Child Psychiatrist or Clinical Psychologist depending on availability of services in your area.

GOODENOUGH DRAW – A – PERSON TEST

DIRECTIONS: "I want you to make a picture of a person. Make the very best picture that you can. Take your time and work very carefully. Try very hard and see what a good picture you can make."

TIME: No time limit. Usually 10 minutes will suffice with young children. This test is to be used primarily as a screening device. The drawings of bright children more than 10 years old or those who have had drawing lessons will result in an invalid evaluation of the child's intellectual potential.

SCORING

CLASS A Preliminary Stage in which the drawing cannot be recognized as a human figure:

1. Aimless uncontrolled scribbling – score 0.
2. Lines somewhat controlled – approaches crude geometrical form – score 1.

CLASS B All drawings that can be recognized as attempts to represent the human figure. Each point is scored plus or minus. One credit for each point scored plus and no half credits given.

GROSS DETAIL

1. Head present
2. Legs present.
3. Arms present
4. Trunk present
5. Length of trunk greater than breadth.
6. Shoulders are indicated (abrupt broadening of trunk below neck)

ATTACHMENTS

1. Both arms and legs attached to trunk.
2. Arms and legs attached to trunk at correct points.
3. Neck present.
4. Outline of neck continuous with that of head, trunk, or both.

HEAD DETAIL

1. Eyes present (one or two)
2. Nose present
3. Mouth present
4. Nose and mouth in two dimensions, two lips shown.
5. Nostril shown
6. Hair shown
7. Hair on more than circumference of head and non-transparent – better than a scribble.

CLOTHING

1. Clothing present (any clear representation of clothing)
2. Two articles of clothing non transparent (ex. Hat, trousers)
3. Entire drawing free from transparencies – sleeves and trousers must be shown.
4. Four articles of clothing definitely indicated. *should include 4 – hat, shoes, coat, shirt, necktie, belt, trousers*
5. Costume complete with incongruities *business suit, soldier's costume and hat, sleeves trousers and shoes must be shown*

HAND DETAIL

1. Fingers present (any indication)
2. Correct number of fingers shown
3. Fingers in two dimensions – length greater than breadth, angle subtended not greater than 180 degrees
4. Opposition of thumb clearly defined
5. Hand shown distinct from fingers and arm

JOINTS

1. Arm joint shown – elbow, shoulder, or both
2. Leg joint shown – knee, hip, or both

PROPORTION

1. Head not more than ½ or less than 1/10 of trunk
2. Arms equal to trunk but not reaching knee
3. Legs not less than trunk not more than twice trunk size
4. Feet in 2 dimensions – not more than 1/3 or less than 1/10 of leg
5. Both arms and lens in two dimensions

MOTOR COORDINATION

1. Lines firm without marked tendency to cross, gap, or overlap.
2. All lines firm with correct joining.
3. Outline of head without obvious irregularities. Develop beyond first crude circle. Conscious control apparent.
4. Trunk outline. Score same as #3.
5. Arms and legs without irregularities. 2 dimensions and no tendency to narrow at point of junction with trunk.
6. Features symmetrical (more likely to credit in profile drawings)

FINE HEAD DETAIL

1. Ears present (2 in full face, 1 in profile)
2. Ears present in correct position and proportion.
3. Eye details – brow or lashes shown.
4. Eye detail – pupil shown.
5. Eye detail – proportion. Length greater than width.
6. Eye detail – glance – only plus in profile.
7. Chin and forehead shown.

PROFILE

1. Projection of chin shown – usually + in profile.
2. Heel clearly shown
3. Body profile – head, trunk, and feet without error.
4. Figure shown in true profile without error or transparency.

SCORE	MA	SCORE	MA	SCORE	MA	SCORE	MA
1	3-3	14	6-6	27	9-9	40	13-0
2	3-6	15	6-9	28	10-0	41	13-3
3	3-9	16	7-0	29	10-3	42	13-6
4	4-0	17	7-3	30	10-6	43	13-9
5	4-3	18	7-6	31	10-9	44	14-0
6	4-6	19	7-9	32	11-0	45	14-3
7	4-9	20	8-0	33	11-3	46	14-6
8	5-	21	8-3	34	11-6	47	14-9
9	5-3	22	8-6	35	11-9	48	15-0
10	5-6	23	8-9	36	12-0	49	15-3
11	5-9	24	9-0	37	12-3	50	15-6
12	6-0	25	9-3	38	12-6	51	15-9
13	6-3	26	9-6	39	12-9		

IN FINDING THE IQ OF DELAYED CHILDREN WHO ARE > 13 YEARS OLD, THE CHRONOLOGICAL AGE SHOULD BE TREATED AS 13 ONLY, AND THE IQ RECORDED AS "OR BELOW."

IT IS NOT WISE TO ATTEMPT TO USE THIS TEST WITH BRIGHT CHILDREN OF MORE THAN 12 YEARS OF AGE.

Chapter 6: Specific Learning Disorder

Specific learning disorder is a neurodevelopmental disorder which affect the brain's ability to perceive or process verbal or nonverbal information efficiently and accurately.

DSM-5 Diagnostic Criteria

A. Difficulties learning as indicated by the presence of at least 1 of the following for at least 6 months, despite provision of adequate intervention:
1. Inaccurate or slow and effortful word reading.
2. Difficulty understanding the meaning of what is read.
3. Difficulties with spelling.
4. Difficulties with written expression.
5. Difficulties mastering number sense, number facts, or calculation.
6. Difficulties with mathematical reasoning.

B. The affected academic skills are below expected for the individual's chronological age and cause significant interference with academic performance or ADL as confirmed by standardized achievement measures and comprehensive clinical assessment.

C. May begin during school-age years but may not become fully manifest until later, when the academic requirements exceed the child's limited capacities.

D. Not better accounted for by intellectual disability, sensory impairments, mental or neurological disorders, psychosocial adversity or inadequate educational exposure.

In Specific Learning Disorder more than one domain may be affected:

- Impairment in reading which affects word reading accuracy, reading rate or fluency and reading comprehension. *Dyslexia* is an alternative term used. Dyslexia is characterized by problems with accurate or fluent word recognition, poor decoding and poor spelling abilities.
- Impairment in written expression which affects spelling accuracy, grammar and punctuation accuracy and clarity or organization of written expression
- Impairment in mathematics which affects number sense, memorization of arithmetic facts, accurate calculation and reasoning. *Dyscalculia* is an alternative term used.

Commonly co-occurs with other neurodevelopmental/psychiatric disorders

- ADHD
- Language Impairment, Speech Sound Disorder
- Developmental coordination disorder,
- Autism Spectrum Disorder
- Anxiety disorders

Some first signs suggestibe of dyslexia	
Preschool and Kindergarten	
Language	• May have difficulty pronouncing words and slow to add new vocabulary words • May be unable to recall the right word • Trouble learning nursery rhymes or playing rhyming • Trouble learning to recognize letters of the alphabet (important predictor of later reading skills: recognition of letters of alphabets starts before decoding)
Memory	• Difficulty remembering rote information (name, phone number, address)
Fine motor skills	• Fine motor skills may develop more slowly than in other children
Lower Grades in School	
Language	• Delayed decoding abilities for reading • Trouble following directions • Poor spelling and using of pronouns, verbs
Memory	• Slow recall of facts • Organizational problems • Slow acquisition of new skills
Attention	• Impulsive, easily distractible and careless errors
Fine motor skills	• Unstable pencil grip • Trouble with letter formation
Visual skills	• Confuses words, e.g. at –to, does –goes, etc • Consistent reading and spelling errors • Transposes number sequence, maths signs (+,- X/=)
Middle Grades of School	
Language	• Poor reading comprehension • Trouble with word problems • Lack of verbal participation in class
Memory	• Slow or poor recall of math facts and failure of automatic recall
Attention	• Inconsistency and poor ability to discern relevant details
Fine motor skills	• Fist-like or tight pencil grip • illegible, slow or inconsistent writing
Visual skills	• May reverse sequences (e.g.: soiled for solid)

Higher Grades in School	
Language	• Weak grasp of explanation • Poor written expressions • Trouble summarizing
Memory	• Trouble studying for test • Slow work pace
Attention	• Memory problems due to poor attention • Mental fatigue
Fine motor skills	• Less significant
Visual skills	• Misreads information • Trouble taking multiple choice questions • Difficulty with sequencing (maths, music and science: physics)

MANAGING CHILDREN WITH SPECIFIC LEARNING DISORDER

History

- What are the learning problems, when they were noted?
- Current problems faced at school
- Developmental history (esp. speech and language, fine motor)
- Family history (esp. speech delay and learning disorders)
- Significant birth and medical history (prematurity, perinatal asphyxia)
- Assessment of school work (esp. exam papers and teacher's report)
- Interventions and extra support received

Physical Examination

- Growth parameters , microcephaly
- Visual and Hearing impairment
- Syndromic facies, Neurocutaneous stigmata
- Complete neurological examination.
- Developmental assessment: Look for difficulties in coordination, motor sequencing and balance, fine motor (handwriting, copying shapes and patterns), receptive and expressive language, reading, and comprehension of written instructions, phonological awareness, verbal short term and verbal working memory and observation of behaviour (attention, task avoidance)

Investigations

- Depends on clinical presentation. Most children with Specific Learning Disorders do not require any investigations.
- Specific assessment (Dyslexia Early Screening Test) if available. Standardized Cognitive Assessment (Wechsler Intelligence Scale for Children) when diagnosis is unclear.

Differential Diagnosis

- Intellectual Disability
- Inadequate academic exposure
- Learning difficulties due to neurological or sensory disorders. (paediatric stroke, traumatic brain injury, hearing or visual impairment)
- Neurocognitive disorders where difficulties manifest as regression from a former state.
- Attention-deficit/hyperactivity disorder. ADHD can co-occur with specific learning disorder.

Management

- School placement: Discuss with parents on placement in mainstream/ inclusive/integrated class, registration as a child with special needs.
- Extra support: Tuition, intervention centres depending on availability. Most effective when provided in one-to-one or small-group setting.
- Occupational therapy for fine motor and visual perceptual training.
- Speech therapy for speech and language impairments.

Suggestions for School Based Interventions

- Phonics-based reading program, teaching link between spoken and written sounds
- Multi-sensory approach to learning
- Learning via audiotape or videotape
- Supported reading of increasingly difficult text, writing exercises and comprehension strategies
- Arrange for readers and extra time for exams (will need letter to school)

Features of Dyslexia that can be elicited in the General Paediatric Clinic Setting
(Refer to tables in following pages)

- Assessment needs to be done in accordance to the child's level of cooperation (may require more than 1 visit)
- This is not a standardized, validated assessment. When in doubt refer to a Developmental Paediatrician or an Educational Psychologist, depending on availability of services.

At the end of the assessment, please answer these 2 questions below, and tick the appropriate column.

Question	Yes	No
1. Does the limitation in reading, spelling and writing cause significant learning difficulty in school?		
2. From your clinical assessment do you agree that the IQ of the child is appropriate for age?		

If the answer to the **both the above questions is "yes"** then the probable diagnosis is **Specific Learning Disorder.**

Skill	Features	Examples	How to Test in Clinic
Reading	Unable to read appropriately for age	Give age appropriate passage or books	Listen to the child read aloud from his or her own grade level reader. (Keep a set of graded readers available in your clinic)
	Child may appear visibly tired after reading for only a short time		
	Reading will be slow, labored, inaccurate reading of even single words (ensure that there is no visual cues while doing this)	Single Word Reading • Boy • Chair • Kite • Hope	Show single words as suggested and ask child to read.
	Unable to read unfamiliar words or pseudo words and usually will try to guess or make up words because of some familiarity.	• Pilau = Pulau • Karusi = Kerusi • Maja = Meja	
Phonological processing / awareness	Difficulty in differentiating words that sounds alike	• Mana • Nama • Mama • Dapat • Padat	Consider the educational background of the child
Letter Indentification	Difficulty to name letters of the alphabet	A, B, C, D, E . . .	Prepare a table of alphabets and ask child to read out (ensure you point to the alphabets that you want the child to read). Take note that child maybe able to recite from memory

Skill	Features	Examples	How to Test in Clinic
Letter-Sound Association	Difficulty identifying words beginning with the same letter	• Doll, Dog, etc • Buku, buka, etc	
Segmentation	Difficulty in identifying word that would remain if a particular sound were removed	• What remains if the /k/ sound was taken away from "cat" = at • What remains if the /Ta/ sound taken away from "table"= ble • What remains if the /p/ sound was taken away from "paku" = aku • What remains if the sound /ma/ sound taken away from "mata" = ta	
Short term Verbal memory (eg, recalling a sentence or a story that was just told)	Difficulty recalling a sentence or a story that was just told	Narrate story to the child then ask questions like: • Apa nama kuching Ali? • Tompok suka makan apa? • Di mana Ali pergi memancing?	Have a short story which goes like this: "Ali ada seekor kuching bernama Tompok. Tompok suka makan ikan. Ali pergi memancing ikan di sungai dan memberikan ikan itu kepada Tompok."

Skill	Features	Examples	How to Test in Clinic
Rapid Naming	Difficulty in rapidly naming a continuous series of familiar objects, digits, letters, or colors	Use flash cards with pictures only, colours or numbers	Can use numbers for rapid naming or to test ability of remembering numbers in a reverse order. Ask child to name colours. If child not be able to do so ask child to point to a particular colour in a book. Usually the child will not have difficulty in doing so.
Expressive vocabulary or word retrieval	Difficulty in listing out name of animals or objects		Give me the names of animals you know
Rote memory	Difficulty in memorizing non-meaningful facts (facts that are not personally interesting and personally relevant)	• Multiplication tables • Days of the week or months of the year in order	Ask child to recite simple multiplication table or to say out days of the week or months of the year in order.
Sequencing steps in a task	Difficulty in performing task that needs sequencing	• Tying shoelaces • Printing letters: can't remember the sequence of pencil strokes necessary to form that letter. May write a in an odd way	

Skill	Features	Examples	How to Test in Clinic
Spelling	Difficulty in spelling even simple words that is age appropriate	• Buku, meja, mata, sekolah, etc	Ask child to do simple spelling with 2 syllables first if able to do then proceed to multisyllable words
Directionality	Left-Right confusion Up-Down confusion	• Substitution : b-p or d-q, n-u, and m-w • Confusion about directionality words: First-last, before-after, next-previous, over-under	
Dysgraphia	Poor, nearly illegible handwriting or difficulty in writing on a straight line. Difficulty in differentiating small or big letters. Unusual spatial organization of the page.	• Words may be widely spaced or tightly pushed together. • Margins are often ignored.	Observe school workbook for writing problems.
Copying	Difficulty in copying from blackboard Takes a long time to copy and copied work will have a lot of mistakes	• Tying shoelaces • Printing letters: can't remember the sequence of pencil strokes necessary to form that letter. May write a in an odd way	Observe school workbook which needs copying

Chapter 7: The H.E.A.D.S.S. Assessment

A Psychosocial Interview for Adolescents

Introduction

Adolescence is the developmental phase between childhood and adulthood and is marked by rapid changes in physical, psychosocial, sexual, moral and cognitive growth.

Dr. Cohen refined a system for organizing the developmentally-appropriate psychosocial history that was developed in 1972 by Dr. Harvey Berman.

The approach is known by the acronym **HEADSS** (**H**ome, **E**ducation /employment, peer group **A**ctivities, **D**rugs, **S**exuality, and **S**uicide/depression). It was subsequently expanded to **HEEADSSS** by adding **E**ating and **S**afety.

Preparing for the Interview

Parents, family members, or other adults should not be present during the HEADSS assessment unless the adolescent specifically gives permission, or asks for it.

Starting the interview

1. *Introduction*
   Set the stage by **introducing yourself** to the adolescent and parents. If the parents are present before the interview, **always introduce yourself to the adolescent first.**
2. *Understanding of Confidentiality*
   Ask the adolescent to **explain** their understanding of confidentiality.
3. *Confidentiality Statement*
   After the adolescent has given you his/her views, acknowledge his/her response and add your views accordingly (confidentiality statement), based on the particular situation.

The HEADSS assessment Items are in listed in the following pages

Suggestions for ending interviews with adolescents

- give them an opportunity to express any concerns you have not covered, and ask for feedback about the interview.
- ask if there is any information you can provide on any of the topics you have discussed. Try to provide whatever educational materials young people are interested in.

Item	Examples of Questions
Home	• Who lives at home with you? Where do you live? Do you have your own room? • How many brothers and sisters do you have and what are their ages? • Are your brothers and sisters healthy? • Are your parents healthy? What do your parents do for a living? • How do you get along with your parents, your siblings? • Is there anything you would like to change about your family?
Education	• Which school do you go to? What grade are you in? Any recent changes in schools? • What do you like best and least about school? Favourite subjects? Worst subjects? • What were your most recent grades? Are these the same or different from the past? • How much school did you miss last/this year? Do you skip classes? Have you ever been suspended? • What do you want to do when you finish school? • How do you get along with teachers? How do you get along with your peers? • Inquire about "bullying".
Employment	• Are you in any full time or part time job?
Eating	• What do you like and not like about your body? • Has there been any recent change in your weight? • Have you dieted in the last one year? How? How often? • How much exercise do you get on an average day ?Week? • Do you worry about your weight? How often? • Does it ever seem as though your eating is out of control? • Have you ever made yourself throw-up on purpose to control your weight?

Item	Examples of Questions
Activities	• Are most of your friends from school or somewhere else? Are they the same age as you? • Do you hang out with mainly people of your same sex or a mixed crowd? • Do you have a lot of friends? • Do you see your friends at school and on weekends, too? • Do you do any regular sport or exercise? Hobbies or interests? • How much TV do you watch? What are your favourite shows? • Dave you ever been involved with the police? Do you belong to a group or gang?
Drugs	• When you go out with your friends, do most of the people that you hang out with drink or smoke? Do you? How much and how often? • Have you or your friends ever tried any other drugs? Specifically, what? • Do you regularly use other drugs? How much and how often?
Sexuality	• Have you ever been in a relationship? When? • Have you had sex? Number of partners? Using contraception? • Have you ever been pregnant or had an abortion? • Have you ever been checked for a sexually transmitted infection (STI)? • Knowledge about STIs and prevention? • For females: Ask about menarche, last menstrual period (LMP), and menstrual cycles. Also inquire about breast self examination (BSE) practices. • For males: Ask about testicular self-examination (TSE) practices.

Item	Examples of Questions
Suicide, Depression	• Do you have difficulties to sleep? Has there been any change in your appetite recently? • Do you mix around well others? Do you have hopeless or helpless feelings? • Have you ever attempted suicide?
Safety	• Have you ever been seriously injured? Do you always wear a seatbelt in the car? • Do you use safety equipment for sports and or other physical activities (for example, helmets for biking)? • Is there any violence in your home? Does the violence ever get physical? • Have you ever been physically or sexually abused? • Have you ever been bullied? Is that still a problem? • Have you gotten into physical fights in school or your neighborhood? Are you still getting into fights?

Chapter 8: End of Life Care in Children

Introduction

Paediatric palliative care is 'an active and total approach to care embracing physical, emotional and spiritual elements. It focuses on quality of life for the child and support for the family and includes management of distressing symptoms, provision of respite and care through death and bereavement'. [1]

When the disease trajectory of the child has reached the final days, actively dying is generally defined as the hours or days preceding imminent death during which time, the patient's physiologic functions wane.[2]

Signs and symptoms that a child is actively dying: [3,4,5,6]

- Behaviour and mental state– profound tiredness and weakness, reduced interest towards surroundings, feeling irritable, hallucination, lack of concentration, restlessness.
- Breathing – changes in breathing pattern or noisy breathing
- Circulation – signs of reduced peripheral circulation (skin colour and capillary refill time)
- Oral intake and elimination – difficulty in swallowing medicine, reduced interest in food and fluid intake, reduced urine and stool output.

During this phase, the following are principles of care

For the Child

- Aim to provide good symptom management – refer to section on "Symptom control in dying children".
- Symptom Care Plan – an individualized step-approached care plan based on distress symptoms which may occur during the active dying phase, with steps of symptom management for family or local medical team and contact information for further consultation with key palliative care providers.
- Communication – provides clear, understandable, consistent, up-to-date, either verbally or in written form for the child based on topics important to them, by taking into account their age and level of understanding, and the concerns of parents or carers. If possible, the child should be involved in all aspects of decision-making, including Advanced Care Planning.
- Provides regular opportunity to discuss with the children about their emotional, psychological and spiritual concerns[13] either by direct discussion, or through play, art and music activities.
- Discontinuation of unnecessary interventions such as routine observations, routine blood tests, and the use of intravenous or subcutaneous fluids and rationalisation of prescribed medicines.

For Parents/Carers/Family members

- Revision of Advance Care Planning – the care plan should be reviewed regularly, at appropriate intervals. It should contain :
  - Demographic information about the children and their family
  - Up-to-date contact information of both parents/carers and key involved professionals
  - A statement about who has the responsibility for giving consent
  - A summary of the life-limiting condition
  - An agreed approach of providing information to the children and their family
  - An outline of the child's ambitions and wishes
  - Agreed treatment plans and objectives
  - Education plans, if relevant
  - Record of discussion about preferred place of care and death, management of life-threatening events (personal resuscitation plan)
  - A distribution list for the Advance Care Plan
- Discuss and provide information about funeral arrangements.
- Provide parents/carers the information of professional contacts (including ambulance services and key palliative care providers) in the event of further deterioration and death at home.
- Revisit the parents/carers' understanding of the methods of home medication administration.
- Offer parents/carers the support and guidance of how to talk about the impending death of their child with other siblings
- Provides parents/carers the access to respite care, if available.
- Offer school visit to meet with the staff of the school of the children and their siblings if necessary. It provides the chance for school staff to address their concerns regarding their care and support for the child or siblings in the educational setting.
- Based on availability of resources and parents/carers concerns, they should be provided with financial support, spiritual or chaplaincy support and emotional support by the named key providers.
- After the death of the child, parents/carers should be provided information and support regarding process of transferring home (if died in hospital), registration of death, organ donation, and the subsequent plan for bereavement support.

For the Child's and Carer's Environment

- The child and their parents/carers should be offered hospice referral (if available and agreed by the child and the parents/carers), as well as the continued communication with local shared care hospital or community teams if their preferred place of care and death is at home.
- Ambience, private room /environment should be provided (if available) which allow the family members to have free access to visit the child in hospital.

Pain - Nociceptive		

Signs and Symptoms
• Somatic pain – well localized, deep or superficial, may described as aching, stabbing, throbbing or pressure.
• Visceral pain – poorly localized, may described as cramping, aching, sharp, referred pain to shoulder tip.
	Possible Causes /Issues
	• Somatic pain: stimulation of skin, muscle or bone receptors (eg: pressure sores, muscle spasm, bone metastasis)
	• Visceral pain: from infiltration, distension or compression of thoracic or abdominal viscera (eg: liver capsule, bowel colic)
	• Various Contributing Factors:
	  • Biological (eg: musculoskeletal)
	  • Environmental (eg: noise)
	  • Psychological (eg: anxiety, depression)
	  • Social, spiritual, cultural (eg: loneliness)
		Management
		Pain assessment tool[15] and pain diary according to child's developmental ability
		Non-Pharmacology
		• Relaxation (reduce noise, music, guided imagery, physical contact e.g. hold, touch, massage)
		• Local hot/cold applications
		• Comfort measures (e.g. sucrose for neonates)
		Pharmacology
		• Analgesia: Following WHO Guideline[14]
		• 2. Adjuvant- Steroids, NSAIDs, radiotherapy, palliative chemotherapy, biphosphonate

Pain - Neuropathic		
Signs and Symptoms • Paresthesia, altered sensation e.g. shooting, sharp intense, burning • Temperature irregulation • Pain to light touc h(allodynia)	**Possible Causes /Issues** • Treatment related neuropathy • Infiltrating malignancy	**Management** Pain assessment and non-pharmacology management: same as nociceptive pain *Pharmacology* • Anticonvulsant: Gabapentin/Pregabalin • Anti-depressant: Amitriptyline • Capsaicin cream 0.075% /Menthol aqueous cream • Lidocaine 5% transdermal patch • Corticosteroids e.g. Dexamethasone (tumour infiltrate)

Agitation		
Signs and Symptoms • Agitated (restless, irritability, aggressive behaviour, crying) • Delirium (confusion, disrupted attention, disordered speech, hallucinations)	**Possible Causes /Issues** • Medical disorders (disease related, pain, hypoxia, electrolyte imbalance, dehydration, urinary retention, constipation) • Psychology (fear, anxiety, depression) • Side effects of medication (eg ketamine)	**Management** *Non-Pharmacology* • Reassurence patient and their family • Promote calm and peach environment (e.g. reduce noise and lighting, provide familiar objects/people) *Pharmacology* • Treat the reversible causes • Benzodiazepines (eg midazolam, lorazepam) • Neuroleptics (e.g. Haloperidol, Levomepromazine)
Pain - Neuropathic		
Signs and Symptoms • Episodes of vacant attacks • Facial or eye twitching • Loss of consciousness • Bradycardia, apnoea, cyanosis • Aura (e.g. unusual smell/feeling) • Loss of bladder/bowel contro • Post-ictal sleep	**Possible Causes /Issues** • Disease related • Raised intracranial pressure • Fever • Drug reactions • Sleep deprivation • Pain • Electrolyte imbalance • To differentiate from abnormal non-seizure movements (eg: dystonic spasms)`	**Management** *Non-Pharmacology* • Include seizure management in ACP • Explain to parents on identification of seizure and home management (written guideline) • Maintain airway

		Pharmacology • Treat reversible causes • Short acting benzodiazepine (if seizure >5 mins) e.g. buccal midazolam/rectal diazepam/IV lorazepam • Consider PR paraldehyde if seizure deos not stop • To review/consider start regular anticonvulsant (e.g. levetiracetam/phenytoin) • For refractory terminal seizures, consider midazolam or phenobarbitone infusion
Excessive Airway Secretions		
Signs and Symptoms • Excessive swallowing • Drooling • Noisy Breathing • Recurrent chest infections	**Possible Causes /Issues** • Swallow impairment due to disease • Excessive hypotonia (disease, medication) • Reduced level of consciousness • Pneumonia • Side effects of medication (eg ketamine)	**Management** *Non-Pharmacology* • Semi-recumbent positioning • Effective oral care including cleaning teeth • Use barrier cream to protect lower chin (e.g. Vaseline) • Consider oral suction and postural drainage *Pharmacology* • Consider treat pneumonia with oral antibiotic • Consider antimuscarinic agents (e.g. Scopolamine patch, Glycopyrronium bromide) if secretions not thick • For thick secretions, consider nebulised saline

Difficulty in Breathing		
Signs and Symptoms • Tachypnoea, chest recession • Tracheal tug • Cyanosis, tachycardia • Tired /Fatigue • Laboured breathing	**Possible Causes /Issues** • Lung: Infection, malignancy, effusion, pneumothorax, Upper airway obstruction • Cardiac: failure, SVC obstruction, embolism • Extrathoracic: massive ascites, anaemia • Psychology: Anxiety/Panic	**Management** *Non-Pharmacology* • Position: Sit upright/ leaning forward over pillow • Air: open window, use fan (blow to face) • Relaxation techniques • Distraction and mirroring (face to face support slowing of breathing) • Pacing in walk/activities (more rest) *Pharmacology* • Treat reversible causes: Infection, anaemia, ascites, pleural effusion, pneumothorax (chest tube) • Secretion management (see symptom above) • Consider anxiolytics/sedative agents for anxiety: Midazolam, lorazepam • Consider trial of oxygen supplementation (if SPO_2 < 92%) • Low dose opioids to relieve dyspnea sensation (15%-30% of pain dosage). • Keep mouth moist • Diuretics for heart failure

Nausea and Vomiting		
Signs and Symptoms • Signs of raised Intracranial pressure (eg: headache, sleepy) • Abdominal: No bowel open, bile vomitus, abdominal pain • Dehydration (dry mouth, reduce urine output, sunken eye)	**Possible Causes /Issues** • Disease or treatment related • Constipation/intestinal obstruction • Raised Intracranial pressure • Infection • GORD • Trigger: cough, movement, food, smells, anticipatory	**Management** *Non-Pharmacology* • Assess trigger factors • Hot/cold packs for abdominal pain • Encourage small amount of diet/fluid as tolerable • Consider nasogastric tube if indicated *Pharmacology* • Treat reversible causes (reduce or change causative treatment/medicine, laxative for constipation) • Regular anti-emetics (choice guided by causes) and review symptoms by 24-48 hours • Consider Intravenous/subcutaneous fluid if dehydrated • Consider anti-reflux medication • Consider Dexamethasone (post chemo/tumour control)

Bleeding		
Signs and Symptoms • Pallor, bruises, lethargy, agitated, dehydration, confusion • Haematemesis • Haemoptysis • Epistaxis • Malaena • Bleeding from stoma, drains, gums	**Possible Causes /Issues** • Disease /treatment related (e.g. malignancy) • Clotting deficiency or DIVC (sepsis)	**Management** *Non-Pharmacology* • Use soft tooth brush for teeth brushing • Nose bleed: pinch nose + cold compression, consider refer ENT for packing • Use dark coloured towels for large amounts of vomit orcoughed-out blood • Haemostatic dressing (e.g. Alginate) for skin trauma *Pharmacology* • Bleed may be exacerbated by fever: consider antipyretics • Anti-fibrinolytic : eg Tranexamic acid • Vasoconstrictor: eg topical Adrenaline • Catastrophic/terminal bleed: consider sedation and analgesia (eg: midazolam /opioid) for pain, agitation, restlessness distress • Consider blood products transfusion if indicated • Consider radiotherapy for solid tumour bleeding

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Chapter 9: Principles of Transport of the Sick Newborn

Introduction

- Transport of neonates involves pre-transport intensive care level resuscitation and stabilisation and continuing intra-transport care to ensure that the infant arrives in a stable state.
- Organized neonatal transport teams bring the intensive care environment to critically ill infant before, during and after transport.
- Good communication and coordination between the referring and receiving hospital is essential.
- There is rarely a need for haste.
- However, there must be a balance between the benefits of further stabilization versus anticipated clinical complications that may arise due to delay in the transport.

Special Considerations in Neonates

Apnoea
Premature and septic babies are especially prone to apnoea

Bradycardia
Hypoxia causes bradycardia followed by heart block and asystole

Oxygen toxicity to the lungs and retina
especially important in the premature infant

Reversal to fetal circulation (Persistent pulmonary hypertension of the neonate, PPHN)
Precipitating factors: hypoxia, hypercarbia, acidosis, sepsis and hypothermia

Hypothermia
Thermoregulation is less developed, infant has a larger body surface area to mass ratio. If bowels are exposed, heat and fluid loss are compounded by evaporation. The effects of hypothermia are acidosis and subsequent PPHN, impaired immune function and delayed wound healing.

Hypoglycemia
The neonate lacks glycogen stores in liver and fat deposits.

Mode of transport

- Careful consideration must be made as to the mode of transport.
- The best mode of transfer is "in utero", e.g. a mother in premature labour should be managed in a centre with NICU facilities or for an antenatally detected surgical, the mother should be advised to deliver at a centre with paediatric surgical facilities.
- The advantages and disadvantages of road, air (helicopter / commercial airlines) and riverine transport must be considered in each child
- Transport incubators with monitors, ventilators, oxygen and suction equipment are ideal.

Air Transport

Patients can be transported by either commercial airlines with pressurised cabins or by helicopters flying without pressurised cabins at lower altitudes. There are special problems associated with air transport:

- *Changes in altitude* – Reduced atmospheric pressure causes decreased oxygen concentration and expansion of gases. This may be important in infants with pneumothorax, pneumoperitoneum, volvulus and intestinal obstruction. These must be drained before setting off as the gases will expand and cause respiratory distress. Infants requiring oxygen may have increased requirements and become more tachypnoeic at the higher altitude in non-pressurised cabins.
- *Poor lighting* - Can make assessment of child difficult .
- *Noise and Vibration* – May stress the infant and transport team; May also cause interference with the monitors, e.g. pulse oximeters. Use ear muffs if available. It is also impossible to perform any procedures during transport.
- *Limited cabin space* – Limits access to the infant especially in helicopters. Commercial aircraft and helicopters are unable to accommodate transport incubators. The infant is thus held in the arms of a team member.
- *Weather conditions and availability of aircraft* – Speed of transfer may be compromised by unavailability of aircraft/flight or weather conditions. Stress and safety to the infant and team during poor weather conditions needs to be considered.
- *Take off and landing areas* – special areas are required and there will be multiple transfers: hospital – ambulance – helicopter – ambulance - hospital.
- *Finances* – Air transport is costly but essential where time is of essence.

Pre-transport Stabilisation

Transport is a significant stress and the infant may easily deteriorate during the journey. Hypothermia, hypotension and metabolic acidosis has a significant negative impact on the eventual outcome. Procedures are difficult to do during the actual transport. Therefore, pre-transport stabilization is critical.

The principles of initial stabilisation of the neonate

(see tables on following pages)

Airway
Breathing
Circulation, **C**ommunication
Drugs, **D**ocumentation
Environment, **E**quipment
Fluids – electrolytes, glucose
Gastric decompression

The principles of initial stabilisation of the neonate

Airway

Establish a patent airway

Evaluate the need for oxygen, frequent suction (Oesophageal atresia) or an artificial airway (potential splinting of diaphragm).

Security of the airway – The endotracheal tubes (ETT) must be secure to prevent intra-transport dislodgement

Chest X-ray – to check position of the ETT

Breathing

Assess the need for intra-transport ventilation. Does the infant have:

- Requirement of FiO2 60% to maintain adequate oxygenation.
- ABG – PaCO2 > 60mmHg.
- Tachypnoea and expected respiratory fatigue.
- Recurrent apnoeic episodes.
- Expected increased abdominal/bowel distension during air transport.

If there is a possibility that the infant needs mechanical ventilation during the transfer, it is safer to electively intubate and ventilate before transport. Check the position of the Endotracheal tube before setting off.

In certain conditions it may be preferable not to ventilate, e.g. tracheo-oesophageal fistula with distal obstruction. If in doubt, the receiving surgeon/paediatrician should be consulted. If manual ventilation is to be performed throughout the journey, possible fatigue and the erratic nature of ventilation must be considered.

Circulation

Assess:

- Heart rate, Urine output, Current weight compared to birth weight - are good indicators of hydration status of the newborn infant.

Also note that:

- Blood pressure in infants drops just before the infant decompensates.
- Minimum urine output should be 1-2 mls/kg /hr.
- The infant can be catheterised or the nappies weighed (1g = 1 ml urine)
- Ensure reliable intravenous access (at least 2 cannulae) before transport.
- If the infant is dehydrated, the infant must be rehydrated before leaving.

The principles of initial stabilisation of the neonate

Communication

Good communication between referring doctor, transport team and neonatologist / paediatric surgeon aids proper pre-transfer stabilization, coordination, timing of transfer, and preparedness of receiving hospital.

- Inform receiving specialist, emergency department of receiving hospital.
- Provide Name and telephone contact of referring doctor and hospital
- Provide patient details
- Give a clear history, physical findings, provisional diagnosis, investigations
- Detail current management and status of the infant
- Discuss mode of transport, expected departure time, arrival at referral centre
- Decide on destination of the patient (e.g. A&E, NICU, Ward)

Drugs as required

- Antibiotics – needed in most sick neonates
- Analgesia or Sedation – if infant has peritonitis or is intubated
- Inotropes
- Vitamin K
- Sodium bicarbonate

Documentation

- History including antenatal and birth history, physical findings, diagnosis
- Previous and current management
- Previous operative and histopathology notes, if any
- Input/output charts
- Investigation results, X-rays
- Consent – informed and signed by parents for high risk infants and especially if parents are not accompanying child.
- Parents' contact address, telephone numbers, if not accompanying infant.
- 10 mls of Mother's blood for cross match, if she is not accompanying infant.

Environment

Maintain a **Neutral Thermal Environment**

Optimal temperature for the neonate (axilla) – 36.5 ^{0}C– 37.0 ^{0}C.

Prevention of heat loss involves maintaining an optimal ambient temperature as well as covering the exposed surfaces.

- Transport Incubator – would be ideal.
- Wrap limbs of the infant with cotton, metal foil or plastic.
- Do not forget a cotton-lined cap for the head.
- Remove all wet linen as soon as possible.
- Care of exposed membranes. (See section on Abdominal Wall Defects)
- Warm intravenous fluids.
- ELBW placed in polyethylene bags for newborn infants to prevent heat loss by evaporation.

The principles of initial stabilisation of the neonate

Environment (continued)

Special Consideration.
In **Hypoxic Ischaemic Encephalopathy**, *therapeutic hypothermia* may be indicated. Please discuss with receiving neonatal team prior to transfer.

Equipment *(see Table at end of chapter)*

Check all equipment: completeness and function before leaving hospital.

- Monitors- Cardiorespiratory monitor/ Pulse oximeter for transport. If unavailable or affected by vibration, a praecordial stethoscope and a finger on the pulse and perfusion will be adequate.
- Syringe and/or infusion pumps with adequately charged batteries. If unavailable, intravenous fluids prepared into 20 or 50ml syringes can be administered manually during the journey via a long extension tubing connected to the intravenous cannulae.
- Intubation and ventilation equipment; Endotracheal tubes of varying sizes.
- Oxygen tanks – ensure adequacy for the whole journey.
- Suction apparatus , catheters and tubings.
- Anticipated medication and water for dilution and injection.
- Intravenous fluids and tubings. Pre-draw fluids, medication into syringes if required during the journey. Tubings must not cross each other or under tension to avoid dislodgement.

Fluid therapy

Resuscitation Fluid

- Give boluses of 10 - 20 mls/kg over up to 2 hours as per clinical status
- Use Normal Saline or Hartmann's solution.
- If blood loss then use whole blood or pack red cells.

This fluid is also used to correct ongoing measured (e.g. orogastric) or third space losses as required. The perfusion and heart rates are reliable indicators of the hydration.

- If ongoing or anticipated losses in surgical neonates, e.g. gastroschisis, intestinal obstruction, , then use 0.45% Saline + 10% Dextrose
- Watch out for hyponatraemia and hypoglycemia. Always check glucose level via a bedside glucometer before transport and regularly if indicated.

Gastric decompression

- An orogastric tube is required in most surgical neonates, especially in intestinal obstruction, congenital diaphragmatic hernia or abdominal wall defects.
- The oral route is preferred as a larger bore tube can be used without compromising nasal passages (neonates are obligatory nasal breathers).
- As an orogastric tube is easily dislodged, check the position regularly.
- 4 hourly aspiration and free flow of gastric contents is recommended.

Immediately before Departure

- Check vital signs and condition of the infant.
- Check and secure all tubes.
- Check the equipment.
- Re-communicate with receiving doctor about current status and expected time of arrival.
- Ensure parents are updated on their baby's condition pre transport and emotional support is offered during and post transport.

Intra-transport Care

- **Transport Team.** Ideally, there should be a specialised neonatal transport team. Otherwise, a neonatal-trained doctor with/without a neonatal trained staff nurse should escort the infant. A minimum of 2 escorts will be required for a ventilated/critically ill infant. The team should be familiar with resuscitation and care of a neonate.
- **Safety of the team must be a priority.** Insurance, life jackets and survival equipment should be available.
- **Monitoring.** Regular monitoring of vital signs, oxygenation and perfusion of the infant should be performed.
- **Fluids.** Intravenous fluids must be given to the ill infant to prevent dehydration and acidosis during the transport. Boluses need to be given as necessary depending on the haemodynamic assessment . If catheterised, the urine output can be monitored. The orogastric tube should be aspirated and kept on free drainage. Losses are replaced as required.
- **Temperature Regulation.** Check temperature intermittently. Wet clothes should be changed especially in the infant with abdominal wall defects. Disposable diapers and one way nappy liners are useful.

Arrival at the Receiving Hospital

- Reassessment of the infant
- Handover to the resident team

Intrahospital Transport

- Use transport incubator if available.
- Ensure all parties concerned are ready before transfer.
- Send team member ahead to commandeer lifts, clear corridors.
- Ensure patient is stable before transport.
- Skilled medical and nursing staff should accompany patient.
- Ensure adequate supply of oxygen.
- Prepare essential equipment and monitors for transport.
- Ensure venous lines are patent, well secured.
- Infusion pumps should have charged batteries. To decrease bulk of equipment, consider cessation of non-essential infusions.

Pre-Departure Checklist	
Equipment	
	Transport incubator (if available)
	Airway and intubation equipment are all available and working (ET tubes of appropriate size, laryngoscope, Magill forceps)
	Batteries with spares
	Manual resuscitation (Ambu) bags, masks of appropriate size
	Suction apparatus
	Oxygen cylinders-full and with a spare
	Oxygen tubing
	Nasal oxygen catheters and masks, including high-flow masks
	Infusion pumps
	Intravenous cannulae of various sizes
	Needles of different sizes
	Syringes and extension tubings
	Suture material
	Adhesive tape, scissors
	Gloves, gauze, swabs (alcohol and dry)
	Stethoscope, thermometer
	Nasogastric tube of different sizes
	Pulse oximeter
	Cardiac monitor (preferably with ECG leads), if indicated
	Portable Ventilator, if indicated
Patient Status	
	Airway is secured and patent (do a post-intubation chest X-ray before departure to make sure ET tube is at correct position.)
	Venous access is adequate and patent (at least 2 IV lines) and fluid is flowing well.
	Patient is safely secured in transport incubator or trolley.
	Vital signs are charted.
	Tubes - all drains (if present) are functioning and secured .

Pre-Departure Checklist *(continued)*	
Medications	
	Intravenous fluids • 0.9% Normal Saline • Hartmann's solution • 5% Albumin in Normal Saline • 0.18% Saline with 10% Dextrose • 0.45% Saline with10% Dextrose • 10% Dextrose water
	Inotropes • Dopamine • Dobutamine • Adrenaline
	Sedative/ Analgesia • Morphine • Midazolam
	Blood product if indicated
	Others • Atropine • Sodium bicarbonate • Sterile water for injection • Normal saline for injection • Antibiotics if indicated
Documentation	
	Patient notes, referral letter
	X-rays
	Consent form
	Vital signs chart
	Input, Output charts
	Maternal blood (for infant less than 6 months)

Chapter 10: General Pointers for Care and Review of Newborn Infants (NICU)

Checklist for Review of an infant in Intensive Care

- *Age* of infant, if <72 hours state in exact hours of age. Beyond this, state in completed days.
- *Weight* : Note birth weight and current weight. An initial drop in weight is to be expected for newborn infants, term up to 10% BW in the first 3-5 days and preterm up to 15% in first 1 week. Less weight loss is expected with the use of humidified incubators. Abnormal weight gain or losses in the first few days often implicate suboptimal fluid therapy
- *General condition* is to be noted - e.g. ill, unstable, handles poorly, desaturates on handling, stable, active, responsive to handling, improving, or good tone
- *Cardiopulmonary* system.
  - Check for:
    - Adequacy of the blood pressure – an estimate of normal BP for preterm infant is that of the gestational age at birth . However, there is no necessity to treat immediately if the baby is stable, responsive and of good tone. Review after one hour to check for improvement in the BP
    - Signs of poor perfusion (with poor peripheral pulses, rapid pulse, poor capillary refilling and cold peripheries) – but these signs have not been found to be very reliable for hypotension. Hypothermia can also be a cause of poor perfusion
    - Examine for presence of PDA in preterm infants
  - If BP is low and there has been a history of volume loss at birth or risk of sepsis, infuse a fluid bolus of 10 ml/kg of Normal Saline. This may be repeated if there is no improvement. After the 2nd dose of normal saline, 5% albumin can be considered for volume expansion in severely hypotensive infants.

    Caution: Risk of IVH in repeat doses especially in ELBW or ill preterm infants – check first for volume loss or reduced vascular volume due to extravascular fluid losses such as in sepsis or intestinal obstruction. Albumin is required only in severe sepsis such as in NEC.
  - Inotropic agents like adrenaline, dobutamine or dopamine may be needed. Consider hydrocortisone in ill preterm infant at birth if no response to volume or inotropes. Check that there is no iatrogenic hyperventilation as a cause of hypotension.
- *Fluids and Electrolytes*.
  - Is the volume and type of fluid given to the child appropriate?

    Empiric fluid therapy for newborns:
    0-24 hours : 60 ml/kg/day
    24-48 hours : 90ml/kg/day
    48-72 hours : 120ml/kg/day
    > 72 hours : 150 ml/kg/day
  - Lower rate of increment for preterm infants of 20 mls/kg/day. More increment may be needed if evidence of dehydration – excessive weight loss and hypernatraemia >145 mmol/L.

- Generally 10% dextrose is started on the 1st day and sodium and potassium is added on the second/ third day.
- Total parenteral nutrition should be started as soon as possible for the infant below 1000 -1250 grams, preferably within the first day of life. Larger preterm infants may be started on parenteral nutrition if expected to not able to be fed enterally for 5 or more days (e.g. congenital diaphragmatic hernia, omphalocele/gastrochiasis).
- Empirically
  - A preterm baby needs 4-5 mmol/kg/day of sodium and 2-3 mmol/kg/day of potassium.
  - ELBW infants are prone for hyperkalaemia and adjustments should be made based on electrolytes.
  - Term infant 2-3 mmol/kg/day of both sodium and potassium.
- Fluid and electrolyte therapy will be influenced by the child's underlying illness and complications and adjustments will have to be made based on these conditions:
  - intake/output, weight, blood urea and electrolytes (BUSE).
- Monitor BUSE and correct any imbalances after considering the underlying cause.
- Ensure the urine output is > 1 ml/kg/hr .after the first day of life

- *Infection*
  - Is there a possibility of infection? Is the child on antibiotics?
  - Fungal infection should be considered if the infant is a preterm infant who has been on several courses of broad spectrum antibiotics and on total parenteral nutrition.
  - Consider discontinuing antibiotics if the blood culture is negative and the patient improved "too quickly" after starting antibiotics, probably responding to other measures such as dehydration or inadequate ventilatory support.
- Feeding
  - Enteral feeds can be given via oro or nasogastric tube- orogastric tube is preferred in small infants as it prevents blockage of the airway.
  - Encourage expressed breast milk to be started within the first 1-2 days of life.
- *Temperature Control*
  - Use of cling wrap/plastic wrap with cap soon for preterm infants after delivery help to maintain normothermia.
  - Under the radiant warmer, covering the open area of open hoods with cling wrap and increasing water content with a humidifier will help in temperature control and fluid regulation of the ELBW infant.
  - Transfer to a closed humidified incubator as soon as possible.
  - Ensure thermoneutral environment.
  - Humidity is essential to maintain temperature in the extremely preterm infants and reduce excessive weight loss in the first few weeks of life.

- Below is a humidification guide for preterm infants.

26 weeks gestation and below	27-30 weeks gestation
80% Humidity for at least 4 wks (may require higher % to cope with increased sodium)	80% Humidity for at least 2 wks
The infant's skin should have keratinised fully at the end of this period, therefore the humidity can be gradually reduced, as tolerated, to maintain a satisfactory axillary temperature	
Reduce the humidity gradually according to the infant's temperature (70% - 60% - 50%) until 20-30% is reached before discontinuing.	

- *Skin care*
  - A vital component of care especially for the premature infants.
  - Avoid direct plastering onto skin and excessive punctures for blood taking and setting up of infusion lines.
  - Meticulous attention must be given to avoid extravasation of infusion fluid and medication which can lead to phlebitis, ulceration and septicaemia.
  - Group your blood taking together to minimise skin breaks/ breakage of indwelling arterial lines.
  - Observe limbs and buttocks prior to insertion of umbilical lines and at regular intervals afterwards to look for areas of pallor or poor perfusion due to vascular spasm.
- *Central nervous system*
  - Check fontanelle tension and size, condition of sutures i.e. overriding or separated, half-hourly to hourly head circumference monitoring (when indicated e.g. infants with subaponeurotic haemorrhage).
  - Sensorium, tone, movement, responses to procedures e.g. oral suctioning, and presence or absence of seizure should be noted.
- *Ventilation*
  - Check if ventilation is adequate. Is the child maintaining the optimum blood gases? Can we start weaning the child off the ventilator?
  - Overventilation is to be avoided as it may worsen the infant's condition.

Endotracheal tube (ETT) size and position

Infant weight	ETT size	ETT position (oral)[1,2,3]
< 750g	2.5	5.5 - 6 cm
750 - 1000g	2.5	6 - 7 cm
1000g - 2000g	3.0	7 - 8 cm
2000g - 3000g	3.5	8 - 9 cm
> 3000g	3.5-4.0	9 - 10 cm

Note:
- *Finalise ETT position by listening for equal air entry and checking with CXR.*
- *Ensure the tip of the ETT is at T2*
- *The length of ETT beyond the lips should be checked as to be just sufficient for comfortable anchoring and not excessively long so as to reduce dead space*

Suction of ETT
- Performed only when needed, as it may be associated with desaturation and bradycardia.
- During suctioning, the FiO_2 may need to be increased as guided by the SaO_2 monitor during suctioning.
- Remember to reduce to the level needed to keep SaO_2 89-95%.

Umbilical Arterial Catheter (UAC) and Umbilical Venous Catheter (UVC) care
- Do not use iodine to prepare the skin for UAC or UVC placement .
- Do not allow the solution to pool under the infant as it may burn the skin particularly in the very low birthweight infant.
- Change any damp or wet linen under the infant immediately following the procedure.
- Sterile procedure is required for inserting the lines. For other than the time of insertion, Wash hands or use alcohol rub before taking blood from the UAC. Ensure aseptic procedure when handling the hub or 3 way tap of the line to withdraw blood.

UAC position
- Length to be inserted measured from the abdominal wall is **3 x BW(kg) + 9 cm.**
- Confirm with X-ray to ensure that the tip of the UAC is between T6 to T9 or between L3-L4.
- Reposition promptly if the tip is not in the appropriate position. The high positioning of the UAC has been found to be associated with less thrombotic events than the low position.
- The UAC is kept patent with a heparin infusion (1U/ml) at 1 ml/hr and can be attached to the intra-arterial blood pressure monitor.

UVC position

- Length to be inserted measured from the abdominal wall is:
  ½ UAC length as calculated above +1 cm.
- This usually puts the tip above the diaphragm.
- However, this formula is not as accurate as using the shoulder umbilical length (check available graph in the ward).
- The shoulder umbilical length is taken as a perpendicular line dropped from the shoulder to the level of the umbilicus.

Ventilation

- Initial ventilator setting (in most situations):

Total Flow:	8 - 10 litres/min
Peak Inspiratory Pressure (PIP):	20-25 mmHg (lower in ELBW infants and those ventilated for non-pulmonary cause, i. e normal lungs)
Positive End Expiratory Pressure (PEEP):	4 - 5 mmHg
Inspiration Time:	0.3- 0.35 sec
Ventilation rate:	40- 60 / min
FiO_2:	60 to 70% or based on initial oxygen requirement on manual positive pressure ventilation.
When Volume Guarantee is used:	VG = 4 – 6 ml/kg

- The ventilator setting is then adjusted according to the clinical picture, pulse oximetry reading and ABG which is usually done within the 1st hour.
- Note:
  - The I:E ratio should not be inverted (i.e. > 1) unless requested specifically by a specialist.
  - Tailor the ventilation settings to the baby's ABG.

Keep:	pH	7.25 - 7.40
	PaO_2	50 - 70 mmHg for premature infants 60 - 80 mm Hg for term infants
	$PaCO_2$	40 - 60 (NB. the trend is not to 'chase' the $PaCO_2$ by increasing ventilator settings unless there is respiratory acidosis).
	SaO_2	89 - 92% for preterm infants.

- Changing of ventilator settings:
  - To produce an increase in PaO_2 either: -
    - Increase FiO_2 concentration.
    - Increase PEEP.
    - Increase PIP (increases minute volume).
    - *rarely*, increase I/E ratio (prolong inspiration).
- To produce a decrease in $PaCO_2$ either: -
    - Increase Rate (increases minute volume).
    - Decrease I/E ratio (prolong expiration).
    - Increase PEEP in worsening lung disease.
    - Decrease PEEP in recovery phase.
    - Increase Targeted Volume in Ventilation
  - Do the opposite to decrease PaO_2 or to increase $PaCO_2$.
- Minute volume = tidal volume (volume per breath) x rate per minute. Minute volume should be about 0.1 – 0.3L/kg/min
- With volume-limited settings, minute volume can be calculated (use tidal volume = 4-6 ml/kg).
- With pressure-limited mode - increasing peak inspiratory pressure results in increased minute volume.

Sedation and Ventilation

- Avoid the use of paralysing agents as far as possible. Paralysis has been shown to result in poorer lung function, more dependent oedema and longer duration of ventilation.
- Use morphine infusion as an analgesia and sedative, if required.

Consider the following if the child *deteriorates* on ventilation:
Worsening of primary condition, e.g. RDS or congenital pneumonia
Mechanical problems : • ETT Dislodged or Obstructed • ETT displaced/ too deep • Pneumothorax • Ventilator tubes disconnected • Ventilator malfunction
Overventilation of the lung
Pneumonia such as nosocomial pneumonia
PDA or heart failure
Persistent pulmonary hypertension
Pleural effusion

Guidelines for packed red blood cells (PRBCs) transfusion thresholds for preterm neonates.

< 28 days age, *and*	• Assisted ventilation with FiO_2 > 0.3: Hb 12.0 gm/dL or PCV < 40% • Assisted ventilation with FiO_2 < 0.3: Hb 11.0 g/dL or PCV < 35% • CPAP: Hb < 10 gm/dL or PCV <30%
> 28 days age, *and*	• Assisted ventilation: Hb < 10 gm/dL or PCV < 30% • CPAP: Hb < 8 gm/dL or PCV < 25%
Any age, breathing spontaneously, *and*	• On FiO_2 > 0.21: Hb < 8 gm/dL or PCV < 25%* • On Room Air: Hb < 7 gm/dL or PCV < 20%* **Consider transfusion if there is poor weight gain or metabolic acidosis as an indication of tissue hypoxia.*

Guidelines for platelet transfusions in non-immune thrombocytopaenic neonates

Platelet count < 30,000/mm^3	• Transfuse all neonates, even if asymptomatic
Platelet count 30,000/mm^3 - 50,000/mm^3	Consider transfusion in • Sick or bleeding newborns • Newborns <1000 gm or < 1 week of age • Previous major bleeding tendency (IVH grade 3-4) • Newborns with concurrent coagulopathy • Requiring surgery or exchange transfusion
Platelet count 50,000/mm^3 - 99,000/mm^3	• Transfuse only if actively bleeding.

Chapter 11: The Premature Infant

Introduction

- The Premature infant: < 37 weeks gestation
- Low Birth Weight (LBW): < 2500 g
- Very Low Birth Weight (VLBW): < 1500 g
- Extremely Low Birth Weight (ELBW): < 1000 g
- Small for Gestational Age: < 10th centile of birth weight for age.

Early and Late Complications in premature infants
Hypothermia
Respiratory distress syndrome, Apnoea
Hypotension, Patent ductus arteriosus
Intraventricular haemorrhage, Periventricular leukomalacia
Gastrointestinal: Paralytic ileus, Necrotizing enterocolitis
Hypoglycaemia, Hyperglycaemia
Neonatal Jaundice
Hypoprothrombinaemia
Fluid and Electrolyte disorders: hyponatraemia, hyperkalemia, metabolic acidosis
Septicaemia
Anaemia
Osteopaenia of prematurity
Retinopathy of prematurity
Chronic lung disease
Neuro-developmental disability
Psychosocial problems

Management

Before and During Labour

- Before delivery, the resuscitation team should have a pre-delivery briefing including antenatal history and intrapartum history.
- Antenatal counselling can be done if there is sufficient time for selected cases such as those at borderline viability or with antenatal risk factors for a guarded outcome.
- If it is possible, the infant resuscitaire should be prewarmed and temperature in the delivery suite to be increased to 26 degrees celcius to prevent hypothermia.

Adequate Resuscitation

Transfer from Labour Room (LR) to NNU (Neonatal Unit)

- Use prewarmed transport incubator if available. If not the baby must be wiped dry and wrapped in dry linen before transfer. For extremely low birth weight infant, from birth, the infant should be wrapped up to the neck with polyethylene plastic wrap or freezer food plastic bag to prevent evaporative heat loss.
- If infant's respiration is inadequate, initiate CPAP in the delivery suite as soon as possible. If the infant still has poor respiratory effort, intubate patient and continue to ventilate infant during transfer with adequate positive pressure ventilation (either manual ventilation or using a transport ventilator) and pulse oximetry monitoring if available.
- For infants with mild respiratory distress, continue CPAP during transfer.

Admission Routine

- Ensure thermoneutral temperature for infant. An incubator or radiant warmer is necessary for more premature and ill infants.
- Ventilation in NICU is often necessary if ventilated during transfer. However, some infants may take longer to adapt to extrauterine life and they may need only CPAP and not ventilation especially those with no risk factors and who were given a full course of antenatal steroids. For the larger preterm infants above 1250 grams, review the required ventilation to maintain a satisfactory blood gas and consider extubation if the ventilator requirements are low, patient has good tone and good spontaneous respiration.
- Maintain SaO_2 between 90-94% (BOOST II, COT trial, STOP-ROP trial) as excessive or wide oxygen swings can be potentially harmful to the premature infant.
- Bathing can be omitted.
- Head circumference (OFC), length measurements.
- Quickly and accurately examine and weigh the infant.
- Assess the gestational age with Dubowitz or Ballard score when stable (see end of this section for score).
- Monitor temp, HR, RR, BP and SaO_2.

Immediate Care for Symptomatic infants

- Investigations are necessary as indicated and include:
  - Blood gases
  - Blood glucose (dextrostix)
  - Full blood count with differential WBC (and IT ratio if possible)
  - Blood culture.
  - CXR (if respiratory signs and symptoms are present)
- Start on 10% dextrose drip or TPN as soon as possible (refer to TPN chapter)
- Correct anaemia.

- Correct hypotension (keep mean arterial pressure (MAP) > gestational age (GA) in wks). Ensure hyperventilation is not present (a cause of hypotension). If the baby has good tone and is active, observe first as the BP may rise after first few hours of life towards a MAP approximating GA in weeks.
- Correct hypovolaemia: Give bolus fluid only if there is history of blood loss or hypovolemia, not for 'poor perfusion' which may be due to other reasons eg hypothermia. Give 10 ml/kg of Normal Saline over 20-30 mins, or packed cells if anaemic (in babies who are hypovolemic with history of blood loss). Avoid repeat fluid boluses unless there is volume loss. Bolus fluid is not required by babies with good tone and is active on admission.
- Start inotrope infusion if hypotension persists after volume correction. Majority of premature infants do not require ionotropic support at birth. Mean blood pressure is estimated around infant's gestational age but there is some variation. If the baby is well perfused and tone is normal, it is best to observe for an upward trend before giving volume expander or starting on ionotropic support.
- Start antibiotics after taking cultures e.g. Penicillin and Gentamycin
- Start IV Aminophylline or caffeine in premature infants <32-34 weeks
- Maintain SaO_2 at 90-94% and PaO_2 at 50 –70 mmHg.

General Measures for Premature infants

- Monitor vitals signs (colour, temperature, apex beat, respiratory rate). Look for signs of respiratory distress (cyanosis, grunting, tachypnoea, nasal flaring, chest recessions, apnoea). In VLBL and ill infants pulse oximetry and blood pressure monitoring are necessary.
- Check Blood Sugar (see Hypoglycaemia protocol).
- Keep warm in incubator at thermoneutral temperature for age and birth weight. ELBW should preferably have humidified environment at least for the first 3 days.
- Ensure adequate nutrition.
- Provide parental counselling and allow free parental access.
- Infection control: observe strict hand washing practices.
- Immunisation:
  - Hep B vaccine at birth if infant stable and BW is >1.8 kg.
  - Otherwise give before discharge.
  - Ensure BCG vaccine is given on discharge.
  - For long stayers other immunisation should generally follow the schedule according to chronological rather than corrected age.
  - Defer immunisation in the presence of acute illnesses.
- Supplements:
  - At birth: IM Vitamin K (0.5 mg for BW<2.5 kg; 1 mg for BW ≥ 2.5 kg)
  - Once on full feeding, give Infant Multivitamin drops 1 mls OD (continue till fully established weaning diet). For preterm infants, use a formulation with Vit D 400 IU, and Folic acid 0.1 mg OD.
  - Starting at about 4 weeks of life: Elemental Iron 2-3 mg/kg/day – to be continued for 3-4 months.

ICU care and Criteria for Replacement Transfusion in Neonates
See relevant chapter.

Discharge

- Cranial Ultrasound for premature infants ≤ 32 weeks is recommended at:
  - Within first week of life to look for intraventricular haemorrhage (IVH).
  - Around day 28 to look for periventricular leucomalacia (PVL).
  - As clinically indicated.
- Screening for Retinopathy of Prematurity (ROP) at 4-6 weeks of age is recommended for
  - All infants ≤ 32 weeks gestation and equal to 1500g at birth.
  - All preterms < 36 weeks who received oxygen therapy depending on individual risk as assessed by the clinician.
- The infants are discharged once they are well, showing good weight gain, established oral feeding and gestational age of at least 35 weeks.

Prognosis

- Mortality and morbidity are inversely related to gestation and birth weight.
- Complications include retinopathy of prematurity, chronic lung disease, neurodevelopmental delay, growth failure, cerebral palsy, mental retardation, epilepsy, blindness and deafness.
- For situations where the baby is discharged between 34-35 weeks, arrange regular review within the week in the ward or nearest health clinic.

Chapter 12: Late Preterm Infants

Introduction

Late preterm births, defined as births between 34 weeks and 36+6/7 weeks of gestation, comprise the majority of preterm births. Numerous studies show greater mortality and morbidity in late preterm infants compared with term infants.

Management

- All infants at birth must have a carefully documented assessment of gestational age.
- Carefully observe for successful adaptation to extra-uterine life. Initial evaluation should include temperature, respiration and heart rate.
- Admit/ refer to a special care nursery/ neonatal intensive care unit if there is cardiorespiratory instability and infant unable to feed.
- Explain the differences of the term baby and the late preterm baby to parents. Reassure and support them.

Feeding

- Compared with term neonates, late preterm newborns are at increased risk for feeding difficulty and dehydration. Feeding should be supervised and established before discharged home.
- Early feeding should be attempted.
- Encourage breastfeeding on demand.
- Educate and assist the mother to hand express and give EBM after all breastfeeding or feeding attempts in the first few days.
- Check concerns of mother regarding with lactation and refer to lactation nurse.

Thermal control

- Since the late preterm is usually nursed in a cot, monitor the temperature regularly as temperature instability is common.
- Double wrap or use radiant warmer especially soon after birth if temperature is below 36.5^{o}C.
- Ensure that the baby is draped or wrapped well to prevent heat loss while doing skin to skin or breastfeeding.

Hypoglycaemia

- Monitor for clinical signs of hypoglycaemia.

Apnoea

- The incidence of apnea in late-preterm infants is reported to be between 4% and 7%, compared with less than 1% to 2% at term.
- Consider continuous monitoring of the respiration and heart rate when there has been a recent or recurrent apneic episodes.

Jaundice

- Ongoing observation of the baby for clinical signs of jaundice. Late pre term babies are at increased risk of higher elevations of bilirubin at day 5 to 7 of life compared to term babies
- Check transcutaneous bilirubin or serum bilirubin if there is a concern.

Discharge

- Consider discharge if:
  - Maintaining temperature > 24 hours.
  - Established feeding and showing weight gain.
  - No signs of dehydration.
  - No recent apnoea.
- Where feasible, inform local health clinic for weekly weight and monitoring until 40 weeks corrected age.
- Educate parents to contact breastfeeding support group should they encounter any problem with breastfeeding.

Follow up

- Late preterm infants are at increased risk for rehospitalization after the immediate perinatal period especially for poor weight gain, hypernatraemic dehydration and neonatal jaundice.
- Counsel parents to avoid crowded places or family gatherings, and to avoid smoking at home in the first few months after discharge to reduce risk of respiratory infection or sudden infant death
- Give appointment for follow up with the nearest public health clinic within 1-2 weeks after discharge, and a less frequent follow up in the paediatric clinic to monitor growth and development as there is increased risk of long term neurodevelopmental difficulties.

Chapter 13: Enteral Feeding in Neonates

Introduction

- The goal of nutrition is to achieve as near to normal weight gain and growth as possible.
- **Enteral feeding should be introduced as soon as possible.** This means starting in the labour room itself for the well infant.
- **Breast milk is the milk of choice.** All mothers should be encouraged to give breast milk to their newborn babies.
- Normal caloric requirements in: Term infants: 110 kcal/kg/day
  Preterm infants : 120 - 140 kcal/kg/day
- Babies who have had a more eventful course need up to 180kcal/kg/day to have adequate weight gain.

Types of milk for Newborn feeding

There are three choices:

- Expressed breast milk
- Normal infant formula
- Preterm infant formula

Breast Milk

- **Breast milk is preferred** as breast fed babies have a lower risk for necrotising enterocolitis and had better development quotients.
- Freshly expressed human milk has numerous benefits especially for premature babies. Although there is no direct evidence comparing fresh versus frozen mothers' milk, this make sense because of the depletion of commensals, immune cells, immune factors and enzyme activity that occurs during freezing.
- However, expressed breast milk (EBM) alone is not adequate for the nutritional needs of the *very preterm infant* as it has:
  - insufficient calories and protein to for optimal early growth at 20 kcal/30mls.
  - insufficient sodium to compensate for high renal sodium losses.
  - insufficient calcium or phosphate - predisposes to osteopenia of prematurity.
  - insufficient vitamins and iron relative to the needs of a preterm infant.

Human Milk Fortifier (HMF)

- It is recommended to add HMF to EBM in babies < 32 wks or < 1500 grams.
- HMF will give extra calories, vitamins, calcium and phosphate.
- HMF should be added to EBM when the baby is feeding at 100 mls/kg/day.
- Start HMF at concentration of 1 sachet: 50 mls EBM and if this is tolerated for 48 hours, increase to 1:25. Check the dilution as it may vary between different brands.
- VLBW infants on exclusive breastmilk may require sodium supplementation until 32-34 weeks corrected age.

Infant Formula

Infant formula should only be given if there is no supply of EBM. There are 2 types of infant formula: Preterm formula and Normal Term Formula.

- Preterm formula : for babies born < 32 weeks or < 1500 grams.
- Normal infant formula : for babies born ≥ 32 weeks or > 1500 grams.

Strategies of administering enteral feeding

Orogastric Route

- Neonates are obligate nose breathers thus nasogastric tubes can obstruct the nasal passage and compromise breathing. Thus the orogastric route is preferable.

Continuous vs. intermittent bolus feeding

- Bolus fed babies tolerate feeds better and gained weight faster. Babies on continuous feeding have been shown to take longer to reach full feeding but there is no difference in days to discharge, somatic growth and incidence of necrotising enterocolitis (NEC).

Cup feeding

- If the baby is able to suckle and mother is not with the baby, cup feeding is preferable to bottle feeding to prevent nipple confusion.

When to start milk?

- As soon as possible for the well term babies
- However, in very preterm infants there may be an increased risk for NEC if feeding is advanced too rapidly, although early feeds with EBM is to be encouraged. Studies suggest that rapid increments in feeds has a higher risk for NEC than the time at which feeding was started.
- Start trophic feeding preferably within 24 hours if EBM available. Caution in ELBW babies or growth- restricted infants. If by 24-48 hours, and no EBM is available, consider a premature formula milk
- **Minimal enteral feeding (MEF)** is recommended in very preterm infants. The principle is to commence very low volume enteral feeds on day 1 - 3 of life (i.e. 5 - 25 mls/kg/day) for both EBM and formula milk. MEF enhances gut DNA synthesis hence promotes gastrointestinal growth. **This approach allows earlier establishment of full enteral feeds and shorter hospital stays, without any concomitant increase in NEC.**

How much to increase?

- Generally the rate of increment is about 20 to 30 mls/kg/day.
- Well term babies should be given breastfeeding on demand.
- Milk requirements for babies on full enteral feed from birth:

Day 1	60 mls/kg/day
Day 2 – 3	90 mls/kg/day
Day 4 – 6	120 mls/kg/day
Day 7 onwards	150 mls/kg/day

Add 15% if the baby is under phototherapy

- In babies requiring IV fluids at birth: The rate of increment need to be individualized to that baby.
- Babies should be observed for feeding intolerance (vomit or large aspirate) and observe for any abdominal distention before increasing the feed.

What is the maximum volume?

- Target weight gain should be around 15g/kg/day (range 10-25g/kg/day). Less weight gain than this suggests a need to increase calories especially protein calories.. More weight gain than 30g/kg/day should raise the possibility of fluid overload particularly in babies with chronic lung disease.
- Preterm infants
- Increase feed accordingly to 180 to 200 mls/kg/day. (This should only be achieved by Day 10 to Day 14 respectively if baby had tolerated feeds well from Day 1)
  If on EBM, when volume reaches 75 mls/kg/day: add HMF.
- Term infants: allow feeding on demand.

When to stop HMF or Preterm Formula?

- Consider changing preterm to standard formula and stop adding HMF to EBM when babies are breastfeeding on demand or have reached their expected growth curve.
- Preterm with poor weight gain can be given specially formulated post discharge formula for preterm infants. Preterm formula meant for newborn preterm infants should not be given to infants > 2 months post conceptual age in view of potential Vitamin A and D toxicity.

Vitamin and mineral supplementation

- *Vitamins*: a premature infant's daily breast milk/ breast milk substitute intake will not supply the daily vitamin requirement. Multivitamin drop providing Vitamin D 400 IU per day can be given after day 14 of life when on feeding of 150 mls/kg/day. The supplement is continued for 3-4 months post discharge.
- *Iron:* Premature infants have reduced intra uterine iron accumulation and can become rapidly depleted of iron when active erythropoiesis resumes. Therefore babies of birth weight < 2000g should receive iron supplements. Iron is given at a dose of 3 mg/kg elemental iron per day.
  - Ferric Ammonium Citrate (400mg/5mls) contains 86 mg/5 mls of elemental iron.
  - Start on day 28, continue until 3-4 months post discharge or until review
  - Babies who have received multiple blood transfusions may not require as much iron supplementation.

Special Cases

- IUGR babies with reversed end-diastolic flow on antenatal Doppler: Studies have show that these babies are at risk of NEC. Thus feeds should be introduced slowly and initially use only EBM.

COMPOSITION OF VARIOUS MILK

Component		Cow's milk	Standard formula	Mature breastmilk	Preterm formula	Preterm breastmilk
Carbohydrate	g/100ml	4.6	7.5	7.4	8.6	6.4
Fat	g/100ml	3.9	3.6	4.2	4.4	3.1
Protein	g/100ml	3.4	1.5	1.1	2.0	2.7
Casein : Lactalbumin ratio		4:1	2:3	2:3	2:3	2.3
Calories	KCal/100ml	67	67	70	80	74
Sodium	mmol/l	23	6.4	6.4	14	17
Potassium	mmol/l	40	14	15	19	17
Calcium	mg%	124	46	35	77	29
Phosphate	mg%	98	33	15	41	13
Iron	mg%	0.05	0.8	0.08	0.67	

Referrence: Sourabh Dutta, Balpreet Singh, Guidelines for feeding very low birth weight infants; Nutrients 2015,7, 423-442

Chapter 14: Total Parenteral Nutrition for Neonates

Introduction

- Total parenteral nutrition (TPN) is the intravenous infusion of all nutrients necessary for metabolic requirements and growth.
- Earlier introduction and more aggressive advancement of TPN is safe and effective, even in the smallest and most immature infants.
- Premature infants tolerate TPN from day 1 of post-natal life.

The goal of TPN is to

- Provide sufficient nutrients to prevent negative energy and nitrogen balance and essential fatty acid deficiency.
- Support normal growth rates without increased significant morbidity.

Indication for TPN

TPN is usually given for situations below, depending on availability

- Birth weight < 1000 gm
- Birth weight 1000-1500 gm and anticipated to be not on significant feeds for 3 or more days.
- Birth weight > 1500 gm and anticipated to be not on significant feeds for 5 or more days.
- Surgical conditions in neonates: necrotizing enterocolitis, gastroschisis, omphalocoele, tracheo-esophageal fistula, intestinal atresia, malrotation, short bowel syndrome, meconium ileus and diaphragmatic hernia.

PRESCRIPTION

TPN can be delivered using standardised or individualised bags.

Components of TPN

The essential components of parenteral nutrition are:

- Fluids
- Carbohydrate
- Protein
- Lipids
- Electrolytes
- Vitamins
- Trace minerals

Goal is to provide 120-130 KCal/kg/day.

- 10% Dextrose solution provides 0.34 KCal/ml.
- 10% Lipid solution gives 0.9 KCal/ml; 20% lipid solution gives 1.1 KCal/ml.
- Protein/Energy ratio: 3-4 gm/100 KCal is needed to promote protein accretion. A baby given only glucose will lose 1.5 grams body protein/day.

Thus it is important to start TPN within the first 24 hours of life in the smaller preterm infants <1250 grams birth weight.

Fluid

- Fluid is an essential component.
- Usually started at 60-80 ml/kg/day (if newborn), or at whatever stable fluid intake the baby is already receiving.
- Postnatal weight loss of 5 - 15 % per day in the ELBW is acceptable.
- Volumes are increased over the first 7 days in line with the fluids and electrolytes protocol with the aim to deliver 120-150 ml/kg/day by day 7.

Amino acids

- Amino acids prevents catabolism; prompt introduction via TPN achieves an early positive nitrogen balance.
- Decreases frequency and severity of neonatal hyperglycaemia by stimulating endogenous insulin secretion and stimulates growth by enhancing the secretion of insulin and insulin-like growth factors.
- Protein is usually started at 2g/kg/day of crystalline amino acids and subsequently advanced, by 3rd to 4th postnatal day, to 3.0 g/kg/day of protein in term and by 5th day 3.7 to 4.0 g/kg/day in the extremely low birthweight (ELBW) infants.
- Reduction in dosage may be needed in critically ill, significant hypoxaemia, suspected or proven infection and high dose steroids.
- Adverse effects of excess protein include a rise in urea and ammonia and high levels of potentially toxic amino acids such as phenylalanine.

Glucose

- There is a relatively high energy requirement in the ELBW and continuous source of glucose is required for energy metabolism.
- In the ELBW minimum supply rate is 6 mg/kg/min to maintain adequate energy for cerebral function; additional 2-3 mg/kg/min (25 cal/kg) of glucose per gram of protein intake is needed to support protein deposition.
- Maximum rate: 12 - 13 mg/kg/min (lower if lipid also administered) but in practice often limited by hyperglycaemia.
- Hyperglycaemia occurs in 20-80% of ELBW as a result of decreased insulin secretion and insulin resistance, presumably due to to glucagon, catecholamine and cortisol release.
- Hyperglycaemia in the ELBW managed by decreasing glucose administration, administering intravenous amino acids and/or infusing exogenous insulin.
- Glucose administration is started at 6 mg/kg/min, advancing to 12-14 mg/kg/min and adjusted to maintain euglycaemia.
- If hyperglycaemia develops glucose infusion is decreased. Insulin infusion is generally not required if sufficient proteins are given and less glucose is administered during the often transient hyperglycaemia. Insulin infusion, if used for persistent hyperglycaemia with glycosuria, should be titrated to reduce risk of hypoglycaemia.

Lipid

- Lipids prevent essential fatty acid deficiency, provide energy substrates and improve delivery of fat soluble vitamins.
- LBW infants may have immature mechanisms for fat metabolism. Some conditions inhibit lipid clearance e.g. infection, stress, malnutrition.
- Start lipids at 1g/kg/day, at the same time as amino acids are started, to prevent essential fatty acid deficiency; gradually increase dose up to 3 g/kg/day (3.5g/kg/day in ELBW infants). Use smaller doses in sepsis, compromised pulmonary function, hyperbilirubinaemia.
- It is infused continuously over as much of the 24 hour period as practical.
- Avoid concentrations >2g/kg/day if infant has jaundice requiring phototherapy.
- Preparation of 20% emulsion is better than 10% as 20% solutions require less fluid volume and provide a lower phospholipid-to-triglyceride ratio. 10% solution interferes with triglyceride (TG) clearance leading to higher TG and cholesterol values. Use of preparations containing lipids from fish oil and olive oil may reduce the risk of cholestasis with prolonged TPN.
- Heparin at 0.5 to 1 units/mL of TPN solutions can facilitate lipoprotein lipase activity to stabilize serum triglyceride values.
  The final concentration of heparin used may need to decreased to 0.5 units/ml in small neonates receiving larger TPN volumes in order to avoid approaching therapeutic amount.
- Lipid clearance monitored by plasma triglyceride (TG) levels.
  (Max TG concentration ranges from 150 mg/dl to 200 mg/dl).
- Exogenous lipid may interfere with respiratory function.
  Suggested mechanisms include impaired gas exchange from pulmonary intravascular accumulation or impaired lymph drainage resulting in oedema. Lipid may also aggravate pulmonary hypertension in susceptible individuals.
- The syringe and infusion line should be shielded from ambient light.

Electrolytes

- The usual sodium need of the newborn infant is 2-3 mEq /kg/day in term and 3-5 mEq/kg/day in preterm infants after the initial diuretic phase(first 3-5 days). Sodium supplementation should be started after initial diuresis(usually after the 48 hours), when serum sodium starts to drop or at least at 5-6% weight loss. Failure to provide sufficient sodium may be associated with poor weight gain.
- Potassium needs are 2-3 mEq/kg/day in both term and preterm infants. Start when urine output improves after the first 2-3 days of life.

Minerals, Calcium (Ca), Phosphorus (P) And Magnesium

- In extrauterine conditions, intrauterine calcium accretion rates is difficult to attain. Considering long-term appropriate mineralization and the fact that calcium retention between 60 to 90 mg/kg/day suppresses the risk of fracture and clinical symptoms of osteopenia, a mineral intake between 65 to 75 (elemental) mg/kg/day of highly-absorbed calcium and 60 to 75 mg/kg/day of phosphorus could be recommended.
- The optimal ratio of Calcium to Phophorus is generally between 1:1.3 and 1:1.7 by weight and nearly a 1:1 molar ratio.
- Monitoring for osteopaenia of prematurity is important especially if prolonged PN.
- A normal magnesium level is a prerequisite for a normal calcaemia. In well balanced formulations, however, magnesium level does not give rise to major problems.

Trace Elements

- Indicated if PN is administered for ≥ 1 week. Commercial preparations are available.

Vitamins

- Both fat and water soluble vitamins are essential. It should be added to the fat infusion instead of amino-acid glucose mixture to reduce loss during administration.

Administration

- TPN should be delivered where possible through central lines.
- Peripheral lines are only suitable for TPN ≤ 3 days duration and dextrose concentration ≤ 12.5%.
- Peripheral lines are also limited by osmolality (<600 mOsm/L) to prevent phlebitis.
- Percutaneous central line: confirm catheter tip position on X-ray prior to use.
- Ensure strict aseptic technique in preparation and administration of TPN.
- Avoid breakage of the central line through which the TPN is infused, though compatible drugs may be administered if necessary.

Caution

- **Hyperkalaemia.** Potassium is rarely required in first 3 days unless serum potassium < 4 mmol/l. Caution in renal impairment.
- **Hypocalcaemia.** May result from inadvertent use of excess phosphate. Corrects with reduction of phosphate.
- **Never add bicarbonate**, as it precipitates calcium carbonate
- **Never add extra calcium to the burette**, as it will precipitate phosphates.

Complications

- Possible complications with intravenous lines delivering TPN:
- Sepsis - minimized by maintaining strict sterility during and after insertion
- Malposition of the catheter tip. To confirm the catheter tip position is in the appropriate position with an Xray (or where available, with ultrasound imaging) before commencing infusion
- Thrombophlebitis - with peripheral line
- Extravasation into the soft tissue, with risk of tissue necrosis

Monitoring

Before starting an infant on parenteral nutrition, investigation required:

- Full blood count, haematocrit
- Renal profile
- Random blood sugar/dextrostix
- Liver function test, serum bilirubin

Monitoring required :

Laboratory

- Full blood count
- Plasma calcium, magnesium, phosphate. Twice/wk until stable then weekly.
- Triglyceride levels. After dose changes then weekly.
- Liver function test

Clinical

- Blood sugar / dextrostix, 4-6 hrly first 3 days, twice a day once stable.
- Daily weight
- Meticulous care of the catheter site and monitoring for infection.

Chapter 15: The Newborn and Acid Base Balance

The rate of metabolism in infants is twice as great in relation to body mass as in adults, which means twice as much acid is formed which leads to a tendency toward acidosis. Functional development of kidneys is not complete till the end of the first month and hence renal regulation of acid base may not be optimal.

Causes of Acidosis	
Metabolic acidosis	Respiratory acidosis
Renal failure	Asphyxia (injury to respiratory centre)
Septicaemia	
Hypoxia	Obstruction to respiratory tract e.g. secretions, blocked endotracheal tube
Hypothermia	
Hypotension	Respiratory distress syndrome (RDS)
Cardiac failure	Pneumonia
Dehydration	Pulmonary oedema
Hyperkalaemia	Apnoea
Hyperglycaemia	
Anaemia	
Intraventricular haemorrhage	
Drugs (e.g. acetazolamide)	
Metabolic disorders	
Causes of Alkalosis	
Metabolic alkalosis	Respiratory alkalosis
Sodium bicarbonate	Asphyxia (overstimulation of respiratory centre)
Pyloric stenosis	
Hypokalaemia	Over-ventilation while on mechanical ventilation
Drugs (e.g.thiazides and frusemide)	

Effects of acidosis and alkalosis in the body

Acidosis

- Depression of central nervous system (CNS)
- Disorientation and coma.
- Increased depth and rate of respiration in metabolic acidosis and depressed
- respiration in respiratory acidosis.
- High $PaCO_2$ in respiratory acidosis increases cerebral blood flow and risk of intraventricular haemorrhage.

Alkalosis

- Over-excitability of the central nervous system.
- Decreased cerebral blood flow - causing cerebral ischaemia, convulsions

Measurement of Acid Base Status

- Done by analyzing following parameters in an arterial blood gas sample:

Normal values:	
pH	7.34-7.45
$PaCO_2$	5.3-6.0 kpa (40-45 mmHg)
HCO_3^-	20-25 mmol/L
PaO_2	8-10 kpa (60-75 mmHg)
BE	± 5 mmol/L

Interpretation of Blood Gases

- pH < 7.34 : *acidosis*
  - If $PaCO_2$ and HCO_3 are low and base deficit is high: *metabolic acidosis.*
  - If $PaCO_2$ and HCO_3 are high and base excess is high: *respiratory acidosis.*
  - If both $PaCO_2$ and base deficit are high: *mixed metabolic and repiratory acidosis.*
- pH > 7.45: *alkalosis*
  - If $PaCO_2$ is low: *respiratory alkalosis*
  - If HCO_3 and base excess are high: *metabolic alkalosis*

  Acidosis and alkalosis may be partially or fully compensated by the opposite mechanism.
- Low $PaCO_2$: *hypocarbia*; high $PaCO_2$: *hypercarbia*
  Permissive hypercapnia (PCO_2 45-55 mmHg) is an important ventilation technique to reduce the risk of volume trauma and chronic lung disease.
- Low PaO_2: *hypoxaemia*; high PaO_2: *hyperoxaemia*

Management of Metabolic Acidosis and Alkalosis

- Treat underlying cause when possible.
- Do not treat acute metabolic acidosis by hyperventilation or by giving bicarbonate. This may correct pH but has deleterious effects on cardiac output and pulmonary blood flow. The use of sodium bicarbonate in acute resuscitative conditions is not advocated by the current body of evidence.
- Volume expansion (i.e., bolus 10 mL/kg of 0.9% Normal Saline) should not be used to treat acidosis unless there are signs of hypovolemia. A volume load is poorly tolerated in severe acidosis because of decreased myocardial contractility.
- $NaHCO_3$ should be used only in the bicarbonate-losing metabolic aci doses such as diarrhea or renal tubular acidosis.
- Dose of $NaHCO_3$ for treatment of metabolic acidosis can be calculated by: **Dose in mmol of $NaHCO_3$ = Base deficit (mEq) x Body weight (kg) x 0.3**
- Do not give $NaHCO_3$ unless infant is receiving assisted ventilation that is adequate. With inadequate ventilation, $NaHCO_3$ will worsen acidosis from liberation of CO_2.

- For chronic mild metabolic acidosis in small premature infants on hyperalimentation, maximize acetate and minimize chloride in the solution.
- Metabolic alkalosis: **usually iatrogenic in premature infants** - diuretic use, gastrointestinal losses, and occurs in combination with contracted intravascular and extravascular volumes.

Treatment of respiratory acidosis and alkalosis

- A steadily rising $PaCO_2$ at any stage in the disease is an indication that ventilatory assistance is likely to be needed.
- A sudden rise may be an indication of acute changes in the infant's condition e.g. pneumothorax, collapsed lobes, misplaced endotracheal tube. .
  (DOPE mnemonic: Displacement, Obstruction, Pneumothorax and Equipment Failure)
- A swift rise in $PaCO_2$ often accompanied by hypoxia following weaning is often an indication that the infant is not ready for weaning.
- A gradual rise in $PaCO_2$ at the end of the first week in a LBW infant on ventilator may be an indicator of the presence of a patent ductus arteriosus.
- Low $PaCO_2$ in a infant on a ventilator means overventilation, hence treatment is to wean down the ventilation settings.

Interpretation of Blood Gases

Examples of Arterial Blood Gas (ABG) Interpretation

1. A 29 weeks' gestation and 1.1 kg BW infant has RDS. He is 20 hours old and is being nursed on nasal CPAP.

His ABG shows:

pH	7.21
$PaCO_2$	6.6 kPa
PaO_2	7.5 kPa
HCO_3	20 mmol/L
BE	-4 mmol/L

Question (Q): What does the ABG show?
Answer (A): Mild respiratory acidosis due to worsening Respiratory Distress Syndrome.
Q: What is the next appropriate mode of therapy?
A: Mechanical ventilation

2. Below is the ABG of a 10 hour old 28 weeks' gestation infant :

pH	7.22
$PaCO_2$	7.0 kPa
PaO_2	10.0 kPa
HCO_3	17 mmol/L
BE	-8 mmol/L

Q: What does the ABG show?
A: Mixed respiratory and metabolic acidosis

Q: Name a likely diagnosis
A: Respiratory distress syndrome

3. The following is the ABG of a 40 day old 26 weeks' gestation baby:

pH	7.38
$PaCO_2$	8.0 kPa
PaO_2	8.0 kPa
HCO_3	35 mmol/L
BE	+10 mmol/L

Q: What does the ABG show?
A: Compensated respiratory acidosis

Q: What is a likely diagnosis?
A: Chronic lung disease.

4. An infant of 30 weeks' gestation and BW 1.3 kg is on a ventilator. ABG shows:

pH	7.35
$PaCO_2$	3.0 kPa
PaO_2	15.0 kPa
HCO_3	12 mmol/L
BE	-12 mmol/L

Q: Interpret the ABG
A: Compensated metabolic acidosis by respiratory alkalosis and hyperoxaemia

Q: What is your next course of action?
A: Reduce FiO_2, treat any contributory cause of acidosis and wean down ventilation settings.

5. A term infant is being ventilated for meconium aspiration. His ABG is as follows :

pH	7.16
$PaCO_2$	10.0 kPa
PaO_2	6.0 kPa
HCO_3	16 mmol/L
BE	-10 mmol/L

Q: What is likely to have happened?
A: Pneumothorax

Q: What is your interpretation of the ABG
A: Mixed respiratory and metabolic acidosis with hypoxaemia.

6. A 6 day old infant is being ventilated for a cyanotic heart disease. ABG shows :

pH	7.2
$PaCO_2$	4.5 kPa
PaO_2	3.0 kPa
HCO_3	8 mmol/L
BE	-15 mmol/L

Q: What does the ABG show?
A: Metabolic acidosis with severe hypoxaemia.

Q: What is your next course of action ?
A: Consider prostaglandin infusion, confirm heart defect by Echocardiography, consider reducing ventilation.

Pearls
Conversion of kPa to mmHg is a factor of 7.5.

Chapter 16: Neonatal Hypoglycemia

Introduction

- There is no single plasma glucose concentration or duration of hypoglycemia that can predict permanent neurologic injury in high-risk infants. This is because thresholds for specific brain responses to hypoglycaemia occur over a range of glucose levels, and these thresholds can be affected by alternative fuels such as ketone bodies, and by recent antecedent hypoglycaemia.
- Neonatal glucose concentrations decrease after birth, to as low as 30 mg/dL (1.7 mmol/dL) during the first 1 to 2 hours after birth, and then increase to higher and relatively more stable concentrations, generally above 45 mg/dL (2.5 mmol/L) by 12 hours after birth.

Target Plasma Glucose Level

Clinical hypoglycemia is defined as a plasma glucose concentration low enough to cause symptoms and/or signs of impaired brain function.

- Target plasma glucose for neonates remains controversial but is commonly accepted as plasma glucose level > 2.6mmol/L in a term or preterm infant.
- In term infants < 4 hours old, plasma glucose > 1.5mmol/L is acceptable if the infant is well, asymptomatic and tolerating feeds and repeat glucose is > 2.6 mmol/L.
- For infants > 48 hours old, it is recommended to keep plasma glucose level > 3.3mmol/L to be above the threshold for neuroglycopaenic symptoms
- For infants with suspected congenital hypoglycaemia disorder or symptomatic infants, to keep plasma glucose > 3.9mmol/L.
  A higher target level is chosen because of lack of alternative fuels and the risks of undertreatment outweigh the risks of overtreatment.

When Neonatal Hypoglycaemia is suspected, the plasma or blood glucose concentration must be determined immediately. Plasma glucose values (RBS) tend to be 10% - 18% higher than whole blood values (Glucometer/ Dextrostix) because of the higher water content of plasma.

Screening

Blood glucose concentration should only be measured in term babies with clinical manifestations, or who are known to be at risk of hypoglycaemia

Infants who are at increased risk of hypoglycemia and require glucose screening:

- Symptoms of hypoglycemia
- Large for gestational age (even without maternal diabetes)
- Perinatal stress
  - Birth asphyxia/ischemia; caesarean delivery for fetal distress
  - Maternal preeclampsia/eclampsia or hypertension
  - Intrauterine growth restriction (small for gestational age)
  - Meconium aspiration syndrome, erythroblastosis fetalis, polycythemia, hypothermia
- Premature (including late preterm infants) or postmature delivery
- Family history of a genetic form of hypoglycemia
- Congenital syndromes (eg, Beckwith-Wiedemann), abnormal physical features (eg, midline facial malformations, microphallus)

Clinical Signs of Hypoglycaemia

- Jitteriness
- Cyanosis
- Seizures
- Apnoeic episodes
- Tachypnoea
- Weak or high-pitched cry
- Floppiness or lethargy
- Poor feeding
- Eye-rolling

Note: Hypoglycaemia may be asymptomatic therefore monitoring is important for all high risk cases

MANAGEMENT

Screening of At Risk Infants (AT BIRTH)

- Identify at risk infants.
- Well infants who are at risk:
  - Immediate feeding (initial feeding should be given within 1 hour of birth)
  - If necessary, supplement feeding until breastfeeding is established.
  - Initial blood glucose should be done 30 minutes after the first feed
- Sick infants:
  - Check blood glucose on admission and set up IV Dextrose 10% drip 60ml/kg/day.

Management of Hypoglycaemia

- Repeat blood glucose (glucometer,dextrostix) and send for plasma glucose levels (RBS) stat.
- Examine and document any symptoms.
- Note when the last feeding was given.
- If on IV drip, check that IV infusion of glucose is adequate and running well.
- If blood glucose < 1.5mmol/l in the first 4 hours of life or if the infant is symptomatic:
  - Give IV Dextrose 10% at 2-3 ml/kg bolus
  - Followed by IV Dextrose 10% drip at 60-90ml/kg/day (for day 1 of life)
  - If the infant is already on IV Dextrose 10% drip, consider increasing the rate or the glucose concentration (usually require 6-8 mg/kg/min of glucose delivery).
- Within the first 4 hours of life, if blood glucose is 1.5 – 2.5 mmol/l and asymptomatic:
  - Give supplementary feed (EBM or formula) as soon as possible.
  - If blood glucose remains < 2.6 mmol/l and infant refuses feeds, start IV Dextrose 10% drip.

- If infant is already on IV Dextrose 10% drip, consider stepwise increment of glucose infusion rate by 2 mg/kg/min until blood sugar is > 2.6 mmol/L.
- Glucose monitoring (capillary blood sugar - dextrostix, glucometer): If blood glucose is below target level, re-check blood glucose every 30 minutes.
- Once blood glucose is above target level for 2 readings: Monitor hourly x 2, then 2 hourly X 2, then to 3-6 hourly pre feeding, if blood glucose remains normal.

- Start feeding when blood glucose remains stable and increase as tolerated. Reduce the IV Dextrose infusion rate 1 hour after the feeding increment.

Management of Persistent Hypoglycaemia

If hypoglycaemia persists despite IV Dextrose 10% infusion, consult MO/ specialist and for district hospitals, consider early referral.

- Re-evaluate the infant
- Confirm hypoglycaemia with RBS but treat as such based on dextrostix level while awaiting RBS result
- Increase volume by 30ml/kg/day and/or increase dextrose concentration to 12.5% or 15%. Concentrations > 12.5% must be infused through a central line
- If hypoglycaemia still persists despite glucose delivery > 8-10 mg/kg/min, consider Glucagon 0.5-1mg stat (iv, im, s/c) then 5-10mcg/kg/h.
  - Glucagon is only useful where there is sufficient glycogen stores such as in infant of diabetic mothers
  - In high doses (>20mcg/kg/h), glucagon can cause paradoxical insulin secretion and rebound hypoglycemia and should be avoided
- If hypoglycaemia occurs in infants with poor glycogen stores as in IUGR, most SGA babies, or in adrenal insufficiency, increase the glucose infusion rate to 12mg/kg/min.
  If hypoglycaemia persists despite a glucose infusion rate of > 12mg/kg/min, a short course (1-2 days) of IV hydrocortisone 1-2 mg/kg /dose bd or tds may be considered.
  Prolonged hydrocortisone is only beneficial in those with adrenal insufficiency
- A subset of SGA infants have hyperinsulinaemic hypoglycaemia (HH) with sufficient glycogen stores. To determine glucagon responsiveness, a test dose of glucagon im/s/c/iv 0.5mg or 1mg can be given, and if there is a rise of 1.7mmol/L after 10-15 mins, this implies there are sufficient glycogen stores and glucagon infusion can be continued.

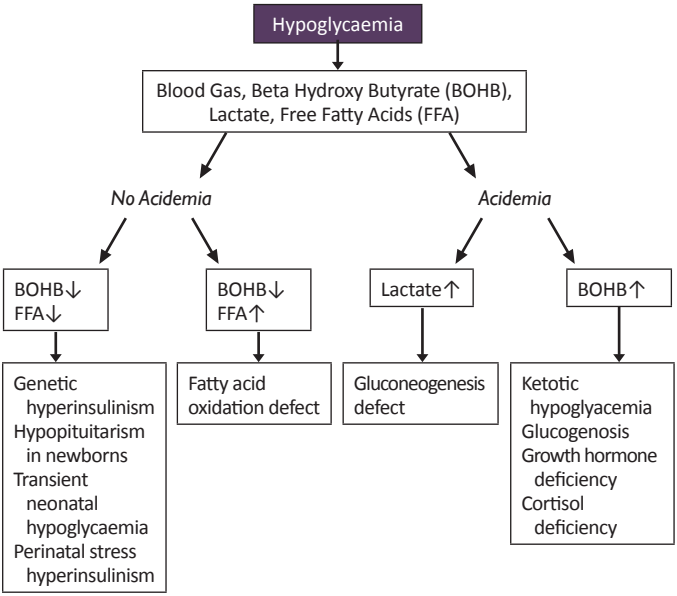
Recurrent or resistant hypoglycaemia

- Consider this if failure to maintain normal blood sugar levels despite a glucose infusion of 15 mg/kg/min, or
- When stabilization is not achieved by 7 days of life. High levels of glucose infusion may be needed in the infants to achieve euglycaemia.
- Consult endocrinologist
- Differential diagnoses include:
  - Hyperinsulinaemic states (e.g. perinatal asphyxia, maternal diabetes mellitus, intrauterine growth restriction, or associated syndromes affecting growth like Beckwith-Wiedemann syndrome, Sotos syndrome)
  - Adrenal insufficiency
  - Galactosaemia
  - Metabolic disorders (e.g. fatty acid oxidation and mitochondrial disorder)
- Investigations
  - Obtain "critical" sampling when plasma glucose < 2.6 mmol/L after 48 hours of life
  - Plasma glucose (RBS)
  - Insulin
  - Blood Gas
  - Serum Lactate
  - Serum Ketones (beta-hydroxybutyrate)
  - Free fatty acid levels
  - Further investigations are directed by the results of these tests (Consult Paediatric Endocrinologist and/or Genetic/Metabolic specialist) e.g. C-peptide, cortisol, growth hormone, ammonia, plasma acylcarnitine and urine for organic acids
  - Take blood investigations before an increase in rate of dextrose infusion when hypoglycaemia persists despite dextrose infusion.

Medical treatment for recurrent or resistant hypoglycaemia

- As per protocol for Management of Persistent Hypoglycaemia.
- PO Diazoxide 5-20mg/kg/day in three divided doses
  - Reduces insulin secretion, therefore useful in hyperinsulinaemia.
  - Can be used in SGA infants with hyperinsulinaemic hypoglycaemia
- Chlorothiazide (use in conjunction with Diazoxide) 5-10mg/kg/day divided into two doses or Hydrochlothiazide 1-2mg/kg/dose bd
- SC Octreotide (synthetic somatostatin) 5-35 µg/kg/day bd/tds or as infusion

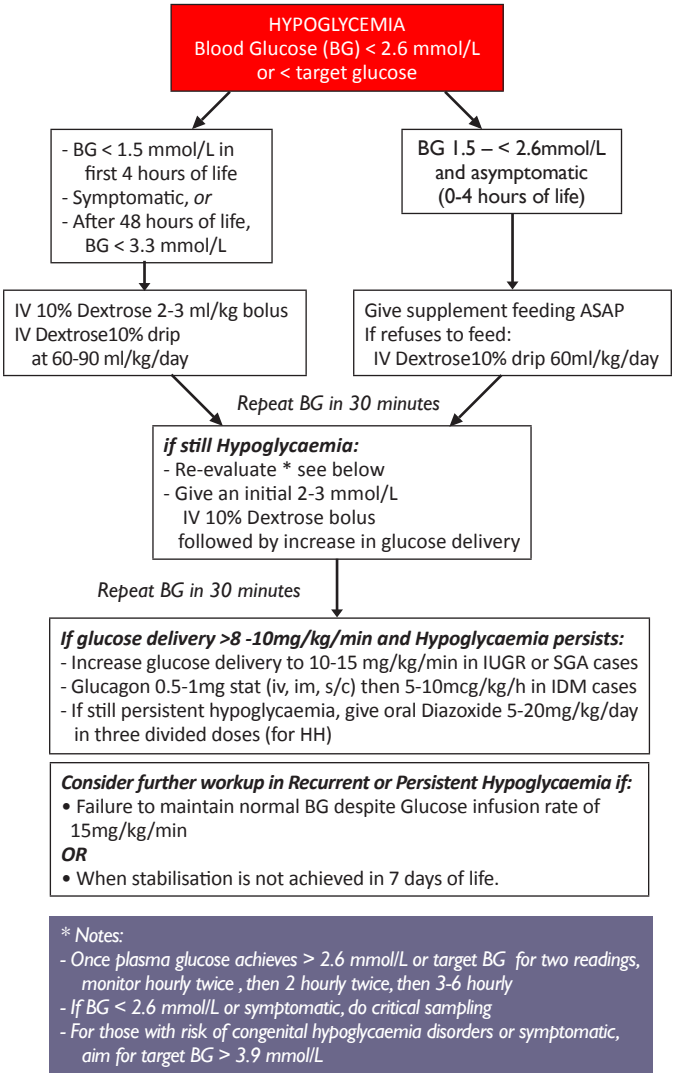
METABOLIC CLUES TO HYPOGLYCEMIA
(adapted from Thornton, et al)



Pearls and Pitfalls in Management

- Depending on severity of hypoglycaemia, maintain some oral feeds as milk has more calories than 10% dextrose.
  Breastfeeding should be encouraged as it is more ketogenic.
- Feed infant with as much milk as tolerated and infuse glucose at a sufficient rate to prevent hypoglycaemia. The dextrose infusion is then reduced slowly while milk feeds is maintained or increased.
- Avoid giving multiple boluses of glucose as they can cause a rapid rise in blood glucose concentration which may be harmful to neurological function and may be followed by rebound hypoglycaemia.
- Any bolus given must be followed by a continuous infusion of glucose. There is no place for treatment with intermittent glucose boluses alone.
- Ensure volume of IV fluid is appropriate for patient taking into consideration concomitant problems like cardiac failure, cerebral oedema and renal failure. If unable to increase volume further, increase dextrose concentration.

MANAGEMENT OF PERSISTENT HYPOGLYCAEMIA



Chapter 17: Neonatal Sepsis

Definition

Neonatal sepsis generally falls into two main categories:

- Early onset: usually acquired from mother with ≥ 1 obstetric complications.
- Late onset: sepsis occurring > 72hours after birth.
  Usually acquired from the ward environment or from the community.

Clinical Features

Risk Factors of Infants and Mother

Any stage

- Prematurity, low birth weight
- Male gender
- Neutropenia due to other causes

Early Onset Sepsis

- Maternal GBS (*Group B Streptococcus*) carrier (high vaginal swab [HVS], urine culture, previous pregnancy of baby with GBS sepsis)
- Prolonged rupture of membranes (PROM) (>18 hours)
- Preterm labour/PPROM
- Maternal pyrexia > 38˚ C, maternal peripartum infection, clinical chorioamnionitis, discoloured or foul-smelling liquor, maternal urinary tract infection
- Septic or traumatic delivery, fetal hypoxia
- Infant with galactosaemia (increased susceptibility to *E. coli*)

Late Onset Sepsis

- Hospital acquired (nosocomial) sepsis
- Overcrowded nursery
- Poor hand hygiene
- Central lines, peripheral venous catheters, umbilical catheters.
- Mechanical ventilation
- Association with indomethacin for closure of PDA, IV lipid administration with coagulase-negative *Staphylococcal* (CoNS) bacteriemia
- Colonization of patients by certain organisms
- Infection from family members or contacts
- Cultural practices, housing and socioeconomic status

Signs and symptoms of Sepsis

- Temperature instability: hypo or hyperthermia
- Change in behaviour : lethargy, irritability or change in tone
  ('baby just doesn't seem right or doesn't look well)
- Skin: poor perfusion, mottling, pallor, jaundice, scleraema, petechiae
- Feeding problems: poor feeding, vomiting, diarrhea, abdominal distension
- Cardiovascular: tachycardia, hypotension
- Respiratory: apnoea, tachypnoea,cyanosis, respiratory distress
- Metabolic: hypo or hyperglycaemia, metabolic acidosis
- Evaluate neonate (late onset sepsis) carefully for primary or secondary foci e.g. meningitis, pneumonia, urinary tract infection, septic arthritis, osteomyelitis, peritonitis, omphalitis or soft tissue infection.

Investigations

- FBC: Hb, TWBC with differential, platelets, Blood culture (>1ml of blood).
- Where available :
  - Serial CRP 24 hours apart
  - Ratio of immature forms over total of neutrophils + immature forms: IT ratio > 0.2 is an early predictor of infection during first 2 weeks of life.
- Where indicated:
  - Lumbar puncture, CXR, AXR, Urine Culture.
  - Culture of ETT aspirate (Cultures of the trachea do not predict the causative organism in the blood of the neonate with clinical sepsis.)

Management

- Empirical antibiotics
  - Start immediately when diagnosis is suspected and after all appropriate specimens taken. Do not wait for culture results.
  - Trace culture results after 48 - 72 hours. Adjust antibiotics according to results. Stop antibiotics if cultures are sterile, infection is clinically unlikely (as in the patient improved due to other reasons such as improving respiratory support or hydration, temperature control)
  - Unnecessary antibiotics use > 5 days increases risk of NEC and nosocomial infection with more resistant organisms or fungal infection in the pre term infants. To consider that not every CXR haziness = pneumonia.
- Empirical antibiotic treatment *(Early Onset)*
  - IV C.Penicillin/Ampicillin and Gentamicin
  - Specific choice when specific organisms suspected/confirmed.
  - Change antibiotics according to culture and sensitivity results
- Empirical antibiotic treatment – *(Late Onset)*
  - For community acquired infection, start on
    - Cloxacillin/Ampicillin and Gentamicin for non-CNS infection, and
    - C.Penicillin and Cefotaxime for CNS infection
- For hospital acquired (nosocomial) sepsis
  - Choice depends on prevalent organisms in the nursery and its sensitivity.
    - For nursery where MRCoNS/ MRSA are common, consider Vancomycin; for non-ESBL gram negative rods, consider cephalosporin; for ESBLs consider carbapenams; for *Pseudomonas* consider Ceftazidime.
    - Anaerobic infections (e.g. Intraabdominal sepsis), consider Metronidazole.
    - Consider fungal sepsis if patient not responding to antibiotics especially if preterm/ VLBW or with indwelling long lines.
- Duration of Antibiotics
  - 7-10 days for pneumonia or proven neonatal sepsis
  - 14 days for GBS meningitis
  - At least 21 days for Gram-negative meningitis
- Consider removing central lines

- Complications and Supportive Therapy
  - Respiratory: ensure adequate oxygenation (give oxygen, ventilator support)
  - Cardiovascular: support BP and perfusion to prevent shock.
  - Hematological: monitor for DIVC
  - CNS: seizure control and monitor for SIADH
  - Metabolic: look for hypo/hyperglycaemia, electrolyte, acid-base disorder
- Therapy with IV immune globulin had no effect on the outcomes of suspected or proven neonatal sepsis.

- Surfactant therapy for respiratory distress syndrome (RDS) is standard care for preterm infants, based on numerous randomised controlled trials demonstrating decreased mortality.
- Surfactant therapy reduces mortality rates most effectively in infants < 30 weeks and those of birthweight < 1250 gm.
- The guideline below is to address how to optimally use surfactant and in which subpopulation of preterm infants.
- The approach should be an individualised one based on clinical appraisal as given in the guideline below.
- Not all preterm infants have RDS and many of them initially have sufficient
- surfactant to establish relatively normal ventilation before other factors such as hypothermia, atelectasis or ventilation trauma inactivates the surfactant.
- The use of antenatal steroids has also reduced the incidence of RDS.

Who to give surfactant to?

- **Depressed preterm infants who have no spontaneous respiration after 30 seconds of ventilation** with T-piece resuscitator or resuscitation bag with CPAP attachment and pressure manometers, and thus require positive pressure ventilation (PPV).
- **Preterm infants below 28 weeks gestation** who are given only CPAP from birth in delivery room, i.e. the infant has spontaneous respiration and good tone at birth. Surfactant to be given within 30 minutes after birth. Decision as to whether to leave the patient intubated after surfactant depends on the lung compliance, severity of RDS and degree of prematurity
- **Preterm infants between 28-32 weeks** – to have CPAP from birth in delivery room. To assess requirement for surfactant in NICU based on oxygen requirement of FiO_2 > 30% and respiratory distress.
  To consider INSURE technique – INtubate, SURfactant, Extubate to CPAP
- **More mature or larger infants** should also be given surfactant if the RDS is severe i.e. arterial alveolar (a/A) PO_2 ratio of <0.22 or Fraction of inspired (FiO_2) > 0.5

$$\text{Calculation for a/A } PO_2 \text{ ratio : } \frac{PaO_2 \text{ (mmHg)}}{(760\text{-}47)FiO_2 - PaCO_2 \text{ (mmHg)}}$$

- To be considered in **severe meconium aspiration syndrome with type II respiratory failure** – to be used prior to high frequency oscillatory ventilation and nitric oxide to allow the lungs to "open" optimally.

Timing of therapy

- Attempts to treat with surfactant before the infant can breathe resulted in more bronchopulmonary dysplasia than early treatment in delivery room because it interferes with initial stabilisation of the infant. Therefore surfactant delivery within the first minute of life is not indicated.

- The first dose has to be given as early as possible to the preterm infants requiring mechanical ventilation for RDS. The repeat dose is given 4-6 hours later if FiO_2 is still > 0.30 with optimal tidal volume settings forthose below 32 weeks and if FiO_2 > 0.40 and CXR still shows moderate to severe RDS ("white" CXR) for those infants > 32 weeks gestational age.

Types of surfactant and dosage

There are two types of surfactant currently available in Malaysia

- Survanta , a natural surfactant, bovine derived
  Dose : 4 ml/kg per dose.
- Curosurf , a natural surfactant, porcine derived (not in Blue Book)
  Dose: 1.25 mls/kg per dose.
- Infasurf, a natural surfactant, bovine derived
  Dose: 3 mls/kg

Method of administration

- Insert a 5 Fr feeding tube that has been cut to a suitable length so as not to protrude beyond the tip of the ETT on insertion, through the ETT. If the surfactant is given soon after birth, it will mix with foetal lung fluid and gravity will not be a factor. Therefore no positional changes are required for surfactant given in delivery room.
  Surfactant is delivered as a bolus as fast as it can be easily be pushed through the catheter. Usually this takes 2 aliquots over a total of a few minutes.
- Continue PPV in between doses and wait for recovery before the next aliquot, with adjustments to settings if there is bradycardia or desaturation. Administration over 15 minutes has been shown to have poor surfactant distribution in the lung fields.
- Alternatively the surfactant can be delivered through the side port on ETT adaptor without disconnecting the infant from the ventilator. There will be more reflux of surfactant with this method.

Monitoring

- Infants should be monitored closely with a pulse oximeter and regular blood gas measurements. An indwelling intra-arterial line wiould be useful. Ventilator settings must be promptly wound down to reduce the risk of pneumothorax and ventilator induced lung injury.
- Consider extubation to CPAP if the oxygen requirement is less than 30% and there are minimal pressure requirements.

Chapter 19: Neonatal Encephalopathy

Neonatal Encephalopathy (NE) is a clinical syndrome of disturbed neurological function, caused by failure to make a successful transition to extrauterine gas exchange.

- Manifests as difficulty in initiating and maintaining spontaneous respiration, depression of muscle tone and reflexes, depressed consciousness and often seizures.
- Moderate or severe NE occurs in 2/1000 live births; usually affects full term infants.
- The terminology NE is preferred to Hypoxic Ischemic Encephalopathy (HIE) unless it is possible to document a significant hypoxic-ischemic insult in the peripartum or intrapartum period.
- Causes of NE other than HIE are CNS malformation, intracranial haemorrhage, intracranial infection, cerebral infarction/stroke, metabolic disorders, drug toxicity, drug withdrawal, electrolyte imbalances, and seizure disorders.
- Risk factors for neonatal encephalopathy were mainly seen in the antenatal period (69%) as compared to the intrapartum period (25%) in a large Western Australian study. Only 4% were due to intrapartum hypoxia.

Criteria suggestive of HIE in the newborn

1. Early onset of moderate or severe encephalopathy in newborn > 35 weeks gestational age. (If aEEG available – amplitude range- lower below 5, higher below 10, i.e. low amplitude aEEG, suggest more severe encephalopathy)

AND

2. Neonatal signs consistent with an intrapartum or peripartum event 3 :

- Arterial cord pH < 7.00
- Apgar score of less than 5 at 5 and 10 minutes of life
- Evidence of multiorgan system dysfunction within 72 hours of birth
- Neuroimaging evidence of acute brain injury seen on brain MRI (done within a week to 10 days) consistent with hypoxia–ischemia

Type and timing of contributing factors that are consistent with intrapartum timing

- A sentinel hypoxic or ischemic event occurring immediately before or during labor and delivery
- Foetal heart rate pattern that becomes abnormal during labour or after a sentinel event

AND

3. The absence of an infectious cause, a congenital malformation of the brain, an inborn error of metabolism or other condition, which could explain the encephalopathy.

When more of the elements from each of the item categories in the table are met, it becomes increasingly more likely that peripartum or intra-partum hypoxia–ischemia played a role in the pathogenesis of neonatal encephalopathy.

- According to the American College of Obstetrician and Gynaecologist's Task Force on Neonatal Encephalopathy and Cerebral palsy, there is no definitive test or set of markers that accurately identifies, with high sensitivity and specificity, an infant in whom neonatal encephalopathy is attributable to an acute intrapartum event.

Staging of Neonatal Hypoxic Ischaemic Encephalopathy (HIE)

Can be done by using modified Sarnat Staging. This is mainly used in term infants or infants > 35 weeks gestation. It is not useful in premature infants.

Modified Sarnat Classification

Often NE does not fit into one single Sarnat staging, common staging used is as 1-2 or 2-3.

Modified Sarnat Classification			
	Mild HIE(Stg I)	Moderate HIE (Stg II)	Severe HIE (Stg III)
Level of consciousness	Hyperalert	Lethargy	Stupor/Coma
Muscle Tone	Normal/ Hypotonia	Hypotonia	Flaccid
Complex reflexes Suck Moro	 Normal / Poor Exaggerated	 Weak / Absent Weak / Incomplete	 Absent Absent
Seizures	Absent	Common	Frequent/ difficult Control
Prognosis	Good, recover within 24hours	Abnormal & untreated lead to cerebral palsy	Severely abnormal, may lead to death or severe handicap

Thompson Encephalopathy Score

- The severity of encephalopathy can be assessed using the modified Thompson Score
- To commence cooling therapy as soon as the Thompson score is ≥ 7 from birth to 6 hours, and the baby fulfils other criteria for therapeutic hypothermia. (see Chapter on therapeutic hypothermia).
- To monitor on an hourly basis until decision to cool is made, i.e. Thompson score increases progressively to >7

Thompson Encephalopathy Score				
Score	0	1	2	3
Tone	Normal	Hyper	Hypo	Flaccid
LOC	Normal	Hyperalert, stare	Lethargic	Comatose
Seizures	None	< 3/day	>2/day	
Posture	Normal	Fisting, cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent ± bites	
Respiration	Normal	Hyperventilation	Brief apnea	IPPV (apnea)
Fontanelle	Normal	Full, not tense	Tense	

Date						
Time						
Tone						
LOC						
Fits						
Posture						
Moro						
Grasp						
Suck						
Respiration						
Fontanelle						
TOTAL						

Chapter 20: Hypothermia Therapy for Neonates ≥35 Weeks Gestation With Moderate or Severe Hypoxic Ischaemic Encephalopathy (HIE)

All four criteria must be met before cooling is commenced

- Newborn Infant born ≥ 35 weeks gestation
- < 6 hrs post birth
- Evidence of asphyxia as defined by the presence of at least 2 of the following 4 Criteria:
  - Apgar scores < 6 at 10 min or continued need for resuscitation with positive pressure ventilation +/- chest compressions at 10min after birth
  - Any acute perinatal event that may result in HIE (i.e. Placental abruption, cord prolapse, severe FHR (Foetal Heart Rate) abnormality etc.)
  - Cord pH < 7.0 or base deficit of -12mmol/L or more
  - If cord pH is not available, arterial pH <7.0 or BE > -12mmoL/L within 60 min of birth
- The baby has Thompson Score > 7 or seizures

Exclusion criteria

- Oxygen requirement > 80% that is not responsive to treatment
- Major lethal congenital abnormalities
- Severe clinical coagulopathy (including low platelet counts) not responsive to treatment
- Baby unlikely to survive. This should be discussed with and decided by the neonatologist

When to start cooling

- Cooling should be started as soon as possible after resuscitation is completed.
- Current evidence suggests that cooling is unlikely to be beneficial if started more than 6-8 hours after birth.

Before cooling

- Ensure adequate resuscitation and support for the neonate including airway, breathing, circulation and dextrose
- Avoid hyperthermia > 37°C as this can increase the risk of adverse outcome.

Methods of cooling

- Total body cooling (with therapeutic hypothermia device)
- Selective head cooling
- Passive cooling +/- active cooling (with cool packs)

PASSIVE COOLING

This is a process of allowing the infant to cool down of their own accord through the removal of the usual interventions undertaken to keep infants warm.

Aims

- To achieve an axillary temperature between 33.5°C and 34.5°C or rectal temperature between 33°C and 34°C within 60 minutes of commencing cooling.
- To target hypothermia initially with passive cooling.
- If rectal temperature remains > 35°C or axillary temp >35.5°C within 60 minutes of starting, then active cooling should be commenced.
- To cool baby for 72 hours then rewarm slowly over 12 hours.

Procedure

- Infant must be nursed on open bed with warmer off (DO NOT nurse infant in incubator).
- Nurse infant naked: NO clothes, cap or any wraps. Leave nappy unfastened
- Full cardiopulmonary monitoring and O_2 saturation monitor.
- Record: Time of commencement of passive cooling and rectal (wherever possible) or axillary temperature every 15 minutes.
- If rectal temperature drops < 33.5°C (axillary temperature below 34°C) set radiant warmer on servo-control mode at the lowest temperature to maintain axillary temperature at 33.5-34.5°C or rectal temperature at 33.0 – 34.0°C.

ACTIVE COOLING WITH ICE PACKS

Active cooling must only be started if passive cooling has been underway for 1 hour and the infant's rectal temperature is >35°C (axillary temp >35.5°C).

Aims

- To achieve target temperature range within 1 hour

Procedure

- Use cool packs from the fridge, NEVER frozen. Always wrap cool packs in cotton bags. They should never be applied directly to the skin.
- Cold packs can be placed under the shoulders/upper back under the head and/or across the chest/body but not in the axilla where the accuracy of temperature monitoring.
- Refer to Table for number of cool packs to be used and the algorithm in next pages.
- Aim for rectal temperature 33 - 34°C within the first hour of cooling. For axillary temperature, aim for 33.5 – 34.5°C.
- Record time of initiating active cooling and monitor temperatures every 15 minutes.
- If rectal temp drops to <34°C (axillary temp <34.5°C), remove all cool packs and repeat temperature in 15 minutes.
- If rectal temperature continues to fall <33.5°C (axillary temp <34°C), set radiant warmer on servo-control mode at the lowest temperature to maintain rectal temp at 33.0 – 34.0°C (axillary temp at 33.5-34.5°C).

Active cooling with ice packs		
Rectal Temperature algorithm (Axillary temp in brackets)	Number of cool packs to be applied	Areas to apply
>35.0°C (>35.5°C)	2*	under shoulders, along sides
34.0 – 35.0°C (34.5 -35.5°C)	I	along sides
<34.0°C (<34.5°C)	0	Nil

NB: Having more than 2 packs prevents radiant loss of heat into the environment and makes it more difficult to cool the baby.

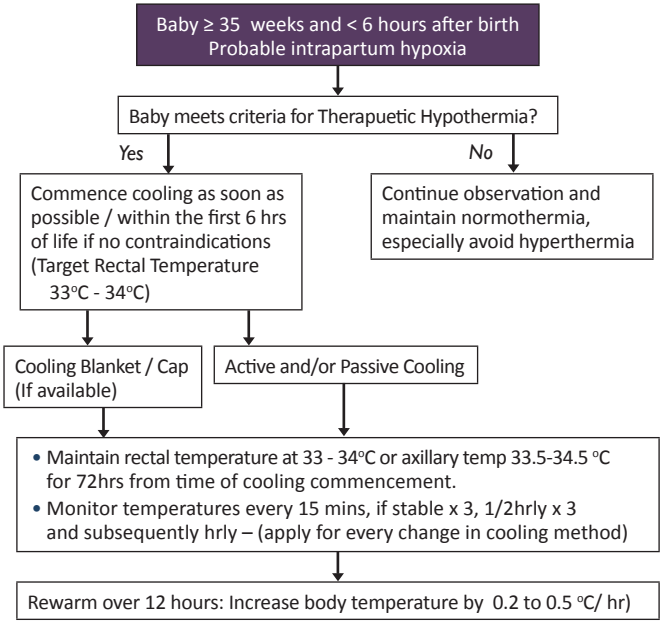
Application of Rectal Thermistor Probe

- Insert Rectal Thermistor/Probe at least 5 cm into anus.
- Secure the probe at the 10 cm (first marking) measurement with tape to the upper inner thigh.
- Note: The probe must be at least 5cm into the anus to accurately measure the baby's core temperature.
- Connect rectal probe to cable, temperature module and monitor
- Set temperature alarm limits at 33°C (low) and 34°C (high) during the cooling period.
- Record time of initiating Active Cooling and monitor Rectal Temperatures every 15 minutes.

Duration of therapeutic cooling.

- Normal cooling should be continued for 72 hrs from the commencement of cooling.
- Consider stopping cooling early if there is:
  - Persistent hypoxemia in 100% oxygen
  - Life- threatening coagulopathy despite treatment
  - An arrhythmia requiring medical treatment (not sinus bradycardia), or
  - If palliative care considered and after mutual agreement between parents and senior clinicians.

THERAPEUTIC HYPOTHERMIA FLOW CHART



REWARMING

Aim

- To rewarm slowly over about 12 hours and to avoid making the baby hyperthermic.

Method

- Apply skin probe and turn the radiant warmer on with the servo set at 34.5°C.
- Increase the set temperature by 0.5°C every 2 hours until reach 36.2 to 36.5°C and rectal temperature is 37°C (It should take up to 12 hours for rewarming)**.
- Monitor axillary temperatures frequently as the rectal temperature approaches the target range. Monitor infant's temperature carefully for 24 hours after normothermia has been achieved to prevent rebound hyperthermia.

NB : Rewarming can occur too rapidly so babies need close monitoring. If baby is rewarming too rapidly increase set temperature by 0.5°C every 4 hrs instead of 2 hourly. Avoid hyperthermia.

Ongoing Monitoring

- Continuous BP, HR and rectal temperature monitoring
- aEEG monitoring if available. aEEG can be helpful in predicting outcome and identifying seizure activity
- Blood Gas (arterial access is usually obtained); 4 hourly at least initially then as required by clinical state (includes glucose, ionised calcium and if possible lactate). Maintain normocarbia and normal oxygen saturation
- Electrolytes; 8-12 hourly initially then as required by clinical state but at least daily until day 3-5
- Full blood count; 12 hrly initially then as required by clinical state but at least daily until day 3-5
- INR and APPT clotting studies; on day 1 and then, if abnormal, daily until day 5 or stable
- LFT on day 2 and 5
- Hypotension: Treatment with volume replacement and/or inotropes should be considered if the mean arterial blood pressure is < 40 mm Hg. A bolus of 10-20 ml/kg of normal saline may be given initially and if the BP remains low, consider using inotropes (either dopamine or dobutamine). Avoid multiple fluid boluses unless volume loss in view of possible impaired cardiac output
- Renal Impairment: As a guide infants with history of perinatal hypoxia will require about 60 ml/kg/day. Infants in renal failure should receive a total of 30 ml/kg/day plus any measured losses.
  Boluses of 0.9% saline may be required to avoid hypovolaemia if diuresis occurs in the infant or if vasodilation occurs during rewarming.
- Enteral Feeding: Enteral feeding can be cautiously introduced and advanced slowly once the initial biochemical and metabolic disturbance are corrected, usually after about 24 hours.
- Sedative Therapy: Signs of distress include tachycardia, facial grimacing and irritability. A heart rate consistently above 110 bpm in cooled infants suggests that infant may be distressed. Ventilated infants may be sedated with morphine infusion 10µg/kg/hr. Morphine may be discontinued after 24-48 hours to lessen the risk of accumulation and toxicity

Side effects / Complications / Precautions

- Sinus bradycardia - usually transient and reversible
- Decreased blood pressure - usually transient and reversible
- Increased oxygen requirement
- Mild thrombocytopenia
- Increased bleeding tendency
- Prolonged drug half-life - morphine (only need half the amount) and phenobarbitone (usually stat dose sufficient – to monitor levels if more doses delivered)
- Too rapid rewarming causing peripheral vasodilatation and hypotension

Chapter 21: Neonatal Seizures

Introduction

- A seizure is a paroxysmal behavior caused by hypersynchronous discharge of a group of neurons. The neonatal period is the most frequent time to have seizures.
- Seizures are the most common manifestation of neurological dysfunction in the newborn. The increased susceptibility to seizures may be explained by birth factors (e.g. hypoxia ischemia, birth trauma) and developmental factors (excitatory effect of Gamma-Amino Butyric Acid (GABA) in immature brain).
- Neonates may also exhibit paroxysmal non-epileptic events than can mimic seizures and it is important to differentiate them from the following:
  - Jitteriness-stimulus sensitive and aborts with gentle limb flexion
  - Benign neonatal sleep myoclonus-only occurs in sleep and aborts with arousal
  - Startle disease (Hyperekplexia)-excessive startle, stimulus sensitive jerks and generalized muscle rigidity

Clinical Manifestation	Jitteriness	Seizure
Abnormality of gaze or eye movement	0	+
Movements exquisitely stimulus sensitive	+	0
Predominant movement	Tremors[1]	Clonic, jerking[2]
Movements stop with passive flexion of affected limb	+	0
Autonomic changes (tachycardia, high BP, apnoea, salivation, cutaneous vasomotor phenomena)	0	+

Footnote: 1, Tremors – alternating movements are rhythmical and of equal rate and amplitude; 2, Clonic, jerking – movements with a fast and slow component

Adapted from JJ Volpe: Neurology in the Newborn 4th Edition. Page 188

Classification of Neonatal Seizures		
Clinical Seizure	EEG seizure	Manifestation

Subtle	Common	• **Ocular phenomena**
		  • Tonic horizontal deviation of eyes common in term infants.
		  • Sustained eye opening with fixation common in preterm infants.
		  • Blinking.
		• **Oral-buccal-lingual movements**
		  • Chewing common in preterm infants.
		  • Lip smacking, cry-grimace.
		• **Limb movements**
		  • Pedaling, stepping, rotary arm movements
		• **Apnoeic spells** common in term infants

Clonic Focal Multifocal	 Common Common	 Well localized clonic jerking, infant usually not unconscious Multifocal clonic movements; simultaneous, in sequence or non-ordered (non-Jacksonian) migration
Tonic Focal Generalized	 Common Uncommon	 Sustained posturing of a limb, asymmetrical posturing of trunk or neck • Tonic extension of upper and lower limbs (mimic decerebrate posturing) • Tonic flexion of upper limbs and extension of lower limbs (mimic decorticate posturing) • Those with EEG correlates; autonomic phenomena, e.g. increased BP are prominent features.
Myoclonic Focal, Multifocal Generalized	 Uncommon Common	 Well localized, single or multiple, migrating jerks usually of limbs Single/several bilateral synchronous jerks or flexion movement more in upper than lower limbs.
Note: *Subtle seizures are easily missed and requires correlation with EEG *Focal clonic seizures may suggest a localized cerebral injury eg perinatal stroke *Generalized tonic seizures are the commonest seizure type in preterm IVH		

Aetiology			
Cause	Usual Age at Onset	Preterm	Term
Hypoxic-ischemic encephalopathy	< 3 days	+++	+++
Metabolic			
Hypoglycemia	< 2 days	+	+
Hypocalcemia			
Early-onset	2 – 3 days	+	+
Late-onset	> 7 days	+	
Drug Withdrawal	< 3 days	+	+
Pyridoxine (Vitamin B6) Dependency	< 1 day		
Intracranial infection			
Bacterial meningitis (E. coli, Group B Strep, Listeria)	< 3 days	++	+
Viral Encephalitis (Herpes Simplex, Enterovirus)	> 3 days	++	
Intrauterine Infection	> 3 days	++	++
Cerebral Vascular			
Intraventricular hemorrhage	< 3 days	++	
Primary subarachnoid bleed	< 1 day		++
Subdural/epidural hematoma	Variable		++
Focal Ischemic Necrosis (Stroke)	Variable		+
Sinus Thrombosis	Variable	++	++
Developmental defects			
Neuronal migration disorders and cortical dysplasia	Variable	+	+
Epilepsy Syndromes			
Epileptic Encephalopathies (Early Myoclonic Epilepsy (EME), Ohtahara syndrome)	> 7 days		+
Benign Familial Neonatal Seizures (BFNS)	< 3 days		+
Benign Neonatal seizures (non familial)	> 5 days		+

* (Relative Frequency: +++ = most common; ++ = less common; + = least common. If no +, then uncommon.)

Management

- Thorough history, physical examination and neurophysiological assessment with amplitude integrated EEG (aEEG)/ continuous video electroencephalography (cEEG) is often required in newborns at risk for seizures. Abnormal initial EEG background may predict higher seizure risk in newborns with HIE.
- It is very important to delineate whether the abnormal movements/ paroxysmal events are seizures. Where applicable correlation with aEEG is desirable as this avoids unnecessary and potential side effects with antiepileptic drugs (AED).
- Controversies regarding extent of treatment (i.e. whether to stop all clinical or electrographic seizures) exist. It is desirable to eliminate electroclinical and electrographic graphic seizures especially if they:
  - Are prolonged –more than 2-3 minutes.
  - Are frequent– more than 2-3 per hour.
  - Disrupt ventilation and/or blood pressure homeostasis
- In acute setting, administer antiepileptic drugs intravenously to achieve rapid onset of action and predictable blood levels in order to achieve serum levels in the normal therapeutic range.
- Maintenance therapy is usually not required if loading doses of anticonvulsant drugs are able to control seizures.
- A prolonged duration of AED maintenance (6-12 weeks) following acute neonatal seizures may be considered in the following circumstances:
- Higher probability of seizure recurrence (stroke and hemorrhage)
- Abnormal neonatal neurological examination upon discharge
- Abnormal EEG background upon discharge
- Routine maintenance AED is not recommended as some AEDs (phenobarbitone and phenytoin) have neuroapoptotic properties.

Outcome

The outcome following neonatal seizures depends primarily on the underlying cause. The presence of both clinical (except focal clonic) and electrographic seizures often indicates brain injury and coupled with abnormal EEG background are important determinants for adverse outcome.

Prognosis according to aetiology of neonatal seizures

Neurological disorder	Normal Development (%)[1]
Hypoxic Ischemic Encephalopathy	50
Severe Intraventricular Haemorrhage with periventricular hemorrhagic infarction	10
Hypocalcaemia *Early onset* (depends on prognosis of complicating illness, if no neurological illness present prognosis approaches that of later onset) *Later onset* (nutritional type)	50 100
Hypoglycemia	50
Bacterial meningitis	50
Malformation of Cortical Development	0

Footnote:1, Prognosis based cases with the stated neurological disease when seizures are a manifestation.This will differ from overall prognosis of the disease.

Additional investigations when aetiology of seizures are still unknown

Blood	Urine	Imaging	CSF
VBG, Lactate, Ammonia Plasma Amino acid Biotinidase enzyme assay (DBS)# Plasma Copper & ceruloplasmin Serum Transferrin isoform (TIEF)# Plasma Very long chain fatty acid (VLCFA) & Phytanic acid# Acylcarnitine profile # (DBS)	Urine Organic Acid Urine sulphite and sulphocysteine Urine purine/ pyrimidine Urine P6C*#	Ultrasound Brain CT Brain MRI Brain +/-MRS# ±MRA/MRV & diffusion studies	Biochemistry/ gram stain/ culture/latex agglutination CSF Lactate Viral studies CSF Amino acid# (Pair with serum)

 # To discuss with Neurologist or Metabolic specialist before sending sample.
DBS = Dried blood spot , *P6C- piperideine-6-carboxylate

Neonatal amplitude-integrated EEG (aEEG): Points to consider

- Continuity
- Amplitude of lower margin (Normal > 5μV) & upper margin (Normal>10μV)

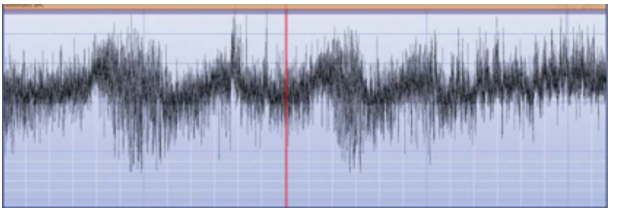
Sleep-wake cycling

- Seizures

RECOGNIZABLE PATTERNS OF TERM NEONATAL AEEG

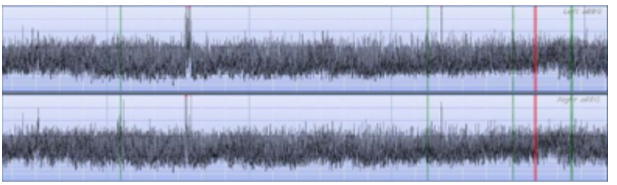
- Normal

Continuous Normal Voltage

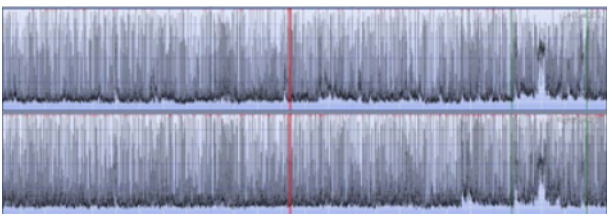


- Abnormal

Discontinuous Normal Voltage

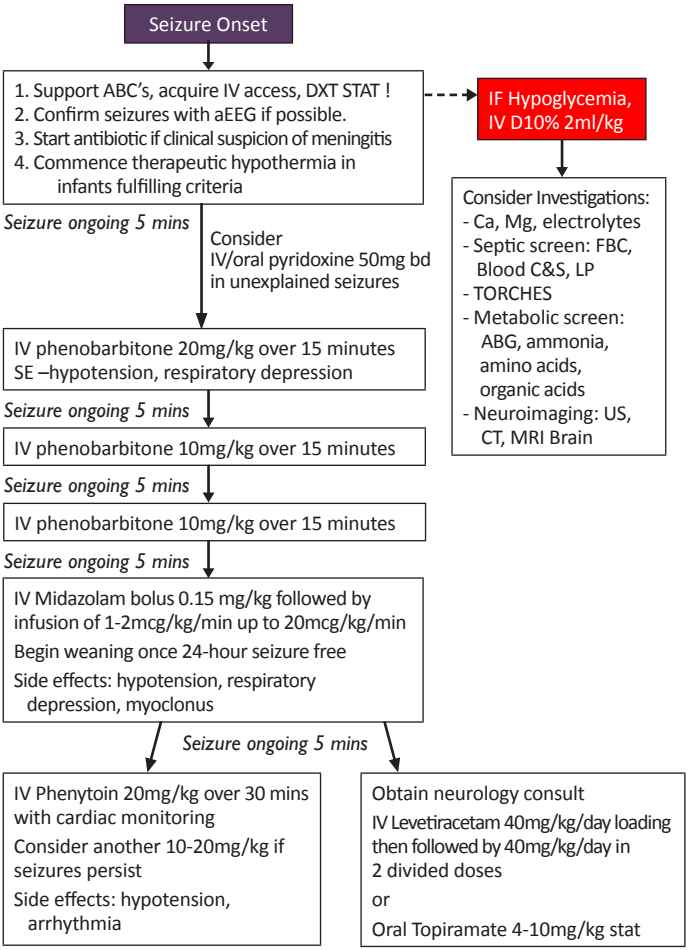


Burst suppression



Suppression

GUIDELINES FOR THE MANAGEMENT OF SEIZURES IN NEONATES AGE ≤ 1 MONTH, GESTATIONAL AGE ≥ 35 WEEKS



Chapter 22: Neonatal Jaundice

Introduction

Jaundice can be detected clinically when the level of bilirubin in the serum rises above 85 µmol/l (5mg/dl).

Causes of neonatal jaundice

- Haemolysis due to ABO or Rh-isoimmunisation, G6PD deficiency, microspherocytosis, drugs.
- Physiological jaundice.
- Cephalhaematoma, subaponeurotic haemorrhage.
- Polycythaemia.
- Sepsis septicaemia, meningitis, urinary tract infection, intra-uterine infection.
- Breastfeeding and breastmilk jaundice.
- Gastrointestinal tract obstruction: increase in enterohepatic circulation.

Risk factors for Severe Neonatal Jaundice
Prematurity
Low birth weight
Jaundice in the first 24 hours of life
Mother with blood Group O or Rhesus Negative
G6PD deficiency
Rapid rise of total serum bilirubin
Sepsis
Lactation failure in exclusive breastfeeding
High predischarge bilirubin level
Cephalhaematoma or bruises
Babies of diabetic mothers
Family history of severe NNJ in siblings

Approach to an infant with jaundice

History

- Age of onset.
- Previous infants with NNJ, kernicterus, neonatal death, G6PD deficiency.
- Mother's blood group (from antenatal history).
- Gestation: the incidence of hyperbilirubinaemia increases with prematurity.
- Presence of abnormal symptoms such as apnoea, difficulty in feeding, feed intolerance and temperature instability.

Physical examination

- General condition, gestation and weight, signs of sepsis, hydration status.
- Signs of acute bilirubin encephalopathy (ABE) should be assessed for in all babies with severe NNJ (see BIND score)
- Pallor, plethora, cephalhaematoma, subaponeurotic haemorrhage.
- Signs of intrauterine infection e.g. petechiae, hepatosplenomegaly.
- Cephalo-caudal progression of severity of jaundice.

The adequacy of breastfeeding, weight and hydration status of all babies should be assessed during the first week of life. Babies with weight loss > 7% should be referred for further evaluation and closely monitored for jaundice

Bilirubin Induced Neurological Dysfunction (BIND score)			
Clinical Signs	Score	Date	Time
Mental Status			
Normal	0		
Sleepy but arousable; decreased feeding	1		
Lethargy, poor suck and/or irritable/jittery with strong suck	2		
Semi-coma, apnoea, unable to feed, seizures, coma	3		
Muscle Tone			
Normal	0		
Persistent mild to moderate hypotonia	1		
Mild to moderate hypertonia alternating with hypotonia, beginning arching of neck and trunk on stimulation	2		
Persistent retrocollis and opisthotonus - bicycling or twitching of hands and feet	3		
Cry Pattern			
Normal	0		
High pitched when aroused	1		
Shrill, difficult to console	2		
Inconsolable crying or cry weak or absent	3		
TOTAL BIND SCORE			

- **Advanced ABE (score 7 - 9):** urgent bilirubin reduction intervention is needed to prevent further brain damage and reduce the severity of sequelae
- **Moderate ABE (score 4 - 6):** urgent bilirubin reduction intervention is likely to reverse this acute damage
- **Mild ABE (score 1 - 3):** subtle signs of ABE

Note: An abnormal or 'referred' Auditory Brainstem Response (ABR) is indicative of moderate ABE. Serial ABR may be used to monitor progression and reversal of acute auditory damage and could be indicative of the effectiveness of bilirubin reduction strategy.

Methods of Detecting Jaundice:

- Visual Assessment (Kramer's rule)
- Transcutaneous Bilirubinometer (TcB) – if TcB levels are more than 200umol/l (12mg/dl), total serum bilirubin (TSB) should be obtained. TcB is not to be used for patients on phototherapy.
- Total Serum Bilirubin

All newborn babies should be visually assessed for jaundice at every opportunity.

Visual Assessment of Neonatal Jaundice (Kramer's rule)			
Area of the Body	Level	Range of Serum Bilirubin	
		µmol/L	mg/dL
Head and neck	1	68 - 133	4 - 8
Upper trunk (above umbilicus)	2	85 - 204	5 - 12
Lower trunk and thighs (below umbilicus)	3	136 - 272	8 - 16
Arms and lower legs	4	187 - 306	11 - 18
Palms and soles	5	≥ 306	≥ 18

Management

- Indications for referral to hospital:
- Jaundice within 24 hours of life.
- Jaundice below umbilicus (corresponds to serum bilirubin 200-250 µmol/L).
- Jaundice extending to soles of feet: **Urgent referral as it is a sign of severe NNJ.**
- Family history of significant haemolytic disease or kernicterus.
- Any unwell infant with jaundice.
- Prolonged Jaundice of >14 days.
- Infants with conjugated hyperbilirubinaemia should be referred to a hospital as soon as possible.
- Infants with unconjugated hyperbilirubinaemia can be investigated and referred only if the jaundice does not resolve or a definitive cause found.

(ref **Chapter 24 Prolonged Jaundice in the Newborn**).

Investigations

- In babies with severe hyperbilirubinaemia, early-onset neonatal jaundice (<24 hours) or rapid rise of TSB (>8.5 µmol/L/h or >0.5 mg/dL/h), further laboratory evaluation may be required to ascertain underlying cause and extent of haemolysis. This may include:
  - G6PD testing (if not screened)
  - mother's and baby's blood groups
  - a direct Coombs test
  - a full blood count ± peripheral blood picture
  - a reticulocyte count
  - a septic workup (if infection is suspected)
- All babies should be screened for Glucose-6-phosphate dehydrogenase (G6PD) deficiency. The results should be reviewed within 24 hours.
- G6PD enzyme assays may be considered in babies suspected to have G6PD deficiency but with normal/indeterminate Fluorescent Spot Test.

Treatment

Use of sunlight exposure to reduce jaundice should be avoided due to risk of dehydration and sunburn.

Phototherapy

- Phototherapy is the mainstay of treatment in NNJ. There are many types of devices that can be used to provide phototherapy such as fluorescent tubes, Light Emitting Diode (LED), fibreoptic and halogen bulbs.
- Effective phototherapy is achieved with optimal irradiance and adequately exposed body surface area rather than the number of phototherapy units.
- Effective phototherapy consist of :
  - blue light range (400 - 500 nm)
  - irradiance of minimum of 15 µW/cm²/nm for conventional phototherapy
  - irradiance of minimum of 30 µW/cm²/nm for intensive phototherapy
  - distance of the light source not exceeding 30 - 50 cm from the baby
- Phototherapy should be commenced when total serum bilirubin reaches the phototherapy threshold for neonatal jaundice*.
- Irradiance of phototherapy units (non-Light Emitting Diode type) should be regularly checked.
- Overhead phototherapy is preferred to underneath phototherapy.
- Babies should be placed in the supine position with adequate exposure.
- Phototherapy should be started at a lower threshold in preterm and low birth weight babies.
- Light Emitting Diode phototherapy is preferred in preterm babies.
- Once the baby is on phototherapy, visual observation as a means of monitoring is unreliable. Serum bilirubin levels must guide the management

Care of babies during phototherapy

- Babies should be regularly monitored for vital signs including temperature and hydration status.
- Babies should be adequately exposed.
- Babies' eyes should be covered to prevent retinal damage.
- Breastfeeding should be continued.
- Turn off photolights and remove eyepads during feeding and blood taking.

Prevention of severe neonatal jaundice

- All babies discharged <48 hours after birth should be seen by a healthcare provider in an ambulatory setting or at home within 24 hours of discharge.
- For babies with severe jaundice admitted for treatment, early follow-up is needed to detect rebound jaundice after discharge.
- Predischarge screening should be used to prevent severe neonatal jaundice (NNJ) in late preterm and term babies.
- Clinical risk factor assessment or/and predischarge bilirubin levels [transcutaneous bilirubin or total serum bilirubin (TSB)] can be used as predischarge screening.
- Universal predischarge bilirubin screening may be considered for all babies if resources are available.
- All G6PD deficient babies should be admitted and monitored for NNJ during the first five days of life. A TSB should be done if there is clinical jaundice.
- Term G6PD deficient babies with birth weights >2500 g may be discharged earlier on day four of life if the TSB is <160 µmol/L (9 mg/dL), and followed-up closely.

Follow up

- Babies with acute bilirubin encephalopathy should have long-term follow-up to monitor for neurodevelopmental sequelae.
- Term and late preterm babies with TSB >20 mg/dL (342 µmol/L) or exchange transfusions should have Auditory Brainstem Response (ABR) testing done within the first three months of life. If the ABR is abnormal, the baby should be referred soon to the audiologist for early intervention and neurodevelopmental follow-up should be continued.
- Healthy term and late preterm babies with non-haemolytic hyperbilirubinaemia and TSB <25 mg/dL (428 µmol/L) may be followed-up at the primary care level.
- Preterm babies with jaundice should be followed-up for neurodevelopmental sequelae as per follow-up plans for all preterm babies.

TSB LEVELS FOR PHOTOTHERAPY AND EXCHANGE TRANSFUSION IN BABIES ≥35 WEEKS GESTATION

adapted from AAP Guidelines

Age	LOW RISK >38 weeks and well		MEDIUM RISK >38 weeks with risk factors, or 35 - 37 weeks + 6 days and well		HIGH RISK 35 - 37 weeks + 6 days with risk factors	
Hours of life	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)
*6	5(80)	17((290)	4(60)	14(240)	2(30)	13(220)
*12	6(100)	18(310)	5(80)	15(260)	3(50)	14(240)
24	9(154)	19(325)	7(120)	17(291)	5(86)	15(257)
48	12(205)	22(376)	10(171)	19(325)	8(137)	17(291)
72	15(257)	24(410)	12(205)	21(359)	10(171)	18.5(316)
96	17(291)	25(428)	14(239)	22.5(385)	11(188)	19 (325)
>96	18(308)	25(428)	15(257)	22.5(385)	12(205)	19 (325)

- *Start intensive phototherapy at TSB of 3 mg/dL (51 µmol/L) above the level for conventional phototherapy or when TSB increasing at >0.5 mg/dL (8.5 µmol/L) per hour.*
- *Risk factors are isoimmune haemolytic disease, G6PD deficiency, asphyxia and sepsis.*

The AAP exchange transfusion guidelines for babies ≥35 weeks gestation recommend:

- *ET if baby shows signs of ABE or if TSB ≥5 mg/dL (85 µmol/L) above the ET levels.*
- *ET if TSB rises to ET levels despite intensive phototherapy in hospitalised babies.*
- *For readmitted babies without signs of ABE, if the TSB is above the ET levels, repeat TSB every 2 - 3 hours and consider ET if it is not expected to drop below ET levels after 6 hours of intensive phototherapy.*

PHOTOTHERAPY AND EXCHANGE TRANSFUSION LEVELS FOR PRETERM INFANTS ≤ 34 WEEKS GESTATION

adapted from NICE Guidelines

Age	23 weeks		24 weeks		25 weeks	
Hours of life	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)
6	2.5(45)	5(90)	2.5(45)	5(90)	3(50)	6(100)
12	3 (55)	6(105)	3.5(60)	6.5(110)	3.5(60)	6.5(110)
24	4.1 (70)	7.6(130)	4.1 (70)	7.9 (135)	4.7 (80)	8.2 (140)
48	5.9 (100)	10.5(180)	6.5 (110)	10.9 (185)	6.5 (110)	11.1 (190)
72	7.6 (130)	13.5 (230)	8.2(140)	14.0(240)	8.8 (150)	14.6 (250)
96	7.6 (130)	13.5 (230)	8.2(140)	14.0 (240)	8.8(150)	14.6 (250)

Age	26 weeks		27 weeks		28 weeks	
Hours of life	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)
6	3(50)	6(100)	3(50)	6(100)	3(50)	6(100)
12	3.5(60)	6.5(110)	3.5(60)	6.5(110)	3.5(60)	6.5(110)
24	4.7(80)	8.2(140)	4.7(80)	8.2(140)	5.3 (90)	8.8(150)
48	7.0(120)	11.7 (200)	7.6(130)	12.0(205)	7.6(130)	12.3(210)
72	9.4 (160)	15.2 (260)	10.0(170)	15.8 (270)	10.5(180)	16.4(280)
96	9.4 (160)	15.2 (260)	10.0(170)	15.8(270)	10.5 (180)	16.4 (280)

Age	29 weeks		30 weeks		31 weeks	
Hours of life	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)
6	3(50)	6(100)	3(50)	6(100)	3(50)	6(100)
12	3.8(65)	6.7(115)	3.8(65)	6.7(115)	4(70)	7 (120)
24	5.3 (90)	8.8(150)	5.6(95)	8.8(150)	5.9 (100)	9.1(155)
48	8.2(140)	12.9 (220)	8.5(145)	12.9(220)	9.1(155)	13.5(230)
72	11.1 (190)	17.0 (290)	11.7(200)	17.5 (300)	12.3(210)	18.1(310)
96	11.1(190)	17.0 (290)	11.7(200)	17.5(300)	12.3 (210)	18.1 (310)

Age	32 weeks		33 weeks		34 weeks	
Hours of life	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)	Conventional Phototherapy TSB mg/dL (µmol/L)	Exchange Transfusion TSB mg/dL (µmol/L)
6	3(50)	6(100)	3(50)	6(100)	3(50)	6(100)
12	4(70)	7 (120)	4(70)	7 (120)	4(70)	7 (120)
24	5.9 (100)	9.4(160)	5.9(100)	9.4(160)	6.5(110)	10.0(170)
48	9.4(160)	14.0 (240)	10.0(170)	14.3(245)	10.0(170)	14.6(250)
72	12.9(220)	18.7(320)	13.5(230)	19.3 (330)	14.6(240)	20.0(340)
96	12.9(220)	18.7(320)	13.5(230)	19.3(330)	14.6 (240)	20.0 (340)

Chapter 23: Exchange Transfusion

Introduction

- Exchange transfusion (ET) is indicated for severe hyperbilirubinaemia.
- Kernicterus has a 10% mortality and 70% long term morbidity.
- Neonates with significant neonatal jaundice should be monitored closely and treated with intensive phototherapy.
- Mortality within 6 hours of ET ranged from zero death to 3 - 4 per 1000 exchanged term infants. Causes of death includes kernicterus itself, necrotising enterocolitis, infection and procedure related events.

Indications

Double volume exchange

- Blood exchange transfusion to lower serum bilirubin level and reduce the risk of brain damage associated with kernicterus.
- Hyperammonimia
- To remove bacterial toxins in septicaemia.
- To correct life-threatening electrolyte and fluid disorders in acute renal failure.

Partial exchange transfusion

- To correct polycythaemia with hyperviscosity.
- To correct severe anaemia without hypovolaemia.

Preparation of infant

- Signed Informed Consent from parent.
- Ensure resuscitation equipment is ready and available.
- Stabilise and maintain temperature, pulse and respiration.
- Obtain peripheral venous access for maintenance IV fluids.
- Proper gentle restraint.
- Continue feeding the child; Omit only the LAST feed before ET.
- If < 4 hours from last feed, empty gastric contents by NG aspiration before ET.

Type of Blood to be used

- Rh isoimmunisation: ABO compatible, Rh negative blood.
- Other conditions: Cross-match with baby and mother's blood.
- In Emergencies if Blood type unkown (rarely): 'O' Rh negative blood.

Procedure (Exchange Transfusion)

- Volume to be exchanged is 2x the infant's total blood volume (2x80mls/kg).
- Use (preferably irradiated) **Fresh Whole Blood preferably < 5 days old** or reconstituted Packed Red Blood Cells and FFP in a ratio of 3:1.
- Connect baby to a cardiac monitor.
- Take baseline observations (either via monitor or manually) and record down on the Neonatal Exchange Blood Transfusion Sheet.

  The following observations are recorded every 15 minutes: apex beat, respiration, oxygen saturation.
- Doctor performs the ET under aseptic technique using a gown and mask.

- Cannulate the umbilical vein to a depth of NOT > 5-7cm in a term infant for catheter tip to be proximal to the portal sinus (for push-pull technique ET through UVC). Refer to section on procedure for umbilical vein cannulation.
- Aliquot for removal and replacement – 5-6 mls/ kg (Not more than 5-8% of blood volume) Maximum volume per cycle - 20 mls for term infants, not to exceed 5 ml/kg for ill or preterm infants.
- At the same time the nurse keeps a record of the amount of blood given or withdrawn, and medications given (see below).

Isovolumetric or continuous technique

- Indication: where UVC cannulation is not possible e.g. umbilical sepsis, failed cannulation.
- Blood is replaced as a continuous infusion into a large peripheral vein while simlutaneously removing small amount blood from an arterial catheter at regular intervals, matching the rate of the infusion closely - e.g. in a 1.5 kg baby, total volume to be exchanged is 240 mls.
- Delivering 120mls an hour allowing 10 ml of blood to be removed every 5 mins for 2 hours.
- Care and observation for good perfusion of the limb distal to the arterial catheter should be performed as per arterial line care

Points to note

- **Pre-warm blood to body temperature using a water bath.** Avoid other methods, e.g. placing under radiant warmer, massaging between hands or placing under running hot water, to minimise preprocedure hemolysis of donor blood. Shake blood bag gently every 5-10 cycles to prevent settling of red blood cells.
- Rate of exchange: 3 -4 minutes per cycle *(1 minute 'out', 1 minute 'in', 1-2 minute 'pause' excluding time to discard blood and draw from blood bag).*
- Syringe should be held vertical during infusion 'in' to prevent air embolism.
- Total exchange transfusion duration should be 90-120 minutes utilising 30-35 cycles.
- Begin the exchange transfusion with an initial removal of blood, so that there is always a deficit to avoid cardiac overload.
- Routine administration of calcium gluconate is not recommended.
- Remove the UVC after procedure unless a second exchange transfusion is anticipated and there was difficulty inserting the UVC.
- Continue intensive phototherapy after the procedure.
- Repeat exchange transfusion may be required in 6 hours for infants with high rebound SB.
- Feed after 4 hours if patient is well and a repeat exchange transfusion is not required.
- If child is anemic (pre-exchange Hb <12 g/dL) give an extra aliquot volume of blood (10 mls/kg) at the end of exchange at a rate of 5 mls/kg/hr after the exchange transfusion.
- If the infant is on any IV medication , to readminister the medication after exchange transfusion.

Investigations

Pre-exchange (1st volume of blood removed)

- Serum Bilirubin
- FBC
- Blood C&S (via peripheral venous blood; UVC to reduce contamination)
- HIV, Hepatitis B (baseline)
- Others as indicated

Post-exchange
(Discard initial blood remaining in UVC before sampling)

- Serum Bilirubin
- FBC
- Capillary blood sugar
- Serum electrolytes and Calcium
- Others as indicated

Post ET Management

- Maintain intensive phototherapy.
- Monitor vital signs:
  Hourly for 4 - 6 hours, and
  4 hourly subsequently.
- Monitor capillary blood sugar:
  Hourly for 2 hours following ET.
- Check serum Bilirubin:
  4 - 6 hours after ET.

Follow-up

- Long term follow-up to monitor hearing and neurodevelopmental assessment.

Complications of Exchange Transfusion
Catheter related
Infection
Haemorrhage
Necrotising enterocolitis
Air embolism
Vascular events
Portal, Splenic vein thrombosis (late)
Haemodynamic problems
Overload cardiac failure
Hypovolaemic shock
Arrhythmia (catheter tip near sinus node in right atrium)
Electrolyte/Metabolic disorders
Hyperkalemia
Hypocalcemia
Hypoglycaemia or Hyperglycaemia

Partial Exchange Transfusion

- To correct hyperviscosity due to polycythaemia.
  Assuming whole blood volume is approximately 80 ml/kg

$$\text{Volume exchanged (mL)} = \text{Blood volume} \times \frac{(\text{Initial PCV} - \text{Desired PCV})}{\text{Initial PCV}}$$

- To correct severe anemia without hypovolaemia

$$\text{Packed Cell vol (ml) required} = 80 \text{ ml} \times \text{Bwt(kg)} \times \frac{[\text{Desired Hb} - \text{Initial Hb}]}{22\text{g/dL} - \text{Hb}_w}$$

Where Hb_w is reflection of the Hb removed during partial exchange transfusion:
$Hb_w = [Hb\ desired + Hb\ initial]/2$

Chapter 24: Prolonged Neonatal Jaundice

Definition

Visible jaundice (SB >85 µmol/L or 5 mg/dL) that persists beyond 14 days of life in a term baby (≥ 37 weeks) or 21 days in a preterm baby (≥35 weeks to < 37 weeks).

Causes of prolonged neonatal jaundice

- It may be unconjugated or conjugated hyperbilirubinaemia.
- Conjugated hyperbilirubinaemia is defined as the direct (conjugated) fraction of bilirubin more than 34 µmol/L (2mg/dL), or more than 15% of the total bilirubin.

Causes of Prolonged Jaundice

Unconjugated Hyperbilirubinaemia	Conjugated Hyperbilirubinaemia
Septicaemia Urinary tract infection Breast milk jaundice Hypothyroidism *Hemolysis:* • G6PD deficiency • Congenital spherocytosis Galactosaemia Gilbert syndrome	*Biliary tree abnormalities:* • Biliary atresia - extra, intra-hepatic • Choledochal cyst • Paucity of bile ducts • Alagille syndrome, non-syndromic Idiopathic neonatal hepatitis syndrome Septicaemia Urinary tract infection Congenital infection (TORCHES) *Metabolic disorders* • Citrin deficiency • Galactosaemia • Progressive familial intrahepatic cholestasis (PFIC) • Alpha-1 antitrypsin deficiency Total Parenteral Nutrition

- *The early diagnosis and treatment of biliary atresia and hypothyroidism is important for favourable long-term outcome of the patient.*
- *All babies with conjugated hyperbilirubinaemia must be referred to a paediatric department urgently to exclude biliary atresia.*

Breast Milk Jaundice

- Breast milk jaundice is very common and remains a diagnosis of exclusion.
- Infant must be well, gaining weight appropriately and breast-feed well.
- The stool must be yellow with a normal physical examination.
- Management is to continue breast-feeding, to give warning signs to parents and to review them periodically during 1 month and 2 months old immunization or at any subsequent medical examinations.

Biliary Atresia

- The exclusion of biliary atresia remains the main aim in the management of prolonged neonatal jaundice. All workup and referrals must be expedited (before 4-6 weeks old) for any suspected cases.
- The important clinical features of biliary atresia are persistent or late onset jaundice, conjugated hyperbilirubinaemia, pale stools, firm liver and hepatosplenomegaly.
- With early diagnosis and biliary drainage through a Kasai procedure by 4-6 weeks of age, successful long-term biliary drainage is achieved in >80% of children. In later surgery good bile flow is achieved only in 20-30%.
- Liver transplantation is indicated if there is failure to achieve or maintain bile drainage.
- Serum gamma glutamyl transpeptidase (GGT) – Good discriminating test between non-obstructive and obstructive causes of neonatal hepatitis. A significantly elevated GGT (few hundreds) with a pale stool strongly favours biliary obstruction whereas, a low/normal GGT with significant cholestasis suggests non obstructive causes of neonatal hepatitis
- Ultrasound of liver – Must be done after at least 4 hours of fasting. Dilated intrahepatic bile ducts (poor sensitivity for biliary atresia) and an absent, small or contracted gall bladder even without dilated intrahepatic ducts is highly suspicious of extra hepatic biliary atresia in combination with elevated GGT and pale stool. A normal gall bladder usually excludes biliary atresia BUT if in the presence of elevated GGT and pale stool, biliary atresia is still a possibility. An experienced sonographer would be able to pick up Choledochal Cyst, another important cause of cholestasis.

Neonatal Hepatitis Syndrome

Exclude other (especially treatable) causes of neonatal hepatitis syndrome.

Metabolic causes (see also **Chapter 94 Inborn Errors of Metabolism**)

Classical Galactosaemia

- Diagnosis can be done using dried blood spots for total blood galactose and galactose-1-uridyl transferase level (GALT).
- This is usually sent in combination with acylcarnitine profile in a single filter paper to IMR biochemistry.
- Urine reducing sugar may be positive in infants who are on lactose containing formula or breastfeeding.
- A recent blood transfusion will affect GALT assay accuracy (false negative) but not so much so on the total blood galactose and urine reducing sugar.
- This condition is treatable with galactose free formula.

Citrin Deficiency

- An important treatable cause of neonatal hepatitis among Asians.
- Investigations MAY yield elevated total blood galactose but normal galactose-1-uridyl transferase (GALT) *(i.e. secondary Galactosemia).*
- Elevated citrulline in plasma amino acids and dried blood spot amino acids .
- Treatable with galactose free formula (if there is secondary galactosaemia) with medium chain triglyceride (MCT) supplementation.
- *Note: Use lithium heparin container to send plasma amino acids.*

Tyrosinaemia type I

- Treatable with NTBC *(2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione).*
- Urine organic acids specifically looking for presence of succinylacetone is highly specific for this condition. Take particular attention of sending urine organic acids *frozen and protected from light* (i.e. covered plain urine container) to maintain the accuracy of the test.

Neonatal Haemochromatosis

- This needs to be excluded in infants presenting with liver failure within first weeks of life.
- Significantly elevated serum ferritin (few thousands) is characteristic.
- Diagnosis is confirmed by presence of iron deposits in extra hepatic tissue, e.g. lip tissue (iron deposits in minor salivary glands). Lip biopsy can be safely performed even in severely coagulopathic infants where liver biopsy is contraindicated.
- Treatment with combination of immunoglobulins, desferral and anti-oxidant cocktails is potentially life saving (avoid liver transplant which at present is not an option for neonatal onset liver failure).
- Antenatal intravenous immunoglobulin prevents recurrence in subsequent children.

Primary bile acid synthesis disorder

- Suspect if cholestasis, low GGT and low cholesterol.
- Serum bile acids is a good screening tool (ensure patient is not on ursodeoxycholic acid < 1 week prior to sampling).
- Definite diagnosis requires urine bile acids analysis (available at specialized laboratory in UK).
- Treatment with cholic acid (not ursodeoxycholic acid) confers excellent outcome in all subtypes.

Peroxisomal biogenesis disorders

- Cholestasis may be part of the manifestation.
- Plasma very long chain fatty acids (VLCFA) is elevated.

Mitochondrial depletion syndrome

- Suspect in presence of other neurological signs e.g. rotatory nystagmus, hypotonia and elevated blood lactate. Metabolic/genetic consult for further diagnostic evaluation.

Infective causes

- Septicaemia
- Urinary tract infection
- Herpes simplex virus infection
  - Consider in infants with liver failure within first few weeks of life.
  - IV Acyclovir therapy while waiting for Herpes IgM results in affected infants may be justified.
- Hepatitis B virus infection
  - Can potentially present as early infantile liver failure but incidence is rare.
  - Presence of positive Hepatitis B surface antigen, positive Hepatitis B virus envelope antigen and high viral load confirms the diagnosis.

Alagille syndrome

- Consider in infants who have cardiac murmurs or dysmorphism.
- One of the parents is usually affected (AD inheritance, variable penetrance)
- Affected infants might not have typical dysmorphic features at birth due to evolving nature of the syndrome.
- Important screening tests include :
- Slit eye lamp examination: look for posterior embryotoxon.
  - May also help to rule out other aetiologies in neonatal hepatitis syndrome, e.g. retinitis in congenital infection, cataract in galactosaemia.
  - Vertebral x ray: To look for butterfly vertebrae.
  - Echocardiography: look for branched pulmonary artery stenosis.
  - Other known abnormalities - ASD, valvular pulmonary stenosis.
- Gene test: JAG1 gene mutation which can be done at IMR (EDTA container).*(Consult Geneticist Prior to Testing)*

Idiopathic Neonatal Hepatitis Syndrome

- Follow up with LFT fortnightly.
- Watch out for liver failure and bleeding tendency (vitamin K deficiency).
- Repeat Hepatitis B and C virus screening at 6 weeks.
- Most infants with idiopathic neonatal hepatitis in the absence of physical signs of chronic liver disease usually make a complete recovery.

Initial Approach and Management

- All babies MUST be screened for prolonged neonatal jaundice (clinical jaundice is adequate), at day 14 for term babies (≥ 37 weeks) and day 21 for preterm babies (≥35 weeks to < 37 weeks).
- Once prolonged jaundice is diagnosed, the baby must be referred to a medical officer (in any hospital or health clinic) the same day or the next working day.
- Clinical assessment remains the mainstay in the approach to babies with prolonged neonatal jaundice. Risk stratification into high, moderate or low risk groups are recommended.
- This is done by:
  - Clinical assessment
    e.g. feeding method, weight, STOOL COLOUR and presence of hepatosplenomegaly

  AND
  - Important laboratory investigations
    i.e. serum bilirubin with direct and indirect bilirubin.

Subsequent management of these babies will depend on the risk groups.
See Table on next page.

Laboratory investigations

- Total Serum Bilirubin with Direct/ indirect Bilirubin remains the most important laboratory investigation for prolonged neonatal jaundice. TSB alone or heel prick capillary bilirubin is NOT helpful in the management of prolonged jaundice.
- Other initial tests that are simple and helpful for babies who are low risk but persistent jaundice beyond 3 weeks of age would be:
  - Repeat of SB with direct/ indirect
  - FBC + reticulocyte count
  - Free T4 & TSH
  - Urine Dipstick and Microscopy

Management of Prolonged Neonatal Jaundice for Babies ≥ 35 weeks by Risk Groups (at the point of diagnosis in any health facilities)

High Risk	Moderate Risk	Low Risk
Positive Clinical Features/ Lab Results • ILL/ Septic Looking • Respiratory Distress • Poor Feeding • Lethargy • Poor Perfusion	Positive Clinical Features/ Lab Results • Conjugated Hyperbilirbubinaemia • Severe Jaundice- TSB > 300µmol/L • New Onset Jaundice (esp after Day 7) • Pale Stools • Dark Yellow Urine (stains diapers) • Poor Weight Gain • Hepatosplenomegaly *To also consider:* • Bottle fed > 50% • Jaundice >1 mth not investigated before • Other suspected medical condition • Significant family history	Positive Clinical Features/ Lab Results • None, i.e. • Well babies with good weight gain, exclusively breast fed (or >50%), bright yellow stool with normal physical examination • Breast milk jaundice
Management	Management	Management
• Stabilize Airway, Breathing, Circulation • Refer to Paediatrician Immediately	• Refer to Paediatric Team • Same day or next working day	Can be managed and followed up at primary care level or hospitals without specialists. *Term babies >37 wks* Day 14: • S. Bilirubin with Direct/ Indirect bilirubin *If still jaundice, Day 21:* • S. Bilirubin with Direct/ Indirect bilirubin, • FBC + reticulocytes • UFEME + microscopy • Free T4, TSH *Preterm babies ≥ 35 to < 37 weeks* To work up 1 week later than term babies.

Well, low risk babies DO NOT need heel prick capillary bilirubin till jaundice resolves. Warning signs for parents and RME (routine medical examination) at 1 mth and 2 mths in health clinics, looking at the same clinical features be a good safety netting.*

Refer to Paediatric Team if conjugated hyperbilirubinaemia, warning signs*, SB> 300umol/L, abnormal lab results, jaundice more than 2 months or any features in the high or moderate risk category.

**Unwell, pale stool, dark yellow urine, new onset of jaundice, persistent jaundice > 2 months*

Further Management of Prolonged Neonatal Jaundice by Paediatric Team

Workup for Unconjugated Hyperbilirubinaemia (mainly for infection, hypothyroidism and hemolytic disorder)	
Clinical Features	Investigations
FOR ALL BABIES	SB with direct/ indirect, FBC + reticulocyte counts, Free T4 & TSH, Urine Dipstick and Microscopy
PLUS	
Predominantly (>50%) formula fed babies	Liver function test, Full blood picture, Urine C+S
Family history	As accordingly
Poor weight gain	Urine C+S, Consider for admission
Pallor	Full blood picture, Blood group, Coombs, G6PD
Hepatosplenomegaly	Liver function test, Full blood picture, Urine C+S, TORCHES, Metabolic screening
Pale stool	*See section on conjugated hyperbilirubinaemia*

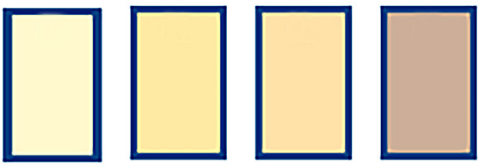
Workup for Conjugated Hyperbilirubinaemia (mainly for biliary atresia and neonatal hepatitis)	
Areas	Investigations
FOR ALL BABIES	SB with direct/ indirect, FBC + reticulocyte counts Free T4 & TSH, Urine Dipstick and Microscopy
PLUS	
Clinical	**Stool colour observation for 3 days**
Radiology	**Ultrasound HBS**, *CXR/ spine x-ray for butterfly veterbrae, HIDA scan, ECHO if murmur*
Biochemistry	**Liver function test, SB with direct/ indirect, Gamma GT,** Ca, PO_4, **Lipid profile**, coagulation profile, blood sugar, **serum ferritin**, serum bile acids
Microbiology	**VDRL**, Blood C+S, **Urine dipstick+microscopy, Urine culture**
Virology	**TORCHES, Hep B/C**, Urine for CMV
Metabolic	**Blood spot for total galactose, GAL-1-PUT; amino acids & acyl-carnitines; alpha-1-antitrypsin, plasma amino acids.** **Urine for reducing sugars,** amino acids **and organic acids.**
Endocrine	**Thyroid function test**
Histology	Liver biopsy
Opthalmology	Look for embryotoxon chorioretinitis/septo-optic dysplasia
Please refer to the text above for more information on the individual tests	

Infant Stool Colour Chart

Adapted from 'Jaundice in the Newborn Baby',
Children's Liver Disease Foundation, UK (www.childliverdisease.org)

Healthy Stools

Suspect Stools



Digital printing or photocopying of this colour chart will alter its colours

Chapter 25: Apnoea in the Newborn

Definition

- **Apnea of prematurity** is defined as sudden cessation of breathing that lasts for at least 20 seconds or is accompanied by bradycardia or oxygen desaturation (cyanosis) in an infant younger than 37 weeks' gestational age.
- It usually ceases by 43 weeks' postmenstrual age but may persist for several weeks beyond term, especially in infants born before 28 weeks' gestation with this risk decreasing with time.

Classification

Types:

- *Central:* absence of respiratory effort with no gas flow and no evidence of obstruction.
- *Obstructive:* continued ineffective respiratory effort with no gas flow
- *Mixed central and obstructive:* most common type

Aetiology

Symptomatic of underlying problems, commoner ones of which are:

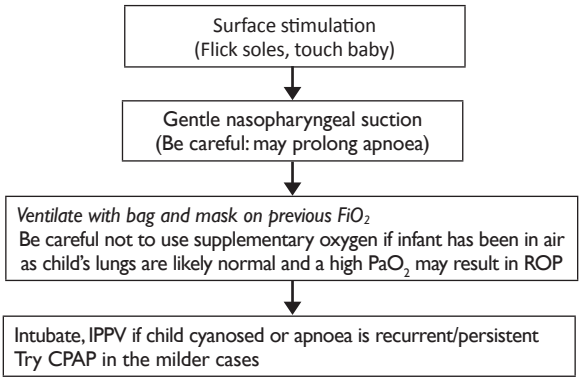
- Respiratory conditions (RDS, pulmonary haemorrhage, pneumothorax, upper airway obstruction, respiratory depression due to drugs).
- Sepsis
- Hypoxaemia
- Hypothermia
- CNS abnormality (e.g. IVH, asphyxia, increased ICP, seizures)
- Metabolic disturbances (hypoglycaemia, hyponatraemia, hypocalcaemia)
- Cardiac failure, congenital heart disease, anaemia
- Aspiration/ Gastro-oesophageal reflux
- Necrotising ennterocolitis, Abdominal distension
- Vagal reflex: Nasogastric tube insertion, suctioning, feeding

Differentiate from Periodic breathing

- Regular sequence of respiratory pauses of 10-20 sec interspersed with periods of hyperventilation (4-15 sec) and occurring at least 3x/ minute, not associated with cyanosis or bradycardia.
- Benign respiratory pattern for which no treatment is required.
- Respiratory pauses appear self-limited, and ventilation continues cyclically.
- Periodic breathing typically does not occur in neonates in the first 2 days of life

Management

- Immediate resuscitation.



- Review possible causes (as above) and institute specific therapy, e.g. septic workup if sepsis suspected and commence antibiotics
  Remember to check blood glucose via glucometer.
- Management to prevent recurrence.
  - Nurse baby in thermoneutral environment.
  - Nursing prone can improve thoraco-abdominal wall synchrony and reduce apnoea.
  - Variable flow NCPAP or synchronised NIPPV can reduce work of breathing and reduce risk of apnoea.
  - Monitoring:
    - Pulse Oximeter
    - Cardio-respiratory monitor
  - Drug therapy
    - Methylxanthine compounds:
    - Caffeine citrate (preferred if available)
    - IV Aminophylline or Theophylline.
- Start methylxanthines prophylactically for babies < 32 weeks gestation.
  For those > 32 weeks of gestation, give methylxanthines if babies have apnoea.
  To stop methylxanthines if :
  - Gestation > 34 weeks
  - Apnoea free for 1 week when the patient is no longer on NCPAP
- Monitor for at least 1 week once the methylxanthines are stopped.
  After discharge , parents should be given advice for prevention of SIDS:
  - Supine sleep position.
  - Safe sleeping environments.
  - Elimination of prenatal and postnatal exposure to tobacco smoke.

Chapter 26: Vascular Spasm and Thrombosis

Thromboembolism (TE) is being increasingly recognised as a significant complication of intravascular catheters in sick newborn infants. Many factors contribute to neonatal catheter-related thrombosis, including the small caliber of the vessel, endothelial damage, abnormal blood flow, design and site, duration of catheterisation and composition of the infusate, in addition to the increased risk of thrombus formation in sick infants. Sepsis and catheters are the most common correlates of thrombosis in the NICU.

Risk factors for neonatal thrombo-embolism
Maternal Risk Factors
Infertility
Oligohydramnios
Prothrombotic disorder
Pre-eclampsia
Diabetes
Intrauterine growth restriction
Chorioamnionitis
Prolonged rupture of membranes
Autoimmune disorders
Delivery Risk Factors
Emergent Caesarean section
Fetal heart rate abnormalities
Instrumentation
Neonatal Risk Factors
Central catheters
Congenital heart disease
Sepsis
Birth asphyxia
Respiratory distress syndrome
Dehydration
Congenital nephritic/nephrotic syndrome
Necrotizing enterocolitis
Polycythemia
Pulmonary hypotension
Prothrombotic disorders
Surgery
Extracorporeal membrane oxygenation
Medications steroids, heparin)

Definitions

- *Vascular spasm* – transient, reversible arterial constriction, triggered by intravascular catheterisation or arterial blood sampling. The clinical effects of vascular spasm usually last < 4 hours from onset, but the condition may be difficult to differentiate from the more serious TE. The diagnosis of vascular spasm may thus only be made retrospectively on documenting the transient nature of the ischaemic changes and complete recovery of the circulation.
- *Thrombosis* – complete/partial occlusion of arteries/veins by blood clot(s).

Assessment

Clinical diagnosis

- Peripheral arterial thrombosis/ vasospasm – pallor or cyanosis of the involved extremity with diminished pulses or perfusion.
- Central venous line (CVL) associated venous thrombosis – CVL malfunction, superior vena cava (SVC) syndrome, chylothorax, swelling and livid discolouration of extremity.
- Aortic or renal artery thrombosis – systemic hypertension, haematuria, oliguria.

Diagnostic imaging

- Contrast angiography is the "gold standard", but difficult to perform in critically ill neonates and requires infusion of radiocontrast material that may be hypertonic or cause undesired increase in vascular volume.
- Doppler ultrasonography – portable, non-invasive, useful to monitor progress over time. False positive and false negative results may occur, as compared to contrast angiography.

Additional diagnostic tests

- Obtain detailed family history in all cases of unusual or extensive TE.
- In the absence of predisposing risk factors for TE, consider investigations for thrombophilic disorders in severe and neonatal onset: anticardiolipin, antithrombin III, protein C, protein S deficiency.

Management of vascular spasm

- Immediate measures to be taken:
  - Lie the affected limb in horizontal position
  - If only one limb is affected, warm (using towel) opposite unaffected leg to induce reflex vasodilatation of the affected leg.
  - Maintain neutral thermal environment for the affected extremity, i.e. keep heat lamps away from the area.
- Inform the paediatrician immediately.
- Consider removing the catheter. If mild cyanosis of the fingers or toes is noted after insertion of an arterial catheter, but peripheral pulses are still palpable, a trial of reflex vasodilatation with close observation is reasonable – check continuously to see that the cyanosis is improving within a few minutes. **A white or "blanched" appearing extremity is an indication for IMMEDIATE removal of the catheter.**
- Other risk factors contributing to thrombosis includes dehydration, sepsis, and polycythaemia. These factors may need to be corrected immediately.
- Maintain good circulatory volume. If there is no immediate improvement with removal of catheter, try volume expansion 10 mls/kg of normal saline.
- Topical nitroglycerine – using patch or topical 2% ointment at a dose of 4 mm/kg body weight, applied as a thin film over the affected body area; may be repeated after 8 hours. Monitor for hypotension and be prepared to treat immediately.

- If the limb ischaemia persists for > 1 hour without any improvement, refer urgently to the radiologist/surgeon.
  An urgent doppler ultrasound scan is needed to ascertain whether the limb ischaemia is caused by vasospasm or thrombosis.

Management of catheter-related thromboembolism

- Management of vascular TE may involve one or more of the following: supportive care, anticoagulation, fibrinolytic therapy, surgical intervention.
- Treatment for neonates is highly individualised and is determined by the extent of thrombosis and the degree to which diminished perfusion to the affected extremity or organ affects function.
- Consultation with a paediatric haematologist, orthopaedic or vascular surgeon may be required.
- Initial management
  - As for vascular spasm for peripheral arterial ischaemia
  - Removal of catheter as soon as blanching is seen.
  - Supportive care – correct volume depletion, electrolyte abnormalities, anaemia and thrombocytopaenia; treat sepsis.
- Anticoagulant/ thrombolytic therapy
  - The risk of serious bleeding associated with antithrombotic therapy in neonates must be balanced against the possibility of organ or limb loss or death without appropriate treatment. Adequate randomised trials to guide therapy in neonates are not available.
  - Contraindications:
    - Major surgery within the last 10 days.
    - Major bleeding: intracranial, pulmonary, gastrointestinal.
    - Pre-existing cerebral ischaemic lesions.
    - Invasive procedures within 3 days
    - Known history of heparin induced thrombocytopaenia or allergy to heparin.
  - Relative contraindications –
    - Platelet count < 50,000 $X10^9$/L; (100,000 $X10^9$/L for ill neonates)
    - Fibrinogen levels<100mg/dL
    - Severe coagulation factor deficiency
    - INR > 2
    - Hypertension

    Note: anticoagulation/thrombolytic therapy can be given after correcting these abnormalities.
  - Precautions:
    - no arterial punctures
    - no subcutaneous or IM injections
    - no urinary catheterisations
    - avoid aspirin or other antiplatelet drugs
    - monitor serial ultrasound scans for intracranial haemorrhage

- Anticoagulants
  - Standard or unfractionated heparin (UFH)
    - UFH should be limited to clinically significant thromboses with the goal of preventing clot expansion or embolism.
    - Anticoagulant, antithrombotic effect limited by low plasma levels of antithrombin in neonates. For dosage see Table below.
    - Optimal duration is unknown but therapy is usually given for 5-14 days
    - Monitor thrombus closely during and following treatment.
    - Complications: Bleeding (2% major haemorrhage rate), heparin-induced thrombocytopaenia. Due to UFH' short half life, cessation of infusion usually resolves any bleeding. If not correct any coagulation deficiencies
    - Antidote: Protamine sulphate if anti-factor Xa > 0.8 u/ml: see Table on next page for dosage. One mg of protamine neutralises 100U UFH
    - Anti- Factor X activity (if available) aimed at 0.3-0.7 U/mL.
    - Baseline aPTT is prolonged at birth and aPTT prolongation is not linear with heparin anticoagulant effect. Therefore Anti factor X activity more effectively monitors UFH use in newborn infants.

Recommended dosing of unfractionated heparin (UFH)

Clinical indication	Traditional dosing	Current recommended dosing
Asymptomatic or symptomatic thrombus but non-limb threatening	*Bolus dose* 75 U/kg IV over 10 mins *Maintenance dose* 28 U/kg/h	**<28 wks GA** *Bolus dose* 25 U/kg IV over 10 mins *Maintenance dose* 15 U/kg/h **28-37 wks GA** *Bolus dose* 50 U/kg IV over 10 mins *Maintenance dose* 15 U/kg/h **> 37 wks GA** *Bolus dose* 100 U/kg IV over 10 mins *Maintenance dose* 15 U/kg/h

Monitoring:
- Maintain anti-factor Xa level of0.03-0.7 U/ml (PTT 65s)
- Check anti-factor Xa level 4 h after loading dose and 4 h after each change in infusion rate
- Full blood count, platelet count, and coagulation screening (including APTT, PT and fibrinogen) should be performed before starting UFH therapy
- Platelet count and fibrinogen levels should be repeated daily for 2-3 days once therapeutic levels are achieved and at least twice weekly thereafter

Adjustment of UFH according to aPTT after loading and initial maintenance				
aPTT	Bolus	Hold (mins)	% rate change	Repeat aPTT
<50	50 U/kg for term	0	+10	4 hours
50-59		0	+10	4 hours
60-85		0	0	next day
85-95		0	-10	4 hours
96-120		30	-10	4 hours
>120		60	-15	4 hours
Once aPTT is in therapeutic range, a full blood count and aPTT can be checked daily or as clinically indicated				

Recommended dosing of protamine for reversal of heparin therapy	
Heparin: Time since last dosing	Protamine dose
< 30 min	1 mg/100 u heparin received
30-60 min	0.5 - 0.75 mg/100 u heparin received
60-120 min	0.375 - 0.5 mg/100 u heparin received
>120 min	0.25 - 0.375 mg/100 u heparin received
Maximum dose	50 mg
Infusion rate	10 mg/ml solution; rate < 5 mg/min

- Low molecular weight heparin (LMWH)
  - Advantages: Subcutaneous administration. Heparin induced thrombocytopaenia is rarely associated with LMWH.
  - Although adverse effects are rare, major complications such as haematoma at site of injection, intracranial haemorrhage have been described
  - Antidote: Omit 2 doses if an invasive procedure is required. Protamine is partially effective, dosage 1mg/100U heparin given within the last 3-4 hrs

Note : LMWH have specific activity against factor Xa so therapy is monitored using anti-FXa and not APTT. However, monitoring of anti-FXa levels may not presently be available in most laboratories..

Recommended dosing of low molecular weight heparin (LMWH)		
Clinical indication	Traditional dosing	Current recommended dosing
Asymptomatic or symptomatic thrombus but non-limb threatening	Subcutaneous (SC) 1.5 mg/kg q 12h	**Term neonates** SC 1.7 mg/kg q 12h **Preterm neonates** SC 2.0 mg/kg q 12h

Monitoring:
- Goal of anti-factor Xa levels of 0.5-1.0 U/mL
- Check level 4 hours after second dose and then weekly
- If infants with high haemorrhagic profile, use dosing of SC 1mg/kg q 12 h
- Guidelines for adjusting LMWH therapy are published in other sources

- Thrombolytic agents
  - Consider thrombolytic agents (r-tPA: recombinant tissue plasminogen activator, streptokinase) if there is limb/life threatening thrombus (monitoring- see table below).
  - Supplementation with plasminogen in the form of FFP is recommended to ensure adequate thrombolysis
  - Thrombi that have been present for several days may be resistant to thrombolysis with failure rates up to 50%
  - Simultaneous infusion of UFH is recommended to inhibit clot propagation
  - Monitoring
    - Monitor fibrinogen levels, thrombin time and plasminogen levels, (if on UFH - coagulation profile) before starting, 4-6 hours after starting and 12-24 hourly thereafter.
      Imaging studies of thrombus before initiation, 4-6 hours after starting and every 12-24 hours to allow discontinuation of treatment as soon as clot lysis is achieved.
    - Maintain fibrinogen >100-150mg/dL with cryoprecipitate (1U/5kg)
    - Platelet count –before initiation, 4-6 hourly after starting treatment, every 12-24 hourly thereafter – minimum of 50,000-100,000 $x10^9$/dL dependant on bleeding risk
    - Cranial imaging before initiation and then daily
    - Complications: bleeding, embolization. Have compresses and localised thrombin available for localised bleeding
  - No IM injections, no arterial punctures, no urinary catheterisation, no rectal temperature

Thrombolytic regimen in neonates		
Drug	IV bolus dose	IV Maintenance dose
Streptokinase	1000 units/kg	1000 units/kg/hr
Urokinase	4,400 U/kg over 20 mins	4,400 units/kg/hr for 6-12 hrs
r-Tissue plasminogen activator	0.06 mg/kg/h	Slow dose escalation 0.015 - 0.24 mg/kg/h if required

Chapter 27: Patent Ductus Arteriosus in the Preterm

Introduction

Gestational age is the most important determinant of the incidence of patent ductus arteriosus (PDA). The other risk factors for PDA are lack of antenatal steroids, respiratory distress syndrome (RDS) and need for ventilation.

Clinical Features

- Wide pulse pressure/ bounding pulses
- Systolic or continuous murmur
- Tachycardia
- Lifting of xiphisternum with heart beat
- Hyperactive precordium
- Apnoea
- Increase in ventilatory requirements

Complications

- Congestive cardiac failure
- Intraventricular haemorrhage (IVH)
- Pulmonary haemorrhage
- Renal impairment
- Necrotising enterocolitis
- Chronic lung disease

Management

- If cardiac ECHO available, confirm presence of PDA and absence of duct dependent cardiac abnormality.
- Supportive therapy:
  - Adequate positive end-expiratory pressure (PEEP) to reduce left-to-right ductal flow and improve systemic blood flow.
  - Maintenance of hematocrit at 35 to 40 percent.
  - Fluid restriction (be careful not to compromise on nutrition/growth and systemic perfusion).
  - Avoidance of loop diuretics (eg. frusemide) as far as possible. Use thiazide diuretics (e.g. hydrochlorothiazide) instead if indicated.
- Pharmacologic closure
  - Indicated for preterm infants with haemodynamically significant PDA, especially if still requiring ventilator support
  - Indomethacin (IV or oral 0.2mg/kg/dose daily dose for 3 days)
  - Ibuprofen (IV or oral; day one - 10mg/kg/dose, day two - 5mg/kg/dose, day three - 5 mg/kg/dose administered by syringe pump over 15 minutes at 24 hour intervals). After day 14 of life, recommended dosage is 14 mg/kg (Day1), 7 mg/kg (day 2), 7 mg/kg (day 3)
  - Paracetamol (IV or oral 15mg/kg/dose 6 hourly for 3 to 7 days)
  - Current available data shows paracetamol as a promising agent for pharmacologic closure of PDA, but further conclusive data is needed before it can be recommended for routine use. Recommended use in clinically significant PDA when NSAID's are relatively contraindicated.

- Contraindications:
  - Infant is proven or suspected to have infection that is untreated
  - Bleeding, especially active gastrointestinal or intracranial
  - Platelet count < 60 x 109 /L
  - NEC or suspected NEC
  - Duct dependent congenital heart disease
  - Impaired renal function
- Monitor:
  - Urine output and renal function. If urine output <0.6 ml/kg/hr after a dose is given, withhold next dose until output back to normal.
  - For GIT complications e.g. gastric bleeding, perforation.
  - For hyperbilirubinemia, especially if using ibuprofen.
- Surgical ligation
  - Persistence of a symptomatic PDA and failed pharmacological treatment
  - If medical treatment fails or contraindicated
- In older preterm infant who is asymptomatic, i.e. only cardiac murmur present in an otherwise well baby – no treatment required. Follow-up as necessary. Most PDA in this group will close spontaneously.

Pearls and Pitfalls in Management

- There is a higher success rate in closure of PDA if indomethacin is given in the first two weeks of life.
- Ensure oral suspension is freshly prepared and well mixed before serving.
- IV indomethacin is unstable once the vial is opened.
- For infants who fail to respond to initial pharmacological therapy, a second course results in 40 percent rate of ductal closure.

Chapter 28: Persistent Pulmonary Hypertension of the Newborn

Definition

Persistent pulmonary hypertension (PPHN) of the newborn is a syndrome of failed circulatory adaption at birth. It is characterised by

- Elevated pulmonary vascular resistance (PVR) resulting in decrease pulmonary flow
- Right to left shunting of deoxygenated blood across the PFO and PDA result in differential cyanosis. Oxygen saturation in the lower limb is 5-10% lower than right upper limb.
- Labile hypoxaemia with marked change in oxygen saturation with minimal or no change in settings of ventilator due to changes in the volume of R to L shunt.

Classification

- *Underdevelopment*: hypoplastic vasculature e.g. congenital diaphragmatic hernia, pulmonary hypoplasia in oligohydramnios secondary to renal disease or chronic leakage of amniotic fluid.
- *Maldevelopment*: normal lung with remodeled pulmonary vasculature as in idiopathic PPHN, chronic fetal hypoxia
- *Maladaptation*: parenchymal lung diseases e.g. Meconium Aspiration Syndrome (MAS), Pneumonia/sepsis, Respiratory Distress Syndrome (RDS), asphyxia
- *Intrinsic Obstruction*: polycythaemia with intravascular obstruction and increase PVR.

Diagnosis

- PPHN is clinically suspected in near term or term infants who have variable oxygen saturation.
- Physical Examination - some of the infants may have signs of respiratory distress. Single loud second heart sound.
- Differential pre and post ductal oxygen saturation (between 5-10%). Lack of differential does not preclude PPHN.
- ABG – Hypoxaemia disproportional to degree of lung disease.
- 2D Echocardiography with colour flow doppler confirm diagnosis with right to left shunting at PFO and PDA.
- Hyperoxia test if no 2D Echo available: PaO_2>150 mmhg in 100% FiO_2 for 5-10 min excludes most CHD. A PaO_2 < 150 mmhg doesn't exclude CHD or PPHN.
- Chest x-ray – evidence of underlying parenchymal disease eg MAS, RDS, pneumonia. Oligaemic lung fields in idiopathic PPHN.
- FBC with differential to evaluate for high hematocrit level (polycythaemia) and risk of underlying infection.

Differential Diagnosis

- Differentiating PPHN from cyanotic heart disease soon after admission is important.
- Preductal and postductal oxygen saturations of more than 5-10% or PaO_2 differences of 10-20 mmHg between right upper limb and lower limbs helps to differentiate PPHN from structural heart disease.
- The diagnosis is confirmed with 2D Echocardiography which may not be available in all hospitals.

Management

PPHN management involves restoration of the cardiopulmonary adaptation and to minimise ventilator- and oxygen-induced pulmonary injury.
This includes treatment of the underlying disease, maintenance of normal systemic BP, decrease pulmonary vascular resistance and ensure adequate tissue oxygenation.

- Supportive care –
  - Maintain normothermia, correct metabolic and hematologic abnormalities e.g. hypoglycemia, hypocalcaemia, polycythaemia and acidosis
  - Minimal stimulation
  - Sedation may be necessary to avoid agitation and asynchrony with ventilator support; morphine infusion 10-20 mcg/kg/hr.
  - In systemic hypotension, a fluid bolus of 10ml/kg of normal saline followed by dopamine 5-20 mcg/kg/min or noradrenaline of 0.05 – 1 mcg/kg/min. Noradrenaline may improve lung function in PPHN through a decrease in pulmonary/systemic pressure ratio and improved cardiac performance.
- Mechanical ventilation
  - Conventional " gentle" ventilation strategies with optimal PEEP and relatively low PIP or tidal volume (tv) for adequate lung expansion and limit volutrauma or barotrauma.
  - Switch to HFOV If high PIP and high TV are required to maintain $PaCO_2 < 60$ mmHg.
  - Target PaO_2 55-80 mmHg, $PaCO_2$ 40-60 mmHg and pH 7.30-7.45.
- Surfactant therapy improves oxygenation in PPHN secondary to parenchymal lung disease - RDS, MAS and pneumonia
- Inhaled Nitric Oxide
  - Potent vasodilator and selectively dilates the pulmonary circulation without decreasing systemic BP.
  - Initiation of iNO for severe PPHN with oxygenation index (OI) > 15-25 at 20 ppm.
  - Wean iNO gradually to prevent rebound pulmonary vasoconstriction.
  - Wean FiO_2 first to below 60% and if PaO_2 can be maintained then wean iNO by 5 ppm every 4 hours. Once iNO is 5 ppm, wean by 1 ppm every 4 hours.

- In centers without iNO, sildenafil may be a life saving alternative but safety and effectiveness has not been established in large RCT. Until further evidence is available, the initial dosing strategy would include initiating therapy with oral sildenafil at 0.5 mg/kg/dose 6-hourly and if no response, increasing the dose up to a maximum of 2 mg/kg/dose. Response time varies from 20 minutes to 3 hours after oral administration. Duration of treatment is not yet well defined, and one approach is to stop the medication after a clear response and improvement. The treatment should also be discontinued after 6-8 doses if there is no improvement, and reduction in dose or stopping treatment if hypotension develops despite inotropic support.
- Milrinone improvse oxygenation in neonates with iNO resistant PPHN in the presence of ventricular dysfunction.
- Intravenous magnesium sulphate can cause reduction of pulmonary artery pressures in animal studies. Only observational studies are available showing it can be helpful in infants. It is associated with systemic hypotension. In centers without iNO, magnesium sulphate may be used. A loading dose of 200 mg/kg $MgSO_4$ is given intravenously over 20 minutes followed by continuous infusion at the rate of 20- 100 mg/kg/h to obtain a serum magnesium level between 3 - 5.5 mmol/l. Inotropes may be required to keep mean arterial blood pressure between 40-45 mmHg. Some of the studies commenced on dopamine 5-10mcg/kg/min prior to starting magnesium therapy.
- ECMO is a supportive measure that allows the neonatal heart and lung to recover from the underlying disease in iNO resistant PPHN. Not available in this country.
- Newer therapies – Superoxide dismutase, arginine and citrulline are under investigation.
- Developmental outcomes – long term multidisciplinary follow up is necessary as PPHN is associated with neurodevelopmental, cognitive and hearing abnormalities.

Chapter 29: Ophthalmia Neonatorum

Definition

Conjunctivitis occurring in newborn during 1st 4 weeks of life with clinical signs of erythema and oedema of the eyelids and palpebral conjunctivae, purulent eye discharge with one or more polymorph nuclear per oil immersion field on a Gram stained conjunctival smear.

Diagnosis

- Essentially a clinical diagnosis
- Laboratory diagnosis to determine aetiology
  - Eye swab for Gram stain (fresh specimen to reach laboratory in 30 mins)
  - Gram stain of intracellular gram negative diplococci - high sensitivity and specificity for *Neisseria gonorrhoea.*
  - Eye swab for culture and sensitivity.
  - Conjunctival scrapping for indirect fluorescent antibody identification for *Chlamydia*.

Aetiology

Bacterial

Gonococcal

- Most important bacteria by its potential to damage vision.
- Typically presents with profound chemosis, edema of the eyelid and abundant purulent discharge which may be blood-tinged from superficial haemorrhage, within first few days of life.
- If left untreated, gonorrheal ON can lead to corneal scarring, ulceration, panophthalmitis and perforation of the globe within 24 hours
- The infant should be evaluated for disseminated gonococcal infection (e.g. arthritis, sepsis, meningitis)
- Treatment:
  - Systemic:
    - Ceftriaxone 25-50mg/kg (max. 125mg) IV or IM single dose, or
    - Cefotaxime 100 mg/kg IV or IM single dose.
      (preferred if premature or hyperbilirubinaemia present)
  - Disseminated infections :
    - Ceftriaxone 25-50mg/kg/day IV or IM in single daily dose for 7 days,
      or Cefotaxime 25mg/kg/dose every 12 hours for 7 days.
  - Documented meningitis : 10-14 days
  - Local: Irrigate eyes with sterile normal saline initially every 15 mins and then at least hourly as long as necessary to eliminate discharge.
    Frequency can be reduced as discharge decreases.
    Topical antibiotics is optional.

Non- Gonococcal

- Includes *Coagulase negative staphylococci, Staphylococcus aureus, Streptococcus viridans, Haemophilus, E.coli, Klebsiella species* and *Pseudomonas*. Most are hospital acquired conjunctivitis which can be treated with topical antibiotics except for pseudomonas.
- Ophthalmia neonatorum caused by *Pseudomonas* is rare but may cause corneal perforation, endophthalmitis and blindness. These infants need assessment by an ophthalmologist and require a combination of systemic and topical aminoglycosides with occasional subconjunctival injection.
- Treatment:
- Local: Chloramphenicol, gentamicin eye ointment 0.5%, both eyes (Change according to sensitivity, duration according to response), or In non- responsive cases refer to ophthalmologist and consider Fucithalmic, Ceftazidime 5% ointment bd to qid for a week.
- Eye toilet (refer as above).

Chlamydial

- Replaced N. gonorrhoea as most common aetiology associated with sexually transmitted infections (STI).
- Unilateral or bilateral conjunctivitis with peak incidence at 2 weeks of life.
- Treatment:
  - Erythromycin 50mg/kg/d in 4 divided doses for 2 weeks
    - Caution - association with hypertrophic pyloric stenosis
    - May need repeat course of erythromycin for further 2 weeks if poor response as elimination after first course ranges from 80-100%
  - If subsequent failure of treatment, use Trimethoprim-sulfamethazole 0.5ml/kg/d in 2 doses for 2 wks (Dilution 200mg SMZ/40mg TM in 5 mls).
  - Systemic treatment is essential. Local treatment may be unnecessary if systemic treatment is given.

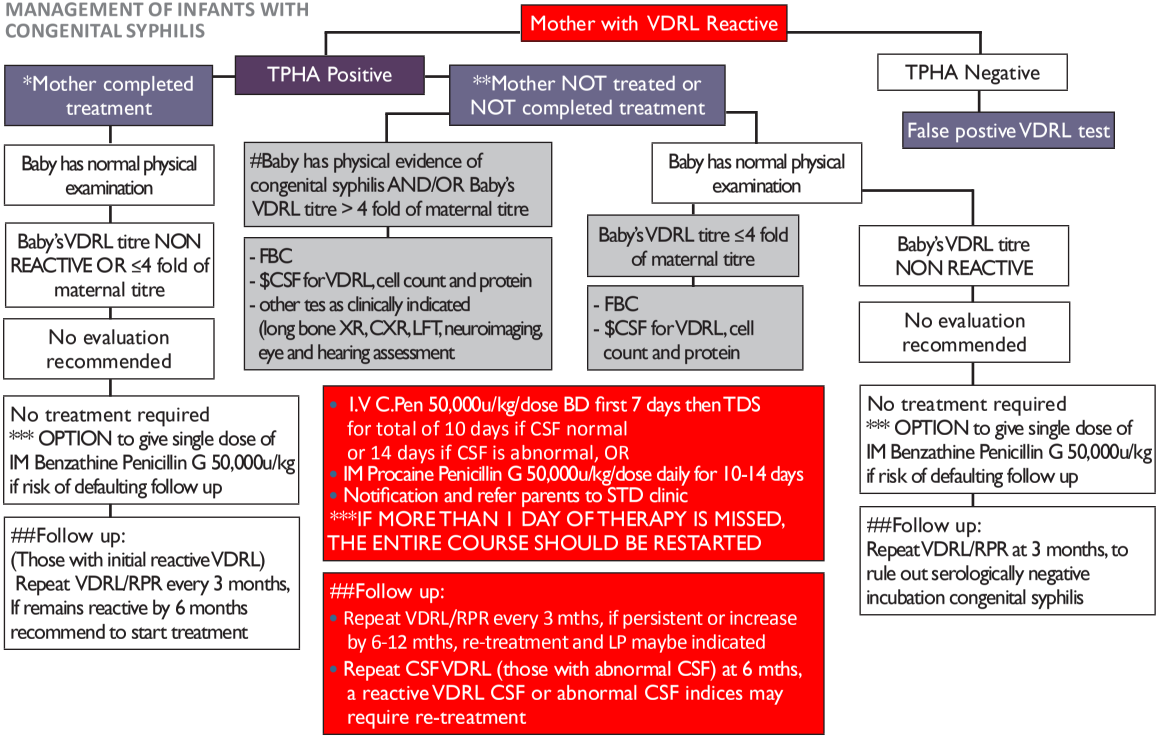
Herpes simplex virus

- Herpes simplex keratoconjunctivitis usually presents 6-14 days after birth with a generalized infection with skin, eye and mucosal involvement.
- These infants need a lumbar puncture and assessment by an ophthalmologist
- May have vesicles around the eye and corneal involvement
- Systemic treatment
  - IV acyclovir 30mg/kg/d divided tds for 2 weeks.

Important Notes

- Refer patients to an ophthalmologist for assessment.
- Ophthalmia neonatorum due to gonococcal or *chlamydia trachomatis* infection is a notifiable disease
- Check VDRL of the infant to exclude associated congenital syphilis and screen for C. trachomatis and HIV.
- Screen both parents for gonococcal infections, syphilis and HIV.
- Parents should be referred to STD clinic for further management.
- On discharge, infants should be seen in 2 weeks with a repeat eye swab gram stain and C&S.

MANAGEMENT OF INFANTS WITH CONGENITAL SYPHILIS



Footnotes to algorithm on previous page:

* Mother completed treatment is defined as
  - Mother had received adequate penicillin regime
  - Treatment completed more than 30 days prior to delivery with no possibility or reinfection AND
  - Documented 4-fold decrease in VDRL/RPR titre OR VDRL/RPR titre remained low and stable i.e VDRL < 1:2; RPR < 1:4

** Mother is considered as "not completed treatment" if one of these criteria is met
  - No or inadequate treatment
  - Treatment with non-penicillin regime
  - Treatment completed less than 30 days before delivery
  - No documented 4-fold decrease in VDRL titre
  - High likelihood of reinfection

Clinical features of congenital syphilis: non-immune hydrops, IUGR, jaundice, hepatosplenomegaly, rhinitis, skin rash, pseudoparalysis of extremity

**$** CSF analysis : Recommended value of 5 WBCs/mm^3 and protein of 40mg/dL as the upper limits of normal for "non traumatic tap".

Follow up of patients:
  - All sero-reactive infants should receive careful follow up examination and serologic testing (VDRL/RPR) every 2-3 month until the test becomes non- reactive or the titre has decreased 4-fold.
  - VDRL/RPR titre should decline by age of 3 month and should be non-reactive by age of 6 month if the infants was not infected or was infected but adequately treated.
  - If the VDRL/RPR titre are stable or increase after 6-12 month, the child should be evaluated and treated with a 10-day course of parenteral Penicillin G.
  - For infants whose initial CSF evaluations are abnormal should undergo a repeat lumbar puncture in 6 months. A reactive CSF VDRL test or abnormal CSF indices that cannot be attributed to other ongoing illness required re-treatment for possible neurosyphilis. If CSF is improving, monitor with follow-up serology.

Additional Notes:

- VDRL/RPR test on venous blood sample as umbilical cord may be contaminated with maternal blood and could yield a false-positive result.
- Tetracycline, doxycycline or erythromycin does not have an established and well-evaluated high rate of success as injection penicillin in the treatment of syphilis.
- Penetration of tetracycline, doxycycline and erythromycin into CSF is poor.

Chapter 31: Perinatally Acquired Varicella and Postnatal exposure to Varicella infection

Introduction

- In maternal infection (onset of rash) within 7 days before and 7 days after delivery 17-30% develops neonatal varicella with lesions appearing 5-10 days of life. Mortality can be as high as 20% since these infants have not acquired maternal protecting antibodies. Cause of death is due to severe pulmonary disease or widespread necrotic lesions of viscera.
- When maternal varicella occurs 7-21 days before delivery, lesions typically appear in the first 4 days of life and prognosis is good with no associated mortality. The mild course is probably due to the production and transplacental passage of maternal antibodies that modify the course of illness in newborns.
- Infants born to mothers who develop varicella between 7 days before delivery or 7 days after delivery should receive as prophylaxis
  - Varicella Zoster immunoglobulin (VZIG) 125 IU i/m as soon as possible after delivery or within 96 hours of initial exposure (to reduce the occurrence of complications and fatal outcomes). Attenuation of disease might still be achieved with administration of VariZIG™ up to 10 days after exposure.
  - For infants born to mothers who develop varicella between 5 days before and 2 days post delivery, add IV acyclovir 15 mg/kg/dose over 1 hour every 8hrly (total 45 mg/kg/day) for 5 days.
  - If Zoster immunoglobulin is not available give
    IV Immunoglobulin 400 mg/kg (this is less effective) AND
    IV Acyclovir 15 mg/kg/dose over 1 hour every 8hrly (total 45 mg /kg/day) for 5 days.
  - On sending home, warn parents to look out for new vesicles or baby being unwell, for 28 days after exposure. If so, parents to bring the infant to the nearest hospital as soon as possible (62% of healthy such neonates given VZIG after birth)
- If vesicles develop, give Acyclovir 15 mg/kg/dose over 1 hour every 8hrly (total 30-45 mg /kg/day) for 7-10 days.
- Women with varicella at time of delivery should be isolated from their newborns, breast-feeding is contraindicated. The newborn baby can receive expressed breast milk in the meantime and breast-feeding commenced when all the mother's lesions have crusted.
- Neonates with varicella lesions should be isolated from other infants but not from their mothers.
- It has been generally accepted that passive immunization of the neonate can modify the clinical course of neonatal varicella but it does not prevent the disease and, although decreased, the risk of death is not completely eliminated
- Infants whose mothers develop Zoster before or after delivery have maternal antibodies and they will not need VZIG.
- Recommend immunisation of family members who are not immune.

Assessing the significance of varicella exposure

- The index case could be the health care professional, a family member or a patient
- There should be close contact with the index case:
  - Maternal/neonatal contact.
  - Contact between health care professional or family member and patient
  - Contact in the same room, including large open wards, for 15 minutes or more.
  - Face to face contact, as in conversation.

Postnatal exposure to varicella in the hospital

- Give VZIG within 96 hours to those who have been exposed if they fit the following criteria:
  - All babies born at < 28 weeks gestation or who weighed < 1000g at birth irrespective of maternal history of chickenpox. This group has increased risk of severe varicella up to 6 weeks after birth.
  - All preterm babies born at ≥28 weeks gestation whose mothers have not had chickenpox or whose status is unknown.
  - Infants with significant non-maternal exposure to VZV within the first 7 days of their life if mother have never had varicella infection
  - All immunocompromised patients such as those undergoing immunosuppressive therapy, have malignant disease or are immunodeficient, severe underlying skin disorder.
- Note that infants who are more than 60 days old or has been given blood transfusion may be VZIG negative even though there is a positive history of maternal varicella – to counsel parents to observe for varicella lesions so baby can be treated early
- Monitor at risk patient up till end of incubation period i.e. 28 days post initial exposure. Non-immunocompromised patient who can be monitored closely at home and have easy access to hospital, can be discharged earlier.
- Isolate patient who has varicella infection and susceptible patients who have been exposed to the virus. Treatment of symptomatic patients with acyclovir as above.
- Screen exposed, susceptible hospital staff for skin lesions, fever, headache and systemic symptoms. They are potentially infective 10-21 days after exposure and should be placed on sick leave immediately should any symptoms or skin lesion arise. If possible, they can also be reassigned during the incubation period to areas where the patients are not as susceptible or non-patient care areas.

Other notes

- In hospitals, airborne transmission of VZV has been demonstrated when varicella has occurred in susceptible persons who have had no direct contact with the index case-patient.
- Incubators are not positive pressure air flow & therefore do not provide isolation. Neonates may not be protected given that they are frequently open for nursing purposes.

- All staff should preferably be screened, and susceptible staff vaccinated for varicella before commencing work in neonatal, oncology and ICU wards. If not, they should receive post exposure vaccination as soon as possible unless contraindications exist such as pregnancy. Post-exposure VZIG to be given to non-immune pregnant staff up to 10 days post initial exposure to prevent complications in the mother and may reduce the risk of foetal varicella syndrome.
- The use of VZIG following exposure does not necessarily prevent varicella and may prolong the incubation period by > 1 week and hence signs or symptoms should be observed for 28 days post exposure.
- VZIG is not presently recommended for healthy full-term infants who are exposed postnatally, even if their mothers have no history of varicella infection. To emphasise to parents to bring back early for treatment with acyclovir if any skin lesion appears within the next 3 weeks.

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Chapter 32: Asthma

The International Studies on Asthma And Allergy (ISAAC) has shown that the prevalence of asthma among school age children is 10%.

Definition

- Chronic airway inflammation leading to increase airway responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or early morning.
- Often associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.
- Reversible and variable airflow limitation as evidenced by >15% improvement in PEFR (Peak Expiratory Flow Rate), in response to administration of a bronchodilator.

Important Points to Note in:	
Clinical History	*Physical Examination*
Current symptoms Pattern of symptoms Precipitating factors Present treatment Previous hospital admission Typical exacerbations Home/ school environment Impact on life style History of atopy Response to prior treatment Prolonged URTI symptoms Family history	*Signs of chronic illness* Harrison's sulci Hyperinflated chest Eczema / dry skin Hypertrophied turbinates *Signs in acute exacerbation* Tachypnoea Wheeze, rhonchi Hyperinflated chest Accessory muscles Cyanosis Drowsiness Tachycardia
Note: Absence of Physical Signs Does Not Exclude Asthma!	

Diagnosis of asthma in children younger than 5 years old

A diagnosis of asthma in young children is largely based on symptoms patterns combined with a careful clinical history and physical findings. A positive family history or positive history of atopy may be predictive.

Features suggesting of asthma in children younger than 5 years old

- Cough: recurrent or persistent non-productive cough that worsens at night or accompanied by wheezing or breathlessness. Cough occurring in the absence of respiratory infections, usually with laughing, crying or exposure to tobacco smoke.
- Wheezing: Recurrent wheezing during sleep or with triggers such as activity, laughing, crying or exposure to tobacco smoke or air pollution
- Difficult or heavy breathing or shortness of breath occurring with exercise, laughing or playing.
- Reduced activity: not running, playing, or laughing at the same intensity as other children.
- Past or family history of allergic disease or history of asthma in first degree relative.
- Therapeutic trial with low dose inhaled steroids: Clinical improvement during 2-3 months of controller treatment and worsening when treatment is stopped.

Key indications for referral of children younger than 5 years old for further diagnostic investigations:

- Failure to thrive
- Neonatal or very early onset of symptoms especially associated with failure to thrive
- Vomiting with respiratory symptoms
- Continuous wheezing
- Failure to respond to controller medications
- No associations of symptoms with typical triggers such as URTI
- Focal or cardiovascular signs or finger clubbing
- Hypoxaemia outside context of viral illness

MANAGEMENT OF CHRONIC ASTHMA

Patients with a new diagnosis of asthma should be properly evaluated as to their degree of asthma severity:

Evaluation of the background of newly diagnosed asthma	
Category	**Clinical Parameters**
Intermittent	• Daytime symptoms less than once a week • Nocturnal symptoms less than once a month • No exercise induced symptoms • Brief exacerbations not affecting sleep and activity • Normal lung function
Persistent (Threshold for preventive treatment)	
Mild Persistent	• Daytime symptoms more than once a week • Nocturnal symptoms more than twice a month • Exercise induced symptoms • Exacerbations > 1x/month affecting sleep, activity • PEFR / FEV_1 > 80%
Moderate Persistent	• Daytime symptoms daily • Nocturnal symptoms more than once a week • Exercise induced symptoms • Exacerbations > 2x/month affecting sleep, activity • PEFR / FEV_1 60 - 80%
Severe Persistent	• Daytime symptoms daily • Daily nocturnal symptoms • Daily exercise induced symptoms • Frequent exacerbations > 2x/month affecting sleep, activity • PEFR / FEV_1 < 60%

Note

- *This division is arbitrary and the groupings may merge. An individual patient's classification may change from time to time.*
- *There are a few patients who have very infrequent but severe or life threatening attacks with completely normal lung function and no symptoms between episodes. This type of patient remains very difficult to manage.*
- *PEFR = Peak Expiratory Flow Rate; FEV_1 = Forced Expiratory Volume in One Second.*

- In 2006, the Global Initiatives on Asthma (GINA) has proposed the management of asthma from severity based to control based. The change is due to the fact that asthma management based on severity is on expert opinion rather than evidence based, with limitation in deciding treatment and it does not predict treatment response.
- Asthma assessment based on levels of control is based on symptoms and the three levels of control are well controlled, partly control and uncontrolled.
- Patients who are already on treatment should be assessed at every clinic visit on their control of asthma

Levels of Asthma Control (GINA 2006)			
Characteristics	*Controlled* All of the following:	*Partly Controlled* *Any* measure present in *any* week:	*Uncontrolled*
Daytime symptoms	None	> 2 per week	≥ 3 features of partly controlled asthma present in any week
Limitation of activities	None	Any	
Nocturnal symptoms or Awakenings	None	Any	
Need for Reliever	None	> 2 per week	
Lung function test	Normal	< 80% predicted or personal best	
Exacerbations	None	≥ 1 per year	One in *any* week

Prevention

Identifying and avoiding the following common triggers may be useful

- Environmental allergens
  - These include house dust mites, animal dander, insects like cockroach, mould and pollen.
  - Useful measures include damp dusting, frequent laundering of bedding with hot water, encasing pillow and mattresses with plastic/vinyl covers, removal of carpets from bedrooms, frequent vacuuming and removal of pets from the household.
- Cigarette smoke
- Respiratory tract infections - commonest trigger in children.
- Food allergy - uncommon trigger, occurring in 1-2% of children
- Exercise
  - Although it is a recognised trigger, activity should not be limited. Taking a β_2-agonist prior to strenuous exercise, as well as optimizing treatment, are usually helpful.

Drug Therapy

Drug Therapy: Delivery systems available & recommendation for different ages.				
Age (years)	Oral	MDI + Spacer	MDI + Mask + Spacer	Dry Powder Inhaler
< 5	+	+	-	-
5 – 8	-	+	-	-
> 8	-	+	+	+
Note: *MDI = Meter dose inhaler* *Mask used should be applied firmly to the face of the child*				

Treatment of Chronic Asthma

Asthma management based on levels of control is a step up and step down approach as shown in the table below:

Management Based On Control				
← Reduce			Increase →	
STEP 1 Intermittent	**STEP 2** Mild Persistent	**STEP 3** Moderate Persistent	**STEP 4** Severe Persistent	**STEP 5** Severe Persistent
As needed rapid acting β_2-agonist	As needed rapid acting β_2-agonist			
Controller Options	*Select one*	*Select One*	*Add one / more*	*Add one / both*
	Low dose inhaled steroids	Low dose ICS + long acting β_2-agonist	Medium / High dose ICS + long acting β_2-agonist	Oral Glucocorticoids lowest dose
	Leukotriene modifier	Medium / High dose ICS	Leukotriene modifier	Anti-IgE
		Low dose ICS + Leukotriene modifier	SR Theophylline	
		Low dose ICS + SR Theophylline		
Footnote: ICS, Inhaled Corticosteroids; SR, Sustained Release.				

Drug Dosages for Medications used in Chronic *Asthma*		
Drug	Formulation	Dosage
Relieving Drugs		
β_2-agonists		
Salbutamol	Oral Metered dose inhaler Dry powder inhaler	0.15 mg/kg/dose TDS-QID/PRN 100-200 mcg/dose QID/PRN 100-200 mcg/dose QID/PRN
Terbutaline	Oral	0.075 mg/kg/dose TDS-QID/PRN 250-500 mcg/dose QID/PRN 500-1000 mcg/dose QID/PRN (maximum 4000 mcg/daily)
Fenoterol	Metered dose inhaler	200 mcg/dose QID/PRN
Ipratropium Bromide	Metered dose inhaler	40-60mcg /dose TDS/QID/PRN
Preventive Drugs		
Corticosteroids		
Prednisolone	Oral	1-2 mg/kg/day in divided doses
Beclomethasone Diproprionate Budesonide	Metered dose inhaler Dry powder inhaler	<400 mcg/day : low dose 400-800 mcg/day : Moderate 800-1200 mcg/day: High
Fluticasone Propionate	Metered dose inhaler Dry powder inhaler	<200 mcg/day : Low 200-400 mcg/day : Moderate 400-600 mcg/day : High
Ciclesonide	Metered dose inhaler	160 microgram daily 320 microgram daily
Sodium Cromoglycate	Dry powder inhaler Metered dose inhaler	20mg QID 1-2mg QID or 5-10mg BID-QID
Theophylline	Oral Syrup Slow Release	5 mg/kg/dose TDS/QID 10 mg/kg/dose BD
Long acting β_2-agonists		
Salmeterol	Metered dose inhaler Dry powder inhaler	50-100 mcg/dose BD 50-100 mcg/dose BD
Combination agents		
Salmeterol / Fluticasone	Metered dose inhaler Dry powder inhaler	25/50mcg, 25/125mcg, 25/250mcg 50/100mcg,50/250mcg, 50/500mcg
Budesonide / Formoterol	Dry powder inhaler	160/4.5mcg, 80/4.5mcg
Antileukotrienes (Leukotriene modifier)		
Montelukast	Oral	4 mg granules 5mg/tablet on night chewable 10mg/tablet ON

Note:

- Patients should commence treatment at the step most appropriate to the initial severity. A short rescue course of Prednisolone may help establish control promptly.
- Explain to parents and patient about asthma and all therapy
- Ensure both compliance and inhaler technique optimal before progression to next step.
- Step-up; assess patient after 1 month of initiation of treatment and if control is not adequate, consider step-up after looking into factors as above.
- Step-down; review treatment every 3 months and if control sustained for at least 4-6 months, consider gradual treatment reduction.

Monitoring

During each follow up visit, three issues need to be assessed. They are:

- Assessment of asthma control based on:
  - Interval symptoms.
  - Frequency and severity of acute exacerbation.
  - Morbidity secondary to asthma.
  - Quality of life.
  - Peak Expiratory Flow Rate (PEFR) or FEV_1 monitoring.
- Compliance to asthma therapy:
  - Frequency.
  - Technique.
- Asthma education:
  - Understanding asthma in childhood.
  - Reemphasize compliance to therapy.
  - Written asthma action plan.

Patients with High Risk Asthma are at risk of developing near fatal asthma (NFA) or fatal asthma (FA) . This group of patients need to be identified and closely monitored which includes frequent medical review (at least 3 monthly), objective assessment of asthma control with lung function on each visit, review of asthma action plan and medication supply, identification of psychosocial issues and referral to a paediatrician or respiratory specialist.

MANAGEMENT OF ACUTE ASTHMA

Assessment of Severity

Initial (Acute assessment)

- Diagnosis
  - symptoms e.g. cough, wheezing. breathlessness , pneumonia
- Triggering factors
  - food, weather, exercise, infection, emotion, drugs, aeroallergens
- Severity
  - respiratory rate, colour, respiratory effort, conscious level

Chest X Ray is rarely helpful in the initial assessment unless complications like pneumothorax, pneumonia or lung collapse are suspected.

Initial ABG is indicated only in acute severe asthma.

Management of acute asthma exacerbations

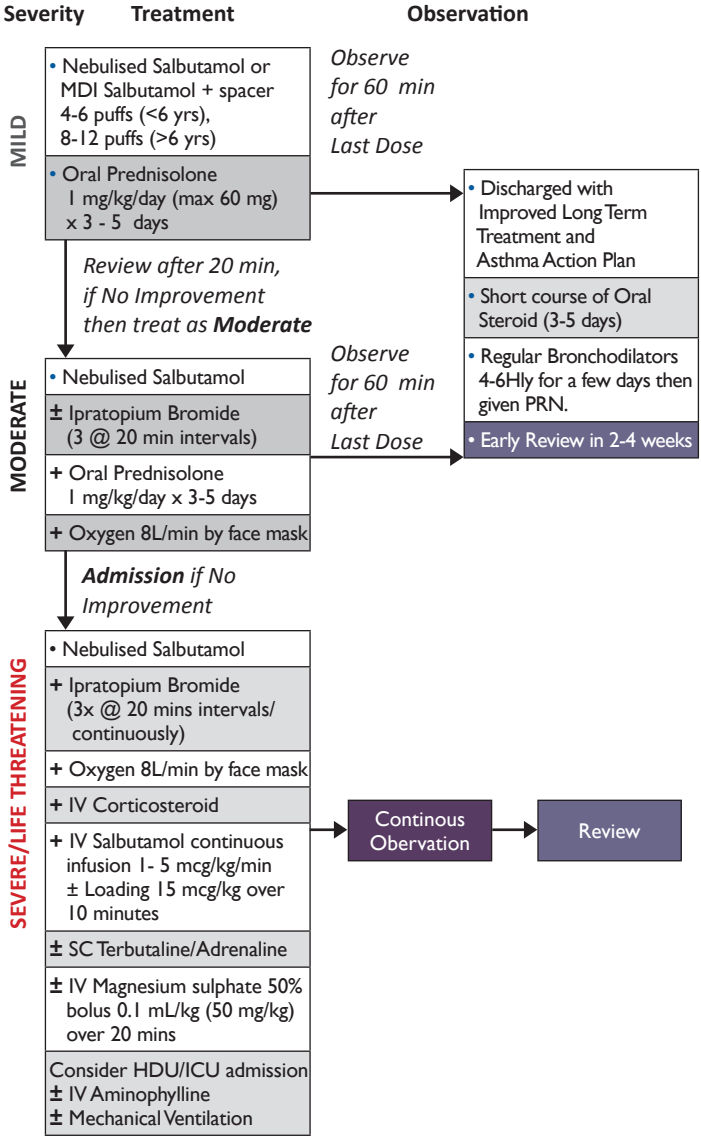
- Mild attacks can be usually treated at home if the patient is prepared and has a personal asthma action plan.
- Moderate and severe attacks require clinic or hospital attendance.
- Asthma attacks require prompt treatment.
- A patient who has brittle asthma, previous ICU admissions for asthma or with parents who are either uncomfortable or judged unable to care for the child with an acute exacerbation should be admitted to hospital.

Criteria for admission

- Failure to respond to standard home treatment.
- Failure of those with mild or moderate acute asthma to respond to nebulised β_2-agonists.
- Relapse within 4 hours of nebulised β_2- agonists.
- Severe acute asthma.

The Initial Assessment is the First Step in the Management of Acute Asthma				
Severity of Acute Asthma Exacerbations				
Parameters	**Mild**	**Moderate**	**Severe**	**Life Threatening**
Breathless	When walking	When talking *Infant:* Feeding difficulties	At rest *Infant:* Stops feeding	
Talks in	Sentences	Phrases	Words	Unable to speak
Alertness	Maybe agitated	Usually agitated	Usually agitated	Drowsy/ confused/ coma
Respiratory rate	Normal to Mildly Increased	Increased	Markedly Increased	Poor Respiratory Effort
Accessory Muscle usage / retractions	Absent	Present - Moderate	Present – Severe	Paradoxical thoraco-abdominal movement
Wheeze	Moderate, often only end expiratory	Loud	Usually loud	Silent chest
SpO_2 (on air)	>95%	92-95%	<92%	Cyanosis & <92%
Pulse /min	< 100	100-120	>120 (>5yrs) >160 (infants)	Bradycardia
PEFR[1]	>80%	60-80%	<60%	Unable to perform
Footnote: *1 , PEFR after initial bronchodilator, % predicted or of personal best*				

MANAGEMENT OF ACUTE EXARCERBATION OF BRONCHIAL ASTHMA IN CHILDREN



Footnotes on Management of Acute Exacerbation of Asthma:

1. Monitor pulse, colour, PEFR, ABG and O_2 Saturation.
   Close monitoring for at least 4 hours.
2. Hydration - give maintenance fluids.
3. Role of Aminophylline debated due to its potential toxicity.
   To be used with caution, in a controlled environment like ICU.
4. IV Magnesium Sulphate : Consider as an adjunct treatment in severe exacerbations unresponsive to the initial treatment. It is safe and beneficial in severe acute asthma.
5. Avoid Chest physiotherapy as it may increase patient discomfort.
6. Antibiotics indicated only if bacterial infection suspected.
7. Avoid sedatives and mucolytics.
8. Efficacy of prednisolone in the first year of life is poor.
9. On discharge, patients must be provided with an Action Plan to assist parents or patients to prevent/terminate asthma attacks.
   The plan must include:
   a. How to recognize worsening asthma.
   b. How to treat worsening asthma.
   c. How and when to seek medical attention.

- Salbutamol MDI vs nebulizer
  < 6 year old: 6 x 100 mcg puff = 2.5 mg Salbutamol nebules.
  > 6 year old: 12 x 100 mcg puff = 5.0 mg Salbutamol nebules.

Drug Dosages for Medications used in Acute *Asthma*		
Drug	Formulation	Dosage
β_2-agonists		
Salbutamol	Nebuliser solution 5 mg/ml or 2.5 mg/ml nebule	0.15 mg/kg/dose (max 5 mg) or < 2 years old : 2.5 mg/dose > 2 years old : 5.0 mg/dose
	Intravenous	Continuous : 500 mcg/kg/hr Bolus: 5-10 mcg/kg over 10 min Infusion: Start 0.5-1.0 mcg/kg/min, increase by 1.0 mcg/kg/min every 15 min to a max of 20 mcg/kg/min
Terbutaline	Nebuliser solution 10 mg/ml, 2.5 mg/ml or 5 mg/ml respule	0.2-0.3 mg/kg/dose, or < 20 kg: 2.5 mg/dose > 20 kg: 5.0 mg/dose
	Parenteral	5-10 mcg/kg/dose
Fenoterol	Nebuliser solution	0.25-1.5 mg/dose
Corticosteroids		
Prednisolone	Oral	1-2 mg/kg/day in divided doses (for 3-7 days)
Hydrocortisone	Intravenous	4-5 mg/kg/dose 6 hourly
Methylprednisolone	Intravenous	1-2 mg/kg/dose 6-12 hourly
Other agents		
Ipratropium bromide	Nebuliser solution (250 mcg/ml)	< 5 years old : 250 mcg 4-6 hourly > 5 years old : 500 mcg 4-6 hourly
Aminophylline	Intravenous	6 mg/kg slow bolus (if not previously on theophylline) followed by infusion 0.5-1.0 mg/kg/hr
Montelukast	Oral	4 mg granules 5mg/tablet on night chewable 10mg/tablet ON

Chapter 33: Viral Bronchiolitis

Aetiology and Epidemiology

- A common respiratory illness especially in infants aged 1 to 6 months old
- Respiratory Syncytial Virus (RSV) remains the commonest cause of acute bronchiolitis in Malaysia.
- Although it is endemic throughout the year, cyclical periodicity with annual peaks occur, in the months of November, December and January.

Clinical Features

- Typically presents with a mild coryza, low grade fever and cough.
- Tachypnoea, chest wall recession, wheeze and respiratory distress subsequently develop. The chest may be hyperinflated and auscultation usually reveals fine crepitations and sometimes rhonchi.
- A majority of children with viral bronchiolitis has mild illness and about 1% of these children require hospital admission.

Guidelines for Hospital Admission in Viral Bronchiolitis

	Home Management	Hospital management
Age < than 3 months	No	Yes
Toxic – looking	No	Yes
Chest recession	Mild	Moderate/Severe
Central cyanosis	No	Yes
Wheeze	Yes	Yes
Crepitations on auscultation	Yes	Yes
Feeding	Well	Difficult
Apnoea	No	Yes
Oxygen saturation	> 95%	< 93 %
High risk group	No	Yes

Chest X-ray

- A wide range of radiological changes are seen in viral bronchiolitis:
  - Hyperinflation (most common).
  - Segmental collapse/consolidation.
  - Lobar collapse/consolidation.
- A chest X-ray is *not routinely required*, but recommended for children with:
  - Severe respiratory distress.
  - Unusual clinical features.
  - An underlying cardiac or chronic respiratory disorder.
  - Admission to intensive care.

Management

General measures

- Careful assessment of the respiratory status and oxygenation is critical.
- Arterial oxygenation by pulse oximetry (SpO_2) should be performed at presentation and maintained above 93%.
  - Administer supplemental humidified oxygen if necessary.
- Monitor for signs of impending respiratory failure:
  - Inability to maintain satisfactory SpO_2 on inspired oxygen > 40%, or a rising pCO_2.
- Very young infants who are at risk of apnoea require greater vigilance.
- Blood gas analysis may have a role in the assessments of infants with severe respiratory distress or who are tiring and may be entering respiratory failure.
- Routine full blood count and bacteriological testing (of blood and urine) is not indicated in the assessment and management of infants with typical acute bronchiolitis .

Nutrition and Fluid therapy

- *Feeding.* Infants admitted with viral bronchiolitis frequently have poor feeding, are at risk of aspiration and may be dehydrated. Small frequent feeds as tolerated can be allowed in children with moderate respiratory distress. Nasogastric feeding, although not universally practiced, may be useful in these children who refuse feeds and to empty the dilated stomach.
- *Intravenous fluids* for children with severe respiratory distress, cyanosis and apnoea. Fluid therapy should be restricted to maintenance requirement of 100 ml/kg/day for infants, in the absence of dehydration.

Pharmacotherapy

- The use of 3% saline solution via nebulizer has been shown to increase mucus clearance and significantly reduce hospital stay among non-severe acute bronchiolits. It improves clinical severity score in both outpatients and inpatients populations.
- *Inhaled β_2-agonists.* Pooled data have indicated a modest clinical improvement with the use of β_2-agonist. A trial of nebulised β_2-agonist, given in oxygen, may be considered in infants with viral bronchiolitis. Vigilant and regular assessment of the child should be carried out.
- *Inhaled steroids*. Randomised controlled trials of the use of inhaled or oral steroids for treatment of viral bronchiolitis show no meaningful benefit.
- *Antibiotics* are recommended for all infants with
  - Recurrent apnoea and circulatory impairment.
  - Possibility of septicaemia.
  - Acute clinical deterioration.
  - High white cell count.
  - Progressive infiltrative changes on chest radiograph.
- Chest physiotherapy using vibration and percussion is not recommended in infants hospitalized with acute bronchiolitis who are not admitted into intensive care unit.

Chapter 34: Viral Croup

Aetiology and epidemiology

- A clinical syndrome characterised by barking cough, inspiratory stridor, hoarse voice and respiratory distress of varying severity.
- A result of viral inflammation of the larynx, trachea and bronchi, hence the term *laryngotracheobronchitis.*
- The most common pathogen is parainfluenza virus (74%), (types 1, 2 and 3). The others are Respiratory Syncytial Virus, Influenza virus types A and B, Adenovirus, Enterovirus, Measles, Mumps and Rhinoviruses and rarely *Mycoplasma pneumoniae* and *Corynebacterium Diptheriae.*

Clinical Features

- Low grade fever, cough and coryza for 12-72 hours, followed by:
- Increasingly bark-like cough and hoarseness.
- Stridor that may occur when excited, at rest or both.
- Respiratory distress of varying degree.

Diagnosis

- Croup is a clinical diagnosis. Studies show that it is safe to visualise the pharynx to exclude acute epiglotitis, retropharyngeal abscess etc.
- In severe croup, it is advisable to examine the pharynx under controlled conditions, i.e. in the ICU or Operation Theatre.
- A neck Radiograph is not necessary, unless the diagnosis is in doubt, such as in the exclusion of a foreign body.

Assessment of severity

Clinical Assessment of Croup (Wagener)

- *Severity*
  - Mild: Stridor with excitement or at rest, with no respiratory distress.
  - Moderate: Stridor at rest with intercostal, subcostal or sternal recession.
  - Severe: Stridor at rest with marked recession, decreased air entry and altered level of consciousness.
- Pulse oximetry is helpful but not essential
- Arterial blood gas is not helpful because the blood parameters may remain normal to the late stage. The process of blood taking may distress the child.

Management

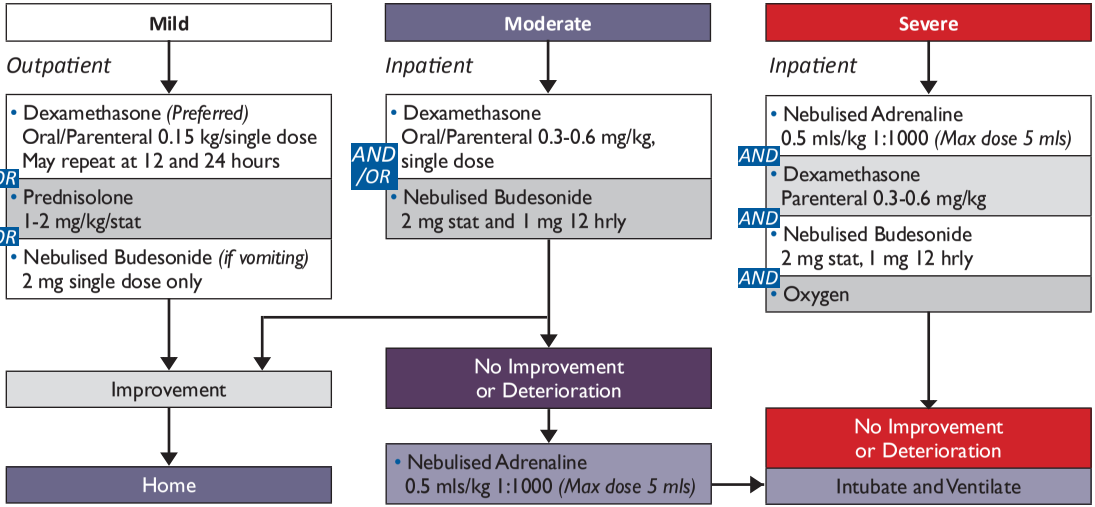
Indications for Hospital admission

- Moderate and severe viral croup.
- Age less than 6 months.
- Poor oral intake.
- Toxic, sick appearance.
- Family lives a long distance from hospital; lacks reliable transport.

Treatment (ref Algorithm on next page)

- The sustained action of steroids combined with the quick action of adrenaline may reduce the rate of intubation from 3% to nil.
- Antibiotics are not recommended unless bacterial super-infection is strongly suspected or the patient is very ill.
- IV fluids are not usually necessary except for those unable to drink.

ALGORITHM FOR THE MANAGEMENT OF VIRAL CROUP



Footnote:

- The decision to intubate under controlled conditions (in Operation Theatre or Intensive Care Unit, with standby for tracheostomy) is based on clinical criteria, often from increasing respiratory distress.
- Indications for oxygen therapy include: 1. severe viral croup; 2. percutaneous SpO_2 < 93%
- With oxygen therapy, SpO_2 may be normal despite progressive respiratory failure and a high $PaCO_2$. Hence clinical assessment is important.

Definition

There are two clinical definitions of pneumonia:

- *Bronchopneumonia*: a febrile illness with cough, respiratory distress with evidence of localised or generalised patchy infiltrates.
- *Lobar pneumonia*: similar to bronchopneumonia except that the physical findings and radiographs indicate lobar consolidation.

Aetiology

- Specific aetiological agents are not identified in 40% to 60% of cases.
- It is often difficult to distinguish viral from bacterial disease.
- The majority of lower respiratory tract infections are viral in origin, e.g. Respiratory syncytial virus, Influenza A or B, Adenovirus, Parainfluenza virus.
- A helpful indicator in predicting aetiological agents is the age group. The predominant bacterial pathogens are shown in the table below:

Pathogens for Pneumonia

Age	Bacterial Pathogens
Newborns	*Group B streptococcus, Escherichia coli, Klebsiella species, Enterobacteriaceae*
Infants 1- 3 months	*Chlamydia trachomatis*
Preschool age	*Streptococcus pneumoniae, Haemophilus influenzae type b, Staphylococcal aureus* Less common: Group A *Streptococcus, Moraxella catarrhalis, Pseudomonas aeruginosa*
School age	*Mycoplasma pneumoniae, Chlamydia pneumoniae*

Assessment of Severity in Pneumonia

Age < 2 months	Age 2 months - 5 years
Severe Pneumonia	**Mild Pneumonia**
• Severe chest indrawing	• Tachypnoea
• Tachypnoea	**Severe Pneumonia**
	• Chest indrawing
Very Severe Pneumonia	*Very Severe Pneumonia*
• Not feeding	• Not able to drink
• Convulsions	• Convulsions
• Abnormally sleepy, difficult to wake	• Drowsiness
• Fever, or Hypothermia	• Malnutrition

Assessment of severity of pneumonia

The predictive value of respiratory rate for the diagnosis of pneumonia may be improved by making it age specific. Tachypnoea is defined as follows :

< 2 months age: > 60 /min
2- 12 months age: > 50 /min
12 months – 5 years age: > 40 /min

Investigations and assessment

Children with bacterial pneumonia *cannot be reliably distinguished* from those with viral disease on the basis of any single parameter: Clinical, laboratory or chest X-ray findings.

- *Chest radiograph*
  - Indicated when clinical criteria suggest pneumonia.
  - Does not differentiate aetiological agents.
  - Not always necessary if facilities are not available or if pneumonia is mild.
- *White blood cell count*
  - Increased counts with predominance of polymorphonuclear cells suggests bacterial cause.
  - Leucopenia suggests either a viral cause or severe overwhelming infection.
- *Blood culture*
  - Non-invasive gold standard for determining the precise aetiology.
  - Sensitivity is low: Positive blood cultures only in 10%-30% of patients.
  - Do cultures in severe pneumonia or if poor response to first line antibiotics.
- *Pleural fluid analysis*
  - If there is significant pleural effusion, a diagnostic pleural tap will be helpful.
- *Serological tests*
  - Serology is performed in patients with suspected atypical pneumonia, i.e. *Mycoplasma pneumoniae, Chlamydia, Legionella, Moraxella catarrhalis*
  - Acute phase serum titre > 1:160 or paired samples taken 2-4 weeks apart with a 4 fold rise is a good indicator of *Mycoplasma pneumoniae* infection.
  - This test should be considered for children aged five years or older.

Assessment of oxygenation

- Objective measurement of hypoxia by pulse oximetry avoids the need for arterial blood gases. It is a good indicator of the severity of pneumonia.

Criteria for hospitalization

- Community acquired pneumonia can be treated at home
- Identify indicators of severity in children who need admission, as pneumonia can be fatal. The following indicators can be used as a guide for admission:
  - Children aged 3 months and below, whatever the severity of pneumonia.
  - Fever (more than 38.5 ^{o}C), refusal to feed and vomiting
  - Fast breathing with or without cyanosis
  - Associated systemic manifestation
  - Failure of previous antibiotic therapy
  - Recurrent pneumonia
  - Severe underlying disorder, e.g. Immunodeficiency

Antibiotics

- When treating pneumonia, consider clinical, laboratory, radiographic findings, as well as age of the child, and the local epidemiology of respiratory pathogens and resistance/sensitivity patterns to microbial agents.
- Severity of the pneumonia and drug costs also impact on selection of therapy.
- Majority of infections are caused by viruses and do not require antibiotics.

Bacterial pathogens and Recommended antimicrobial agents.

Pathogen	Antimicrobial agent
Beta-lactam susceptible	
Streptococcus pneumonia	Penicillin, cephalosporins
Haemophilus influenzae type b	Ampicillin, chloramphenicol, cephalosporins
Staphylococcus aureus	Cloxacillin
Group A *Streptococcus*	Penicillin, cephalosporin
Other organisms	
Mycoplasma pneumoniae	Macrolides, e.g. erythromycin, azithromycin
Chlamydia pneumoniae	Macrolides, e.g. erythromycin, azithromycin
Bordetella pertussis	Macrolides, e.g. erythromycin, azithromycin

INPATIENT MANAGEMENT

Antibiotics

For children with severe pneumonia, the following antibiotics are recommended:

Suggested antimicrobial agents for inpatient treatment of pneumonia	
First line	*Beta-lactams*: Benzylpenicillin, moxycillin, ampicillin, amoxycillin-clavulanate
Second line	*Cephalosporins*: Cefotaxime, cefuroxime, ceftazidime
Third line	*Carbapenem*: Imipenam
Other agents	*Aminoglycosides*: Gentamicin, amikacin

- *Second line antibiotics* need to be considered when :
  - There are no signs of recovery
  - Patients remain toxic and ill with spiking temperature for 48 - 72 hours
- A macrolide antibiotic is used in pneumonia from *Mycoplasma* or *Chlamydia*.
- A child admitted with severe community acquired pneumonia must receive parenteral antibiotics. In severe cases of pneumonia, give combination therapy with a second or third generation cephalosporins and macrolide.
- Staphylococcal infections and infections caused by Gram negative organisms such as *Klebsiella* have been frequently reported in malnourished children.

Staphylococcal infection

- *Staphylococcus aureus* is responsible for a small proportion of cases.
- A high index of suspicion is required because of the potential for rapid deterioration. It chiefly occurs in infants with a significant risk of mortality.
- Radiological features include multilobar consolidation, cavitation, pneumatocoeles, spontaneous pneumothorax, empyema, pleural effusion.
- Treat with high dose Cloxacillin (200 mg/kg/day) for a longer duration
- Drainage of empyema often results in a good outcome.

Necrotising pneumonia and pneumatocoeles

- It is a result of localized bronchiolar and alveolar necrosis.
- Aetiological agents are bacteria, e.g. *Staphylococcal aureus, S. Pneumonia, H. Influenza, Klebsiella pneumonia* and *E. coli*.
- Give IV antibiotics until child shows signs of improvement.
- Total antibiotics course duration of 3 to 4 weeks.
- Most pneumatocoeles disappear, with radiological evidence resolving within the first two months but may take as long as 6 months.

Supportive treatment

- *Fluids*
  - Withhold oral intake when a child is in severe respiratory distress.
  - In severe pneumonia, secretion of anti-diuretic hormone is increased and as such dehydration is uncommon. Avoid overhydrating the child.
- *Oxygen*
  - Oxygen reduces mortality associated with severe pneumonia.
  - It should be given especially to children who are restless, and tachypnoeic with severe chest indrawing, cyanosis, or is not tolerating feeds.
  - Maintain the SpO_2 > 95%.
- *Cough medication*
  - Not recommended as it causes suppression of cough and may interfere with airway clearance. Adverse effects and overdosage have been reported.
- *Temperature control*
  - Reduces discomfort from symptoms, as paracetamol will not abolish fever.
- *Chest physiotherapy*
  - This assists in the removal of tracheobronchial secretions: removes airway obstruction, increase gas exchange and reduce the work of breathing.
  - No evidence that chest physiotherapy should be routinely done.

OUTPATIENT MANAGEMENT

- In children with mild pneumonia, their breathing is fast but there is no chest indrawing.
- Oral antibiotics can be prescribed.
- Educate parents/caregivers about management of fever, preventing dehydration and identifying signs of deterioration.
- The child should return in two days for reassessment, or earlier if the condition is getting worse.

Chapter 36: Empyema Thoracis

Introduction

- A condition with pus formation in the pleural cavity
- Common pathogens include *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes* and *Hemophilus influenza*. Occasionally gram negative bacilli like *Salmonella* species.
- Tuberculosis should be considered in unresolving empyema thoracis.

Stages of a parapneumonic effusion

Stage 1: EXUDATIVE (24-72 Hours): Pleuritis and inflammation. Simple clear exudative fluid

Stage 2: FIBROPURULENT (7-10 days): Complicated pleural effusion or pus fluid. Deposition of fibrin clots or fibrin membrane. May have septation or loculation.

Stage 3: ORGANIZING (2-4 weeks): Fibroblast grows on parietal and pleural surface. Intra-pleural fibrin membrane transform to web of thick and non-elastic pleural peel.

Pleural drainage with Intrapleural fibrinolytic agent therapy (Urokinase or Streptokinase)

- Used in late Stage 1 or early Stage 2: facilitates drainage of fluid, reduces length of hospital stay and avoids surgical intervention in some children.
- Not beneficial in advanced stage like Stage 3.
- Complications of intrapleural fibrinolytic therapy are uncommon:
  - fever, haemorrhage, pain and allergic reaction
  - generally safe when used cautiously
- Contraindicated in haemothorax, pneumothorax and hypersensitive to intra-pleural fibrinolytic agents.

Technique for intrapleural fibrinolytic therapy

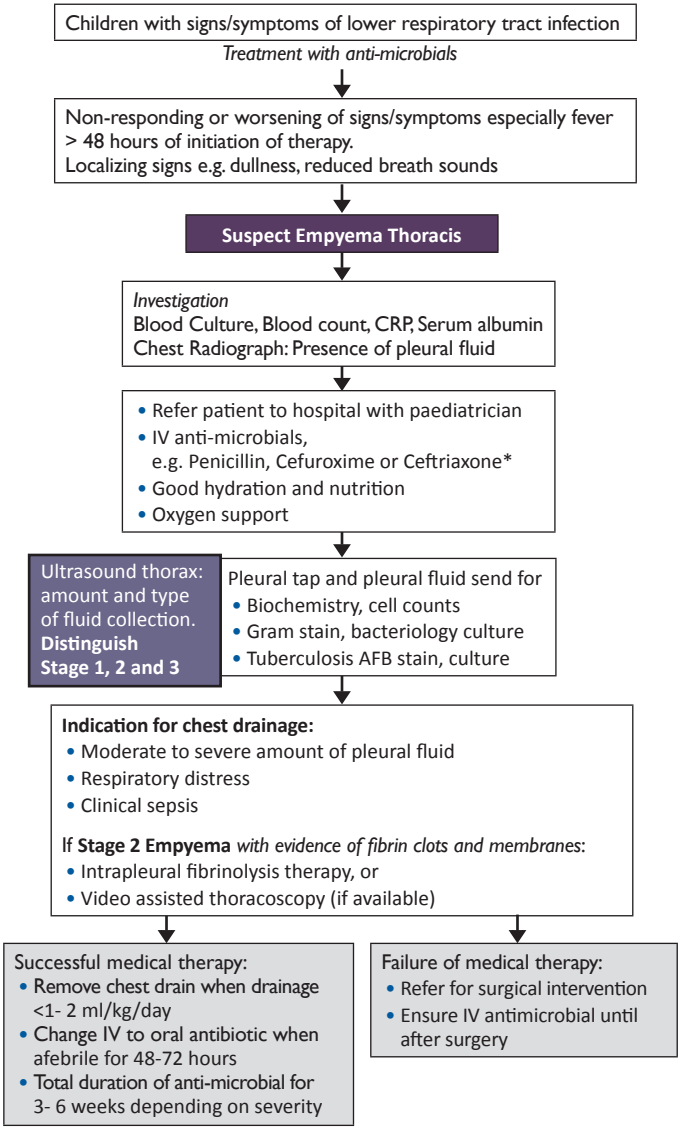
- Confirm presence of intrapleural fluid collection by chest radiograph and ultrasound of the thorax.
- Insert chest drainage under sedation (general anesthesia, if available) on the site of fluid collection. The type of pleural drain may be the pigtail catheter (under ultrasound guidance) or conventional chest tube determined by the availability and expertise.
- Identification of intra-pleural fibrinolytic agent is required and adjust the dosage according to patient's weight (Table 1).
- Instillation of the fibrinolytic agent.
- Clamp chest drainage for 4 hours.
- During the period of clamping, ambulate the patient or reposition the patient regularly.
- After 4 hours, release the clamp and drain the fluid.
- Monitor for side effects.
- Repeat Steps 4-7 once or twice a day according to patient's condition
- Repeat chest radiograph after the last drainage. Daily chest radiograph or ultrasound is not recommended.
- Remove the chest drain when it drains less than 1-2 ml/kg/day.

Table 1: Recommended dosage for intra-pleural fibrinolytic therapy			
Intrapleural Fibrinolytic Agent	Dose (weight > 10 kg)	Dose (weight ≤ 10 kg)	Duration
Urokinase	10,000 units in 40 ml normal saline. Give twice a day.	40,000 units in 40 ml normal saline. Given twice a day.	3 days
Streptokinase	25,000 units/ kg in 50 ml normal saline. Given daily.	250,000 units in 50 ml normal saline. Given daily.	3-5 days
Alteplase (Tissue plasminogen activator)	0.1 mg/kg in 10 ml normal saline. Given daily.	0.1mg/kg (Max 6 mg) in 1ml/kg normal saline (Max 50 ml). Given daily.	3 days

Surgical intervention in Empyema Thoracis

- Video-assisted Thoracoscopic Surgery (VATS)
- Thoracotomy with debridement and decortication

FLOW CHART FOR MANAGING EMPYEMA THOARACIS



** Note: 1. In young children, Cloxacillin may be used for Staphylococus infection.*
2. Carbapenems may be used if poor response to Penicillin or Cephalosporins.

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Chapter 36 Empyema Thoracis

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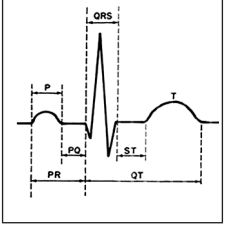
Chapter 37: Paediatric Electrocardiography

Age related changes in the anatomy and physiology of infants and children produce normal ranges for electrocardiographic features that differ from adults and vary with age. Awareness of these differences is the key to correct interpretation of paediatric ECG.

ECG should be interpreted systematically

- Heart rate, Rhythm
- P wave axis, amplitude, duration
- PR interval
- QRS axis, amplitude, duration
- ST segment and T waves
- QT interval and QTc
  (QTc = measured QT interval / square root of R-R interval)

The ECG cycle



Normal values for Heart rate in children		
Age	Heart Rate (bpm)	
	Mean	Range
< 1 day	119	94 – 145
1 – 7 days	133	100 – 175
3 – 30 days	163	115 – 190
1 – 3 months	154	124 – 190
3 – 6 months	140	111 – 179
6 – 12 months	140	112 – 177
1 – 3 years	126	98 – 163
3 – 5 years	98	65 – 132
5 – 8 years	96	70 – 115
8 – 12 years	79	55 – 107
12 – 16 years	75	55 – 102

Normal values in Paediatric ECG				
Age	PR interval (ms)	QRS duration (ms)	R wave (S wave) amplitude (mm)	
			Lead V1	Lead V6
Birth	80 – 160	< 75	5 - 26 (1 - 23)	0 - 12 (0 - 10)
6 months	70 – 150	< 75	3 - 20 (1 - 17)	6 - 22 (0 - 10)
1 year	70 – 150	< 75	2 - 20 (1 - 20)	6 - 23 (0 - 7)
5 years	80 – 160	< 80	1 - 16 (2 - 22)	8 - 25 (0 - 5)
10 years	90 – 170	< 85	1 - 12 (3 - 25)	9 - 26 (0 - 4)

Age Group	ECG Characteristics
Premature infants (< 35 weeks gestation)	• Left & posterior QRS axis. • Relative LV dominant; smaller R in V1, taller R in V6.
Full term infant	• Right axis deviation (30° to 180°) RV dominant. • Tall R in V1, Deep S in V6, R/S ratio > 1 in V1. • T wave in V1 may be upright for 48 hours.
1 to 6 months	• Less right axis deviation (10° to 120°). • RV remains dominant. • Negative T waves across right praecordial leads.
6 months to 3 years	• QRS axis < 90°. • R wave dominant in V6. • R/S ratio ≤ 1 in V1.
3 to 8 years	• Adult QRS progression in praecordial leads. • LV dominant, Dominant S in V1, R in V6. • Q wave in V5-6 (amplitude < 5 mm).

Important normal variants

- T wave inversion of right praecordial leads (V1 – V3): normal findings from day 2 of life until late teens. An upright T wave in V1 before 8 years old is indicative of RVH.
- Q wave may be seen in leads I, aVL, V5 and V6 provided amplitude < 5 mm.
- RSR' pattern of right praecordial leads: normal in children provided QRS duration < 10 msec and R' amplitude < 15 mm (infants) or 10 mm (children.)
- Elevated J point: normal in some adolescents.

Criteria for Right Ventricular Hypertrophy

- R > 20 mm in V1 at all ages
- S > 14 mm (0 to 7 days); > 10mm (1 week - 6 mths); > 7mm (6 mths - 1 year); > 5mm (> 1 year) in V6.
- R/S ratio > 6.5 (0 - 3 mths); 4.0 (3 - 6 mths); 2.4 (6 mths - 3 years); 1.6 (3 to 5 years); 0.8 (6 to 15 years) in V1
- T wave upright in V4R or V1 after 72 hrs of life
- Presence of Q wave in V1

Criteria for Left Ventricular Hypertrophy

- S > 20 mm in V1
- R > 20mm in V6
- S (V1) + R (V6) > 40mm over 1 year of age; > 30mm if < 1year
- Q wave > 4 mm in V5-6
- T wave inversion in V5-6

Chapter 38: Congenital Heart Disease in the Newborn

Introduction

- Congenital heart disease (CHD) encompass a spectrum of structural abnormalities of the heart or intrathoracic vessels.
- Commonly presents in the newborn with central cyanosis, heart failure, sudden collapse or heart murmur.

Central Cyanosis

- Bluish discoloration of lips and mucous membranes.
- Caused by excess deoxygenated haemoglobin (> 5 Gm/dL), confirmed by pulse oxymetry (SpO_2 < 85%) or ABG.

Causes of Cyanosis in the Newborn
Cyanotic Heart Disease
Obstructed pulmonary flow
Pulmonary atresia, Critical pulmonary stenosis, Tetralogy of Fallot
Discordant ventriculo-arterial connection
Transposition of great arteries.
Common mixing
Single ventricle, Truncus arteriosus, Tricuspid atresia, Total anomalous pulmonary venous drainage
Primary Pulmonary Disorders
Parenchymal disease
Meconium aspiration syndrome, Respiratory distress syndrome, Congenital pneumonia
Extraparenchymal disease
Pneumothorax, Congenital diaphragmatic hernia
Persistent pulmonary hypertension of newborn
Primary
Secondary
Meconium aspiration, Perinatal asphyxia, Congenital diaphragmatic hernia
Severe polycythaemia
Methaemoglobinuria

Heart Failure

Clinical presentation may mimic pulmonary disease or sepsis:

- Tachypnoea
- Tachycardia
- Hepatomegaly
- Weak pulses

Causes of Heart Faliure in the Newborn
Structural Heart Lesions
Obstructive Left Heart lesions
Hypoplastic left heart syndrome, critical aortic stenosis, severe coarctation of aorta
Severe Valvular Regurgitation
Truncal arteriosus with truncal valve regurgitation
Large Left to Right Shunts
Patent ductus arteriosus, ventricular septal defects, truncus arteriosus, aortopulmonary collaterals
Obstructed Pulmonary Venous Drainage
Total anomalous pulmonary venous drainage
Myocardial Diseases
Cardiomyopathy
Infant of diabetic mother, familial, idiopathic
Ischaemic
Anomalous origin of left coronary artery from pulmonary artery, perinatal asphyxia
Myocarditis
Arrhythmia
Atrial flutter, SVT, congenital heart block
Extracardiac
Severe anaemia
Neonatal thyrotoxicosis
Fulminant sepsis

Sudden Collapse

Can be difficult to be distinguished from sepsis or metabolic disorders:

- Hypotension
- Extreme cyanosis
- Metabolic acidosis
- Oliguria

Challenges and Pitfalls

- Cyanosis is easily missed in the presence of anaemia.
- Difficulty to differentiate cyanotic heart disease from non-cardiac causes
- Indistinguishable clinical presentations between left heart obstructive lesions and severe sepsis or metabolic disorders.
- Possibility of congenital heart disease not considered in management of sick infant.

Congenital heart lesions that may present with sudden collapse
Duct-dependent systemic circulation
Coarctation of aorta, Critical aortic stenosis, Hypoplastic left heart syndrome, Interrupted aortic arch
Duct-dependent pulmonary circulation
Pulmonary atresia with intact ventricular septum, Tricuspid atresia with pulmonary atresia, Single ventricle with pulmonary atresia, Critical pulmonary stenosis
Transposition of great arteries without septal defect
Obstructed total anomalous pulmonary drainage

Clinical Approach to Infants with Congenital Heart Disease

History

- Antenatal scans (cardiac malformation, fetal arrhythmias, hydrops).
- Family history of congenital heart disease.
- Maternal illness: diabetes, rubella, teratogenic medications.
- Perinatal problems: prematurity, meconium aspiration, perinatal asphyxia.

Physical Examination

- Dysmorphism: Trisomy 21, 18, 13; Turner syndrome, DiGeorge syndrome.
- Central cyanosis.
- Differential cyanosis.
- Tachypnoea.
- Weak or unequal pulses.
- Heart murmur.
- Hepatomegaly.

Bedside Test: Pulse Oximetry

- Any reading < 95% or discrepancy > 3% between upper & lower limbs should alert further evaluation.

Investigations

- Chest X-ray
- Hyperoxia test:
  - Administer 100% oxygen via headbox at 15 L/min for 15 mins.
  - ABG taken from right radial artery.
  - Cyanotic heart diseases: pO_2 < 100 mmHg; rise in pO_2 is < 20 mmHg. (note: in severe lung diseases & PPHN, pO_2 can be < 100 mmHg).
- Echocardiography.

General principles of management

- Initial stabilization: secure airway, adequate ventilation, circulatory support
- Correct metabolic acidosis, electrolyte derangements, hypoglycaemia; prevent hypothermia.
- Empirical treatment with IV antibiotics.
- Early cardiology consultation.
- IV Prostaglandin E infusion if duct-dependent lesions suspected:
  - Starting dose: 10 – 40 ng/kg/min; maintenance: 2 – 10 ng/kg/min.
  - Adverse effects: apnoea, fever, hypotension.
- If unresponsive to IV prostaglandin E, consider:
  - Transposition of great arteries, obstructed total anomalous pulmonary. venous drainage.
  - Blocked IV line.
  - Non-cardiac diagnosis.
- Arrangement to transfer to regional cardiac center once stabilized.
- The cardiologist will decide on further management depending on the echocardiography findings.

Summary of The Clinical Approach to Cyanotic Newborns					
Cause	History, Signs	Chest X-ray	ABG	Hyperoxia test	Echocardiography
Cyanotic Heart Disease	No/mild Respiratory distress. Heart murmur.	Abnormal heart size and pulmonary vasculature	Low PCO_2	No rise in PO_2	Usually diagnostic
Primary Lung Disease	Respiratory distress	Abnormal lungs	Low PO_2 Hgh PCO_2	PO_2 >100mmHg	Normal
Persistent Pulmonary Hypertension	Suggestive history (MAS, asphyxia, sepsis)	Maybe abnormal (lungs)	Differential cyanosis	Inconclusive	Right to left shunt across PFO or PDA
Methemoglbinemia	Normal	Normal	Normal	PO_2 >100mmHg	Normal
MAS, meconium aspiration syndrome; PFO, patent foramen ovale; PDA, patent ductus arteriosus					

Specific Management Strategies For Some Common Lesions

LEFT TO RIGHT SHUNTS

Atrial septal defects (ASD)

Small defects:

- No treatment.

Large defects:

- Elective closure at 4-5 years age.

Ventricular septal defects (VSD)

Small defects:

- No treatment; high rate of spontaneous closure.
- SBE prophylaxis.
- Yearly follow up for aortic valve prolapse, regurgitation.
- Surgical closure indicated if prolapsed aortic valve.

Moderate defects:

- Anti-failure therapy if heart failure.
- Surgical closure if:
  - Heart failure not controlled by medical therapy.
  - Persistent cardiomegaly on chest X-ray.
  - Elevated pulmonary arterial pressure.
  - Aortic valve prolapse or regurgitation.
  - One episode of infective endocarditis.

Large defects:

- Early primary surgical closure.
- Pulmonary artery banding followed by VSD closure in multiple VSDs.

Persistent ductus arteriosus (PDA)

Small PDA:

- No treatment if there is no murmur
- If murmur present: elective closure as risk of endocarditis.

Moderate to large PDA:

- Anti-failure therapy if heart failure
- Timing, method of closure (surgical vs transcatheter) depends on symptom severity, size of PDA and body weight.

CYANOTIC HEART LESIONS

Tetralogy of Fallot (TOF)

- Most TOFs suitable for single stage surgical repair at 1 to 2 years age
- Indications for modified Blalock Taussig shunt:
  - Hypercyanotic spells or severe cyanosis < 6 months age when child is too young for total repair.
  - Small pulmonary arteries; to promote growth before definitive repair
  - Anomalous coronary artery crossing in front of right ventricular outflow tract - precludes transannular incision; repair with conduit required at later age.
- Following surgical repair, patients need life-long follow up for late right ventricular dysfunction; some may require pulmonary valve replacement.

Tetralogy of Fallot with pulmonary atresia

- IV prostaglandin E infusion is often required during early neonatal period
- Further management strategy depends on the anatomy of the pulmonary arteries and presence of aortopulmonary collaterals.

Transposition of the great arteries (TGA)

Simple TGA (intact ventricular septum)

- IV Prostaglandin E infusion promotes intercirculatory mixing at PDA.
- Early balloon atrial septostomy (BAS) if restrictive interatrial communication.
- Surgical repair of choice: arterial switch operation at 2 to 4 weeks age
- Left ventricular regression may occur if repair not performed within 4 weeks of life.

TGA with VSD:

- Does not usually require intervention during early neonatal period; may develop heart failure at 1 to 2 months age.
- Elective one-stage arterial switch operation + VSD closure < 3 months age.

TGA with VSD and PS:

- Blalock Taussig shunt during infancy followed by Rastelli repair at 4 to 6 years age.

Chapter 39: Hypercyanotic Spell

Introduction

Sudden severe episodes of intense cyanosis caused by reduction of pulmonary flow in patients with underlying Tetralogy of Fallot or other cyanotic heart lesions. This is due to spasm of the right ventricular outflow tract or reduction in systemic vascular resistance (e.g. hypovolaemia) with resulting increased in right to left shunt across the VSD.

Clinical Presentation

- Peak incidence age: 3 to 6 months.
- Often in the morning, can be precipitated by crying, feeding, defaecation.
- Severe cyanosis, hyperpnoea, metabolic acidosis.
- In severe cases, may lead to syncope, seizure, stroke or death.
- There is a reduced intensity of systolic murmur during the spell.

Management

- Treat this as a *medical emergency.*
- Knee-chest/squatting position:
  - Place the baby on the mother's shoulder with the knees tucked up underneath.
  - This provides a calming effect, reduces systemic venous return and increases systemic vascular resistance.
- Administer 100% oxygen
- Give IV/IM/SC morphine 0.1 – 0.2 mg/kg to reduce distress and hyperpnoea.

If the above measures fail:

- Give IV Propranolol 0.05 – 0.1 mg/kg slow bolus over 10 mins.
- Alternatively, IV Esmolol 0.5 mg/kg slow bolus over 1 min, followed by 0.05 mg/kg/min for 4 mins.
  - Can be given as continuous IV infusion at 0.01 – 0.02 mg/kg/min.
  - Esmolol is an ultra short acting beta blocker
- Volume expander (crystalloid or colloid) 20 ml/kg rapid IV push to increase preload.
- Give IV sodium bicarbonate 1 – 2 mEq/kg to correct metabolic acidosis.
- Heavy sedation, intubation and mechanical ventilation.

In resistant cases, consider

- IV Phenylephrine (0.01 – 0.02 mg/kg slow bolus) / Noradrenaline infusion (0.1 – 0.5 mcg/kg/min) to increase systemic vascular resistance and reduce right to left shunt.
- Emergency Blalock Taussig shunt.

Other notes:

- A single episode of hypercyanotic spell is an indication for early surgical referral (either total repair or Blalock Taussig shunt).
- Oral propranolol 0.2 – 1 mg/kg/dose 8 to 12 hourly should be started soon after stabilization while waiting for surgical intervention.

Chapter 40: Heart Failure

Definition

Defined as the inability to provide adequate cardiac output to meet the metabolic demand of the body.

Causes of heart failure

- Congenital structural heart lesions: more common during infancy.
- Primary myocardial, acquired valvular diseases: more likely in older children.

Causes of Heart Failure	
Congenital heart disease	Acquired valvular disease
Left to right shunt lesions	• Chronic rheumatic valvular diseases
• VSD, PDA, AVSD, ASD	• Post infective endocarditis
Obstructive left heart lesions	Myocardial disease
• Hypoplastic left heart syndrome,	*Primary cardiomyopathy*
• Coarctation of aorta, aortic stenosis	• Idiopathic, familial
Common mixing unrestricted pulmonary flow	*Secondary cardiomyopathy*
• Truncus arteriosus, TAPVD, tricuspid atresia	• Arrhythmia-induced: congenital heart block, atrial ectopic tachycardia
• TGA, single ventricle, pulmonary atresia with VSD,	• Infection: post viral myocarditis, Chagas disease
• Large aortopulmonary collateral	• Ischaemic: Kawasaki disease
Valvular regurgitation	• Myopathic: muscular dystrophy,
• AV valve regurgitation, Ebstein anomaly	• Pompe disease, mitochondrial dis.
• Semilunar valve regurgitation	• Metabolic: hypothyroidism
Myocardial ischaemia	• Drug-induced: anthracycline
• Anomalous origin of left coronary artery from pulmonary artery.	• Others: iron overload (thalassaemia)
	Acute myocarditis
	• Viral, rheumatic, Kawasaki disease

Clinical presentation

- Varies with age of presentation.
- *Symptoms* of heart failure in infancy:
  - Feeding difficulty: poor suck, prolonged time to feed, sweating during feed.
  - Recurrent chest infections.
  - Failure to thrive.

- *Signs* of heart failure in infancy:
  - Resting tachypnoea, subcostal recession.
  - Tachycardia, Poor peripheral pulses, poor peripheral perfusion.
  - Hyperactive praecordium, praecordial bulge.
  - Hepatomegaly.
  - Wheezing.
- Common signs of heart failure in adults, i.e. increased jugular venous pressure, leg oedema and basal lung crackles are ***not usually*** found in children.

Treatment

General measures

- Oxygen supplementation, propped up position
- Keep warm, gentle handling.
- Fluid restriction to ¾ normal maintenance if not dehydrated or in shock
- Optimize caloric intake; low threshold for nasogastric feeding; - consider overnight continuous infusion feeds.
- Correct anaemia, electrolyte imbalance, treat concomitant chest infections.

Antifailure medications

- Frusemide (loop diuretic)
  - Dose: 1 mg/kg/dose OD to QID, oral or IV
  - Continuous IV infusion at 0.1 – 0.5 mg/kg/hour if severe fluid overload
  - Use with potassium supplements (1 - 2 mmol/kg/day) or add potassium sparing diuretics.
- Spironolactone (potassium sparing diuretic, modest diuretic effect)
  - Dose: 1 mg/kg/dose BD
- Captopril
  - Angiotensin converting enzyme inhibitor, afterload reduction agent
  - Dose: 0.1 mg/kg/dose TDS, gradual increase up to 1 mg/kg/dose TDS
  - Monitor potassium level (risk of hyperkalaemia)
- Digoxin
  - Role controversial
  - Useful in heart failure with excessive tachycardia, supraventricular tachyarrhythmias.
- IV inotropic agents - i.e. Dopamine, Dobutamine, Adrenaline, Milrinone
  - Use in acute heart failure, cardiogenic shock, post-op low output syndrome.

Specific management

- Establishment of definitive aetiology is of crucial importance
- Specific treatment targeted to underlying aetiology. Examples:
  - Surgical/transcatheter treatment of congenital heart lesion.
  - Pacemaker implantation for heart block.
  - Control of blood pressure in post-infectious glomerulonephritis.
  - High dose aspirin ± steroid in acute rheumatic carditis.

Chapter 41: Acute Rheumatic Fever

Introduction

- An inflammatory disease of childhood resulting from untreated *Streptococcus pyogenes* (group A streptococcus) pharyngeal infections.
- Peak incidence 5 to 15 years; more common in females.

Diagnostic criteria for Acute Rheumatic Fever		
Major Criteria	Minor Criteria	Investigations
Carditis	Fever (Temp > 38 °C)	FBC: anaemia, leucocytosis
Polyarthritis, aseptic monoarthritis or polyarthralgia	ESR > 30 mm/h or CRP > 30 mg/L	Elevated ESR and CRP
		Throat swab, ASOT
		Blood culture
Chorea	Prolonged PR interval	CXR, ECG.
Erythema marginatum		Echocardiogram
Subcutaneous nodules		

Making the Diagnosis:

- Initial episode of ARF:
  2 major criteria or 1 major + 2 minor criteria,
  \+ *evidence of a preceding group A streptococcal infection*
- Recurrent attack of ARF: (known past ARF or RHD)
  2 major criteria or 1 major + 2 minor criteria or 3 minor criteria,
  \+ *evidence of a preceding group A streptococcal infection*

Note:

1. Evidence of carditis: cardiomegaly, cardiac failure, pericarditis, tachycardia out of proportion to fever, pathological or changing murmurs.

2. Abbrevations: ARF, Acute Rheumatic Fever; RHD, Rheumatic Heart Disease

Treatment

Aim to suppress inflammatory response so as to minimize cardiac damage, provide symptomatic relief and eradicate pharyngeal streptococcal infection

- Bed rest. Restrict activity until acute phase reactants return to normal.
- Anti-streptococcal therapy:
  - IV C. Penicillin 50 000U/kg/dose 6H
    or Oral Penicillin V 250 mg 6H (<30kg), 500 mg 6H (>30kg) for 10 days
  - Oral Erythromycin for 10 days if allergic to penicillin.
- Anti-inflammatory therapy
  - *mild / no carditis:*
    Oral Aspirin 80-100 mg/kg/day in 4 doses for 2-4 weeks, tapering over 4 weeks.
  - *pericarditis, or moderate to severe carditis:*
    Oral Prednisolone 2 mg/kg/day in 2 divided doses for 2 - 4 weeks, taper with addition of aspirin as above.

- Anti-failure medications
  - Diuretics, ACE inhibitors, digoxin (to be used with caution).

Important:
Consider early referral to a Paediatric cardiologist if heart failure persists or worsens during the acute phase despite aggressive medical therapy. Surgery may be indicated.

Secondary Prophylaxis of Rheumatic Fever

- IM Benzathine Penicillin 0.6 mega units (<30 kg)
  or 1.2 mega units (>30 kg) every 3 to 4 weeks.
- Oral Penicillin V 250 mg twice daily.
- Oral Erythromycin 250 mg twice daily if allergic to Penicillin.

Duration of prophylaxis

- Until age 21 years or 5 years after last attack of ARF whichever was longer.
- Lifelong for patients with carditis and valvular involvement.

Chapter 42: Infective Endocarditis

Introduction

Infective endocarditis is defined as infection of the endocardial surface of the heart which frequently involves the heart valves. It is associated with high mortality and severe complications. Early and accurate diagnosis is crucial to allow appropriate treatment to improve outcomes and reduce mortality.

Diagnosis

- A high index of suspicion is warranted in any patients with underlying risk factors who present with unexplained fever (90%), loss of appetite and weight loss.
- Heart murmurs are found in up to 85% of patients. Some may present with complications such as heart failure (up to 58%) and embolic events (25%).
- Young infants and immunocompromised patients may not have fever.
- Pre-existing risk factors:
  - Congenital heart disease; whether unrepaired or repaired
  - Prosthetic heart valves and intracardiac devices
  - Previous history of infective endocarditis
  - Native valvular heart diseases such as rheumatic heart disease
  - Presence of chronic intravenous access such as indwelling central venous catheters, chemoports and haemodialysis catheters
  - Immunocompromised patients
- The diagnosis of IE requires combination of clinical features, microbiological findings and identification of endocardial involvements and extracardiac complications by imaging tools.

Blood cultures

- Remains the cornerstone of diagnosis of IE
- At least 3 sets (to increase yield and reduce false positive rate by skin contaminants)
- There is no necessity to wait for spikes of fever (due to continuous nature of bacteraemia)
- Should be taken at 30 mins intervals between samples
- Should be obtained from peripheral veins and not from central venous catheter using aseptic technique
- Should be taken before commencement of antibiotics
- Each set should include 1 aerobic and 1 anaerobic bottle with minimal of 3 ml of blood

Echocardiography

- Transthoracic echocardiogram (TTE) should be performed as soon as possible when IE is suspected
- Findings suggestive of IE include vegetation, abscess, pseudoaneurysm, new dehiscence of prosthetic valve, fistula, valve leaflet perforation and aneurysm
- Sensitivity and specificity of TTE are strongly affected by patient's acoustic window and operator's experience

- If clinical suspicion of IE remains high despite an initial negative TTE, a repeat TTE or transoesophageal echocardiogram (TEE) is recommended within a week
- In children, TEE requires general anaesthesia and risk versus benefit must be carefully considered
- TEE is advisable in cases with prosthetic valves, prosthetic cardiac material and those with poor TTE acoustic window
- TTE is recommended at completion of antibiotic treatment to assess treatment response

Newer Imaging Modalities

- Cardiac CT: detection of intracardiac abscesses, pseudoaneurysms and degree of paravalvular extension, splenic abscesses and intracranial mycotic aneurysms
- Brain MRI: detection of ischaemic lesions, microbleeds and mycotic aneurysms
- Nuclear Imaging: supplementary roles in difficult cases such as prosthetic valve endocarditis

Modified Duke Criteria

These criteria can be used as a guide to diagnose IE with an overall sensitivity of 80%. It is not to replace good clinical judgement to treat each individual patients appropriately.

Definite IE	*Pathological Criteria* • Microorganisms demonstrated by culture or histology of a vegetation, a vegetation that has embolized or intracardiac abscess specimen OR • Pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis *Clinical Criteria* • 2 major criteria OR • 1 major criteria and 3 minor criteria OR • 5 minor criteria
Possible IE	• 1 major criteria and 1 minor criteria OR • 3 minor criteria
Rejected IE	• Firm alternate diagnosis OR • Resolution of symptoms suggesting IE with antibiotic therapy for ≤ 4 days OR • No pathological evidence of IE at surgery or autopsy, with antibiotic therapy ≤ 4 days OR • Does not meet criteria for possible IE as above

Clinical Crietria	
Major criteria	

Blood culture positive for IE	• Typical microorganisms consistent with IE from 2 separate blood cultures
	  • Viridans streptococci, Streptococcus gallolyticus/ bovis, HACEK* group, Staphylococcus aureus OR
	  • Community-acquired enterococci in the absence of a primary focus OR
	• Microorganisms consistent with IE from persistently positive blood cultures
	  • ≥ 2 positive blood cultures of blood samples drawn > 12h apart OR
	  • All of 3 or majority of ≥ 4 separate cultures of blood (with first and last samples drawn ≥ 1h apart)
	• Single positive blood culture for Coxiella burnetti or phase I IgG antibody titre > 1:800

Imaging positive for IE	• Echocardiogram positive for IE
	  • Vegetation
	  • Abscess, pseudoaneurysm, intracardiac fistula
	  • Valvular perforation or aneurysm
	  • New partial dehiscence of prosthetic valve
	• Abnormal activity around the site of prosthetic valve implantation detected by 18F-FDG PET/CT or radiola-belled leukocytes SPECT/CT
	• Definite paravalvular lesions by cardiac CT

Minor criteria	
• Predisposition: predisposing heart condition or IV drug use • Fever > 38°C • Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, Janeway's lesions • Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor • Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE	
* The HACEK group of bacteria (Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species) are a small, heterogeneous group of fastidious, gram-negative bacteria that frequently colonize the oropharynx	

MANAGEMENT

Antimicrobial Therapy

General principles:

- Use bactericidal instead of bacteriostatic agents
- Initial high dose parenteral route to achieve high bactericidal effects
- Adequate duration to ensure complete eradication (4 to 6 weeks)

Antibiotic Regimens for Initial Empirical Treatment

- *Community-acquired native valves or late prosthetic valves endocarditis*

  IV Ampicillin 200 – 300 mg/kg/day in 4 – 6 divided dose (max 12 g/day)
  +
  IV Gentamicin 1 mg/kg 8 hourly
  +
  IV Cloxacillin 200 mg/kg/day in 4 – 6 divided dose (max 12 g/day)

- *Community-acquired native valves or late prosthetic valves endocarditis (allergic to penicillin)*

  IV Vancomycin 40 mg/kg/day in 2 – 3 divided dose (max 2 g/day)
  +
  IV Gentamicin 1 mg/kg 8 hourly

- *Early prosthetic valve endocarditis*

  IV Vancomycin 40 mg/kg/day in 2 – 3 divided doses (max 2 g/day)
  +
  IV Gentamicin 1 mg/kg 8 hourly
  +
  Oral Rifampicin 20 mg/kg/day divided in 3 doses (max 900 mg/day)

- *Nosocomial and healthcare associated endocarditis*

  IV Vancomycin 40 mg/kg/day in 2 – 3 divided doses (max 2 g/day)
  +
  IV Gentamicin 1 mg/kg 8 hourly
  ±
  IV Cefepime 50 mg/kg 8 hourly (max 6 g/day)

- Once the causative microorganism is identified and sensitivity pattern obtained, the empirical regimen should be switched to definitive regimen

Antibiotic Regimens for Definitive Treatment of Infective Endocarditis

Penicillin-susceptible viridans streptococci, Streptococcus gallolyticus/bovis (MIC ≤ 0.125 µg/ml)

Antibiotics:

EITHER

- Penicillin G IV 200,000 – 300,000 U/kg/day in 4 – 6 divided doses (max 12 – 18 MegaU/day)
- Ampicillin IV 200 – 300 mg/kg/day in 4 – 6 divided doses (max 2 g/day)
- Ceftriaxone IV 100 mg/kd/day in 1 – 2 divided doses (max 4 g/day)

Duration: 4 weeks (native valve) 6 weeks (prosthetic valve)

If allergic to Penicillin:

- Vancomycin IV 40 mg/kg/day in 2 – 3 divided doses (max 2 g/day)

Duration: 4 weeks (native valve) 6 weeks (prosthetic valve)

Relatively resistant to Penicillin viridans streptococci, Streptococcus gallolyticus/bovis (MIC 0.125 – 2 µg/ml)

Antibiotics:

EITHER

- Penicillin G IV 200,000 – 300,000 U/kg/day in 4 – 6 divided doses (max 12 – 18 MegaU/day)
- Ceftriaxone IV 100 mg/kd/day in 1 – 2 divided doses (max 4 g/day)

Duration: 4 weeks (native valve) 6 weeks (prosthetic valve)

PLUS

- Gentamicin IV 1 mg/kg 8 hourly

Duration: 2 weeks (native valve) 6 weeks (prosthetic valve)

If allergic to Penicillin:

- Vancomycin IV 40 mg/kg/day in 2 – 3 divided doses (max 2 g/day)

Duration: 4 weeks (native valve) 6 weeks (prosthetic valve)

PLUS

- Gentamicin IV 1 mg/kg 8 hourly

Duration: 2 weeks (native valve) 6 weeks (prosthetic valve)

Methicillin-susceptible staphylococci (MSSA); native valve

Antibiotics:

- Cloxacillin IV 200 – 300 mg/kg/day in 4 – 6 divided doses (max 12 g/day)

Duration: 2 – 4 weeks (right-sided IE); 4 – 6 weeks (left sided IE)

If allergic but non-anaphylactic reactions to Penicillin:

- Cefazolin IV 100 mg/kg/day in 3 divided doses (max 2 g/day)

Duration: 4 -6 weeks

If anaphylactic reactions to Penicillin

- Vancomycin IV 40 mg/kg/day in 2 – 3 divided doses (max 2 g/day)

Duration: 4 -6 weeks

Antibiotic Regimens for Definitive Treatment of Infective Endocarditis

Methicillin-resistant staphylococci (MRSA); native valve

Antibiotics:

EITHER

- Vancomycin G IV 40 mg/kg/day in 2 – 3 divided doses (max 2 g/day)
- Daptomycin IV 10 mg/kg daily

Duration: 4 - 6 weeks

Note: Daptomycin is superior to Vancomycin for MIC > 1 mg/L

PLUS

- Gentamicin IV 1 mg/kg 8 hourly

Duration: 2 weeks (native valve) 6 weeks (prosthetic valve)

Methicillin-susceptible staphylococci (MSSA); prosthetic valve

Antibiotics:

- Cloxacillin IV 200 – 300 mg/kg/day in 4 – 6 divided doses (max 12 g/day)

Duration: 4 - 6 weeks

PLUS

Rifampicin PO 20 mg/kg/day in 3 divided doses (max 900 mg/day)

Duration: 4 - 6 weeks

PLUS

Gentamicin IV 1 mg/kg 8 hourly

Duration: 2 weeks

Note:

- Use Cefazolin if non-anaphylactic reactions to Penicillin
- Use Vancomycin if anaphylactic reactions to Penicillin
- Start Rifampicin 3 – 5 days after Cloxacillin

Methicillin-resistant staphylococci (MRSA); prosthetic valve

Antibiotics:

- Vancomycin IV 60 mg/kg/day in 2 – 3 divided doses (max 2 g/day)

PLUS

Rifampicin PO 20 mg/kg/day in 3 divided doses (max 900 mg/day)

PLUS

Gentamicin IV 1 mg/kg 8 hourly

Duration: ≥ 6 weeks

Note:

- Start Rifampicin 3 – 5 days after Vancomycin

Antibiotic Regimens for Definitive Treatment of Infective Endocarditis

Enterococcus spp

Antibiotics:

- Ampicillin IV 300 mg/kg/day in 4 – 6 divided doses (max 2 g/day)

Duration: 4 - 6 weeks

PLUS

Gentamicin IV 1 mg/kg 8 hourly

Duration: 2 - 6 weeks

OR

Ceftriaxone IV 100 mg/kg/day in 1 – 2 divided doses (max 4 g/day)

Duration: 6 weeks

Note: 6 weeks duration is recommended for patients

- Symptoms > 3 months
- Prosthetic valve

HACEK

Antibiotics:

Ceftriaxone IV 100 mg/kg/day in 1 – 2 divided doses (max 4 g/day)

OR

Ampicillin/Sulbactam IV 200 – 300 mg/kg/day ampicillin dose in 4 – 6 divided doses

Duration: 4 weeks (native valve), 6 weeks (prosthetic valve)

Candida spp

Antibiotics:

Amphotericin B IV 1 mg/kg daily

±

Flucytosine PO 100 – 150 mg/kg in 4 divided doses

Duration: At least 6 weeks after surgery

Note:

- Valve replacement is mandatory
- Step down therapy with oral Fluconazole 6 – 12 mg/kg daily for susceptible organism in stable patient after blood clearance of *Candida*

SURGICAL INTERVENTIONS

Surgical intervention is indicated in the following cases:

- Heart failure: severe valvular regurgitation, obstruction or fistula causing refractory pulmonary oedema, cardiogenic shock or severe heart failure symptoms.
- Uncontrolled infection: infection caused by fungi, local extension of infection (abscess, pseudoaneurysm, fistula, enlarging vegetation), persistent positive blood cultures despite appropriate antibiotic therapy and prosthetic valve endocarditis caused by staphylococci or non-HACEK gram-negative bacteria.
- Prevention of embolism: Left-sided vegetation > 10 mm after 1 or more embolic episode, very large vegetation > 30 mm.

Antimicrobial Prophylaxis for Infective Endocarditis

Cardiac conditions with increased risk of infective endocarditis for which antibiotic prophylaxis is indicated:

- Prosthetic cardiac valves, including transcatheter valve and those with prosthetic material used for cardiac valve repair
- Native valvular heart diseases such as rheumatic heart disease
- Previous episode of infective endocarditis
- Congenital heart diseases
  - Any type of unrepaired cyanotic CHD, including those with palliative shunts and conduits
  - During the first 6 months following surgical or transcatheter treatment of CHD with prosthetic material or devices
  - Repaired CHD with residual shunt or valvular regurgitation adjacent to site of a prosthetic material or device (which inhibit endothelialization)

Although antibiotic prophylaxis is not routinely recommended for patients with other cardiac conditions not listed above, they should be advised of the importance of dental and cutaneous hygiene. General preventive measures include:

- At least once a year dental follow up
- Prompt disinfection of any wounds
- Appropriate antibiotic therapy for any focus of bacterial infection
- Discourage piercing and tattooing
- Limit the use of infusion catheters and invasive procedures whenever possible. Strict adherence of care bundles for central and peripheral cannulae

Procedures which require IE prophylaxis

- Under most circumstances, the pre-procedural antibiotic prophylaxis as per routine surgical practice is adequate as IE prophylaxis.
- If pre-procedural antibiotic is not routinely given, the following recommendations should be used:

Prophylaxis indicated	Prophylaxis not indicated
Dental procedures	
Any procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa. Examples • Extractions • Periodontal procedures, subgingival scaling, root planning • Replanting avulsed teeth or implant placement	• Local anaesthetic injections in non-infected tissues • Treatment of superficial caries • Dental X-rays • Following shedding of deciduous teeth • Orthodontic bracket placement and adjustment of fixed appliances • Removal of sutures • Supragingival plague removal
Respiratory tract procedures	
• Invasive respiratory tract procedures which involve incision or biopsy of respiratory mucosa • Drainage of abscess	• Endotracheal intubation • Flexible bronchoscopy without biopsy
Gastrointestinal and Genitourinary procedures	
Only for those with established infection	• Transoesophageal echocardiography • Gastroscopy, colonoscopy • Cystoscopy • Vaginal or caesarean delivery • Intrauterine contraception device implantation
Skin and soft tissue procedures	
Only for those with established infection	

Recommended antibiotic for IE prophylaxis	
Situation	Antibiotic
No history of allergic to penicillin/ ampicillin	Amoxicillin or Ampicillin 50 mg/kg orally or IV
Allergic to penicillin/ampicillin	Clindamycin 20 mg/kg orally or IV

- A single dose of antibiotic recommended above should be given 30 – 60 minutes before the procedure.
  Second dose is not required after the procedure.

Chapter 43: Kawasaki Disease

Introduction

- A systemic febrile condition affecting children usually < 5 years old.
- Aetiology remains unknown, possible bacterial toxins or viral agents with genetic predisposition.
- Also known as mucocutaneous lymph node syndrome.

Diagnostic Criteria for Kawasaki Disease
Fever lasting at least 5 days.
At least 4 out of 5 of the following: • Bilateral non-purulent conjunctivitis. • Mucosal changes of the oropharynx (injected pharynx, red lips, dry fissured lips, strawberry tongue). • Changes in extremities (oedema and/or erythema of the hands or feet, desquamation, beginning periungually). • Rash (usually truncal), polymorphous but non vesicular. • Cervical lymphadenopathy.
Illness not explained by other disease process.

Clinical Pearls

Diagnosis of Classical KD is based on the clinical features above.
Other helpful signs in making the diagnosis:

- Irritability, altered mental state, aseptic meningitis
- Erythema or induration at the BCG site
- Perianal excoriation
- Transient arthritis
- Diarrhoea, vomiting, abdominal pain
- Hepatosplenomegaly
- Hydrops of gallbladder
- Sterile pyuria

Investigations

- Full blood count - anaemia, leucocytosis, thrombocytosis.
- ESR and CRP are usually elevated.
- Serum albumin < 3g / dl; Raised alanine aminotransaminase
- Urine > 10 wbc / hpf
- Chest X-ray, ECG
- Echocardiogram in the acute phase; Repeat at 6-8 wks/earlier if indicated.

Note:

- Most important complication is coronary vasculitis, usually within 2 weeks of illness, affecting up to 25% of untreated children.
- Usually asymptomatic, it may manifest as myocardial ischaemia, infarction, pericarditis, myocarditis, endocarditis, heart failure or arrhythmia.

Incomplete Kawasaki Disease

Incomplete KD should be considered in any infant/child with prolonged unexplained fever, fewer than 4 of the principal clinical features, and compatible laboratory or echocardiographic findings.
Higher risk of coronary artery dilatation or aneurysm occurring.

Echocardiography is indicated in patients who have prolonged fever with:

- two other criteria
- subsequent unexplained periungual desquamation
- two criteria + thrombocytosis
- rash without any other explanation

Atypical Kawasaki Disease

For patients who have atypical presentation, such as renal impairment, that generally is not seen in Kawasaki Disease.

Treatment

Primary treatment

- IV Immunoglobulins 2 Gm/kg infusion over 10 - 12 hours.
  Therapy < 10 days of onset effective in preventing coronary vascular damage.
- Oral aspirin (anti-inflammatory dose) 30-50mg/kg/day in 3 divided doses till day 14 of illness or until patient is afebrile for 2-3 days.

Maintainence:

- Oral Aspirin 3-5 mg/kg daily (anti-platelet dose) for 6 - 8 weeks or until ESR and platelet count normalise.
- If coronary aneurysm present, then continue aspirin until resolves.

Kawasaki Disease not responding to Primary Treatment
Defined as persistent or recrudescent fever ≥ 36hrs after completion of initial dose of IV Immunoglobulins.

Treatment

- Repeat IV Immunoglobulins 2 Gm/kg infusion over 10 - 12 hours

Vaccinations

- The use of Immunoglobulins may impair efficacy of live-attenuated virus vaccines. Delay these vaccinations for at least 11 months.

Prognosis

- Complete recovery in children without coronary artery involvement.
- Most (80%) 3-5 mm aneursyms resolve; 30% of 5-8 mm aneurysms resolve.
- Prognosis worst for aneurysms > 8 mm in diameter.
- Mortality in 1 - 2 %, usually from cardiac complications within 1 - 2 months of onset.

Risk stratification and long term follow up after Kawasaki Disease				
Risk Level	**Treatment**	**Physical Activity**	**Follow up**	**Invasive Testing**
Level I No coronary artery changes	None beyond 6-8 weeks	No restrictions beyond 6-8 weeks	Cardiovascular risk assessment, counselling at 5yr intervals	None
Level II Transient coronary artery ectasia; none after 6-8 wks	None beyond 6-8 weeks	No restrictions beyond 6-8 weeks	Cardiovascular risk assessment, counselling at 3 - 5yr intervals	None
Level III One small-medium coronary artery aneurysm, major coronary artery.	Low dose aspirin until aneurysm regression documented	Age <11 yr old: No restriction beyond 6-8 weeks . Avoid contact sports if on aspirin	Annual echocardiogram and ECG, and cardiovascular risk assessment counselling	Angiography if non-invasive test suggests ischemia
Level IV > 1 large or giant coronary artery aneurysm, or multiple or complex aneurysms in same coronary artery, without destruction.	Long term aspirin and warfarin (target INR 2.0-2.5) or LMWH in giant aneurysms	Avoid contact sports	Biannual echocardiogram and ECG; Annual stress test	Angiography at 6-12 mo or sooner if indicated; Repeated study if non-invasive test, clinical or laboratory findings suggest ischemia
Level V Coronary artery obstruction.	Long term aspirin; Warfarin or LMWH if giant aneurysm persists. Also consider beta-blockers	Avoid contact sports	Biannual echocardiogram and ECG; Annual stress test	Angiography to address therapeutic options
LMWH, low molecular weight heparin				

Chapter 44: Viral Myocarditis

Introduction

- Defined as inflammation of the myocardium with myocellular necrosis.
- Viruses are found to be most important cause of acute myocarditis. Other causes include Mycoplasma, typhoid fever, diphtheria toxins etc.

Clinical presentation

- Vary from asymptomatic ECG abnormalities to acute cardiovascular collapse, even sudden death.
- There may be prodromal symptoms of viremia, including fever, myalgia, coryzal symptoms or gastroenteritis.
- The diagnosis is made clinically, with a high index of suspicion, with the following presentation that cannot be explained in a healthy child:
  - Tachycardia, Respiratory distress, Other signs of heart failure, Arrhythmia.

Useful Investigations for Myocarditis
Electrocardiogram (ECG)
• Sinus tachycardia, Non-specific ST segment , Pathological Q wave, low QRS voltages (<5mm in any precordial lead), T wave inversion.
• Arrhythmia
• Heart block, ventricular ectopics
Chest x-ray
• Cardiomegaly (normal heart size doesn't exclude myocarditis)
• Pleural effusion
Echocardiography *Findings often varied and non-specific, although rarely entirely normal*
• Global left ventricular dilatation and Hypocontractility
• Pericardial effusion
• Functional mitral regurgitation
Need to exclude other structural abnormalities, especially coronary artery anomalies.
Cardiac biomarkers
Troponin T , Troponin I, Creatinine kinase (CK) and CK-MB
Microbiological studies, including polymerase chain reaction (PCR)
Enterovirus 71, coxsackie B virus, adenovirus, parvovirus B19, cytomegalovirus, echovirus, Mycoplasma, Salmonella typhi
Contrast enhanced MRI
Myocardial oedema, focal enhancement, regional wall motion abnormalities.
Endomyocardial biopsy

Fulminant myocarditis

- Children with fulminant myocarditis presented with heart failure with cardiogenic shock requiring inotropic or mechanical circulatory support.
- They may have history of fever, distinct onset of heart failure symptoms within a 1- to 2-day period, and a history consistent with viral illness within the 2 weeks before hospitalization.
- Mortality in fulminant myocarditis is high. Fulminant myocarditis may benefit from early mechanical ventilation, prompt and aggressive pharmacological treatment.

Management

- Depends on the severity of the illness. Patients with heart failure require intensive monitoring and haemodynamic support.
- Treatment of heart failure: see **Chapter on Heart Failure.**
- Consider early respiratory support, mechanical ventilation in severe cases.

Specific treatment

- Treatment with IV immunoglobulins and immunosuppressive drugs have been studied but the effectiveness remains controversial and routine treatment with these agents cannot be recommended at this moment.
- However only in *Fulminant myocarditis*, immunoglobulin therapy has been suggested to correlate with a favourable outcome, even though it is yet to be supported with meta analysis studes in children.
  Suggested dose is 1g/kg per day over 10 hours infusion for 2 days.

Prognosis

- One third of patients recover.
- One third improve clinically with residual myocardial dysfunction.
- The other third does poorly and develops chronic heart failure, which may cause mortality or require heart transplantation.

BRADYARRHYTHMIA

Sinus node dysfunction

- Criteria for sinus bradycardia (Table below):

ECG criteria	
Age Group	Heart Rate
Infants to < 3 years	<100 bpm
Children 3 – 9 years	< 60 bpm
Children 9 – 16 years	< 50 bpm
Adolescents > 16 years	< 40 bpm
24 hours Ambulatory ECG criteria	
Age Group	Heart Rate
Infants to 1 year of age	< 60 bpm sleeping, < 80 bpm awake
Children 1 – 6 years	< 60 bpm
Children 7 – 11 years	< 45 bpm
Adolescents, young adults	< 40 bpm
Highly trained athletes	< 30 bpm

Systemic causes of sinus bradycardia:

- Hypoxia
- Sepsis
- Acidosis
- Intracranial lesions
- Hypothyroidism
- Anorexia nervosa
- Electrolytes abnormalities i.e. hypokalaemia, hypocalcaemia, hypomagnesaemia

Causes of sinus node dysfunction

- Right atrial dilatation due to volume loading
- Cardiomyopathies
- Inflammatory conditions: myocarditis, pericarditis, rheumatic fever
- Post atrial surgery: Mustard, Senning, Fontan, ASD closure, cannulation for cardiopulmonary bypass

Atrioventricular block

Classification

- 1st degree - prolonged PR interval
- 2nd degree
  - Mobitz type 1 (Wenckebach): progressive PR prolongation before dropped AV conduction.
  - Mobitz type 2: abrupt failure of AV conduction without prior PR prolongation.
  - High grade – 3:1 or more AV conduction.
- 3rd degree (complete heart block): AV dissociation with no atrial im pulses conducted to ventricles.

Note: 2nd degree (Type 2 and above) and 3rd degree heart block are *always* pathological

Aetiology

- Congenital – in association with positive maternal antibody (anti-Ro and anti-La); mother frequently asymptomatic
- Congenital heart diseases: atrioventricular septal defect (AVSD), congenital corrected transposition of great arteries (L-TGA), left atrial isomerism
- Congenital long QT syndrome
- Surgical trauma: especially in VSD closure, TOF repair, AVSD repair, Konno procedure, LV myomectomy, radiofrequency catheter ablation
- Myopathy: muscular dystrophies, myotonic dystrophy, Kearns-Sayre syndrome.
- Infection: diphtheria, rheumatic fever, endocarditis, viral myocarditis

Acute Management: Symptomatic Bradycardia with Haemodynamic Instability

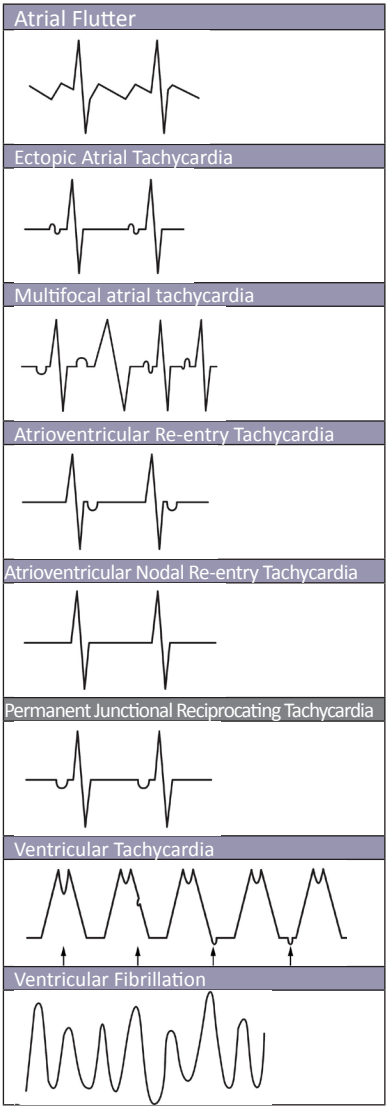
- Treat the underlying systemic causes of bradycardia
- Drugs:
  - IV Atropine
  - IV Isoprenaline infusion
  - IV Adrenaline infusion
- Transcutaneous pacing if available.
- Patients who are not responding to initial acute management should be referred to cardiologist for further management.
- Emergency transvenous pacing or permanent pacing may be required.

Classification

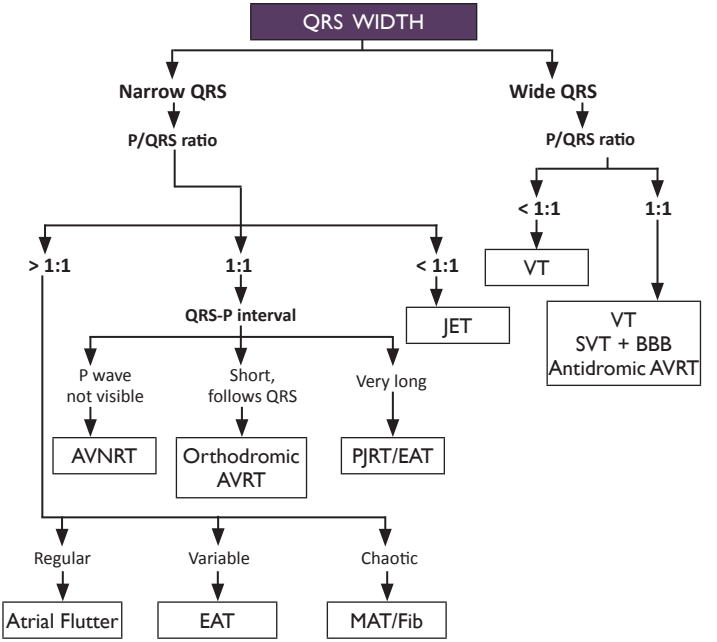
- Atrial tachycardia: AF, EAT, MAT
- Conduction system tachycardia or supraventricular tachycardia: AVRT, AVNRT, PJRT
- Ventricular tachycardia: VT, VF

Description

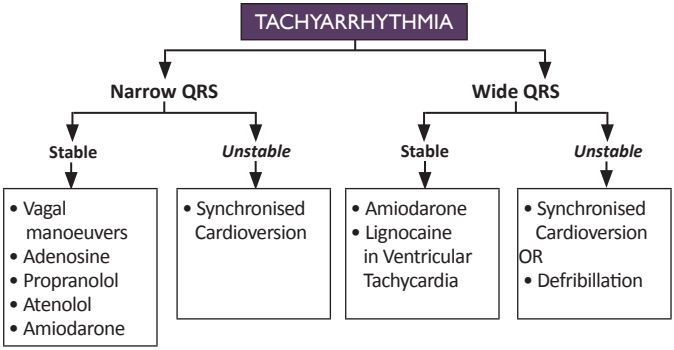
- *Atrial flutter (AF)*
  - Saw tooth flutter waves
  - Variable AV conduction
- *Ectopic Atrial Tachycardia (EAT)*
  - Abnormal P wave axis.
  - P wave precedes QRS.
  - Variable rate.
  - "Warm up" and "cool down" phenomenon.
- *Multifocal Atrial Tachycardia (MAT)*
  - Irregularly irregular
  - Multiple different P wave morphologies, bizarre, chaotic.
  - No two RR intervals the same
- *Atrioventricular Re-entry Tachycardia (AVRT)*
  - P wave follows QRS.
- *Atrioventricular Nodal Re-entry Tachycardia (AVNRT)*
  - P wave not visible, superimposed on QRS.
- *Permanent Junctional Reciprocating Tachycardia (PJRT)*
  - Inverted P waves in II, III, aVF appear to precede QRS complex.
  - Long RP interval.
- *Ventricular tachycardia (VT)*
  - Wide QRS complex.
  - P wave may be dissociated from the QRS complex.
- Ventricular fibrillation (VF)
  - chaotic, irregular rhythm.



ALGORITHM FOR IDENTIFYING TACHYARRHYTHMIA



Abbrevations. VT, ventricular tachycardia; JET, junctional ectopic tachycardia; SVT, supraventricular tachycardia; BBB, bundle branch block; Fib, fibrillation. AVRT, atrioventricular re-entry tachycardia; AVNRT, atrioventricular nodal re-entry tachycardia; PJRT, permanent junctional reciprocating tachycardia; EAT, ectopic atrial tachycardia; MAT, multifocal atrical tachycardia;



Narrow QRS complex tachycardia

Haemodynamically stable

- Vagal manoeuvers:
  - Icepack/iced water for infants: apply to face for a max of 30 seconds .
  - Valsalva manoeuvers if child is old enough (blow into a pinched straw).
- IV Adenosine: 0.1mg/kg (max 6mg) rapid push. Increase by 0.1mg/kg every 2 mins until tachycardia terminated or up to a maximum of 0.5mg/kg (maximum: 18 mg).

NB: to record and print the ECG during administration the IV adenosine

- IV Propranolol 0.02mg/kg test dose, then 0.1mg/kg over 10 minutes.
- IV Amiodarone: 25mcg/kg/min for 4 hours then 5 -15mcg/kg/min until conversion.

Haemodynamically unstable

- Synchronized DC conversion at 0.5 to 1 joule/kg.

Wide QRS complex tachycardia

Haemodynamically stable

- IV Amiodarone (same as above).
- IV Procainamide.
- IV Lignocaine.

Haemodynamically unstable

- Synchronized cardioversion at 0.5 to 1.0 joule/kg.
- In pulseless patients, defibrillate at 2 to 4 joules/kg.

Pitfalls in management

- Consult a cardiologist if these acute measures fail to revert the tachycardia.
- In Wolff-Parkinson-White syndrome, digoxin is contraindicated because paroxysms of atrial flutter or fibrillation can be conducted directly into the ventricle.
- Adenosine unmasks the atrial flutter by causing AV block and revealing more atrial beats per QRS complex.
- In wide QRS complex tachycardia with 1:1 ventriculoatrial conduction, it is reasonable to see if adenosine will cause cardioversion, thereby making a diagnosis of a conduction system dependent SVT.
- A follow up plan should be made in consultation with cardiologist.

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MANAGEMENT OF CONVULSIVE STATUS EPILEPTICUS

Child with SEIZURE

Seizure > 5 mins
Impending Status epilepticus

At Home, In Ambulance

PR Diazepam 0.2- 0.5 mg/kg (Max 10mg)
0.5mg/kg (2-5yrs); 0.3mg/kg (6-11yrs) 0.2mg/kg (12yrs +)
or
Buccal Midazolam 0.2-0.5mg/kg (Max 10 mg)

Seizure 5-30 mins
Established Status epilepticus

In Hospital

Obtain IV access
IV Diazepam 0.2mg/kg slow bolus (at 2 mg/min; maximum 10mg)

Seizures continue > 5 mins after Diazepam

IV Phenytoin 20 mg/kg
(Max Loading dose 1.25 Gm)
Dilute in 0.9% saline;
Max. concentration at 10 mg/ml;
Infuse over 20-30 mins,
with cardiac monitoring.

Ensure
- Ventilation
- Adequate Perfusion (ABC's)
- **Bedside Blood Sugar**
- If on maintenance Phenytoin, then give IV Phenobarbitone
- Monitor blood sugar, electrolytes, blood counts, liver function, blood gases.
- Consider blood culture, toxicology, neuroimaging, antiepileptic drug levels.
- If <2 yrs old, consider IV Pyridoxine 100 mg.

Early Refractory Status epilepticus

CONSULT PAEDIATRICIAN !
Consider One of the following:

Seizures continue > 10 mins after Phenytoin

IV Midazolam 0.2 mg/kg bolus (at 2 mg/min; Max 10 mg), then infusion 3-5 mcg/kg/min up to a max of 15 mcg/kg/min)

IV Phenobarbitone 20 mg/kg
(Max Loading dose 1 Gm)
Infusion at 25- 50 mg/min),

IV Levetiracetam 40 mg/kg infused over 10 minutes, then 20 mg/kg 12 hourly

IV Sodium Valproate 20 mg/kg (Max Loading 1.25 Gm, given over 1-5 mins, at 20-50 mg/min), then infusion 1- 5 mg/kg/hour for 6 - 12 hours)

- Monitor BP, respiration
- Start inotropic support, esp. if given Midazolam or Phenobarbitone
- Arrange for ICU.
- Secure airway, prepare to use mechanical ventilation.
- Titrate Phenobarbitone to achieve burst-suppression pattern on EEG.
- Avoid Sodium Valproate in metabolic encephalopathy.

Seizure >60 mins
Established Refractory Status epilepticus

Discuss with Paediatric Neurologist and Intensivist about inducing coma

Definition (ILAE 2015)

- Status epilepticus (SE) is a condition resulting either from
  - The failure of the mechanisms responsible for seizure termination, or
  - The initiation of mechanisms which lead to abnormally prolonged seizures.
- Types of SE (simplified from ILAE 2015)
  - Convulsive SE (seizures with prominent motor symptoms)
  - Non-convulsive SE (seizures on EEG only)
  - Focal motor SE
- Treatment for convulsive SE should be initiated when there is
  - Continuous seizure or
  - Two or more discrete seizures lasting >5 min, between which there is incomplete recovery (see Algorithm).
- Timing and treatment of NCSE and focal motor SE may be more variable (consult neurologist).

DOs

- Optimize vital functions throughout control of Status Epilepticus.
- Consider intubation early if airway/gas exchange compromised, elevated ICP suspected or if seizures persist >30 minutes.
- Identify and treat underlying cause (commonly: infectious and autoimmune encephalitides, traumatic/ hypoxic injuries, metabolic strokes, specific epilepsy syndromes and AED withdrawal in patients with epilepsy).
- Give adequate loading doses followed by maintenance, drug levels for phenobarbitone and phenytoin are useful to monitor and guide treatment.
- If using multiple drugs, use those with different mechanisms of action and avoid phenytoin and phenobarbitone combination if possible.
- Consider therapeutic hypothermia early in cases of refractory SE.

DON'Ts

- Avoid excessive time lag between doses/steps of treatment.
- Be careful with drugs that may exacerbate certain forms of seizures (e.g. benzodiazepines in tonic SE, carbamazepine in NCSE, valproate/ phenobarbitone in mitochondrial disease).
- Avoid propofol in patients on ketogenic diet and those needing steroids/ catecholamines (risk of propofol infusion syndrome).
- Do not treat ALL abnormal movements and episodes of stiffening as seizures. Movement disorder and dystonia from paroxysmal autonomic instability are common comorbid conditions.
  Hence, video EEG monitoring +/- neurological consult may be required.

Chapter 47: Epilepsy

Definition

- Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition.
- An epileptic seizure is the transient occurrence of clinical manifestation of abnormal excessive or synchronous neuronal activity in the brain.
- An epileptic syndrome is an epileptic disorder characterized by a cluster of signs and symptoms. Syndromes are classified on age of onset, seizure type(s), clinical and developmental features, EEG abnormalities and MRI brain findings. It has therapeutic and prognostic implications.

Operational (Practical) Clinical Definition of Epilepsy

(any of the following conditions):-

- At least two unprovoked (or reflex) seizures occurring >24 h apart.
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
- Diagnosis of an epilepsy syndrome.

Imitators of epilepsy: Paroxysmal non-epileptic events

- The first important step in the management of childhood epilepsy is to differentiate epileptic seizures from paroxysmal non-epileptic events.

Paroxysmal non-epileptic events (seizure mimics)	
Neonates • Apnea • Jitteriness • Benign neonatal sleep myoclonus • Hyperekplexia *Infants* • Breath-holding spells • Benign myoclonus of infancy • Shuddering attacks • Sandifer syndrome (Severe gastro-oesophageal reflux disease) • Benign paroxysmal torticollis of infancy • Abnormal eye movements (e.g. opsoclonus-myoclonus) • Rhythmic movement disorder (e.g. head banging)	*Children* • Breath-holding spells • Vasovagal / cardiac syncope • Migraine • Benign paroxysmal vertigo • Tic disorders and stereotypies • Rhythmic movement disorder • Parasomnias *Adolescents and young adults* • Vasovagal / cardiac syncope • Narcolepsy • Hypnic jerks (sleep starts) • Periodic limb movements of sleep • Paroxysmal dyskinesia • Hemifacial spasm • Psychogenic non-epileptic seizures

APPROACH TO A CHILD WITH A FIRST SEIZURE

Definition

One or multiple unprovoked afebrile seizures within 24 hours with recovery of consciousness between seizures.

Notes:

- 25-50% of first unprovoked seizures in children will recur.
- The child who is neurologically normal, with no history of neurologic illness, and no evident acute cause for the seizure has an approximately 25% risk of a recurrent seizure in the next year, and a nearly 50% risk of seizure over the next 10 to 15 years.
- 70-80% of second seizure will recur.
- Clinical factors associated with an increased risk of recurrent seizures are:-
  - Prior neurologic insult
  - Significant MRI findings
  - Abnormal EEG
- Detailed history to determine if event is a seizure or a paroxysmal non- epileptic event as 30% of patients referred as epilepsy do not have seizures.
- A thorough clinical examination is important to look for any possible underlying aetiology.
- There is a need to exclude acute provoking factors.
- Distinguish between provoked seizures secondary to acute systemic, metabolic or toxic cerebral insult and epilepsy.
- Treating underlying cause of provoked seizures will usually resolve the seizures and long term anti-epileptic therapy is not required.

What Investigations Need To Be Done?

- Routine investigations such as FBC, BUSE, Ca, Mg, RBS if
  - Child unwell (vomiting, diarrhoea etc).
  - Child not 'alert', lethargic or failure to return to baseline alertness.
- Lumbar puncture indicated if there is suspicion of brain infection.
- Toxicology screening considered if there is suspicion of drug exposure.
- EEG is recommended after all first afebrile unprovoked seizures.
  - EEG helps classify seizure type, epilepsy syndrome and predict recurrence.
- Neuroimaging (MRI preferred) indicated for:
  - Persisting postictal focal deficit (Todd's paresis).
  - Condition of child not returned to baseline within several hours after the seizure.

Is Treatment Required?

- Treatment with antiepileptic drug is NOT indicated in all patients with a first afebrile seizure as it does not prevent development of epilepsy or influence long term remission.

APPROACH TO A CHILD WITH EPILEPSY

- The diagnosis of epilepsy is mainly clinical.
- Detailed history of the seizures; i.e. the setting in which the seizure occurs, child's behaviour preceding, during and after the event is critical
- Video (via mobile phone camera) of the actual event is very helpful.
- The antenatal, birth, past medical history, developmental milestones and family history should be recorded meticulously.
- Look for dysmorphism, neurocutaneous signs; do thorough CNS and developmental examination.
- Perform general and systemic examinations to look for clues of underlying aetiology.

Investigations

Are recommended when a second afebrile seizure occurs:

- Full blood count, biochemical investigations such as electrolytes, calcium, magnesium, glucose, liver and renal function tests to exclude metabolic cause and before starting anti-epileptic drug therapy.
- Metabolic and genetic studies in clinically indicated cases with epilepsy, developmental delay where aetiology is not found from history and physical examination.

EEG

- is important to support the clinical diagnosis of epileptic seizures, classify the seizure type and epileptic syndrome, helps in selection of anti-epileptic drug and prognosis.
- EEG during sleep increases yield of abnormalities and is important for those patients with seizures predominantly during sleep.
- A 'normal' EEG does not exclude epilepsy as it is a clinical diagnosis and the yield of abnormalities from a single EEG recording is low.

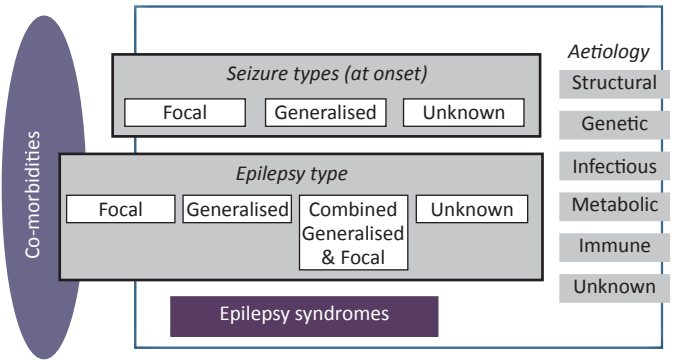
Neuroimaging

- CT scan is indicated only for seizures in emergency setting during acute illness.
- MRI is indicated in:
  - Epilepsy occurring in the first year of life, except febrile seizures.
  - Focal epilepsy except childhood epilepsy with centrotemporal spikes.
  - Developmental delay or regression.
  - Difficult to control / refractory epilepsy.
- MRI is not indicated in:
  - Childhood epilepsy with centrotemporal spikes (previously called Benign Rolandic epilepsy).
  - Idiopathic generalized epilepsies (e.g. Childhood absence epilepsy, Juvenile absence epilepsy, Juvenile myoclonic epilepsy)

  However, MRI should be considered in the above if there are any atypical features or if the seizures are difficult to be controlled.

ILAE* Classification of Seizure Types (expanded version)		
Focal Onset	**Generalised Onset**	**Unknown Onset**
Aware or Impaired Awareness *Motor Onset* automatisms atonic clonic epileptic spasms hyperkinetic myoclonic tonic *Nonmotor Onset* autonomic behavior arrest cognitive emotional sensory **Focal to bilateral tonic-clonic**	*Motor* tonic-clonic clonic tonic myoclonic myoclonic-tonic-clonic myoclonic-atonic atonic epileptic spasms *Nonmotor (absence)* typical atypical myoclonic eyelid myoclonia	*Motor* tonic-clonic epileptic spasms *Nonmotor* behavior arrest **Unclassified**

INTERNATIONAL LEAGUE AGAINST EPILEPSY (ILAE)
FRAMEWORK FOR CLASSIFICATION OF THE EPILEPSIES



Examples of epilepsy syndromes (adapted from ILAE)		
Neonatal period	**Childhood**	**Adolescent - Adult**
Self-limited neonatal seizures Self-limited familial neonatal epilepsy Early myoclonic encephalopathy Ohtahara syndrome	Febrile seizure plus (FS+), Genetic epilepsy with febrile seizure plus (GEFS+) Epilepsy with myoclonic-atonic seizures Childhood absence epilepsy (CAE) Epilepsy with eyelid myoclonias Epilepsy with myoclonic absences Panayiotopoulos syndrome Childhood occipital epilepsy (Gastaut type) Childhood epilepsy with centrotemporal spikes (previously called Benign Rolandic epilepsy) Landau-Kleffner syndrome (LKS) Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) Lennox-Gastaut syndrome Autosomal-dominant nocturnal FLE (Frontal Lobe Epilepsy)	Juvenile absence epilepsy (JAE) Juvenile myoclonic epilepsy (JME) Epilepsy with GTC seizures alone Progressive myoclonic epilepsies (PME) Familial focal epilepsies
Infancy		**Others**
Self-limited familial infantile epilepsy Self-limited non-familial infantile epilepsy West syndrome Dravet syndrome Myoclonic epilepsy in infancy Epilepsy of infancy with migrating focal seizures Myoclonic encephalopathy in non-progressive disorders		Mesial TLE (Temporal Lobe Epilepsy) with hippocampal sclerosis Gelastic seizures with hypothalamic hamartoma Hemiconvulsion-hemiplegia-epilepsy Rasmussen syndrome Reflex epilepsies

Principles of antiepileptic drug (AED) therapy for Epilepsy

- Attempt to classify the seizure type(s) and epilepsy syndrome.
- Treatment recommended if ≥ 2 episodes (recurrence risk up to 80%).
- Monotherapy as far as possible. Choose most appropriate drug based on epilepsy syndrome, seizure type (if epilepsy syndrome not identified yet) and associated comorbidities.
- Increase dose gradually until seizures controlled or maximum dose reached or side effects occur.
- Add on the second drug if first drug failed. Optimise second drug, then try to withdraw first drug. (Alternative monotherapy).
- Rational combination therapy (usually 2 or maximum 3 drugs) i.e. combines drugs with different mechanism of action and consider their spectrum of efficacy, drug interactions and adverse effects.
- Beware of AED-induced seizure aggravation in certain epilepsy syndromes.
- Trial of vitamins and co-factors such as vitamin B6, pyridoxal phosphate, biotin and folinic acid should be considered in infantile epilepsies not responding to AED.
- In children not responding to treatment with 2 AEDs, complete re-evaluation is required for epilepsy surgery / trial of ketogenic diet.
- Risk of carbamazepine-induced hypersensitivity reactions, including Steven-Johnson syndrome and toxic epidermal necrolysis, is increased in patients with the HLA-B*1502 allele – consider testing if test easily available.
- Avoid starting female of childbearing potential with sodium valproate because of risk of teratogenicity and neurodevelopmental impairment to the unborn child, unless other treatments are ineffective or not tolerated.
- Drug level monitoring is not routinely done (except phenytoin), unless non- compliance, toxicity or drug interaction is suspected.
- Vitamin D supplementation should be considered for children with risk factors for Vitamin D deficiency, i.e. those on long term AED therapy, on more than 1 AED and poor sunlight exposure.
- When withdrawal of medication is planned (generally after being seizure-free for 2 years) , consideration should be given to epilepsy syndrome, likely prognosis and individual circumstances before attempting slow withdrawal of medication over 3-6 months (maybe longer if using clonazepam or phenobarbitone).
  If seizures recur, the last dose reduction is reversed and medical advice sought.

Antiepileptic drug options by Epilepsy Syndrome

West syndrome
First Line: Steroid (Prednisolone), Vigabatrin* (first line for Tuberous sclerosis)
Second Line: Nitrazepam, Clonazepam, Clobazam, Valproate, Topiramate, Pyridoxine

Dravet syndrome
First Line: Sodium valproate, Clobazam/Clonazepam
Second Line: Topiramate, Levetiracetam

Lennox-Gastaut syndrome
First Line: Sodium valproate, Lamotrigine
Second Line: Topiramate, Clobazam, Rufinamide*

Childhood absence epilepsy, or other absence epilepsy syndrome
First Line: Sodium valproate, Ethosuximide*
Second Line: Lamotrigine, Levetiracetam

Juvenile myoclonic epilepsy
First Line: Sodium valproate
Second Line: Lamotrigine,(may exacerbate myoclonus), Levetiracetam, Clobazam, Clonazepam, Topiramate

Childhood epilepsy with centrotemporal spikes
First Line: Sodium valproate, Carbamazepine
Second Line: Clobazam, Lamotrigine, Levetiracetam

**Currently not in MOH Drug Formulary*

Selecting antiepileptic drugs according to seizure types

FOCAL SEIZURES
First Line: Carbamazepine , Valproate, Oxcarbazepine*
Second Line: Lamotrigine,Topiramate, Levetiracetam, Clobazam, Phenytoin, Phenobarbitone

GENERALIZED SEIZURES

Tonic-clonic / clonic only
First Line: Valproate
Second Line: Lamotrigine,Levetiracetam,Topiramate, Clobazam, Carbamazepine, Phenytoin

Absence
First Line: Valproate, Ethosuximide
Second Line: Lamotrigine, Levetiracetam

Atonic, tonic
First Line: Valproate
Second Line: Lamotrigine,Topiramate, Clonazepam, Phenytoin

Myoclonic
First Line: Valproate
Second Line: Levetiracetam, Clonazepam, Clobazam, Topiramate,

Antiepileptic drugs that aggravate selected seizure types	
Phenobarbitone	Absence seizures
Clonazepam	Causes tonic status in Lennox-Gastaut syndrome
Carbamazepine	Absence, myoclonic, generalised tonic-clonic seizures
Lamotrigine	Dravet syndrome, Myoclonic seizures in Juvenile Myoclonic Epilepsy
Phenytoin	Absence, myoclonic seizures
Vigabatrin	Myoclonic, absence seizures

Adverse Effects of Antiepileptic Drugs

Carbamazepine
Common side effects: Drowsiness, dizziness, ataxia, diplopia, rashes
Serious side effects: Steven-Johnson syndrome[1], agranulocytosis

Clobazam[2], Clonazepam
Common side effects: Drowsiness, hypotonia, salivary and bronchial hypersecretion, hyperactivity and aggression

Lamotrigine
Common side effects: Dizziness, somnolence, insomnia, rash
Serious side effects: Steven-Johnson syndrome

Levetiracetam
Common side effects: Somnolence, asthenia, dizziness, irritability, behavioural change

Phenobarbitone
Common side effects: Behavioural disturbance, cognitive dysfunction, drowsiness, ataxia, rash

Phenytoin
Common side effects: Ataxia, diplopia, dizziness, sedation, gum hypertrophy, hirsutism, megaloblastic anemia

Sodium valproate
Common side effects: Nausea, epigastric pain, tremor, alopecia, weight gain, hair loss, thrombocytopaenia
Serious side effects: Hepatic toxicity, pancreatitis, encephalopathy

Topiramate
Common side effects: Weight loss, somnolence, mental slowing, word finding difficulty, hypohidrosis, renal calculi

Vigabatrin
Common side effects: Drowsiness, dizziness, mood changes, weight gain
Serious side effects: Peripheral visual field constriction (tunnel vision)

*Footnotes: 1, Steven-Johnson syndrome occurs more frequently in Chinese and Malay children who carry the HLA-B*1502 allele.*
2, Clobazam is less sedative than clonazepam

The patients with "Intractable Epilepsy"

Please re-evaluate for the following possibilities:-

- Is it a seizure or a non-epileptic event?
- Wrong classification of epilepsy syndrome, thus wrong choice of antiepileptic drug.
- Antiepileptic drug dose not optimised.
- Poor compliance to antiepileptic drug.
- Antiepileptic drug aggravating seizures.
- Lesional epilepsy, hence a potential epilepsy surgery candidate.
- Progressive epilepsy or neurodegenerative disorder.

When to refer to Paediatric Neurologist?

Refer immediately (to contact paediatric neurologist)

- Behavioural or developmental regression.
- Infantile spasms.

Refer

- Poor seizure control despite monotherapy with 2 different antiepileptic medications.
- Difficult to control epilepsies beginning in the first two years of life.
- Structural lesion on neuroimaging.

Advice for Parents

- Educate and counsel on epilepsy.
- Emphasize compliance if on an antiepileptic drug.
- Don't stop the medication by themselves. This may precipitate breakthrough seizures.
- In photosensitive seizures: watch TV in brightly lit room.
- Avoid sleep deprivation.
- Use a shower with bathroom door unlocked.
- No cycling in traffic, climbing sports or swimming alone.
- Educate on the emergency treatment for seizure.
- Inform teachers and school about the condition.

First Aid Measures during a Seizure (Advise for Parents/Teachers)

- Do not panic, remain calm. Note time of onset of the seizure.
- Loosen the child's clothing especially around the neck.
- Place the child in a left lateral position with the head lower than the body.
- Wipe any vomitus or secretions from the mouth.
- Do not insert any object into the mouth even if the teeth are clenched.
- Do not give any fluids or drugs orally.
- Stay near the child until the seizure is over and comfort the child as he/she is recovering.

Chapter 48: Febrile Seizures

Definition

- Seizures occurring in association with fever in children between 3 months and 6 years of age, in whom there is no evidence of intracranial pathology or metabolic derangement.
- No comprehensive local epidemiological data. Studies in Western Europe quote a figure of 3-4% of children < 5 years experiencing febrile seizures.

Classification of Febrile Seizures	
Simple Febrile Seizures • Duration < 15 minutes • Generalised seizure. • Does not recur during the febrile episode	*Complex Febrile Seizures* • Duration > 15 minutes • Focal features • >1 seizure during the febrile episode • Residual neurological deficit post-ictally, such as Todd's paralysis

Management

- Not all children need hospital admission. The main reasons are: -
  - To exclude intracranial pathology especially infection.
  - Fear of recurrent seizures.
  - To investigate and treat the cause of fever besides meningitis/encephalitis.
  - To allay parental anxiety, especially if they are staying far from hospital.
- Investigations
  - The need for blood counts, blood sugar, lumbar puncture, urinalysis, chest X-ray, blood culture etc, will depend on clinical assessment of the individual case.
  - Lumbar puncture

    Must be done if : (unless contraindicated - see **Chapter on Meningitis**)
    - Any symptoms or signs suggestive of intracranial infection
    - Persistent lethargy and not fully interactive

    Should be considered if :
    - Age < 12 months old especially if child has not received Hib and pneumococcal immunization
    - Prior antibiotic therapy
  - Serum calcium and electrolytes are rarely necessary.
  - EEG is not indicated even if multiple recurrences or complex febrile seizures.
- Parents should be counselled on the benign nature of the condition.
- Control fever
  - Avoid excessive clothing
  - Use antipyretic e.g. syrup or rectal Paracetamol 15 mg/kg 6 hourly for patient's comfort, though this does not reduce the recurrence of seizures.

- Parents should also be advised on **First Aid Measures during a Seizure.**
  Rectal Diazepam
  - Parents of children with high risk of recurrent febrile seizures including those with febrile status epilepticus should be supplied with Rectal Diazepam (dose : 0.5 mg/kg).
  - They should be advised on how to administer it if the seizures last more than 5 minutes.
- Prevention of *recurrent* febrile seizures.
  Antiepileptic drugs are not recommended for prevention of recurrent febrile seizures because:
  - The risks and potential side effects of medications outweigh the benefits
  - No medication has been shown to prevent the future onset of epilepsy.
  - Febrile seizures have an excellent outcome with no neurological deficit nor any effect on intelligence.

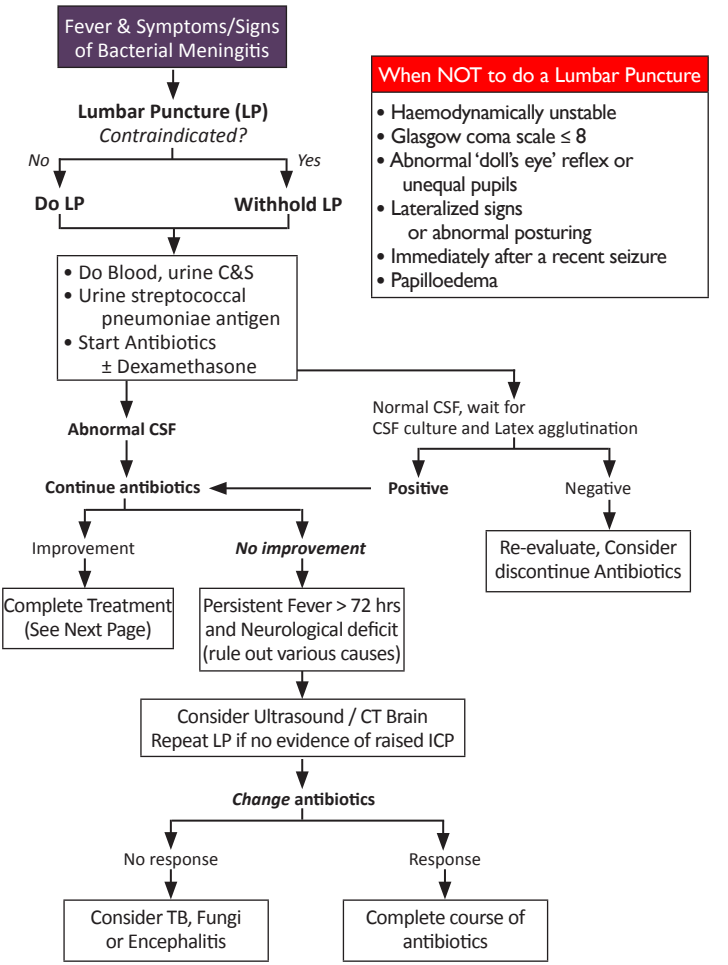
Risk factors for Recurrent Febrile Seizures
• Family history of Febrile seizures • Age < 18 months • Low degree of fever (< 40 °C) during first Febrile seizure. • Brief duration (< 1 hr) between onset of fever and seizure. ** If No risk factor, then < 15 % risk of recurrence* *If ≥ 2 risk factors, then > 30 % risk of recurrence* *If ≥ 3 risk factors, then > 60 % risk of recurrence*
Risk factors for subsequent Epilepsy
• Neurodevelopmental abnormality • Complex febrile seizures • Family history of epilepsy
Prognosis in Febrile Seizures
Febrile seizures are benign events with excellent prognosis • 3 - 4 % of population have Febrile seizures. • 30 % recurrence after 1st attack. • 48 % recurrence after 2nd attack. • 2 - 7 % develop subsequent afebrile seizure or epilepsy. • No evidence of permanent neurological deficits following Febrile seizures or even Febrile status epilepticus.

Chapter 49: Meningitis

Introduction

- Meningitis is still a major and sometimes fatal problem in Paediatrics.
- Morbidity is also high. A third of survivors have sequelae of their disease. However, these complications can be reduced if meningitis is treated early.

APPROACH TO A CHIILD WITH FEVER AND SIGNS/SYMPTOMS OF MENINGITIS



Cerebrospinal fluid values in neurological disorders with fever				
Condition	Leukocytes (mm^3)	Protein (g/l)	Glucose (mmol/l)	Comments
Acute Bacterial Meningitis	100 - >50,000	Usually 1- 5	<0.5 - 1.5	Gram stain may be positive
Partially-treated Bacterial Meningitis	1 - 10,000 Usually high PMN, but may have lymphocytes	> 1	Low	CSF may be sterile in Pneumococcal, Meningococcal meningitis
Tuberculous Meningitis	10 - 500 Early PMN, later high lymphocytes	1- 5	0 - 2.0	Smear for AFB, GeneXpert MTB test + in CSF; High ESR
Fungal Meningitis	50 – 500 Lymphocytes	0.5 - 2	Normal or low	CSF for Cryptococcal Ag
Encephalitis	10 - 1,000	Normal / 0.5-1	Normal	CSF virology and HSV DNA PCR

Recommended antibiotic therapy according to likely pathogen			
Age Group	Initial Antibiotic	Likely Organism	Duration (if uncomplicated)
< 1 month	C Penicillin + Cefotaxime	*Grp B Streptococcus* *E. coli*	21 days
1 - 3 months	C Penicillin + Cefotaxime	*Group B Streptococcus* *E. coli* *H. influenzae* *Strep. pneumoniae*	10 – 21 days
> 3 months	C Penicillin + Cefotaxime, OR Ceftriaxone	*H. influenzae* *Strep. pneumoniae* *N. meningitides*	7 – 10 days 10 – 14 days 7 days

Note:

- Review antibiotic choice when infective organism has been identified.
- Ceftriaxone gives more rapid CSF sterilisation as compared to Cefotaxime or Cefuroxime.
- If Streptococcal meningitis, request for MIC values of antibiotics.

MIC level	*Drug of choice:*
• *MIC < 0.1 mg/L (sensitive strain)*	*C Penicillin*
• *MIC 0.1-< 2 mg/L (relatively resistant)*	*Ceftriaxone or Cefotaxime*
• *MIC > 2 mg/L (resistant strain)*	*Vancomycin + Ceftriaxone or Cefotaxime*

- Extend duration of treatment if complications e.g. subdural empyema, brain abscess.

Use of Steroids to decrease the sequelae of bacterial meningitis

- Best effect achieved if given before or with the first antibiotic dose.
- Dose:
  Dexamethasone 0.15 mg/kg 6 hly for 4 days or 0.4 mg/kg 12 hly for 2 days
- Give steroids if CSF is turbid and patient has not received prior antibiotics.

Supportive measures

- Monitor temperature, pulse, BP and respiration 4 hourly and input/output.
- Nil by month if unconscious.
- Judicious fluid management with careful monitoring to ensure adequate circulating volume while being aware of the possibility albeit uncommon of SIADH. Patient may need more fluid if dehydrated
- If fontanel is still open, note the head circumference daily. Consider cranial ultrasound or CT scan if effusion or hydrocephalus is suspected.
- Seizure chart.
- Daily Neurological assessment is essential.
- Observe for 24 hours after stopping therapy and if there is no complication, patient can be discharged.

If persistent fever in a patient on treatment for meningitis, consider:

- Thrombophlebitis and injection sites e.g. intramuscular abscess.
- Intercurrent infection e.g. pneumonia, UTI or nosocomial infection.
- Resistant organisms. Inappropriate antibiotics or inadequate dosage.
- Subdural effusion, empyema or brain abscess.
- Antibiotic fever.

Follow up (Long term follow up is important)

- Note development of child at home and in school.
- Note head circumference.
- Ask for any occurrence of fits or any behavioural abnormalities.
- Assess vision, hearing and speech.
- Request for early formal hearing assessment in cases of proven meningitis.
- Until child shown to have normal development (usually until 4 years old).

Indications for CT Scan brain (with contrast)

Useful to detect complications

- Prolonged depression of consciousness .
- Prolonged focal or late seizures.
- Focal neurological abnormalities.
- Enlarging head circumference.
- Suspected subdural effusion or empyema.

Indications for Subdural drainage

- Rapid increase in head circumference with no hydrocephalus.
- Focal neurological signs.
- Increased intracranial pressure.
- Suspected subdural empyema.

Prognosis depends on

- Age: worse in younger patients.
- Duration of illness prior to effective antibiotics treatment.
- Causative organism: more complications with *H. influenzae*, *S. pneumoniae.*
- Presence of focal signs.

Chapter 50: Autoimmune Encephalitis

Introduction

- This is a diverse group of neuropsychiatric disorders presenting with acute or subacute progressive decrease in level of consciousness, altered cognition, memory impairment, behavioural/psychiatric manifestations, seizures or movement disorders; either isolated or in combination.
- Antibodies commonly implicated are those against neuronal surface antigens or intracellular antigens.
- The most common antibody detected in children is anti-NMDA receptor antibody (*NMDA: N-methyl-D-aspartate).

Diagnostic criteria for Possible Autoimmune Encephalitis

- All three of the following criteria have been met:
- Subacute onset (rapid progression of < 3 months) of working memory deficits, altered mental status or psychiatric symptoms.
- At least one of the following:
  - New focal CNS findings
  - Seizures (new onset)
  - CSF pleocytosis (> 5 cells/mm3 in white cell count)
  - MRI features suggestive of encephalitis
- Reasonable exclusion of alternative causes

Differential Diagnosis

- CNS infections (bacterial, viral , TB, fungi, SSPE)
- Epileptic disorders
- CNS demyelination (ADEM, multiple sclerosis, neuromyelitis optica)
- CNS vasculitis (primary CNS vasculitis, SLE)
- Hashimoto's encephalopathy
- Neoplastic disorders
- Toxic, metabolic, drug toxicity
- Mitochondrial diseases
- Inborn errors metabolism
- Autistic regression

Investigations

- Serum and CSF for anti-NMDA receptor antibody (at IMR).
- Serum and CSF for other autoantibodies (only available at private lab).
- CSF for biochemistry, cytology, oligoclonal band, IgG index.
- EEG (background slowing , delta brushes ,epileptic activities).
- MRI brain (abnormal signal at medial temporal lobes, cerebral cortex, cerebellum, brainstem, basal ganglia, contrast enhancement. Maybe normal or non-specific).
- Tumour screening (ultrasound scan for ovarian or testicular teratoma).
- Other relevant investigations to rule out the alternative diagnoses.

Diagnostic criteria for anti-NMDA receptor encephalitis

Probable

All three of the following:

- Rapid onset (< 3 months) of at least 4 of the 6 following major groups of symptoms: -
  - Abnormal (psychiatric) behaviour or cognitive dysfunction
  - Speech dysfunction (pressured speech, verbal reduction, mutism)
  - Seizures
  - Movement disorder, dyskinesia, or rigidity/abnormal postures
  - Decreased level of consciousness
  - Autonomic dysfunction or central hypoventilation
- At least one of the following lab study results:
  - Abnormal EEG (focal or diffuse slow, epileptic activity or extreme delta brush pattern)
  - CSF with pleocytosis or oligoclonal bands
- Reasonable exclusion of other disorders
- Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

Definite

- Diagnosis can be made in the presence of one or more of the six major groups of symptoms and positive anti-NMDA receptor antibody test after reasonable exclusion of other disorders.

Treatment (Consult Pediatric Neurologist)

- Immunotherapy:
  - First line
    - IV Methylprednisolone 10mg/kg/dose 8 hourly (up to 1 g daily) for 5 days with iv/oral omeprazole followed by oral prednisolone (1-2 mg/kg/day)

    AND
    - Intravenous immunoglobulin 2 g/kg total over 2-5 days

    AND/OR
    - Plasmapheresis
  - Second line
    - IV cyclophosphamide, IV Rituximab
- Tumour resection (uncommon in children)
- Supportive therapy:
  - Aimed at managing the seizures, movement disorders, behavioural impairment, sleep issues and psychological support for parents

Relapse

- Occur in 20-25% of cases.
- May signify presence of tumour or inadequate treatment.

Chapter 51: Status Dystonicus

Introduction

- Status dystonicus can occur in the context of an acute illness affecting the CNS e.g. hypoxic ischaemic /infective / metabolic encephalopathies or may occur in children with known chronic dystonia (either primary or secondary dystonia such as in cerebral palsy).
- It is a medical emergency with high morbidity and mortality but often under-diagnosed.

Definition

- Increasingly frequent and severe or extreme episodes of generalized dystonia /dystonic spasms (sustained involuntary muscle contraction leading to abnormal postures and movement) which requires urgent hospital admission.

Triggering factors

- Intercurrent illness or infection
- Pain from any source
  - GI (gastro-oesophageal reflux, constipation)
  - Dental (ulcers, caries)
  - Orthopaedic (dislocated hip, fractures)
- Trauma
- Surgical procedures or anaesthetics stressors
- Medications (weaning off or introduction of new medications such as haloperidol, metoclopramide)

Complications of Status Dystonicus

- Severe pain
- Hyperpyrexia
- Exhaustion from sleep deprivation and exertion
- Dehydration with electrolyte disturbance from excessive sweating
- Rhabdomyolysis leading to myoglobinaemia and raised creatine kinase
- Acute renal failure
- Bulbar dysfunction with risk of pulmonary aspiration
- Respiratory failure and death

Biochemical derangements:

- Electrolyte imbalance (hypocalcemia, hyperkalemia)
- Acid-base disturbance
- Elevated creatinine phosphokinase (usually > 1000 IU/L)
- Myoglobinaemia
- Myoglobinuria

Differential diagnosis

- Neuroleptic malignant syndrome
- Serotonin syndrome
- Malignant hyperthermia
- Paroxysmal sympathetic hyperactivity

Initial Management

Airway

- Should be closely monitored and consider elective intubation.
- Feeding via naso-gastric or naso-jejunal tube may be preferred.

Hydration

- Patient should be adequately hydrated and maintenance fluids may need to be increased by an additional 5-20%.
- Secure intravenous access is mandatory in all patients.
- Urine output should be maintained to 1-2 ml/kg/hour or more.
- Monitor for rhabdomyolysis and myoglobinaemia.
- Myoglobinuria (urine dipstick +ve for blood without RBC on microscopy).
- Serum creatine kinase should be measured and repeated 24 and 48 hours later as rise in the level may take 24-28 hours.
- Monitor for renal impairment.
- Urine output and serum electrolytes with urea should be monitored closely daily or more frequently.

Pain and distress

- Appropriate analgesia either oral (paracetamol, non-steroidal analgesics) or intravenous (morphine, midazolam) should be given generously with close monitoring of the patients hemodynamic status.

Sleep

- Sleep is known to relieve dystonia in almost all cases.
- Syrup chloral hydrate (10-50mg /kg/dose, stat or repeated, max 6 hourly)
- Small bolus doses of iv midazolam (0.1-0.2 mg/kg/dose) or
- low dose (0.1-0.5 mcg/kg/min) infusion of iv midazolam has been found to be effective in most cases.

Dystonia specific management (consider referral to paediatric neurologist)

- A number of sedatives and /or muscle relaxants may be useful alone or in combination.
  - Regular syrup chloral hydrate.
  - Midazolam: oral, buccal, iv or iv infusion (or oral / rectal diazepam).
  - Oral baclofen (2.5mg bd – 5mg tds starting dose).
  - Oral benzhexol (0.5mg daily/bd/tds starting dose).
- Extreme care should be taken to monitor children when using combinations of drugs with sedating properties.

Indications for endotracheal intubation and mechanical ventilation

- Airway compromise / respiratory failure.
- Refractory status dystonicus.
- Severe metabolic compromise e.g. renal failure requiring haemodialysis.

Supportive Management

- Treat any known triggers (e.g. Infection, GERD, constipation).
- Address any emotional and psychological contributing factors.
- Appropriate positioning, minimal handling, & reduce environmental stimuli.

Chapter 52: Acute Demyelinating Syndromes

Introduction
These disorders consist of monophasic and polyphasic (recurrent) diseases with acquired immune injury to the white matter in the central nervous system, optic nerve or spinal cord.

Optic neuritis
- Acute loss of vision (decreased visual acuity) of one or both eyes
- Often associated with pain on eye movements and colour desaturation
- A relative afferent pupillary defect is present
- MRI may show swelling and abnormal signal of the optic nerves.

Acute transverse myelitis
- Spinal cord dysfunction, with motor weakness, numbness of both legs.
- and/or arms, often associated with urinary retention.
- Maximal deficits occurring between 4 hours - 21 days after symptom onset.
- MRI may demonstrate swelling +/or abnormal signal in the spinal cord.

Acute Disseminated Encephalomyelitis (ADEM)
- Acute encephalopathy (behavioural change or alteration of consciousness) with multifocal neurological deficits/signs,
  e.g. limb weakness, numbness, cerebellar ataxia, cranial nerve palsy, speech impairment, visual loss, seizures and spinal cord involvement.
- MRI shows multiple areas of abnormal signal in the white matter.
- No other aetiologies can explain the event.

ADEM: Common Differential Diagnoses
• CNS infection   • Bacterial, tuberculous meningitis, viral encephalitis • Clinically isolated syndrome (1st episode of Multiple sclerosis) • Guillain Barré syndrome • Acute stroke • Mitochondrial disorders

Other Investigations (as needed)
- Cerebrospinal fluid - FEME, cultures, oligoclonal bands, Herpes virus PCR (optional: lactate, viral studies).
- Infection screen - virology, mycoplasma, etc.
- Vasculitis screen (ESR, C3,C4, antinuclear factor).
- Evoked potentials - visual, auditory and somatosensory.

Treatment

Supportive measures

- Vital sign monitoring, maintain blood pressure
- Assisted ventilation for "cerebral / airway protection"
- Anticonvulsants for seizures
- Antibiotics / Acyclovir for CNS infections if febrile, awaiting cultures, PCR result.

Definitive immunotherapy

- IV Methylprednisolone 30mg/kg/day (max 1 gm), given daily or in divided doses, for 3 to 5 days.
- Followed by oral Prednisolone 1-2 mg/kg/day (max 60 mg) daily to complete for 2 weeks.
- Give longer course of oral prednisolone for ADEM, and transverse myelitis with residual deficit: high dose (1-2 mg/kg/day) for 3-4 weeks, then to taper the dose gradually over another 2-4 weeks).
- If no response, consider: IV Immunoglobulins 2 gm/kg over 2 - 5 days and/or referral to a paediatric neurologist.

Relapses or Recurrent episodes

- If demyelinating episodes of any type recur in the same patient, refer patient to a paediatric neurologist urgently to workup for CNS demyelinating disorders associated with specific antibody (e.g. anti-NMO and anti-MOG antibodies) or multiple sclerosis.
- Timely treatment for these conditions is essential to improve the long-term outcome.

Chapter 53: Acute Flaccid Paralysis

Introduction

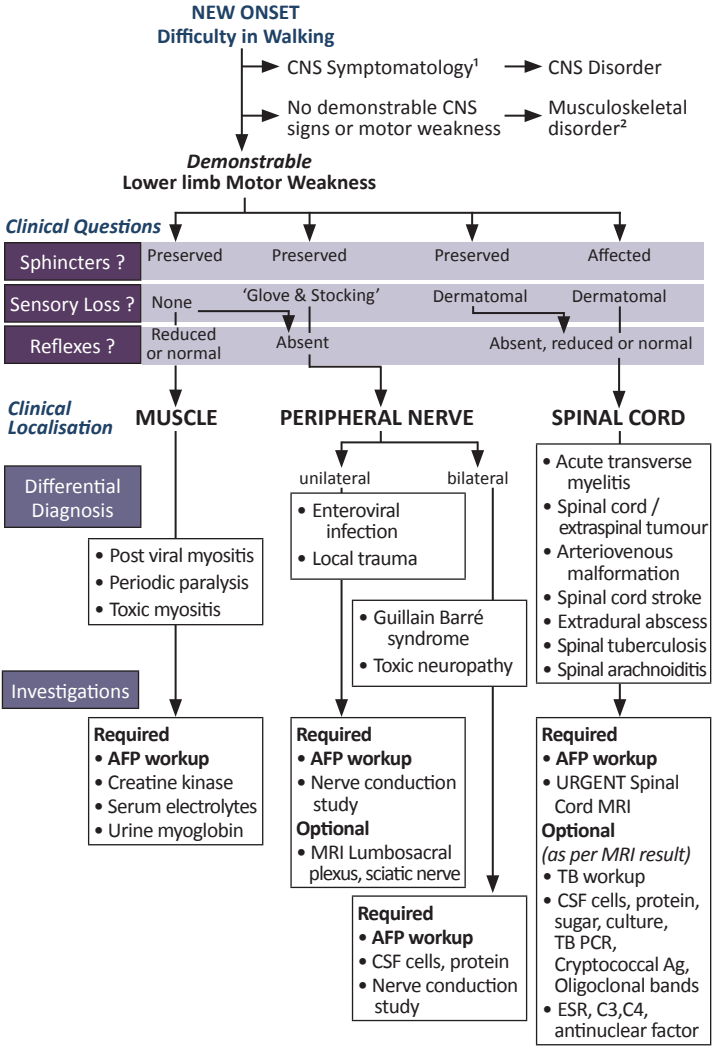
Acute Flaccid Paralysis (AFP) occurs when there is rapid evolution of motor weakness (< than 4 days), with a loss of tone in the paralysed limb. This excludes weakness due to trauma and spastic paralysis.

AFP is a ***medical emergency*** as unnecessary delays can result in death and disability. Children with AFP need to be assessed and managed carefully. A simple algorithm is provided on the next page.

AFP surveillance in children

- Collecting stools for enterovirus in children with AFP is an important part of the Global Polio Eradication Initiative (GPEI).
- For Malaysia to remain a polio-free country we need to prove that none of our cases of AFP are caused by poliovirus infection. To do this we have to report all cases of AFP aged < 15 years, send stools for enterovirus isolation using a standardised protocol, and follow up children with AFP to determine the outcome.

Protocol for AFP surveillance in Malaysia		
Step	**Timing**	**Description**
Case Detection	At diagnosis	• Follow case definition for AFP
Case Reporting	Within 24 hours	• Inform and fax the completed AFP case investigation form to regional health office / health inspector according to local protocol
Timing of stool specimens	Within 2 weeks of onset of paralysis	• 2 stool specimens collected no less than 24 hours apart
Collection of specimens		• Fresh stool. Avoid rectal swabs. (at least 8g – size of an adult thumb). • Place in a sterile glass bottle.
Transport of stools	As soon as able	• Maintain a cold chain of 2 - 8 °C. Transport in frozen ice packs or dry ice. • Ensure stool specimens arrive at IMR within 72 hours of stool collection. • Caution: avoid desiccation, leakage; • Ensure adequate documentation and use AFP Case Laboratory Request Form
Follow up of patients	60 days from paralysis	• To determine whether there is residual paralysis on follow up • To send a second case investigation form with follow-up findings and final diagnosis



Notes: 1. Headache, vomiting, seizures, encephalopathy, cranial nerve deficits, ataxia, brisk tendon reflexes, upgoing plantar response.
2. Soft tissue, joint or bony causes of walking difficulty.

Chapter 54: Guillain Barré Syndrome

Introduction

Guillain Barré syndrome (GBS) is a post-infectious inflammatory disorder affecting the peripheral nerves.

Clinical Pearls on GBS in Children

- Rapidly progressive, bilateral and relatively symmetric weakness of the limbs with decrease or absent reflexes. In atypical cases, weakness may begin in the face or upper limbs, or asymmetrical at onset.
- Sensory symptoms, e.g. limb pain and hyperesthesia, are common.
- Bladder and bowel involvement may occasionally be seen, but is never present at onset and never persistent
  (if so, think of spinal cord disorder)
- CSF protein level and nerve conduction studies may be normal in the first week of illness.
- GBS variants and overlapping syndrome:
  - Miller Fisher syndrome - cranial nerve variant characterised by opthalmoplegia, ataxia and areflexia.
  - Bickerstaff's brainstem encephalitis - acute encephalopathy with cranial and peripheral nerve involvement.

Management

The principle of management is to establish the diagnosis and anticipate / pre-empt major complications.

- A *Clinical* diagnosis can be made by a history of progressive, ascending weakness (< 4 wks) with areflexia, and an elevated CSF protein level and normal cell count ("protein-cellular dissociation").
- Nerve conduction study is *Confirmatory*.

Initial measures

- Give oxygen, keep NBM if breathless. Monitor PEFR regularly
- Admit for PICU / PHDU care, if having:
  - Respiratory compromise (deteriorating PERF).
  - Rapidly progressive tetraparesis with loss of head control.
  - Bulbar palsy.
  - Autonomic and cardiovascular instability.
- Provide respiratory support early with BiPAP or mechanical ventilation

Hughes Functional Scale for GBS	
0	Normal
1	Minor symptoms, capable of running
2	Able to walk up to 10 meters without assistance but unable to run
3	Able to walk 10 meters with assistance of one person, or a walker
4	Unable to walk
5	Requires assisted ventilation

Specific measures

- IV Immunoglobulins (IVIG) 2 gm /kg total over 2 - 5 days in the first 2 weeks of illness, with Hughes functional scale 3 and above or rapidly deteriorating.
- IVIG is as efficacious as Plasma exchange in both children and adults, and is safer and technically simpler.
- 10 % of children with GBS may suffer a relapse of symptoms in the first weeks after improvement from IVIG. These children, may benefit from a second dose of IVIG.

General measures

- Prophylaxis for deep vein thrombosis should be considered for patients ventilated for GBS, especially if recovery is slow.
- Liberal pain relief, with either paracetamol, NSAIDs, gabapentin or opiates.

Important:

If patient shows disease progression or no improvement 4 weeks after the onset of weakness, to refer to paediatric neurologist for further evaluation

consider:

1 INITIAL ASSESSMENT

Airway . . . . . secure airway, endotracheal intubation
Breathing . . . oxygen, artificial ventilation if required
Circulation . . IV bolus, ionotropes, chest compressions
Dextrostix . . correct hypoglycemia promptly

Once stable, monitor HR, BP, Resp rate, SpO_2, urine output

2 WHAT IS THE GCS?

If GCS ≥ 12 . . monitor GCS hourly

If GCS < 12 . . monitor GCS ½ hourly till improves

3 CONSIDER ENDOTRACHEAL INTUBATION IF:

- Airway obstructs if not supported.
- Airway compromised by vomiting.
- Respiratory rate too low for adequate ventilation.
- SpO_2 remains < 92 % despite high flow O_2 and airway opening manouevres.
- Signs of shock even after 40 ml/kg of fluid resuscitation.
- Signs of exhaustion.
- GCS < 8 and deteriorating.

Look for & treat:

SEPSIS **SHOCK** **SEIZURES**

4 RAISED INTRACRANIAL PRESSURE

If Clinically has **Papilloedema**, or if *2 of the following:*

- GCS < 8, or deteriorating GCS
- Unreactive, unequal pupils
- Abnormal doll's eye reflex
- Decorticate, decerebrate posturing
- Abnormal breathing (Cheyne-Stokes, apneustic)

5 CONSIDER AETIOLOGY

- *CNS Infection*
  - Bacterial meningitis
  - Viral encephalitis
  - TB meningitis
  - Brain abscess
  - Cerebral malaria
- *Trauma*
- *Vasculitis*
- *Acute Poisoning*
- *Metabolic disease*
  - Diabetic ketoacidosis
  - Hypoglycaemia, Hyperammonemia
- *Non-accidental injury*
- *Post convulsive state*
- *Hypertensive crisis*
- *ADEM/ANEC*
- Stroke/*Cerebral venous sinus thrombosis*
- *Acute Hydrocephalus*

6 INVESTIGATIONS

Recommended

FBC, urea & electrolytes, glucose
Liver function tests
Serum ammonia, blood gas
Blood cultures
Urinalysis

Sample when ILL:

1-2 ml plasma/serum: separated, frozen & saved
10-20 ml urine: frozen & saved

Optional:

EEG, Vasculitis screen, Toxicology, IEM Screen, Blood film for malaria parasite

Delay Lumbar Puncture

Neuroimaging: Do urgent CT or MRI brain for all children with ↑ ICP when child is stable. Consider MRI brain within 48 hours if possible (if not done at presentation), when the diagnosis is still uncertain.

7 MANAGEMENT

Management of Raised ICP

- Nursing
  - Position head in the midline.
  - Elevate head of bed up to 15-30°.
  - Avoid unnecessary suction, procedures.
  - Avoid hyper or hypothermia.
  - Avoid internal jugular central venous line.
- Ventilation
  - Adequate sedation and analgesia.
  - Maintain good oxygenation, normocapnoea i.e. $PaCO_2$ 4.5 – 5.0 kPa / 35 - 40 mmHg.
  - Avoid excessively high PEEP.
- Fluid and electrolyte balance
  - Keep patient well hydrated.
  - Avoid hypo-osmolar fluid, plain dextrose solutions.
  - Monitor serum sodium and respond accordingly:

  ↓*Na^+*, ↓*urine output:* Consider SIADH, fluid restriction.

  ↓*Na^+*, ↑*urine output:* Consider cerebral salt wasting, replace renal sodium loss.

  ↑*Na^+, polyuria (> 5ml/kg/h)* → *likely central diabetes insipidus:* Fluid replacement and consider desmopressin.
- Maintain cerebral blood flow
  - Keep CPP > 50 mmHg
  - If ↑ BP: do not lower unless hypertensive crisis, acute glomerulonephritis

  [Cerebral Perfusion Pressure (CPP) = Mean Arterial Pressure (MAP) - Intracranial Pressure (ICP)]
- Hyperosmolar therapy
  - Consider IV mannitol or hypertonic saline
  - IV Mannitol 0.25 - 0.5 g/kg. May repeat after 2-6 hour.
  - Avoid prolonged use > 72 hours
  - Hypertonic saline (3% NaCl) 5-10 ml/kg. May repeat 2 ml/kg after 2-6 hours or infusion at 0.1-1.0 ml/kg/hr.
  - Recommended in hypotension but avoid in severe hyponatraemia.
  - Both agents can be used concurrently but keep serum osmolality < 320 mmol/L.
- Surgical decompression

  If medical measures fail, surgical decompression may be indicated (i.e. external ventricular drainage, decompressive hemicraniectomy)

8 OUTCOME

General rules

- Outcome depends on the underlying cause:
  - 1/3 die
  - 1/3 recover with deficits
  - 1/3 recover completely
- Acute complication improve with time e.g. cortical blindness, motor deficits

Chapter 56: Childhood Stroke

Introduction

- The overall incidence of neonatal stroke is 1 in 4,000 live births, while for childhood stroke is 2.5-13 per 100,000 children / year.
- Ischaemic stroke, including arterial ischaemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) is increasingly diagnosed in children.

Arterial Ischaemic Stroke

- Incidence: 2-8 per 100,000 children / year.
- Recurrence occurs in 10-30% of childhood AIS.

Definition

1. Acute onset (may be evolving) of focal ± diffuse neurological disturbance and persistent for 24 hours or more, ***AND***
2. Neuro-imaging showing focal ischaemic infarct in an arterial territory and of maturity consistent with the clinical features.

Clinical features

- Typically sudden, maximal at onset, well in the week before presentation (but may be evolving, waxing & waning).
- Focal deficits : commonest - motor deficits (hemiparesis), sensory deficits, speech / bulbar disturbance, visual disturbance, unsteadiness / gait difficulty.
- Diffuse neurological disturbance : altered consciouness, headache
- Seizures.
- Other non-specific features in neonatal stroke including apnoea, feeding difficulty, abnormal tone.

Potential Risk Factors for Arterial Ischaemic Stroke

Cardiogenic Congenital, acquired heart diseases Cardiac procedure Arrhythmia *Vasculopathy* Dissection, Moyamoya Post-varicella angiopathy Focal / transient cerebral arteriopathy of childhood *Vasculitis* Primary CNS vasculitis Secondary vasculitis (Infective vasculitis, SLE, Takayasu) *Prothrombotic disorders* Inherited thrombophilia Acquired thrombophilia Nephrotic syndrome, malignancy, anti-phospholipid syndrome, L-Asparaginase	*Acute disorders* Head and neck disorder Trauma (may be trivial), Infection - Meningitis, otitis media, mastoiditis, sinusitis Systemic disorders Sepsis, dehydration, asphyxia *Chronic disorders* Iron deficiency anaemia Sickle cell anaemia Metabolic disorders Homocystinuria, Dyslipidaemia, Organic acidaemia, MELAS (Mitochondrial encephalomyopathy, lactic acidosis with stroke-like episodes)

Investigations

- Blood workup :
  - Basic tests: FBC / FBP, renal profile, LFT, RBS, lipid profile, iron assay (as indicated).
  - Thrombophilia screen: PT/PTT/INR, protein C, protein S, anti-thrombin III, factor V Leiden, lupus anti-coagulant, anti-cardiolipin, serum homocysteine level.
  - If perinatal / neonatal stroke: consider mother's thrombophilia screen.
  - Further tests may include MTHFR (methylenetetrahydrofolate reductase), lipoprotein A, Prothrombin gene mutations.
  - Vasculitis workup (if indicated): C3, C4, CRP, ESR, ANA.
  - Further tests may include dsDNA, p-ANCA, c-ANCA.
  - Others: VBG, lactate and urine organic acid (for suspected metabolic aetiologies); CSF sampling (for suspected CNS infection or vasculitis if no contra-indications).
- Cardiac assessment : ECG & Echocardiogram (ideally with bubble study).
- Neuro-imaging (consult radiologist)
- Goals – to ascertain any infarction, haemorrhages, evidence of clots / vasculopathy and to exclude stroke-mimics.
- If stroke is suspected, both brain parenchymal and cervico-cephalic vascular imaging should be considered.

Brain imaging	Cervico-cephalic Vascular Imaging
Cranial Ultrasound If fontanel is open. *CT scan* Quick, sensitive for haemorrhages but may miss early, small and posterior fossa infarcts. *MRI scan (with DWI+ADC)* Better parenchymal details and sensitive for early infarct	*Carotid artery Ultrasound / Doppler* If suspected carotid dissection or stenosis. *MR Angiogram (MRA)* Intracranial vessels (with MRI) & to include neck vessels if suspected cervical vasculopathy. *CT Angiogram / Formal cerebral angiogram* May be considered in certain cases.

Management

- General care
  - Resuscitation: A, B, C's (check Airway, Breathing and Circulation)
  - Admit to ICU if indicated for close vital signs and GCS monitoring. (post-infarction cerebral oedema may worsen 2-4 days after acute tstroke)
  - Workup for the possible underlying risk factor(s) and treat accordingly.
  - If cervical dissection is the likely aetiology (eg : history of head & neck trauma, Marfan syndrome, carotid bruit), apply soft cervical collar.
- Acute neuro-protective care :
  - General measures for cerebral protection.
  - Maintain normothermia, normoglycemia, normovolemia
  - Monitor fluid balance, acceptable BP, adequate oxygenation, treat seizures aggressively.
- Acute Anti-thrombotic therapy :
  - Consult paediatric neurologist (and haematology team if available) for the necessity, choice and monitoring of anti-thrombotic therapy.
  - If stroke due to cardiac disease/procedure, should also consult cardiologist/cardio-thoracic team.
  - If anti-thrombotic is needed, consider anti-coagulation therapy (unfractionated heparin / LMWH) or aspirin. Ensure no contraindications.
- Secondary preventive therapy:
  - If needed, consider Aspirin (3-5mg/kg/day, may be reduced to 1-3mg/kg/day if has side effects.)
  - Duration: generally for 3-5 years but may be indefinitely.
  - Caution with long-term aspirin. (See below)
  - Alternatively, LMWH or warfarin may be used in extra-cranial dissection, intracardiac clots, major cardiac disease or severe prothrombotic disorders.
- Consider steroid for CNS vasculitis.
- Neonatal stroke: Generally, no anti-thrombotic therapy needed except proven cardio-embolic stroke or recurrent AIS.

Contraindications of Anti-thrombotic therapy
• Infarct associated with significant hemorrhage • Large infarct with the worry of secondary haemorrhagic transformation • Uncontrolled hypertension • Other risks for bleeding
Caution with Aspirin
• Reye's syndrome has been linked to use of aspirin during febrile illness. • Reduce aspirin by 50% during fever > 38°C. • Withhold for 3-5 days if suspected/confirmed varicella/influenza infection.

CHILDHOOD CEREBRAL SINO-VENOUS THROMBOSIS (CSVT)

Introduction

- 20-30% of childhood stroke due to CSVT; 30-40 % of CSVT will lead to venous infarcts or stroke.
- More than 50% of venous infarcts are associated with haemorrhages.
- Consider CSVT if infarct corresponds to venous drainage territories or infarct with haemorrhage not due to vascular abnormality.

Clinical features *(Typically sub-acute)*

- Diffuse neurological disturbance:
- Headache, seizures, altered sensorium, features of increased intracranial pressure (papilloedema, 6th cranial nerves palsy).
- Focal deficits if venous infarct.

Risk factors

- Prothrombotic conditions (Inherited, L-asparaginase, nephrotic syndrome).
- Acute disorders (Head & neck trauma / infection, dehydration, sepsis).
- Chronic disorders (SLE, thyrotoxicosis, iron deficiency anaemia, malignancy).

Investigations

- Thrombophilia screen and others depending on possible risk factor(s).

Neuroimaging

- Brain imaging - as in Childhood AIS guidelines.
- Cerebral Venogram
- MRV-TOF (time-of-flight) – flow dropout artefact may be a problem
- CTV – better than MRV-TOF, but radiation exposure is an issue.

Management

- General care and acute neuro-protective care as in AIS.
- Consult Paediatric neurologist for anti-coagulation therapy (ensure no contraindications).
- Consult neuro-surgery if infarct associated with haemorrhage.

Chapter 57: Brain Death

Definition

Brain death is a state when the function of the brain as a whole, including the brain stem is irreversibly lost. A person certified to be brain dead is dead. It is a clinical diagnosis based on the absence of neurologic function with a known irreversible cause of coma.

Diagnosis of brain death *(All to be fulfilled)*

Preconditions:

- Patient is in deep coma, apnoeic and on ventilator.
- Cause of coma fully established and sufficient to explain the status of patient.
- There is irremediable / irreversible brain damage.
- Normotensive for age without volume depletion (systolic BP and MAP in acceptable range for not less than 2 SDs below age appropriate norm).
- Core body temperature >35°C.
- Corrected / treated metabolic disturbances.
- Discontinuation and adequate clearance / elimination of medications that can interfere with the neurologic examination and apnoea test.

Exclusions:

- Preterm neonates < 37 weeks of gestational age.
- Coma due to metabolic or endocrine disturbance, drug intoxication.

Diagnostic Criteria *(All to be fulfilled)*

- Deep coma, unresponsive and unreceptive, Glasgow scale 3/15.
- Apnoeic, confirmed by apnoea test.
- Absent brain stem reflexes confirmed by the following tests:-
  1. Pupillary light reflex.
  2. Oculocephalic reflex.
  3. Motor response in cranial nerve distribution
  4. Corneal reflex
  5. Vestibulo-ocular reflex (caloric test)
  6. Oro-pharygeal reflex
  7. Tracheo-bronchial reflex

Test

(All conditions and exclusions fulfilled before proceeding to examine and test for brain death)

1. *Pupillary light reflex*.

- Mid-position or dilated.
- No response to bright light in both eyes.

2. *Oculocephalic reflex*. (Doll's eye response)

- Testing is done only when no fracture or instability of the cervical spine is apparent.
- The oculocephalic response is elicited by fast, vigorous turning of the head from middle position to 90° on both sides.

3. *Corneal reflex*.

- No blinking response seen when tested with a cotton swab.

4. *Motor response in cranial nerve distribution*.

- No grimacing seen when pressure stimulus applied to the supraorbital nerve, deep pressure on both condyles at level of the temporo-mandibular joint or on nail bed.

5. *Vestibulo-ocular reflex* (Caloric test).

- The test should not be performed if the tympanic membrane is perforated.
- The head is elevated to 30° during irrigation of the tympanum on each side with 50 ml of ice water.
- Allow 1 minute after injection and at least 5 minutes between testing on each side.
- Tonic deviation of the eyes in the direction of cold stimulus is absent.

6. *Oropharyngeal reflex.*

- Absent gag response when the posterior pharynx is stimulated.
- In neonates and infants, sucking and rooting reflexes are also absent.

7. *Tracheo-bronchial reflex*.

- A suction catheter is passed down through the endotracheal tube to the level of the carina or beyond. Lack of cough response to bronchial suctioning should be demonstrated.

8. *Apnoea test*.

- Prerequisites: the patient must be in a stable cardiovascular and respiratory state.
- Adjust ventilator to maintain $PaCO_2$ at or around 40 mmHg.
- Pre-oxygenate with 100% O_2 for 10 minutes.
- Disconnect from ventilator.
- Deliver 100% O_2 via tracheal catheter at 6 L/min
- Monitor O_2 saturation with pulse oximetry
- Measure $PaCO_2$ after 5 minutes and again after 8 minutes if $PaCO_2$ has not exceeded 60 mmHg.
- Re-connect to ventilator after the test.
- Disconnection of the ventilator shall not exceed 10 mins at any one time
- The apnoea test is **positive** when there is no respiratory effort with a $PaCO_2$ of ≥ 60 mmHg.
- If during apnoea testing, there is significant hypotension, marked desaturation or cardiac arrhythmias immediately draw an arterial blood sample, re-connect to ventilator and analyse ABG.
- Should the $PaCO_2$ < 60 mmHg, the result is indeterminate.
- It is left to the discretion of the paediatrician to decide whether to repeat the test or to depend on an ancillary test to finalise the clinical diagnosis of brain death.

Note: For patients with chronic lung disease, the baseline $PaCO_2$ may already be above 40 mmHg. The apnoea test is then considered positive if there is no respiratory effort at a $PaCO_2$ of 20 mmHg above the baseline $PaCO_2$.

Additional criteria for children

- No recommendation can be made for preterm infants <37 weeks of gestational age.
- Beyond this age, the brain death criteria apply but the interval between two examinations is depending on the age of the child.
  - Term newborn (37 weeks gestation) to 30 days of age: at least 24 hours.
  - 31 days – 18 years: at least 12 hours.
- Ancillary study: not required except in cases that
  - Component(s) of the clinical examination and apnoea test cannot be fully completed.
  - There is uncertainty of the examination finding(s).
  - Medication effect may interfere with the evaluation.
  - If required,
    - Term newborn (37 weeks gestation) to 30 days of age: EEG or cerebral blood flow (CBF) study are less sensitive in this age group but CBF may be preferred.
    - 30 days – 18 years: EEG and CBF have equal sensitivity.
  - Reduction of observation period between two examinations: permitted for both age groups if EEG or CBF is consistent with brain death.

Assessment and Certification

- Two specialists who are competent (at least 3 years of postgraduate clinical experience and trained in brain death assessment) in diagnosing brain death are qualified to certify brain death.
- They should preferably be paediatricians, anaesthesiologists, neurologists and neurosurgeons. Doctors involved in organ transplantation are not allowed to certify brain death.
- A repeat assessment and certification must be carried out after the first (with interval between the 2 examinations depending on the age of the child), not necessarily by the same pair of specialists.
- The 'Brain Death Certification form is filled up by the first set of doctors (Doctor A and B) and completed by the 2nd set of doctors (Doctor C and D) or Doctor A and B if the same doctors are performing the repeat test. The time of death will then be declared by the doctors performing the repeat test.
- The time of death is at the time of the 2nd testing. Should the patient's heart stop before the repeat test, that will be taken as the time of death.
- Brain death certification must only be done in areas of the hospital with full facilities for intensive cardiopulmonary care of the comatose patients.

Pitfalls in Assessment / Certification

- Assessment may be difficult in patients with
  - Severe facial trauma
  - Pre-existing pupillary abnormalities
  - Sleep apnoea or severe pulmonary disease with chronic retention of CO_2
  - Certain neurological disorders, e.g. Bickerstaff brainstem encephalitis and locked-in syndrome.
  - Toxic levels of sedative drugs, aminoglycosides, tricyclic antidepressants, anticonvulsants, chemotherapeutic drugs, neuromuscular blocking agents.
- Drug levels are useful if they can be quantified. The drug levels should be in the low to mid therapeutic range prior to neurologic examination to determine brain death
- When the drug or poison cannot be quantified, observe the patients for at least 4 times the elimination T ½ half-life, (provided the elimination of the drug or toxin is not interfered by other drugs or organ dysfunction) and consider performing an ancillary study (EEG/CBF) for brain death
- When the drug is unknown but suspicion of its presence is high, continue to observe the patients for any change in neurological status
- Determination of brain death should be deferred in the presence of severe acidosis or alkalosis as this may point to certain intoxication and potentially reversible medical illness or endocrine crisis.
- Spontaneous and reflex movements have been observed in patients with brain death. The most common are finger jerks, toe flexion sign and persistent Babinski response. These movements are spinal in origin and do not occur spontaneously. They do not preclude the diagnosis of brain death.

Elimination T ½ life for common drugs administered to critically ill paediatric patients which may interfere brain death assessment		
Drugs	Infants and Children	Neonates
Ketamine	2.5 hours	
Thiopentone	10 hours	
Phenobarbitone	Infants: 20-133 hours Children: 37- 73 hours	45-500 hours
Phenytoin	11-55 hours	63-88 hours
Midazolam	2.9-4.5 hours	4-12 hours
Diazepam	1 month-2 years: 40-50 hours 2-12 years: 15-21 hours 12-16 years: 18-20 hours	50-95 hours
Morphine	1-3 months: 6.2 hours 6 months – 2.5 year: 2.9 hours Children: 1-2 hours	7.6 hours
Fentanyl	0.5-14 yrs: 21-24 hours	1-15 hours
Rocuronium	3-12 mo: 1.3 + 0.5 hours 1 to < 3 yrs: 1.1 ± 0.7 hours 3 to < 8 yrs: 0.8 ± 0.3 hours	
Pancuronium	110 minutes	
Vecuroium	41 minutes	65 minutes
Atracurium	17 minutes	20 minutes

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Chapter 58: Approach to A Child with Short Stature

Short stature can be a sign of disease, disability and social stigma causing psychological stress. It is important to have early diagnosis and treatment.

Definition

- Definitions of growth failure:
  - Height below 3rd percentile (-2SD for age and gender).
  - Height significantly below genetic potentials (-2SD below mid-parental
  - target).
  - Abnormally slow growth velocity.
  - Downwardly crossing percentile channels on growth chart (> 18 mths age).
- Average height velocity at different phases:
  - Prenatal growth : 1.2 -1.5 cm / week
  - Infancy :23 - 28 cm / year
  - Childhood : 5 - 6.5 cm / year
  - Puberty : 8.3 cm / year (girls), 9.5 cm / year (boys)
- Measure serial heights to assess the growth pattern and height velocity.

Initial screening evaluation of growth failure

- General tests:
  - FBC with differentials, renal profile, liver function test, ESR, Urinalysis.
- Chromosomal analysis in every short girl.
- Endocrine tests
  - Thyroid function tests.
  - Growth factors: IGF-1, IGFBP-3.
  - Growth hormone stimulation tests if growth hormone deficiency is strongly suspected. (Refer to a Paediatric Endocrine Centre)
- Imaging studies
  - Bone age : anteroposterior radiograph of left hand and wrist.
  - CT / MRI brain (if hypopituitarism is suspected).
- Other investigations depends on clinical suspicion.
  - Blood gas analysis.
  - Radiograph of the spine.

Differential diagnosis of short stature and growth failure	

Healthy but short children
• Familial short stature
• Constitutional growth delay
Intrinsic short stature
• Small for gestational age
• Genetic syndromes
  • Down syndrome
  • Turner syndrome
  • Prader-Willi syndrome
• Skeletal dysplasia
  • Achondroplasia
  • Hypochondroplasia
Systemic diseases
• Infectious: HIV, tuberculosis
• Cardiac disease
• Renal disease
  • Renal tubular acidosis
  • Chronic renal insufficiency
• Gastrointestinal
  • Cystic fibrosis
  • Inflammatory bowel disease
• Central nervous system disease
• Chronic lung disease
• Malignancy
	Endocrinopathies
	• Hypothyroidism
	• Hypopituitarism
	  • Heredity, sporadic, idiopathic
	• Isolated GH deficiency
	  • Birth injury
	  • Craniopharyngioma
	  • Cranial irradiation
	  • Brain tumours
	  • Midline defects
	  • Haemosiderosis
	• GH insensitivity (Laron syndrome)
	• Cushing syndrome, exogenous steroids
	• Poorly controlled diabetes mellitus
	• Precocious puberty
	• Pseudohypoparathyroidism
	• Pseudo-pseudohypo-parathyroidism
	Non-organic aetiology
	• Psychosocial deprivation
	• Nutritional dwarfing

Abbreviation: *GH, Growth Hormone*	

Clinical Approach to children with Short Stature

History

- Antenatal
  - Complications of pregnancy
  - Pre-eclampsia, hypertension
  - Maternal smoking, alcohol
  - Infections
- Birth
  - Gestational age
  - Birth weight and length
  - Mode of delivery (breech, forceps)
  - Apgar score
- Neonatal complications
- Developmental milestones
- Nutrition
  - General well being
  - Appetite, energy, sleep, bowel habits
  - Pattern of growth from birth
- Maternal and child relationship
- Medical history
  - Underlying illness, medications irradiation
- Family History
  - Short stature (3 generations).
  - Age of onset of puberty in family members of the same sex
  - Diseases in the family

Physical Examination

Anthropometry

- Height, weight, head circumference
- Height velocity
- Arm span
- Upper: lower segment Ratio: 1.7 in neonates to slightly <1.0 in adults
- General appearance and behaviour
- Dysmorphism
- Pubertal staging

Family Measurements

Measure height of parents for mid-parental heights (MPH)

Boys : $\frac{\text{Father's height} + (\text{Mother's height} + 13)}{2}$

Girls: $\frac{\text{Mother's height} + (\text{Father's height} - 13)}{2}$

Management

- Treat underlying cause (hypothyroidism, uncontrolled diabetes mellitus, chronic illnesses).
- For children suspected to be GH deficient, refer to Paediatric Endocrinologist for initiation of GH.
- Psychological support for non-treatable causes (genetic / familial short stature; constitutional delay of growth and puberty)
- FDA approved indications for GH treatment in Children:
  - Paediatric GH deficiency
  - Turner syndrome
  - Small for gestational age
  - Chronic renal insufficiency
  - Idiopathic short stature
  - Prader–Willi syndrome
  - AIDS cachexia

GH Treatment

- GH should be initiated by a Paediatric Endocrinologist.
- GH dose: 0.025 - 0.05 mg/kg/day (0.5 - 1.0 units/kg/wk) SC daily at night.
- GH treatment should start with low doses and be titrated according to clinical response, side effects, and growth factor levels.
- During GH treatment, patients should be monitored at 3-monthly intervals (may be more frequent at initiation and during dose titration) with a clinical assessment (growth parameters, compliance) and an evaluation for adverse effects (e.g. impaired glucose tolerance, carpal tunnel syndrome), IGF-1 level, and other parameters of GH response.
- Other biochemical evaluations:
  - Thyroid function
  - HbA1c
  - Lipid profile
  - Fasting blood glucose
- Continue treatment till child reaches near final height, defined as a height velocity of < 2cm / year over at least 9 months (or bone age > 13 years in girls and >14 years in boys).
- Treat other pituitary hormone deficiencies such as hypothyroidism, hypogonadism, hypocortisolism and diabetes insipidus.

Chapter 59: Congenital Hypothyroidism

Introduction

- Incidence of congenital hypothyroidism worldwide is 1:2500 - 4000 live births
- In Malaysia, the incidence is 1:2200 to 3000 from the annual data of National Congenital Hypothyroidism Screening Program.
- It is the commonest preventablecause of mental retardation in children.
- Thyroid hormones are crucial for:
  - Normal growth and development of brain and intel-lectual function, during the prenatal and early postnatal period.
  - Maturation of the foetal lungs and bones.

Causes of Congenital Hypothyroidism

- Thyroid dysgenesis (85%)
  - Athyreosis (30%)
  - Hypoplasia (10%)
  - Ectopic thyroid (60%)
- Other causes (15%)
  - Inborn error of thyroid hormone synthesis (1:30,000)
  - Hypothalamo-pituitary defect (1:100,000)
  - Peripheral resistance to thyroid hormone (very rare)
  - Transient neonatal hypothyroidism (1:100 - 50,000)
  - Endemic cretinism

Signs and symptoms

- Most infants are asymptomatic at birth.
- Subtle clinical features include :
  - Prolonged neonatal jaundice
  - Constipation
  - A quiet baby
  - Enlarged fontanelle
  - Respiratory distress with feeding
  - Absence of one or both epiphyses on X-ray of knees
- If left untreated, overt clinical signs will appear by 3 - 6 months: coarse facies, dry skin, macroglossia, hoarse cry, umbilical hernia, lethargy, slow movement, hypotonia and delayed devel-opmental milestones.
- Most infants with the disease have no obvious clinical manifestations at birth, therefore neonatal screening of thyroid function should be performed on all newborns.

Biochemical diagnosis

- A physiologic surge of TSH occurs within the first 30 minutes of life due to the stress of delivery and exposure to the extrauterine environment.
- Serum TSH levels peak at levels as high as 70 mIU/L within the first 24 hours of life and then usually drop to < 10 mIU/L within the first 3 days of life. Serum levels of TSH are less than 6 mIU/L beyond the neonatal period.
- Following the TSH surge, fT4 increases by approximately 50% at days 1-4 of life, and remains elevated at 7 days of postnatal life. Median concentration of fT3, fT4 and TSH were greatest during the first month of life and subsequently decrease with age.
- Therefore, adult normative values, provided by many general hospital laboratories, differ from those in newborn period and should never be used for the neonates. Normal values according to both gestational and postnatal age up to 28 days of life should be used. Normal serum levels of fT4 and TSH in the first week of life have been published (refer table below), though it should be noted that precise values may vary somewhat, depending on the specific assays used in different laboratories. Refer to your hospital laboratory values for norms according to age.

Level of Cord TSH and fT4

- Cord blood TSH level according to the Malaysian Congenital Hypothyroid Screening Protocol
  - NORMAL: < 20mIU/L or use 97.5th percentile value as determine by the local laboratory or laboratory that used the same analyser
  - BORDERLINE: 20-60 mIU/L
  - HIGH: > 60 mIU/L
- Cord fT4 level:
  - NORMAL : > 15 pmol/l
  - LOW: ≤ 15 pmol/l

Retesting of Patients and management

- Blood samples for confirmation (re-testing) should be *venous* samples and should be taken from the baby *after 72 hours of life*. This is to avoid the TSH surge that occurs from ½ hour after birth to 72 hours of age.
- *Babies for retesting are those with high cord TSH (> 60 mIU/L) or borderline cord TSH (20-60 mIU/L) with low cord fT4 (≤ 15 pmol/l).*
- Ideally, the standard age specific reference range of venous fT4 for specific assays, as in the table above, should be used.

Comparison of fT4 reference intervals of different age groups using different assay systems (from Kapelari et al. *BMC Endocr Disord* 2008; 8: 15.)

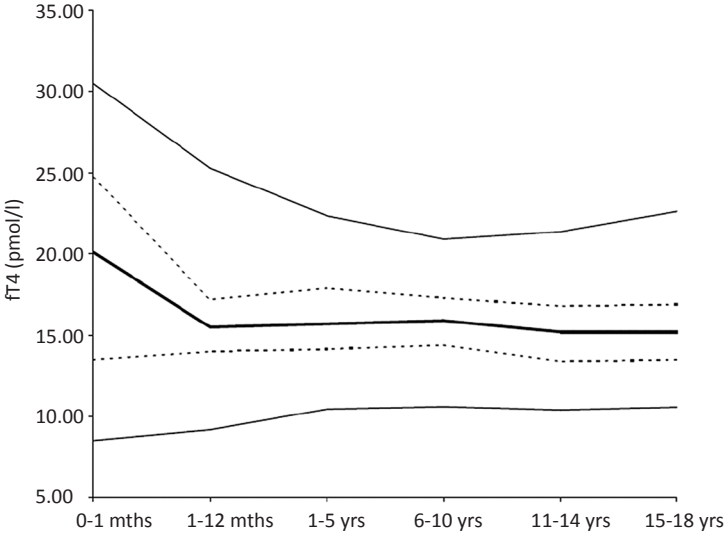
	Soldin et al., 1995 Abbott IMx®	Zurakowski et al., 1999 DELFIA®	Elmlinger et al., 2001 Immulite®	Djemli et al., 2004 Access 2®	Hübner et al., 2002 Advia Centaur®	Kapelari et al., Advia Centaur®
fT4 Age	[mU/L] n = 533	[mU/L] n = 5,558	[mU/L] n = 762	[mU/L] n = 706	[mU/L] n = 460	[mU/L] n = 1,209
1 d – 7 d	F: 11 – 25 M: 10 – 36	n.d.	29.60 – 62.40 – 79.20	F: 11.0 – 13.6 – 22.3	10.8 – 26.8 [a]	8.54 – 20.10 – 30.20
8 d –15 d	F: 8 – 25	n.d.	18.00 – 42.30 – 63.60	M: 9.8 – 12.2 – 23.2	10.9 – 25.5 [b]	
15 d – 1 m	M: 6 – 30	n.d.	n.d.			
1 – 12 m	F: 11 – 24 M: 10 – 26	9.5 – 19.5 – 39.5	11.10 – 19.70 – 27.30	F: 9.0 – 11.3 – 16.1	11.4 – 14.5 – 20.9 [c]	11.95 – 15.50 – 22.51
1 – 2 y				M: 8.7 – 11.7 – 16.2		
2 – 3 y	F: 13 – 22	9.0 – 18.4 – 37.2		n.d.	11.4 – 14.7 – 19.0	11.90 – 15.70 – 20.85
3 – 4 y	M: 12 – 21			n.d.		
4 – 5 y			12.90 – 17.30 – 23.90	n.d.		
5 – 6 y				n.d.		
7 – 8 y	F: 11 – 20	8.3 – 16.9 – 34.1	12.90 – 19.30 – 24.50	n.d.	11.0 – 14.2 – 18.8	11.54 – 15.90 – 19.96

Footnote: M, Male; F, Female; a, 1 d – 3 d; b, 4 d – 30 d; c, 61 d

Comparison of fT4 reference intervals of different age groups using different assay systems (from Kapelari et al. *BMC Endocr Disord* 2008; 8: 15.)

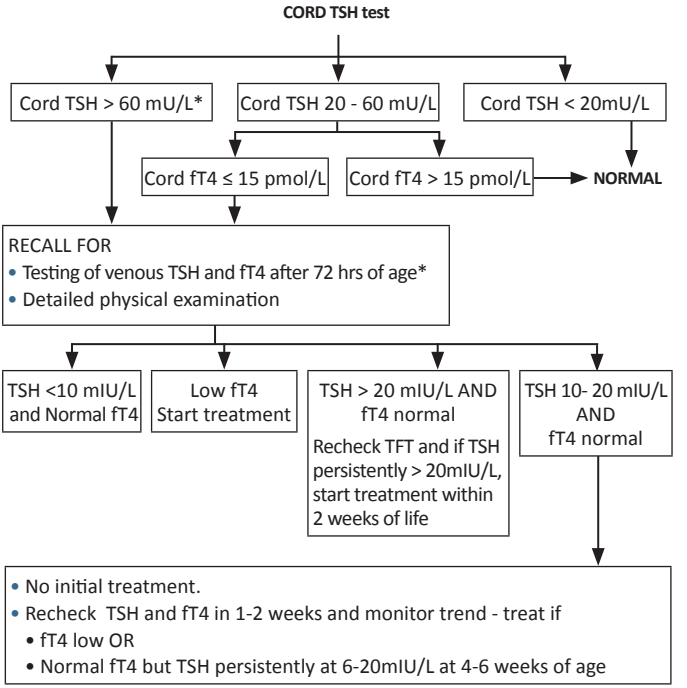
	Soldin et al., 1995 Abbott IMx®	Zurakowski et al., 1999 DELFIA®	Elmlinger et al., 2001 Immulite®	Djemli et al., 2004 Access 2®	Hübner et al., 2002 Advia Centaur®	Kapelari et al., Advia Centaur®
fT4 Age	[mU/L] n = 533	[mU/L] n = 5,558	[mU/L] n = 762	[mU/L] n = 706	[mU/L] n = 460	[mU/L] n = 1,209
9 y – 10 y	M: 10 – 22		10.30 – 17.00 – 23.80	F: 9.6 – 11.6 – 14.5 M: 9.7 – 11.7 – 14.2		
11 y			11.80 – 16.70 – 22.65			
12 y	F: 10 – 19		10.40 – 16.20 – 22.91	F: 8.8 – 10.7 – 13.5	10.8 – 13.6 – 18.7	11.10 – 15.20 – 20.00
13 y	M: 12 – 20	7.6 – 15.5 – 31.5	8.50 – 16.50 – 22.52	M: 8.4 – 10.8 – 13.0		
14 y			12.20 – 16.50 – 23.30			
15 y			9.10 – 17.00 – 23.40		10.7 – 14.4 – 18.7	10.80 – 15.20 – 20.33
16 y	F: 11 – 19		12.90 – 16.70 – 23.30	F: 8.7 – 10.7 – 13.6		
17 y	M: 12 – 20	7.0 – 14.1 – 28.7	11.80 – 17.40 – 22.50	M: 9.5 – 11.8 – 15.0		
18 y – 19 y			9.30 – 14.50 – 20.50	n.d.		

Footnote: M, Male; F, Female; a, 1 d – 3 d; b, 4 d – 30 d; c, 61 d



Age-related reference values for fT4 (both sexes).
The central 95% range (2.5th, 25th, 50th, 75th, and 97.5th percentiles) is shown.
Due to resolution reasons lines start at zero, although no samples were taken within the first hours after birth.
(from Kapelari et al. *BMC Endocr Disord* 2008; 8: 15.)

MANAGEMENT OF CONGENITAL HYPOTHYROIDISM



*Note: In cases with logistic problems and cord TSH > 60 mIU/L, treatment can be started after venous TFT have been taken. Patient shall be recalled to review the TFT results when available. Venous TFT must be collected before starting L-thyroxine. A normal TFT result after administration of L-thyroxine does not rule out congenital hypothyroidism.

Interpretation of the results and decision to treat is as follows:

- Normal venous TSH after 72 hours of life is usually < 10 mIU/l and fT4 is in the normal range. The normal range varies according to the assay method used. Refer to the table above on normal range for various assays.
- If venous TSH taken after 72 hours is >20 mIU/L, and venous FT4 is normal, repeat TFT. Treat for congenital hypothyroidism if TSH persistently >20 or fT4 low for age. Refer urgently to paediatrician if in doubt to consider starting treatment within two weeks of life if TSH persistently above 20 mIU/L (although fT4 normal for age). Trending of TFT should be observed. In certain cases, bone age may be performed (X-ray knee in normal term infants).
- If venous fT4 is below the norm for age, start treatment immediately, regardless of TSH level. Check with your hospital laboratory for age appropriate reference.
- If the venous TSH taken after 72 hours of life 10-20 mIU/L and normal fT4, no initial treatment. Recheck venous TFT after 1-2 weeks and monitor the trend. Check that the TSH continues dropping towards normal for age and the fT4 remains normal. Consider treatment if the result is suggestive of hypothyroidism.
- Beyond 21 days of life in a well baby with a venous fT4 within the limits for age, if the venous TSH remains > 6 mIU/L, to consider discussion with the family, of either initiating thyroxine supplementation immediately and re-challenge at a later stage; or withholding treatment but retesting two weeks later.
- Congenital hypothyroidism screening does not pick up central hypothyroidism where the venous TSH is normal or low and fT4 is low.
- Due to uncertainty of normal range for venous fT4 with different assays in many hospitals, it may be a practice in some hospitals to assume venous fT4 less than 15 pmol/L and TSH > 6-10 mIU/L being abnormal in infants of 1-4 weeks of life, and thus treatment be considered. However, this level of fT4 may possibly underestimate the normal venous fT4 level in the early neonatal life, and overestimate it in the later neonatal period.

TREATMENT

Generally, treatment for congenital hypothyroidism is started (within 2 weeks of life) based on:

- Venous fT4 below norms for age
- Venous TSH persistently more than 20 mIU/L
- In cases with logistic problems and cord TSH > 60 mIU/L, treatment can be started after venous TFT have been taken. Patient shall be recalled to review the TFT results when available.

Timing of treatment

- Should begin immediately after diagnosis, and within 2 weeks of life.
- If features of hypothyroidism are present, treatment is to be started urgently.

Duration

- Treatment is life-long except in children suspected of having transient hypothyroidism.

Preparation

- Brand name rather than generic L-T4 tablets should be used, particularly during infancy and in severe cases.
- The L-thyroxine tablet should be crushed, mixed with small amount of breast milk or water and fed to the infant.
- Tablets should not be mixed with soy formulas or any preparation containing iron (formulas or vitamins), both of which reduce the absorption of T4.

Doses of L- Thyroxine by age

Age	mcg/kg/dose, daily
0 – 3 months	10 – 15
3 – 6 months	8 – 10
6 – 12 months	6 – 8
1 – 5 yr	5 – 6
6 – 12 yr	4 – 5
> 12 yr	2 – 3

Note:

- Average adult dose is 1.6 mcg /kg/day in a 70-kg adult (wide range of dose from 50 - 200 mcg/day).
- L-thyroxine can be given at different doses on alternate days, e.g. 50 mcg given on even days and 75 mcg on odd days will give an average dose of 62.5 mcg/day.
- Average dose in older children is 100 mcg/m^2/day.

Goals of therapy

- To restore the euthyroid state by maintaining a venous fT4 level at the upper half of the normal age-related reference range (Please refer to the reference range of your centre). Ideally, venous TSH levels should be between 0.5-2.0 mIU/L after the first month of life.
- Venous fT4 levels usually normalise within 1-2 weeks, and TSH usually become normal after 1 month of treatment.
- Some infants continue to have high venous TSH concentration (10-20 mIU/L) despite normal venous fT4 values due to resetting of the pituitary-thyroid feedback threshold. However, compliance to medication has to be reassessed and emphasised.

Congenital malformations and syndromes should be systematically sought for in infants with congenital hypothyroidism. A thorough physical examination should be carried out in all neonates with high TSH concentrations for the detection of congenital malformations, particularly those affecting the heart, and in children for the identification of any underlying dysmorphic syndrome or neuro-developmental disorders.

Follow-up

- Monitor growth parameters and developmental assessment (special emphasis on hearing and speech). Ideally, repeated hearing tests should be carried out before school age and as required (even though newborn hearing screening tests has been done).
- Patient (and serum fT4 and TSH) needs to be monitored according to the following schedule: -
  - Age 1 month: Follow up 1-2 weekly until TSH levels normalised
  - Age 1-6 months: Follow up 1-2 monthly
  - Age 6 months - 3 years: Follow up 3-4 monthly
  - Age >3 years: Follow up 6-12 monthly
- Should be more frequent if compliance is questionable or abnormal TFT values, and 4-6 weeks after any change in L-thyroxine dose/formulation.
- Ongoing counselling of parents is important because of the serious consequences of poor compliance.

Re-evaluation of patients likely having transient hypothyroidism

- This is best done at age 3 years when thyroid dependent brain growth is completed at this age.
- Stop L-thyroxine for 4 weeks then repeat thyroid function test: fT4, TSH.
- If the fT4 is low and the TSH value is elevated, permanent primary hypothyroidism is confirmed and imaging studies (thyroid scan, Ultrasound of the thyroid) should be considered to determine the specific aetiology. Thus lifelong treatment is needed.

*Re-evaluation may be considered earlier than 3 years old if the patient is on very low dose of L-thyroxine (e.g. 12.5 mcg OD) while thyroid function tests suggests over-treatment (i.e. TSH suppressed) and eutopic thyroid gland.

Re-evaluation may be waived in those with frequently raised TSH (>10 mIU/L) after the first year of life or already known absent or ectopic thyroid gland.

Screening in special categories of neonates

- Second screening should be considered for the following conditions
  - VLBW babies
  - Sick newborns admitted to NICU such as HIE babies
  - Preterm newborns
  - Multiple births
  - Down syndrome

Cord TSH screening may be normal for these groups of babies and require a repeat screening at 2-4 weeks of age

- Screening of congenital hypothyroidism in neonates with prematurity (<37 weeks gestation):
  - There is relative immaturity of the hypothalamic-pituitary-thyroid axis according to gestational age of infants in utero.
  - Following delivery, the magnitude of increase in fT4 is less in premature infants compared to term infants. Premature babies with congenital hypothyroidism can have a delayed TSH rise despite a normal cord blood TSH.
  - Besides cord blood TSH screening, venous TFT should be performed around 2-4 weeks of age.
  - The interpretation of screening results should take into account the results of all specimens analyzed in a multiple sampling strategy.
  - The criteria defining the results of investigations should be adapted for the analytical parameters measured, the method used, and the age at sampling and maturity (gestational age/birth weight) of the infant.

Babies born to mothers with thyroid disorders

- All newborns of mothers with established or suspected autoimmune thyroid diseases should be evaluated for thyroid dysfunction, followed up and treated if necessary.

Chapter 60: Diabetes Mellitus

Introduction

- Type 1 diabetes mellitus (T1DM) is the most common type of diabetes mellitus in children and adolescents.
- The incidence of type II diabetes mellitus is on the rising trend among young people due to obesity.

Symptoms and Signs of Diabetes Mellitus	
Early	**Late**
Polydipsia Polyuria Weight loss Enuresis (secondary)	Vomiting Dehydration Abdominal pain Hyperventilation due to acidosis Drowsiness, coma

Diagnostic criteria of Diabetes Mellitus

- Classic symptoms[a] of diabetes or hyperglycaemic crisis, with plasma glucose concentration ≥ 11.1 mmol/L
  OR
- Fasting plasma glucose[b] ≥ 7.0 mmol/L
  OR
- Two hour post-load glucose ≥ 11.1 mmol/L in OGTT[c]
  OR
- HbA1c >6.5%[d]

[a] classic symptoms consist of thirst, polyuria, polydipsia, recurrent infection and weight loss.

[b] Fasting is defined as no caloric intake for at least eight hours.

[c] The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g.

[d] The test should be performed in a laboratory using a method that is National Glycohaemoglobin Standardisation Programme certified and standardised to the Diabetes Control and Complications Trial (DCCT) assay

- The diagnosis must be confirmed by repeat blood glucose testing in the absence of unequivocal hyperglycaemia.
- The role of HbA1c alone in the diagnosis of diabetes mellitus remains unclear and diabetes cannot be excluded when the value is <6.5%.

Diagnosis of T1DM

- The diagnosis of diabetes mellitus in children and adolescents should be made based on clinical features and biochemical criteria (World Health Organization criteria*).
- Autoantibodies testing (glutamic acid decarboxylase antibody, anti-islet antibody, insulin autoantibodies and protein tyrosine phosphatase antibody) should be done to confirm the diagnosis of type 1 diabetes mellitus (T1DM).

Clinical features of T1DM and T2DM in children and adolescents		
	T1DM	T2DM
Age of onset	6 months to young adulthood	Usually pubertal or later
Clinical presentation	Most often acute, rapid onset of symptoms	Variable: often insidious onset of symptoms
Autoimmunity	Present	No
Ketosis	Common	Rare
Body habitus	Usually lean but can be overweight following population frequency	Often overweight/obese
Acanthosis nigricans	Typically absent	Commonly present

Management

Principles of insulin therapy

- Daily insulin dosage
  - Daily insulin dosage varies between individuals and changes over time.
  - The correct dose of insulin for any individual is the dose that achieves the best glycemic control without causing obvious hypoglycemia problems, and achieving normal growth (height and weight).
  - Dosage depends on many factors such as: age, weight, stage of puberty, duration and phase of diabetes, state of injection sites, nutritional intake and distribution, exercise patterns, daily routine, results of blood glucose monitoring (BGM), glycated hemoglobin (HbA1c) and intercurrent illness.
- Guidelines on dosage:
  - During the partial remission phase, total daily insulin dose is usually 0.5 IU/kg/day.
  - Prepubertal children (outside the partial remission phase) usually require insulin of 0.7–1.0 IU/kg/day.
  - During puberty, requirements may rise to 1 - 2 IU/kg/day.
  - The total daily dose of insulin is distributed across the day depending on the daily pattern of blood glucose and the regimens that are used.
- The choice of insulin regimen will depend on many factors that include:
  - Age of patient.
  - Duration of diabetes.
  - Lifestyle (dietary patterns, exercise schedules, schooling, work commitments, etc.)
  - Target of metabolic control.
  - Preference of the patient/caregiver.

INTENSIVE INSULIN THERAPY

- Intensive insulin therapy is the preferred regimen in patients with type 1 diabetes mellitus (T1DM).

Basal-bolus regimen

- The basal-bolus regimen (intermediate-acting insulin/long-acting basal once or twice daily and rapid-acting/short-acting boluses with meals and snacks) mimics the physiological insulin secretion.
- Basal insulin constitutes about 40 - 60% of the total daily insulin dose (TDD) requirements; the remainder is pre-prandial rapid-acting/short-acting insulin.

Pump therapy

- Insulin pump therapy is gaining popularity with a variable basal rate and bolus doses with meals.
- Continuous subcutaneous insulin infusion (CSII) results in better metabolic control and lower TDD requirement compared with multiple daily injection (MDI) in short-term.
- In young children 1 - 6 years old with T1DM, insulin pump therapy is a safe and efficacious alternative compared with insulin injection.
- Advantages include potential decrease in hypoglycaemic episodes and improvement in quality of life.

LESS INTENSIVE INSULIN THERAPY

- Less intensive regimen consists of three or less injections a day.
- Three injections daily consist of:
  - Rapid-acting/short-acting and intermediate-acting insulin pre-breakfast.
  - Rapid-acting/short-acting alone pre-lunch or pre-dinner.
  - Intermediate-acting insulin pre-bed.

Premixed insulin is not recommended for paediatric use because of its fixed ratio of insulin components and does not allow flexibility of dosing. However, if patients and their caregivers prefer less injections, self-mixed insulin (rapid-acting/short-acting and intermediate-acting insulin) given twice a day may be acceptable.

Types of Insulin Preparations and their Action Profiles				
Generic name	Onset of action	Peak of action (hr)	Duration of action (hr)	Timing of injection
Rapid-acting insulin • Aspart • Lispro • Glulisine	 10 - 20 min 0 - 15 min 5 - 15 min	 1 - 3 1 1 - 2	 3 - 5 3.5 - 4.5 3 - 5	5-15 min before or immediately after meals
Short-acting insulin	30 min	1 - 4	6 - 8	30 min before meals
Intermediate acting insulin [neutral protamine Hagedorn (NPH)]	1 - 1.5 hour	4 - 12	16 - 23	Pre-breakfast/ pre-bed
Long-acting insulin • Glargine • Detemir	 2 - 4 hour 1 hour	 Peakless Peakless	 20 - 24 17 - 23	Same time everyday at anytime of the day
Premixed human (30% short-acting insulin + 70% NPH)	30 min	Dual	16 - 23	30 - 60 min before meals
Premixed analog • 30% aspart + 70% aspart protamine • 25% lispro + 75% lispro protamine	 10 - 20 min 0 - 15 min	 Dual Dual	 18 – 23 16 - 18	5 - 15 min before meals

Source: Perkhidmatan Diabetes dan Endokrinologi, Kementerian Kesihatan Malaysia. Practical Guide to Insulin Therapy in Type 2 Diabetes Mellitus. Putrajaya: MOH; 2010

INSULIN DOSE ADJUSTMENT

- For patients with T1DM on basal bolus therapy, pre-meal insulin dose may be adjusted based on insulin to carbohydrate ratio (ICR) or insulin sensitivity factor (ISF).
- Detailed record of Self-monitoring of Blood Glucose (SMBG), carbohydrate intake and insulin doses are crucial when making insulin dose adjustments.

Insulin to Carbohydrate Ratio (ICR)

- ICR is defined as the amount of carbohydrate in grams covered by one unit (IU) of rapid-acting or short-acting insulin.
- It can be calculated by using the 500 (for rapid-acting insulin), and 450 (for short-acting insulin) rules.
- ICR for most children are 1:20 or 1:25 However in practice, adolescents may require more insulin and thus giving a higher ICR (e.g. 1:15). ICR is often higher for breakfast due to higher insulin resistance.
- For very young children requiring <10 IU of insulin per day, the 300 - 450 rule may be used.
- The 500 rule for rapid-acting insulin:

  ICR = 500* / (Total daily insulin)

  *450 for short acting insulin (basal and bolus insulin)

Insulin Sensitivity Factor (ISF)

- ISF is defined as the amount of BG in mmol/L reduced by one unit (IU) of rapid-acting or short-acting insulin and used to correct hyperglycaemia.
- The 100 rule for rapid-acting insulin:

  ISF = 100* (Total daily insulin)

  *83 for short-acting insulin (basal and bolus insulin)

Monitoring of glycaemic control

- Self-monitoring of blood glucose (SMBG) should be practised by all children and adolescents with type 1 diabetes mellitus.
- SMBG should be performed four to six times a day and more frequent in certain conditions such as sick day or during exercise.
- It is a good practice to keep a diary to record glucose levels, insulin dosages and dietary details for treatment adjustments.
- This diary should be reviewed regularly by patients, families and healthcare providers.

SMBG allows prompt actions to be taken for optimal treatment and prevention of hypo- or hyperglycaemia when it is performed at the correct timing as below:

- To optimise basal insulin, blood testing should be done at bedtime, during the night (e.g. 3am to detect nocturnal hypoglycaemia and hyperglycaemia) and after the overnight fast (pre-breakfast).
- For immediate adjustment of meal insulin dose, pre-meal blood testing should be done. For subsequent adjustment of meal insulin dose, blood testing should be done pre-meal and two hours postmeal to show levels of BG in response to the meal insulin.
- For glycaemic control during vigorous/prolonged exercise, blood testing should be done before, during and several hours after the exercise.
- Blood testing should be done when hypoglycaemia is suspected. It should also be done during intercurrent illness to prevent hyperglycaemia.

Continuous Glucose Monitoring System

Continuous Glucose Monitoring System (CGMS) uses minimally invasive device to measure SC interstitial fluid glucose every 1 - 5 minutes (continuously). This device is expensive and not affordable to most families.

- Indications for CGMS are:
  - Failure to achieve individual's glycaemic target (HbA1c) despite optimal use of intensive insulin regimens.
  - Suspected nocturnal hypoglycaemia and/or early morning hyperglycaemia.
  - Suspected unrecognised hypoglycaemia e.g. exceptionally low HbA1c without reported hypoglycaemia.
  - Recurrent severe hypoglycaemia and hypoglycaemia unawareness.

Self-monitoring of urinary or blood ketones

- Urine or blood ketones measurement should be monitored during episodes of uncontrolled hyperglycaemia, intercurrent illness (sick days) and impending ketoacidosis:
  - Especially with presence of abdominal pains, vomiting, drowsiness or rapid breathing.
  - When there is persistent BG levels >14 mmol/L (250 mg/dL).
  - However in local setting, the blood ketone strips are expensive and urinary ketone strips for self-monitoring are not widely available or affordable.

Recommendations for HbA1c measurement

- Every patient should have a minimum of one measurement of HbA1c per year, ideally 3 to 6 measurements per year depending on age and degree of glycaemic control.
- The recommended HbA1c target for all patients younger than 18 years is <7.5% (58 mmol/mol).
- Each patient should have their targets individually determined with the goal of achieving a value as close to normal as possible while avoiding severe hypoglycaemia and minimising frequent mild to moderate hypoglycaemia.

Level of control				
Assessment	Ideal (non-diabetic)	Optimal	Suboptimal (action suggested)	High risk (action required)
Clinical assessment Symptoms of hyperglycaemia	No symptoms	No symptoms	Polyuria, polydipsia, enuresis	Blurred vision, poor weight gain, poor growth, delayed puberty, poor school attendance, skin or genital infections, and signs of vascular complications
Clinical assessment Symptoms of hypoglycaemia	No symptoms	No severe hypoglycaemia	Episodes of severe hypoglycaemia	Episodes of severe hypoglycaemia
Biochemical assessment* SMBG values in mmol/L AM fasting or pre-prandial Post-prandial Bedtime	 3.6 - 5.6 4.5 - 7.0 4.0 - 5.6 3.6 - 5.6	 4 – 8 5 - 10 6.7 - 10 4.5 - 9	 >8 10 - 14 <4.2 or >9 <4.2 or >9	 >9 >14 <4.4 or >11 <4.0 or >11
Nocturnal HbA1c DCCT (%) *	<6.5	<7.5**	7.5 - 9.0**	>9.0***
HbA1c IFCC (mmol/mol)**	<48	<58	58 - 75	>75

* HbA1c DCCT: HbA1c according to the DCCT (Diabetic Control and Complication Trial).
** HbA1c IFCC: HbA1c according to the IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) reference.

Diet

- A balance and healthy diet for age is required with dietician involvement.
- Carbohydrate counting should be taught to patients. Insulin dosage should match the carbohydrate intake.

Exercise

- Physical activities should be performed regularly and in a safe manner in patients with type 1 diabetes mellitus.
- Physical activity that significantly improve glycaemic control are:
  - Duration of >60minutes per session.
  - Higher frequency of >3 times in a week.
  - Longer duration programme of >3 months.
  - Combined aerobic and resistance training.

The following steps should be observed regarding physical activity:

- Avoid strenuous physical activity if pre-exercise BG is high (>14mmol/L) with ketonuria or ketonaemia.
- Increase intensity and duration of physical activity in a progressive manner.
- Do not inject insulin in the site that will be heavily involved in muscular activity e.g. not to inject in the thigh before cycling.
- Avoid physical activity exercise at peak action of insulin.
- Consider reducing evening basal insulin.
- Monitor BG in evening and night after physical activity to avoid nocturnal hypoglycaemia.
- Carry some sugar and drink more water.

Diabetic Education

At diagnosis - Survival skills:

- Explanation of how the diagnosis has been made and reasons for symptoms.
- Simple explanation of the uncertain cause of diabetes. No cause for blame.
- The need for immediate insulin and how it will work.
- What is glucose? Normal blood glucose (BG) levels and glucose targets
- Practical skills: insulin injections; blood and/or urine testing, reasons for monitoring.
- Basic dietary advice.
- Recognition and treatment of hypoglycaemia.
- Diabetes during sick days illnesses. Advice not to omit insulin - prevent DKA.
- Diabetes at home or at school including the effects of exercise.
- Psychological adjustment to the diagnosis.
- Details of emergency telephone contacts.

Medic alert

- Wear the medic alert at all times as this may be life saving during an emergency.
- Obtain request forms for a medic alert from the local diabetes educator.

Diabetes support group

- Diabetes Malaysia, Diabetes Resource Centre at regional centre, hospitals.
- Encourage patient and family members to enroll as members of diabetes associations and participate in their activities.

School

- Patients with type 1 diabetes mellitus should have individualised diabetes medical management plan in school/day-care centre.
- The school teachers should be informed about children having diabetes.

Other complications and other associated conditions

- Diabetes complication screening as in Table on next page.
- Monitoring of growth and pubertal development.
- Blood pressure should be monitored at least annually. Blood pressure value should be maintained at the <95th percentile for age or 130/80 mmHg for young adults.
- Screening of thyroid function at diagnosis of diabetes. Then every second year if asymptomatic, no goitre and thyroid autoantibodies negative. More frequent assessment is indicated otherwise.
- In areas of high prevalence for coeliac disease, screening for coeliac disease should be carried out at the time of diagnosis and every second year thereafter. More frequent assessment if there is clinical suspicion of coeliac disease or coeliac disease in first-degree relative.
- Routine clinical examination for skin and joint changes.

Evaluation for complications

- Microalbuminuria: 2 of 3 consecutive urine collections within 3-6 months duration should be used as evidence of microalbuminuria defined as:
  - Albumin excretion rate (AER) 20-200 mcg/min or AER 30-300 mg/day.
  - Albumin/creatinine ratio (ACR) 2.5-25 mg/mmol (males) and 3.5 – 25 mg/mmol (females) on first morning urine specimen; Random ACR is higher.
  - Albumin concentration (AC) 30-300 mg/L (on early morning urine sample).
- Spot urine ACR is closely correlated with 24-hours urine albumin excretion in patients with T1DM ($R2=0.828$, $p<0.001$).
- Abnormal screening tests should be repeated as microalbuminuria may not be persistent.
- When interpreting urine microalbuminuria, false positive results should be considered which may occur in certain conditions (exercise, menstrual bleeding, infections, fever, kidney diseases, marked hyperglycaemia).

Sick Day Management						
Ketones		Blood Glucose				
Blood mmol/L	Urine	5.5 mmol/L	5.5 - 10 mmol/L	>10 - 14 mmol/L	>14 - 22 mmol/L	>22 mmol/L
<0.6	Negative or trace	Do not give extra insulin Recheck BG & ketones in 2 hours	No insulin adjustment needed	Add correction dose of insulin according to ISF	Give extra 5% of TDD or 0.05 IU/kg	Give extra 10% of TDD or 0.1 IU/kg *Repeat if needed*
0.6 - 1.4	Trace, small to moderate	Starvation ketones Extra carb & fluid needed	Starvation ketones Extra carb & fluid needed No insulin adjustment needed	Extra carb & fluid needed Give 5-10% of TDD or 0.05 - 0.1 IU/kg	Give extra 5 - 10% of TDD or 0.05 - 0.1 IU/kg	Give extra 10% of TDD or 0.1 IU/kg *Repeat if needed*
1.5 - 2.9	Moderate to large	High levels of starvation ketones Check BG meter Recheck BG & ketones Extra carb & fluid needed	High levels of starvation ketones Extra carb & fluid needed Give 5% of TDD or 0.05 IU/kg; rpt insulin dose when BG has risen	Extra carb & fluid needed Give 10% of TDD or 0.1 IU/kg	Give extra 10 - 20% of TDD or 0.1 IU/kg; repeat insulin dose after 2 hours if ketones do not decrease	
>3.0	Large	Very high levels of starvation ketones Check BG meter Recheck BG & ketones Extra carb & fluid needed	Very high levels of starvation ketones Extra carb & fluid needed Give 5% of TDD or 0.05 IU/kg; rpt insulin dose when BG has risen	Extra carb & fluid needed Give 10% of TDD or 0.1 IU/kg	Give extra 10 - 20% of TDD or 0.1 IU/kg; repeat insulin dose after 2 hours if ketones do not decrease	
There is an immediate risk of ketoacidosis if the blood ketone level is ≥3.0 mmol/L						

Screening, risk factors, and interventions for vascular complications				
Complications	Screening schedule	Screening methods	Risk factors	Potential interventions
Retinopathy	• Start at age 10 or at onset of puberty if this is earlier, after 2 - 5 years' diabetes duration • Annually thereafter	• Fundal photography or • Mydriatic ophthalmoscopy (less sensitive)	Hyperglycaemia High BP Lipid abnormalities Higher BMI	Improved glycaemic control Laser therapy
Nephropathy	• Start at age 10 or at onset of puberty if this is earlier, after 2 - 5 years' diabetes duration • Annually thereafter	• Urinary albumin: creatinine ratio (ACR) or • First morning urinary albumin concentration or • Timed urine collections for albumin excretion rates (AER)	Hyperglycaemia High BP Lipid abnormalities Smoking	Improved glycaemic control ACEi or ARB BP control
Neuropathy	Unclear	History and physical examination	Hyperglycaemia Higher BMI	Improved glycaemic control
Macrovascular disease	After age 10 years	• Lipid profile every 5 years • BP annually	Hyperglycaemia High BP Lipid abnormalities Higher BMI Smoking	Improved glycaemic control BP control Statins
ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BMI=body mass index; blood pressure (BP)				

Target levels for different parameters to reduce the risk of microvascular and cardiovascular diseases in children and adolescents with type 1 diabetes; the level of evidence are from adult studies.

Parameter	Target Level	Evidence Grade
Haemoglobin A1c (DCCT)	≤ 7.5 % without severe hypoglycaemia	A
Low density lipoprotein cholesterol	< 2.6 mmol/l	A
High density lipoprotein cholesterol	≥ 1.1 mmol/l	C
Triglycerides	< 1.7 mmol/l	C
Blood pressure	< 90th percentile by age, sex, height	C/B
Body mass index	< 95th percentile (non obese)	E
Smoking	None	A
Physical activity	>1 h of moderate physical activity daily	B
Sedentary activities	<2 h daily	B

Abbreviation: DCCT, Diabetes Control and Complication Trials Standard

Chapter 61: Diabetic Ketoacidosis

Diabetic Ketoacidosis (DKA)

- The biochemical criteria for the diagnosis of DKA are
- Hyperglycaemia: blood glucose > 11 mmol/L (> 200 mg/dL)
- Venous pH < 7.3 or bicarbonate <15 mmol/L.
- Ketonaemia and ketonuria.
- The choice of insulin regimen will depend on many factors that include:

Goals of therapy

- Correct dehydration.
- Correct acidosis and reverse ketosis.
- Restore blood glucose to near normal.
- Avoid complications of therapy.
- Identify and treat any precipitating event.

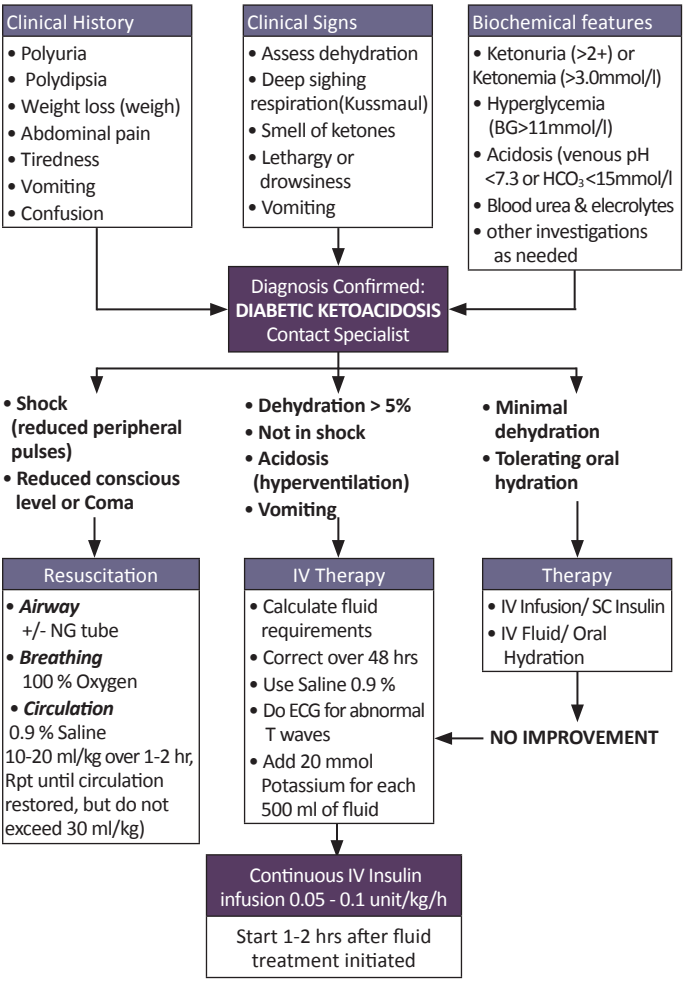
Emergency management

- Bedside confirmation of the diagnosis and determine its cause.
- Look for evidence of infection.
- Weigh the patient. This weight should be used for calculations and not the weight from a previous hospital record.
- Assess clinical severity of dehydration.
- Assess level of consciousness [Glasgow coma scale (GCS)]
- Obtain a blood sample for laboratory measurement of:
  - Serum or plasma glucose
  - Electrolytes, blood urea nitrogen, creatinine, osmolality
  - Venous blood gas (or arterial in critically ill patient)
  - Full blood count
  - Calcium, phosphorus and magnesium concentrations (if possible)
  - HbA1c
  - Blood ketone (useful to confirm ketoacidosis; monitor response to treatment)
- Urine for ketones.
- Appropriate cultures (blood, urine, throat), if there is evidence of infection.
- If laboratory measurement of serum potassium is delayed, perform an electrocardiogram (ECG) for baseline evaluation of potassium status.

Supportive measures

- Secure the airway and give oxygen.
- Empty the stomach via a nasogastric tube.
- A peripheral intravenous catheter or an arterial catherter (in ICU) for painless repetitive blood sampling.
- Continuous cardiac monitoring to assess T waves for evidence of hyper- or hypokalaemia.
- Antibiotics for febrile patients after cultures.
- Catheterization if the child is unconscious or unable to void on demand. (e.g. in infants and very ill young children)

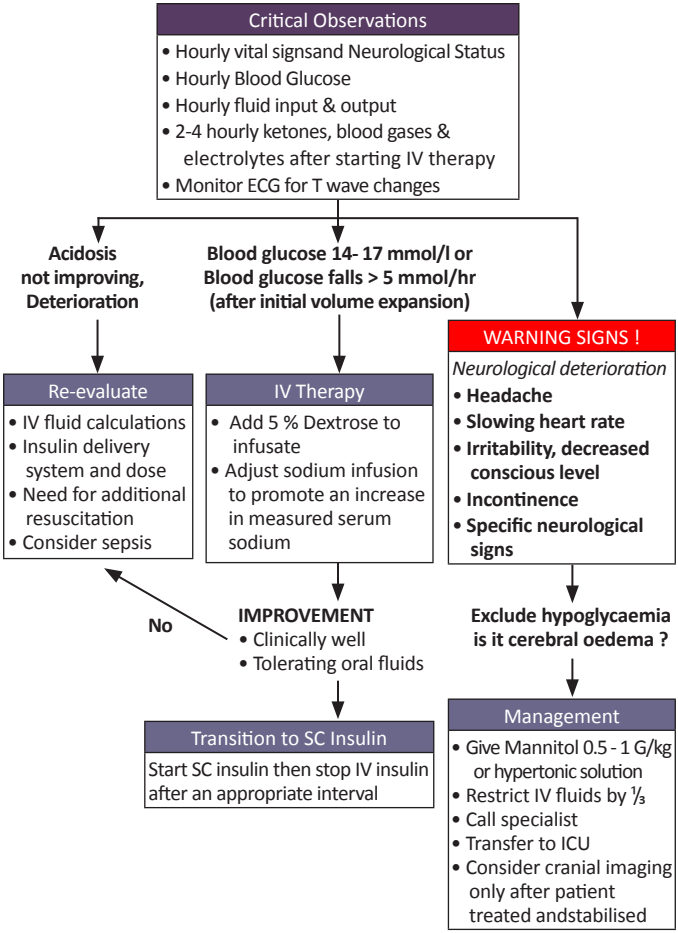
ALGORITHM FOR ASSESSMENT AND MANAGEMENT OF DIABETIC KETOACIDOSIS



DKA is categorised by the severity of acidosis:
- Mild (venous pH <7.3, bicarbonate <15 mmol/L)
- Moderate (venous pH <7.2, bicarbonate <10 mmol/L)
- Severe (venous pH <7.1, bicarbonate <5 mmol/L

Adapted from Dunger et al. Karger Pub. 1999

ALGORITHM FOR ASSESSMENT AND MANAGEMENT OF DIABETIC KETOACIDOSIS (CONT.)



Adapted from Dunger et al. Karger Pub. 1999

Monitoring of DKA

- Hourly (or more frequently as indicated) bedside monitoring
  - Vital signs (pulse rate, respiratory rate and blood pressure)
  - Neurological observations for warning signs and symptoms of cerebral oedema
  - Capillary Blood glucose
  - Insulin dose
  - Accurate fluid input (including oral fluid) and output
- Two to four hourly (or more frequently) laboratory tests
  - Blood glucose
  - Blood gases
  - Serum electrolytes
  - Blood urea nitrogen
  - Serum calcium, magnesium and phosphorus
  - Haematocrit
- Two hourly blood beta-hydroxybutyrate (β-OHB) (capillary blood)

Calculations
• Anion gap = (Na + K) - (Cl + HCO_3)
• Normal value: 12 +/- 2 mmol/L
• In DKA the anion gap is typically 20–30 mmol/L
• An anion gap > 35 mmol/L suggests concomitant lactic acidosis
• Corrected sodium (mmol/L) = measured Na + $\frac{2 \times (\text{plasma glucose} - 5.6)}{5.6}$
• Effective osmolality (mOsm/kg) = 2 x (Na + K) + plasma glucose + urea

Fluids and Salt

Principles of water and salt replacement

- Fluid replacement should begin 1 - 2 hours before starting insulin therapy.
- Patients with DKA have a deficit in extracellular fluid volume that is usually in the range of 5 - 10%.
- Clinical estimates of the volume deficit are subjective and inaccurate. Therefore in moderate DKA, use 5 - <7% and in severe DKA, 7 - 10% dehydration.
- Initial fluid therapy will depend on whether the patient is in:
  - Shock.
  - Severe volume depletion but not in shock (7 -10% dehydration) .
  - Mild to moderate volume depletion (5 - 7% dehydration).

DKA with shock

- In patients with DKA in shock, infuse isotonic saline (0.9% saline) 10 - 20 ml/kg as quickly as possible to restore circulatory volume with reassessment after each bolus.
- Each fluid bolus should be given in 10 ml/kg.

DKA with severe volume depletion but not in shock

- In DKA patients with poor peripheral circulation but not in shock, infuse 10 - 20 ml/kg of isotonic saline over 1 - 2 hours.
- It may be repeated until tissue perfusion is adequate (maximum 30 ml/kg).
- Each fluid bolus should be given in 10 ml/kg.
- Subsequent rehydration and maintenance fluid should be calculated and infused over 48 hours.
- Resuscitation boluses should not be included as part of the total fluid requirement.
- The rate of fluid administration usually do not exceed 1.5 - 2 times the daily maintenance requirement.
- Use isotonic solution (rehydration and maintenance fluid) for at least 4 - 6 hours before switching to a solution that has a tonicity ≥ 0.45% saline.
- The decision to switch solution depends on the patient's hydration status, serum sodium and osmolality. Oral intake can be resumed within 24 hours except in severely ill patients.
- Calculate the corrected sodium (formula as above) and monitor changes.
- Clinical assessment of hydration status and calculated effective osmolality are valuable guides to fluid and electrolyte therapy.
- The aim is to gradually reduce serum effective osmolality to normal.
- Serum sodium level should increase simultaneously as the serum glucose level decreases (sodium should rise by 0.5 mmol/L for each 1 mmol/L decrease in glucose concentration).

DKA with mild to moderate volume depletion

- Isotonic saline bolus infusion is not required in mild to moderate volume depletion of DKA.
- In moderately dehydrated patients, rehydration and maintenance fluid using isotonic saline should be infused over 48 hours.
- The decision to switch solution or reduce the rate of infusion depends on the patient's hydration status, serum sodium and osmolality.
- In patients with mild dehydration, oral fluid can be continued as tolerated. IV fluid may be needed to maintain total daily fluid requirement.

Insulin therapy

- Insulin therapy in DKA should begin with a rate of 0.05 - 0.1 unit/kg/h about 1 - 2 hours after starting fluid replacement therapy.
- Do not administer IV bolus of insulin at the start of therapy. It may increase the risk of cerebral oedema and exacerbate hypokalaemia.
- The dose of insulin should remain at 0.05 - 0.1 unit/kg/h until DKA resolves (pH >7.3, bicarbonate >15 mmol/L, β-OHB <1 mmol/L or closure of the anion gap), which usually takes longer than normalisation of BG levels.
- If no improvement is seen in pH, anion gap or β-OHB concentration, reassess the patient, review insulin therapy and consider other possible causes of impaired response to insulin such as infection or errors in insulin preparation.
- For patients with marked sensitivity to insulin (e.g. young children with DKA), the dose may be decreased provided that metabolic acidosis continues to resolve.
- Adjustment of glucose administration:
  - BG level typically decreases at a rate of 2 - 5 mmol/L/hour, depending on the timing and amount of glucose administration.
  - When BG falls to approximately 14 - 17 mmol/L, 5% glucose should be added to the IV fluid.
  - If BG falls very rapidly (>5 mmol/L/hour) after initial fluid expansion, consider adding glucose even before BG has decreased to 17 mmol/L.
  - While correcting metabolic acidosis with insulin infusion, 10% or even 12.5% dextrose may be needed to prevent hypoglycaemia.

Important

If the blood glucose concentration decreases too quickly or too low before DKA has resolved:
- Increase the amount of glucose administered.
- Do not decrease the insulin infusion.

Potassium replacement

- Children with DKA may have total body potassium deficits between 3 and 6 mmol/kg.
- Potassium replacement is needed irrespective of the serum potassium level unless renal failure is present (refer to Table).
- IV potassium replacement must not exceed 0.5 mmol/kg/hour.
- Electrocardiogramme (ECG) may help to determine whether the child has hypo- or hyperkalaemia. ECG changes:
  - Hypokalaemia: prolonged PR interval, T-wave flattening and inversion, ST depression, prominent U waves and apparent long QT interval.
  - Hyperkalaemia: tall, peaked and symmetrical T waves, and shortening of the QT interval.
- If hypokalaemia persists despite a maximum rate of potassium replacement, the rate of insulin infusion may be reduced.
- Potassium phosphate may be used together with potassium chloride or acetate to avoid hyperchloraemic metabolic acidosis or hypophosphataemia.

Situation (at presentation)	Treatment
Normokalaemia	Start potassium replacement after initial volume expansion and before starting insulin infusion. Commence with 40 mmol/L of potassium per litre in the infusate (1.5 g potassium chloride/500 ml). Subsequent potassium replacement should be based on serum potassium measurements.
Hypokalaemia	Potassium replacement should be started at the time of initial volume expansion at not more than 20 mmol/L of potassium in the infusate and thereafter at 40 mmol/L during rehydration.
Hyperkalaemia	Start potassium replacement only after urine output is documented.

Acidosis

- Bicarbonate therapy may cause paradoxical CNS acidosis, hypokalaemia and increasing osmolality.
- Administration is not recommended except in life threatening hyperkalemia.

Introduction of oral fluids and transition to SC insulin injections

- Oral fluids should be introduced only with substantial clinical improvement (mild acidosis/ketosis may still be present).
- When oral fluid is tolerated, IV fluid should be reduced accordingly.
- When ketoacidosis has resolved (pH > 7.3; HCO3- > 15mmmol/L), oral intake is tolerated, and the change to SC insulin is planned, the most convenient time to change to SC insulin is just before a mealtime.
- e.g. SC regular insulin 0.25 u/kg given before meals (pre-breakfast, pre- lunch, pre-dinner), SC intermediate insulin 0.25 u/kg before bedtime. Total insulin dose is about 1u/kg/day.
- To prevent rebound hyperglycaemia, the first SC injection is given 30 min (with rapid acting insulin) or 1–2 h (with regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed.
- Intensive insulin injections (basal bolus injections) 4 or more times per day are preferable to conventional (twice daily) injections.

Morbidity and mortality

- In national population studies, mortality rate from DKA in children is 0.15–0.30%.
- Cerebral oedema accounts for 60–90% of all DKA deaths
- 10% - 25% of survivors of cerebral edema have significant residual morbidity.
- Other rare causes of morbidity and mortality include:
  Sepsis; hypokalaemia and hyperkalaemia, severe hypophosphataemia; hypoglycaemia; aspiration pneumonia; pulmonary oedema; adult respiratory distress syndrome (ARDS); rhabdomyolysis; acute renal failure and acute pancreatitis.

Cerebral oedema

- Clinically significant cerebral oedema usually develops 4 -12 h after treatment has started, but may occur before treatment or rarely, as late as 24 - 48 h later.
- Clinical diagnosis based on bed side evaluation:
  - One diagnostic criterion or
  - Two major criteria or
  - One major and two minor criteria
- These criteria have a sensitivity of 92% and a false positive rate of only 4%.
- In DKA patient with multiple risk factors to cerebral oedema, mannitol and hypertonic saline should be readily available with the dose calculated beforehand. If neurological status deteriorates acutely, treatment should be given immediately.

Diagnostic Criteria for Cerebral Oedema	
• Abnormal motor or verbal response to pain • Decorticate or decerebrate posture • Cranial nerve palsy (especially III, IV, and VI) • Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes respiration, apneusis)	
Major Criteria	Minor Criteria
• Altered mentation / fluctuating level of consciousness. • Sustained heart rate deceleration (decrease > 20 bpm), not attributable to improved intravascular volume or sleep state. • Age-inappropriate incontinence	• Vomiting • Headache • Lethargy, not easily arousable • Diastolic blood pressure > 90 mmHg • Age < 5 years

Treatment of cerebral oedema

- Prop the patient up at 30 degrees.
- Reduce the rate of fluid administration by one-third.
- Give mannitol 0.5 - 1 g/kg IV over 10-15 min and repeat if there is no initial response in 30 minutes to 2 hours.
- If there is no initial response to mannitol, hypertonic saline (3%), 2.5 - 5 ml/kg over 10-15 minutes may be used as an alternative.
- Consider intubating the patient if there is impending respiratory failure.
- After treatment for cerebral oedema has been started, a cranial CT scan may be considered to rule out other possible intracerebral causes of neurologic deterioration.

Chapter 62: Disorders of Sexual Development

Definition

- Disorders of sexual development(DSD) include various congenital conditions in which there is inconsistency between chromosomal, gonadal and or anatomical sex.

DSD is a Neonatal Emergency

- The commonest cause of DSD is congenital adrenal hyperplasia (CAH).

Major concerns in DSD patients are :-

- Underlying medical issues:
  - Dehydration, salt loss (adrenal crisis).
  - Urinary tract infection.
  - Bowel obstruction.
- Decision on sex of rearing:
  - Avoid wrong sex assignment.
  - Prevent gender confusion.
- Psychosocial issues

General concepts of care

- Gender assignment must be avoided before expert evaluation of patients.
- Evaluation and long-term management must be performed at a centre with an experienced multidisciplinary team (paediatric subspecialists in endocrinology, surgery, and/or urology, psychology/ psychiatry, gynaecology, genetics, neonatology, and social work, nursing and medical ethics).
- Patients and family concerns (eg, social, religion and culture) should be respected and addressed.

Disorders of Sexual Development (DSD)				
Sex Chromosome DSD	46, XY DSD		46, XX DSD	
45, X Turner Syndrome 47, XXY Klinefelter Syndrome and variants 45, X/46, XY Mixed gonadal dysgnesis 46,XX/46,XY chimeric, ovotesticular DSD	*Disorders of Testicular Development* Complete gonadal dysgenesis Partial gonadal dysgenesis Gonadal regession Ovotesticular DSD	*Disorders of Androgen Synthesis/Action* Androgen synthesis defect Luteinzing Hormone receptor defect Androgen insensitivity 5 α-reductase deficiency Disorders of Anti-Mullerian hormone Timing defect Endocrine disrupters Cloacal exstrophy	*Disorders of Ovarian Development* Ovotesticular DSD Testicular DSD (SRY+, dup SOX9) Gonadal dysgenesis	*Fetal Androgen Excess* Congenital adrenal hyperplasia (CAH) 21-Hydroxylase deficiency 11-Hydroxylase deficiency Non-CAH Aromatase deficiency POR gene defect Maternal Luteoma Iatrogenic

EVALUATION

Ideally, the baby or child and parents should be assessed by an experienced multi-disciplinary team.

History

Exclude Congenital Adrenal Hyperplasia in all neonates with DSD

- Parental consanguinity.
- Obstetric : previous abortions, stillbirths, neonatal deaths.
- Antenatal : drugs taken, exogenous androgens, endocrine disturbances.
- Family History: Unexplained neonatal deaths in siblings and close relatives.
- Infertility, genital anomalies in the family.
- Abnormal pubertal development.
- Symptoms of salt wasting during neonatal period.
- Increasing skin pigmentation
- Progressive virilisation

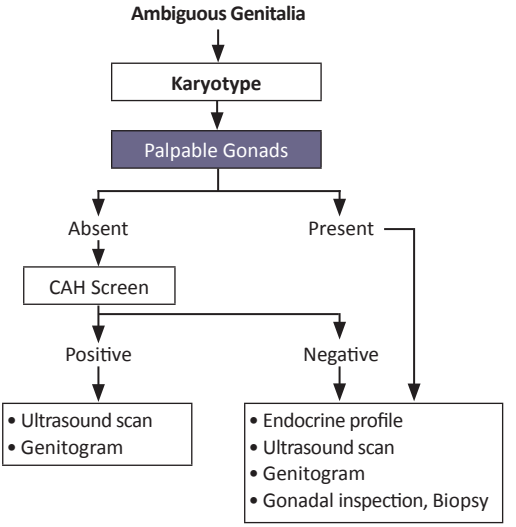
Physical examination

- Hypotension.
- Dehydration.
- Hyperpigmentation.
- Dysmorphism (Turner phenotype, congenital abnormalities).
- Cloacal anomaly.
- Psychosocial behaviour (older children).
- Appearance of external genitalia
  - Size of phallus, erectile tissue.
  - Position of urethral opening (degree of virilisation).
  - Labial fusion or appearance of labio-scrotal folds.
  - Presence or absence of palpable gonads.
  - Presence or absence of cervix (per rectal examination to be performed only by an experienced specialist).
  - Position and patency of anus.

Criteria that suggests DSD include

- Overt genital ambiguity.
- Apparent female genitalia with enlarged clitoris, posterior labial fusion, or an inguinal labial mass.
- Apparent male genitalia with bilateral undescended testes, micropenis, isolated perineal hypospadias.
- Mild hypospadias with undescended testes.
- Family history of DSD, e.g. Complete androgen insensitivity syndrome (CAIS).
- Discordance between genital appearance and a prenatal karyotype.

Most of DSDs are recognized in the neonatal period.
Others present as pubertal delay.

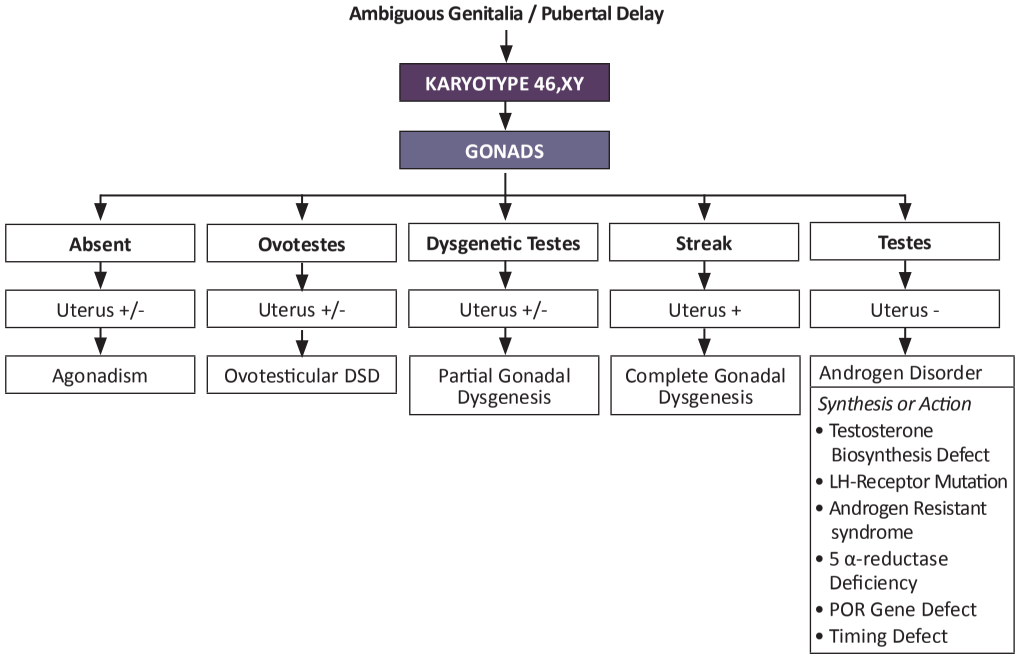


Investigations

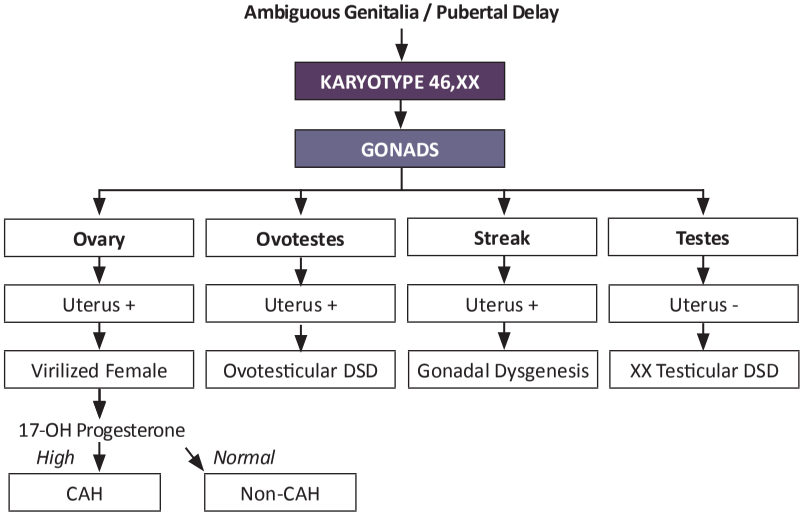
- Chromosomal study, karyotyping with X- and Y-specific probe detection
- Abdominopelvic ultrasound
- Genitogram
- Exclude salt losing CAH
- Serial serum electrolytes in the neonatal period
- Serum 17-hydroxyprogesterone (taken after 24 hours of life)
- Cortisol, renin
- Testosterone, LH, FSH
- Anti-Mullerian hormone (depending on indication and availability)

Additional investigations as indicated:

- LHRH stimulation test.
- hCG stimulation tests (testosterone, dihydrotestosterone (DHT) at Day 1 & 4).
- Urinary steroid analysis.
- Androgen receptor study (may not be available).
- DNA analysis for SRY gene (sex-determining region on the Y chromosome).
- Imaging studies (genitogram).
- Biopsy of gonadal material in selected cases.
- Molecular diagnosis is limited by cost, accessibility and quality control.
- Trial of testosterone enanthate 25 mg IM monthly 3x doses
  - This can be done to demonstrate adequate growth of the phallus and is essential before a final decision is made to raise a DSD child as a male.


Ambiguous Genitalia / Pubertal Delay
KARYOTYPE 46,XY
GONADS
Absent
Uterus +/-
Agonadism
Ovotestes
Uterus +/-
Ovotesticular DSD
Dysgenetic Testes
Uterus +/-
Partial Gonadal Dysgenesis
Streak
Uterus +
Complete Gonadal Dysgenesis
Testes
Uterus -
Androgen Disorder
Synthesis or Action
• Testosterone Biosynthesis Defect
• LH-Receptor Mutation
• Androgen Resistant syndrome
• 5 α-reductase Deficiency
• POR Gene Defect
• Timing Defect

DIAGNOSTIC ALGORITHM OF 46, XX DSD



Management

Goals

- Preserve fertility.
- Ensure normal sexual function.
- Phenotype and psychosocial outcome concordant with the assigned sex.

General considerations

- Admit to hospital. Salt losing CAH which is life threatening must be excluded.
- Urgent diagnosis.
- Do not register the child until final decision is reached.
- Protect privacy of parents and child pending diagnosis.
- Counseling of parents that DSD conditions are biologically understandable.
- Encourage bonding.

Gender Assignment

Gender assignment and sex of rearing should be based upon the most probable adult gender identity and potential for adult function. Factors to be considered in this decision include :-

- Diagnosis .
- Fertility potential.
- Adequacy of the external genitalia for normal sexual function. Adequate
- phallic size when considering male sex of rearing.
- Endocrine function of gonads. Capacity to respond to exogenous androgen.
- Parents' socio-cultural background, expectations and acceptance.
- Psychosocial development in older children.
- Decision about sex of rearing should only be made by an informed family after careful evaluation, documentation, and consultation.

Gender reinforcement

- Appropriate name.
- Appropriate upbringing and dressing.
- Treatment and control of underlying disease e.g. CAH.
- Surgical correction by surgeons specialised in genital surgery.

Assigned female

- Remove all testicular tissue.
- Vaginoplasty after puberty.
- No role for vaginal dilatation in children.

Assigned male

- Orchidopexy.
- Removal of Mullerian structures.
- Surgical repair of hypospadias.
- Gonadectomy to be considered if dysgenetic gonads.

Surgical management

- The goals of surgery are:
  - Genital appearance compatible with gender
  - Unobstructed urinary emptying without incontinence or infections
  - Good adult sexual and reproductive function
- Only surgeons with the expertise in the care of children and specific training in the surgery of DSD should perform these procedures.
- Early genitoplasty is feasible only if the precise cause of DSD has been established and gender assignment has been based on certain knowledge of post-pubertal sexual outcome. Otherwise surgery should be postponed, as genitoplasty involves irreversible procedures such as castration and phallic reduction in individuals raised females and resection of utero-vaginal tissue in those raised male.
- The procedure should be anatomically based to preserve erectile function and the innervations of the clitoris.
- Emphasis in functional outcome rather than a strictly cosmetic appearance.

CONGENITAL ADRENAL HYPERPLASIA (CAH)

Neonatal diagnosis and treatment

- CAH is caused by a variety of enzyme deficiencies in the adrenal cortex.
- About 95% of all CAH is caused by 21-hydroxylase deficiency (21-OHD)
- The incidence is 1:10,000 to 1:15,000.
- The classical form is subdivided into "salt losing" and "simple virilising" forms.
- Patients with simple virilising form may show salt loss during severe illness.
- Non-classical form of CAH has adequate glucocorticoid and mineralocorticoid production to escape diagnosis at birth, but the moderately androgen excess will cause symptoms of hyperandrogenism later in life.

Clinical presentation

Neonatal period

- Clinical presentation of 21-OHD depends on the infant's gender.
  - Female infants have variably virilised genitalia, ranging from:
    - Clitoromegaly or phallus like structure.
    - Displacement of the vaginal opening towards or into the urethra.
    - Posterior fusion of labiae.
    - Scrotalisation of the skin of the labia majora.
    - Variable pigmentation of this area.
    - No palpable gonads.
  - Male infants have apparently normal external genitalia with/without penile enlargement.
- Hyperpigmentation (as common as up to 90%) is seen in both gender.
- Salt loss may manifest at day 5 to day 15 of life with poor feeding, vomiting, dehydration, hypotension and failure to thrive.
  If left undiagnosed, patients can present with adrenal crisis which is a life threatening condition.

Diagnostic approach in infants with suspected 21-OHD

History

- CAH is inherited as an autosomal recessive trait, thus family history is often positive and may include previous unexplained neonatal death.
- Many boys with severe salt losing CAH die undiagnosed, by the end of second and third week of life.
- Parents are generally asymptomatic carriers of the mutated genes. Consanguinity may or may not be noted.

Physical examination

- In a newborn with ambiguous genitalia, CAH due to 21-OHD has to be excluded as it is the most common cause.
- Careful palpation to detect for the presence of gonads should be done as it may indicate a male child rather than a virilised female with CAH.
- Infants with suspected 21-OHD should be observed for symptoms of salt loss.

Newborn screening for CAH

- Neonatal mass screening for 21-hydroxylase deficiency identifies both male and female affected infants, prevents incorrect sex assignment, and decreases mortality and morbidity. However, it is not available yet in Malaysia.

Diagnosis of salt-wasting CAH

Newborn infants with suspected CAH need to be monitored for salt wasting, by:

- Serial sodium, potassium for salt loss (Abnormality may not be apparent in the first few days of life)
- Urea, creatinine to exclude renal disorders
- 17-hydroxyprogesterone, serum cortisol (early morning)
- If salt loss: Investigate as above and measure plasma renin level. In addition, aldosterone, androstenedione, testosterone, DHEAS can be considered.
- For patients with ambiguous genitalia:
  - Ultrasound can be considered to detect uterus and gonads.
  - Genitogram can be helpful to delineate internal reproductive structure.
  - Karyotype can be done for confirmation of likely female infant.

Management of salt losing crisis

- Administration of IV normal saline (0.9%): 10-20 ml/kg over 1 hour to correct hypovolaemic shock. Subsequent rehydrating fluids should contain 0.45 – 0.9% NaCl according to serum sodium levels (with appropriate dextrose concentration in maintenance fluid).
- Administer IV hydrocortisone 100 mg/m^2 stat followed by 25 mg/m^2 six hourly during the acute condition.
- If hypoglycaemia is present, correct with 2 ml/kg of dextrose 10% .
- Continuous cardiac monitoring for hyperkalemic changes, and if necessary severe symptomatic hyperkalemia needs to be corrected urgently (such as resonium, nebulized salbutamol or even glucose and insulin).
- Monitor fluid input and output, vital signs, glucose level, serial serum electrolytes and daily weight.

Treatment of CAH

- The aims of steroid therapy is to replace the adrenal cortisol production and also to suppress abnormal product (adrenal androgens) formation.
- Oral hydrocortisone should be given in 3 divided doses, in the range of 11-15 mg/m^2/day or more to suppress excess adrenal androgen production. During infancy, a higher dose of hydrocortisone up to 25 mg/m^2/day may be needed due to markedly elevated adrenal androgens. Divided or crushed tablets of hydrocortisone should be used instead of syrup.
- Excessive steroid doses may cause growth suppression and Cushingoid features and therefore should be avoided.
- Hydrocortisone is the preferred choice of glucocorticoid replacement, especially in infants and growing children. However, in some patients who has completed their growth, long-acting glucocorticoids (eg. prednisolone) may be considered to improve medication compliance.

- For CAH patients with salt losing:
  - Mineralocorticoid in the form of oral fludrocortisone (0.2 mg daily) should be given.
  - Oral sodium chloride supplements should be given during infancy, at 1-3 g/day (17-51 mEq/day), divided into 4-6 doses.
- All patients on glucocorticoid treatment must have medic alert (card, bracelet or pendant) with them at all times to ensure prompt treatment during emergency.
- Adequate instructions (verbal and written) must be conveyed to the caregivers. Written communications (letter) to relevant health care providers regarding the diagnosis/medication/treatment strategies during acute illness will be kept by the patient/caregivers.
- Appropriate genetic counselling should be given to parents so that proper screening for CAH can be done for future babies.

Monitoring treatment of CAH

- Patients' growth should be monitored by regular plotting of the growth chart. Normal growth rate for age is a sign of adequate treatment.
- Careful physical examination at each visit is important. Presence of oily facial skin, comedones, acne, pubic or axillary hair suggest ongoing under-treatment. Blood pressure and pubertal development (Tanner staging) should be monitored at each visit.
- Bone age acceleration indicates increased growth rate due to ongoing undertreatment.
- Laboratory measurements may include serum 17-OHP, cortisol, testosterone, and PRA or direct plasma renin.
- However, laboratory measurement does not add much guidance to the management as compared to clinical monitoring. Electrolytes may be measured in an unwell child.

Treatment with glucocorticoids during stress/illness

- Parents must be given clear written instruction on higher doses of hydrocortisone during stress/illness (during febrile illness (> 38.5 °C), when vomiting or poor oral intake, after trauma and before surgery).
- During acute illness or stress, oral glucocorticoid dose should be 2-3 times of the usual maintenance dose.
- If patients are unable to take oral steroids, parenteral hydrocortisone will be indicated. A bolus dose is given as shown below.

  First 2 years of age: 0-25mg.

  2-8 years old: 50mg.

  8 years old: 100mg.

  The following daily dose should be 3-4 times the maintenance dose, divided into 3-4 doses per day.

Feminizing surgery

- Feminizing surgery is needed usually for the severely virilised (Prader staging more or equal to 3) females.
- It should be performed by an experienced surgeon in a centre with similarly experienced paediatric endocrinologists, mental health professionals, and social work services.
- There is no randomized control studies of either the best age or the best methods for feminizing surgery.

Psychological issues

- Patients with CAH and psychosocial problems associated with disorders of sexual development should be referred to mental health professionals with specialised expertise in managing such problems.
- During management of patients with CAH, psychosocial risks to the child should be minimized as below:
  - Wrong assignment leading to later gender dysphoria.
  - Risk that baby will be unacceptable to parents leading to impaired bonding.
  - Risk of social/cultural disadvantage to baby.
  - Risk of social isolation, embarrassment.

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Chapter 63: Acute Glomerulonephritis

Introduction

Acute glomerulonephritis (AGN) is an abrupt onset of one or more features of an **Acute Nephritic Syndrome**:

- Oedema e.g. facial puffiness
- Microscopic /macroscopic haematuria (urine: tea-coloured or smoky)
- Decreased urine output (oliguria)
- Hypertension
- Azotemia

Presenting features of AGN

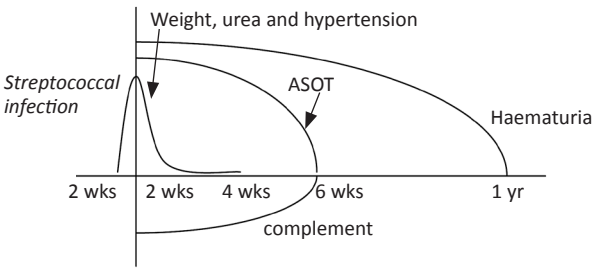
- Acute nephritic syndrome (most common)
- Nephrotic syndrome
- Rapidly progressive glomerulonephritis
- Hypertensive encephalopathy
- Pulmonary oedema
- Subclinical (detected on routine examination)

Causes of Acute Nephritis
Post streptococcal AGN
Post-infectious acute glomerulonephritis (other than Grp A ß-Haemolytic *Streptococci*)
Subacute bacterial endocarditis
Henoch-Schoenlein purpura
IgA nephropathy
Hereditary nephritis
Systemic lupus erythematosus
Systemic vasculitidis

POST STREPTOOCCAL AGN

- The commonest cause of an acute nephritic syndrome is post-infectious AGN, mainly due to post-streptococcal pharynx or skin infection.
- Post streptococcal AGN is commonest at 6 – 10 years age.

Natural History of Acute Post-Streptococcal Glomerulonephritis



Investigation findings in Post-Streptococcal AGN

- Urinalysis and culture
  - Haematuria – present in all patients.
  - Proteinuria (trace to 2+, but may be in the nephrotic range; usually associated with more severe disease.)
  - Red blood cell casts (pathognomonic of acute glomerulonephritis).
  - Other cellular casts.
  - Pyuria may also be present.
- Bacteriological and serological evidence of an antecedent streptococcal infection:
  - Raised ASOT (> 200 IU/ml)
  - Increased anti-DNAse B (if available) – a better serological marker of preceding streptococcal skin infection
  - Throat swab or skin swab
- Renal function test
  - Blood urea, electrolytes and serum creatinine
- Full blood count
  - Anaemia (mainly dilutional)
  - Leucocytosis may be present
- Complement levels
  - C3 level – low at onset of symptoms, normalises by 6 weeks
  - C4 is usually within normal limits in post-streptococcal AGN
- Ultrasound of the kidneys
  - Not necessary if patient has clear cut acute nephritic syndrome

Management

- Strict monitoring - fluid intake, urine output, daily weight, BP *(Nephrotic* chart)
- Penicillin V for 10 days to eliminate β - haemolytic streptococcal infection (give erythromycin if penicillin is contraindicated)
- Fluid restriction to control oedema and circulatory overload during the oliguric phase until child diureses and blood pressure is controlled
  - Day 1 : up to 400 mls/m²/day. Do not administer intravenous or oral fluids if child has pulmonary oedema.
  - Day 2 : till patient diureses – 400 mls/m²/day
    (as long as patient remains in circulatory overload)
  - When child is in diuresis – free fluid is allowed
- Diuretics (e.g. Frusemide) should be given in children with pulmonary oedema. It is also usually needed for treatment of hypertension.
- Diet – no added salt to diet. Protein restriction is unnecessary
- Look out for complications of post-streptococcal AGN:
  - Hypertensive encephalopathy usually presenting with seizures
  - Pulmonary oedema (acute left ventricular failure)
  - Acute renal failure

Management of severe complications of post-streptococcal AGN

Hypertension

- Refer to **Chapter 70: Hypertension in Children**

Pulmonary oedema

- Give oxygen, prop patient up; ventilatory support if necessary.
- IV Frusemide 2 mg/kg/dose stat; double this dose 4 hours later if poor response
- Fluid restriction – withhold fluids for 24 hours if possible.
- Consider dialysis if no response to diuretics.

Acute kidney injury

- Mild renal impairment is common.
- **Severe persistent oliguria or anuria with azotaemia is uncommon.**
- Management of severe acute renal failure: see **Chapter on Acute Kidney Injury.**

Indications for Renal Biopsy

- Severe acute renal failure requiring dialysis.
- Features suggesting a non post-infectious AGN as the cause of acute nephritis.
- Delayed resolution
  - Oliguria for > 2 weeks
  - Azotaemia for > 3 weeks
  - Gross haematuria for > 3 weeks
  - Persistent proteinuria for > 6 months

Follow-up

- For at least 1 year.
- Monitor BP at every visit
- Do urinalysis and renal function to evaluate recovery.
- Repeat C3 levels 6 weeks later if not already normalised by the time of discharge.

Outcome

- Short term outcome: Excellent, mortality <0.5%.
- Long term outcome: 1.8% of children develop chronic kidney disease following post streptococcal AGN. These children should be referred to a paediatric nephrologist for further evaluation and management.

HENOCH- SCHONLEIN PURPURA NEPHRITIS

Definition

- Classic tetrad
  - Rash
  - Abdominal pain
  - Arthritis/arthralgia
  - Glomerulonephritis (20-55% of HSP patients)
- Most common vasculitis of childhood, affects small vessels
- Epidemiology: Predominantly aged 3-15 years; 50% < age 5 years
- Aetiology
  - Underlying cause remains unknown
  - Immune-mediated vasculitis
  - Variety of infectious and chemical triggers proposed as a cause, up to 50% have history of preceding URTI
- Pathophysiology
  - Small-vessel leukocytoclastic vasculitis
  - Tissue deposition of IgA-containing immune-complexes

Diagnostic approach

History

- Rash
  - Palpable purpura, petechiae and ecchymoses
  - Usually symmetrical
  - Gravity/pressure-dependent areas (buttocks and lower limbs in ambulatory children)
- Arthritis/arthralgia
  - Usually affects large joints of lower limbs
  - Occasionally upper limbs
  - Usually no significant effusion or warmth
- Abdominal pain
  - Commonest complication- intussusception
  - Others- GI haemorrhage, bowel ischaemia/ perforation, pancreatitis, protein-losing enteropathy
- Unusual presentations
  - Pulmonary haemorrhage
  - Headaches
  - Seizures

Physical Examination

- Skin lesions
  - Palpable purpura, non-blanching
  - Can occur anywhere on the body, but usually concentrated on the lower extremities
- Polyarthralgia
- Abdominal pain on examination
- Scrotal pain and swelling - 13% of boys

Laboratory Investigations

- Urinalysis
- 24-hour urine protein/ urine protein-creatinine ratio
- Renal profile

Treatment approach

Symptomatic management

- Joint pain
  - Ibuprofen/ paracetamol
- Severe abdominal pain
  - Oral prednisolone.
  - Intravenous corticosteroids if nausea/ vomiting present
- Renal involvement

  Specific treatment in patients with nephrotic-range proteinuria and/or renal impairment (needs referral to nephrologist):
  - Intravenous corticosteroids (pulse dosing)
  - Oral Corticosteroids
  - Oral Cyclophosphamide

Prognosis of HSP nephritis

- Progression to ESRD:
  - 2-3% of those with initial renal involvement, 15-30% with more severe renal disease.
- Children at risk for progression:
  - Nephrotic syndrome
  - Renal insufficiency

Follow-up

- If initial UFEME normal/ only microscopic hematuria, monitor BP and UFEME:
  - Weekly for the first month after disease onset
  - Fortnightly from weeks 5-12
  - Single reviews at 6 and 12 months
- If normal UFEME at 12 months, no need further follow-up.

Indications for referral to Paediatric Nephrologist

- Gross haematuria
- Nephrotic Syndrome
- Acute nephritis
- Proteinuria
- Hypertension
- Deterioration of renal function

Chapter 64: Nephrotic Syndrome

Diagnosis

Nephrotic syndrome is a clinical syndrome of massive proteinuria defined by

- Oedema
- Hypoalbuminaemia of < 25g/l
- Proteinuria > 40 mg/m²/hour (> 1g/m²/day) or
  an early morning urine protein creatinine index of >200 mg/mmol (> 3.5 mg/mg)
- Hypercholesterolaemia

Aetiology

- *Primary or idiopathic* (of unknown cause) nephrotic syndrome is the commonest type of nephrotic syndrome in children.
- *Secondary* causes of nephrotic syndrome include post-streptococcal glomerulonephritis and systemic lupus erythematosus (SLE).

This chapter outlines the management of idiopathic nephrotic syndrome. Management of secondary forms of nephrotic syndrome follows the management of the primary condition.

Investigations at initial presentation

- Full blood count
- Renal profile: Urea, electrolyte, creatinine
- Serum cholesterol
- Liver function tests, particularly serum albumin
- Urinalysis, urine culture
- Quantitative urinary protein excretion
  (spot urine protein: creatinine ratio or 24 hour urine protein)
- *Other investigations* would depend on the age of the patient, associated renal impairment, hematuria, hypertension or features to suggest an underlying *secondary* cause for the nephrotic syndrome.
  These tests include:
  - Antinuclear factor / anti-dsDNA to exclude SLE.
  - Serum complement (C3, C4) levels to exclude SLE, post-infectious glomerulonephritis.
  - ASOT titres to exclude Post-streptococcal glomerulonephritis.
  - Other tests as indicated.

Renal biopsy

- A renal biopsy is not needed prior to corticosteroid or cyclophosphamide therapy. This is because 80% of children with idiopathic nephrotic syndrome have minimal change steroid responsive disease.
- Main indication for renal biopsy is **steroid resistant nephrotic syndrome**, defined as *failure to achieve remission despite 4 weeks of adequate corticosteroid therapy.*
- Other indications are features that suggest non-minimal change nephrotic syndrome:
  - Persistent hypertension
  - Renal impairment, and/or
  - Gross haematuria.

Management

- Confirm that patient has nephrotic syndrome by ensuring that the patient fulfills the criteria above.
- Exclude other causes of nephrotic syndrome. If none, then the child probably has idiopathic nephrotic syndrome.

General management

- A normal protein diet with adequate calories is recommended.
- No added salt to the diet when child has oedema.
- Penicillin V 125 mg BD (1-5 years age), 250 mg BD (6-12 years), 500 mg BD (> 12 years) is recommended at diagnosis and during relapses, particularly in the presence of gross oedema.
- Careful assessment of the haemodynamic status.
  - Check for signs and symptoms which may indicate
    - ***Hypovolaemia:*** Abdominal pain, cold peripheries, poor capillary refill, poor pulse volume with or without low blood pressure; *OR*
    - ***Hypervolaemia:*** Basal lung crepitations, rhonchi, hepatomegaly, hypertension.
  - Fluid restriction - not recommended except in chronic oedematous states.
- Diuretics (e.g. frusemide) are not necessary in steroid responsive nephrotic syndrome but use with caution if required, as may precipitate hypovolaemia.
- Human albumin (20-25%) at 0.5 - 1.0 g/kg can be used in symptomatic grossly oedematous states together with IV frusemide at 1-2 mg/kg to produce a diuresis.

Caution: fluid overload and pulmonary oedema can occur with albumin infusion especially in those with impaired renal function. Urine output and blood pressure should be closely monitored.

General advice

- Counsel patient and parents about the disease particularly with regards to the high probability (85-95%) of relapse.
- Home urine albumin monitoring: once daily dipstix testing of the first morning urine specimen. The patient is advised to consult the doctor if albuminuria ≥ 2+ for 3 consecutive days, or 3 out of 7 days.
- The child is also advised to consult the doctor should he/she become oedematous regardless of the urine dipstix result.
- Children on systemic corticosteroids or other immunosuppressive agents should be advised and cautioned about contact with chickenpox and measles, and if exposed should be treated like any immunocompromised child who has come into contact with these diseases.
- Immunisation:
  - While the child is on corticosteroid treatment and within 6 weeks after its cessation, only killed vaccines may safely be administered to the child.
  - Give live vaccines 6 weeks after cessation of corticosteroid therapy.
  - Pneumococcal vaccine should be administered to all children with nephrotic syndrome. If possible, give when the child is in remission.

- *Acute adrenal crisis*
  - May be seen in children who have been on long term corticosteroid therapy (equivalent to 18 mg/m² of cortisone daily) when they undergo situations of stress.
  - Give Hydrocortisone 2-4 mg/kg/dose TDS or Prednisolone 1 mg/kg/day.

COMPLICATIONS OF NEPHROTIC SYNDROME

Hypovolaemia

- *Clinical features*: Abdominal pain, cold peripheries, poor pulse volume, hypotension, and haemoconcentration.
- *Treatment*: Infuse Human Albumin at 0.5 to 1.0 g/kg/dose fast. If human albumin is not available, other volume expanders like human plasma can be used. Do not give Frusemide.

Primary Peritonitis

- *Clinical features*: Fever, abdominal pain and tenderness in children with newly diagnosed or relapse nephrotic syndrome.
- *Investigations*: Blood culture, peritoneal fluid culture (not usually done)
- *Treatment*: Parenteral penicillin and a third generation cephalosporin

Thrombosis

- Thorough investigation and adequate treatment with anticoagulation is usually needed. Please consult a Paediatric Nephrologist.

CORTICOSTEROID THERAPY

Corticosteroids are effective in inducing remission of idiopathic nephrotic syndrome.

Initial treatment

- Once a diagnosis of idiopathic nephrotic syndrome has been established, oral Prednisolone should be started at:
  - **Initial Prednisolone therapy of 60 mg/m² per day** for 4 weeks (maximum dose of 60 mg/day), followed by
  - **Alternate-day prednisone of 40 mg/m² per day** for 4 weeks (maximum dose of 40 mg/day), *then then taper over 4 weeks and stop.*
- With this corticosteroid regime, 80% of children will achieve remission (defined as urine dipstix trace or nil for 3 consecutive days) within 28 days.
- Children with **Steroid resistant nephrotic syndrome**, defined by failure to achieve response to an initial 4 weeks treatment with prednisolone at 60 mg/m²/ day, should be referred to a Paediatric Nephrologist for further management, which usually includes a renal biopsy.

Treatment of relapses

- The majority of children with nephrotic syndrome will relapse.
- A relapse is defined by *urine albumin excretion > 40 mg/m²/hour or* urine dipstix of ≥ 2+ for 3 consecutive days.
- These children do not need admission unless they are grossly oedematous or have any of the complications of nephrotic syndrome.

Treatment of Initial or Infrequent Relapse

- Induction with Prednisolone at dose of 60 mg/m^2 per day (maximum dose of 60 mg/day) *until remission*
- then 40mg/m^2/EOD (maximum dose 40mg /day) for 4 weeks then stop.

Treatment of frequent relapses

- Defined as ≥ 2 relapses within 6 months of initial diagnosis or
  ≥ 4 relapses within any 12 month period.
- Induction of relapse is with oral Prednisolone as follows:
  - 60 mg/m^2/day (maximum 60 mg/day) ***until remission*** followed by
  - 40 mg/m^2/EOD (maximum 40 mg) for 4 weeks only.
- Taper Prednisolone dose every 2 weeks and keep on *as low an alternate day dose as possible for 6 months.* Should a child relapse while on low dose alternate day Prednisolone, then re-induce with Prednisolone as for relapse.

Treatment of steroid dependent nephrotic syndrome

- Defined as *≥ 2 consecutive relapses occurring during steroid taper or within 14 days of the cessation of steroids.*
- If the child is not steroid toxic, re-induce with steroids and maintain on *as low a dose of alternate day prednisolone as possible.* If the child is steroid toxic (short stature, striae, cataracts, glaucoma, severe cushingoid features) *consider steroid-sparing agents.*

STEROID-SPARING AGENTS

Cyclophosphamide therapy

- Indicated for the treatment of steroid dependent nephrotic syndrome with signs of steroid toxicity; begin therapy when in remission after induction with corticosteroids.
- Parents should be counseled about the effectiveness and side effects of (leucopenia, alopecia, haemorrhagic cystitis, gonadal toxicity).
- Dose: 2-3 mg/kg/day for 8-12 weeks (cumulative dose 168 mg/kg).
- Monitor full blood count and urinalysis 2 weekly.

Relapses post Cyclophosphamide

- Relapses after a course of cyclophosphamide are treated as for relapses following the initial diagnosis of nephrotic syndrome, if the child does not have signs of steroid toxicity.
- Should the relapse occur soon after a course of Cyclophosphamide when the child is still steroid toxic, or if the child again becomes steroid toxic after multiple relapses, then a Paediatric Nephrology opinion should be sought for other steroid-sparing agents.

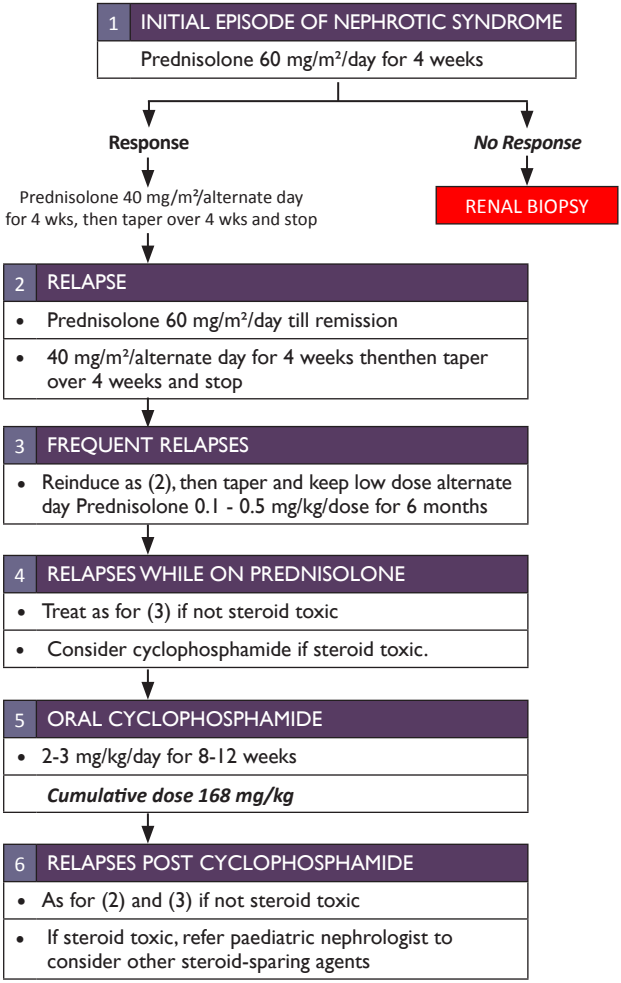
Levamisole

- *Dose*: 2.5mg/kg on alternate days for at least 12 months

Other Steroid-Sparing Agents (need referral to paediatric nephrologist)

- Calcineurin inhibitors: Cyclosporin or Tacrolimus
- Mycophenolate Mofetil (MMF)
- Rituximab

MANAGEMENT OF NEPHROTIC SYNDROME



Breakthrough proteinuria/ Intercurrent infections

- Most common relapse trigger is intercurrent infection.
- In patients on weaning or maintenance alternate day prednisolone: Risk of relapse can be reduced by temporarily increasing the dose from alternate to every day for 3-5 days.
- Usually does not require corticosteroid induction if the child has no oedema, remains well and the proteinuria remits with resolution of the infection. However, if proteinuria persists, treat as a relapse.

A Paediatric nephrology consultation is recommended if:

- Age <12 months or >12 years.
- Persistent hypertension +/- persistent microscopic hematuria.
- Elevated creatinine despite correction of any hypovolemia.
- C3 or C4 below normal range.
- Unclear if nephrotic versus mixed nephritic-nephrotic (e.g. macroscopic haematuria, intravascular fluid overload with hypertension, renal impairment).
- Steroid resistance.
- Needing steroid sparing agents beyond oral Cyclophosphamide/Levamisole.

Steroid resistant nephrotic syndrome

Refer for renal biopsy. Specific treatment will depend on the histopathology.

General management of the Nephrotic state:

- Control of edema:
  - Restriction of dietary sodium.
  - Diuretics e.g. Frusemide, Spironolactone.
- ACE inhibitor e.g. Captopril or Angiotensin II receptor blocker (AIIRB). e.g. Losartan, Irbesartan, to reduce proteinuria.
  - Monitor BP and renal profile 1-2 weeks after initiation of ACE inhibitor *or AIIRB.*
- Control of hypertension: antihypertensive of choice - ACE inhibitor/AIIRB.
- Penicillin prophylaxis.
- Monitor renal function.
- Nutrition: normal dietary protein content, salt-restricted diet.
- Evaluate calcium and phosphate metabolism.

Chapter 65: Acute Kidney Injury

Definition

- Acute kidney injury (AKI) was previously called acute renal failure.
- Abrupt rise in serum creatinine level and decreased glomerular filtration rate resulting in inability of the kidneys to regulate fluid and electrolyte balance.

Clinical features

- Of underlying cause.
- Oliguria (< 300 ml/m²/day in children; < 1 ml/kg/hour in neonates)
- Non-oliguria.
- Clinical features arising from complications of AKI
  e.g. seizures, acute pulmonary oedema
- Important to consider pre-renal failure as a cause of oliguria.
- In pre-renal failure, the kidney is intrinsically normal and the tubules are working to conserve water and sodium appropriately.
- In acute tubular necrosis (ATN) the damaged tubules are unable to conserve sodium appropriately.

Common causes of Acute Kidney Injury

Pre-Renal	***Renal,or Intrinsic***
Hypovolaemia • Dehydration, bleeding Third space loss • Nephrotic syndrome, burns Distributive shock • Dengue shock, sepsis syndrome Cardiac • Congestive heart failure • Cardiac tamponade ***Post-Renal*** Posterior urethral valves Acute bilateral ureteric obstruction Acute obstruction in solitary kidney	Glomerular Infection related Systemic lupus erythematosus Acute glomerulonephritis Tubulointerstitial Acute tubular necrosis • Hypoxic-ischaemic injury • Aminoglycosides, chemotherapy Toxins, e.g. • Myoglobin, haemoglobin Venom • Bee sting Tumour lysis, Uric acid nephropathy Infection, pyelonephritis Vascular • ACE-inhibitors • Vascular lesions • Haemolytic uremic syndrome • Renal vein thrombosis

Investigations

- Blood:
  - Full blood count.
  - Blood urea, electrolytes, creatinine.
  - Blood gas.
  - Serum albumin, calcium, phosphate.
- Urine: biochemistry and microscopy.
- Imaging: renal ultrasound scan (urgent if cause unknown).
- Other investigations as determined by cause.

MANAGEMENT

Prevention

- Identify patients at risk of AKI. They include patients with the following:
  - Prematurity, asphyxia, trauma, burns, post-surgical states, other organ failures (eg heart, liver), pre-existing renal disease, malignancy (leukaemia, B-cell lymphoma).
- Monitor patients-at-risk actively with regards to renal function and urine output.
- Try to ensure effective non-dialytic measures, which include:
  - Restoring adequate renal blood flow.
  - Avoiding nephrotoxic agents if possible.
  - Maximizing renal perfusion before exposure to nephrotoxic agents.

Fluid balance

In Hypovolaemia

- Fluid resuscitation regardless of oliguric / anuric state
- Give crystalloids e.g. isotonic 0.9% saline / Ringer's lactate 20 ml/kg fast (in < 20 minutes) after obtaining vascular access.
- Transfuse blood if haemorrhage is the cause of shock.
- Hydrate to normal volume status.
- If urine output increases, continue fluid replacement.
- If there is no urine output after 4 hours (confirm with urinary catheterization), monitor central venous pressure to assess fluid status.

See **Chapter on Shock for details of management.**

In Hypervolaemia / Fluid overload

Features of volume overload include hypertension, raised JVP, displaced apex beat, basal crepitations, hepatomegaly and increasing ventilatory requirements.

- If necessary to give fluid, restrict to insensible loss (400 ml/m²/day or 30ml/kg in neonates depending on ambient conditions).
- IV Frusemide 2 mg/kg/dose (over 10-15 minutes), maximum of 5 mg/kg/dose *or* IV Frusemide infusion 0.5 mg/kg/hour.
- Dialysis if no response or if volume overload is life-threatening.

Euvolaemia

- Once normal volume status is achieved, give insensible loss plus obvious losses (urine / extrarenal).
- Monitor fluid status: weight, BP, heart rate, nutritional needs, intake/output.

Hypertension

- Usually related to fluid overload and/or alteration in vascular tone.
- Choice of anti-hypertensive drugs depends on degree of BP elevation, presence of CNS symptoms of hypertension and cause of renal failure. A diuretic is usually needed.

Metabolic acidosis

- Treat if pH < 7.2 or symptomatic or contributing to hyperkalaemia.
- **Bicarbonate deficit = 0.3 x body weight (kg) x base excess (BE)**
- Ensure that patient's serum calcium is > 1.8 mmol/L to prevent hypocalcaemic seizures with Sodium bicarbonate therapy.
- Replace half the deficit with IV 8.4% Sodium bicarbonate (1:1 dilution) if indicated.
- Monitor blood gases.

Electrolyte abnormalities

Hyperkalaemia

- Definition: serum K^+ > 6.0 mmol/l (neonates) and > 5.5 mmol/l (children).
- Cardiac toxicity generally develops when plasma potassium > 7 mmol/l.
- Regardless of degree of hyperkalaemia, treatment should be initiated in patients with ECG abnormalities from hyperkalaemia.

ECG changes in Hypokalemia

- Tall, tented T waves
- Prolonged PR interval
- Widened QRS complex
  - Flattened P wave
  - Sine wave (QRS complex merges with peaked T waves)
- VF or asystole

Hyponatraemia

- Usually dilutional from fluid overload.
- If asymptomatic, fluid restrict.
- Dialyse if symptomatic or the above measures fail.

Hypocalcaemia

- Treat if symptomatic (usually serum Ca^{2+} < 1.8 mmol/L), and if Sodium bicarbonate is required for hyperkalaemia, with IV 10% Calcium gluconate 0.5 ml/kg, given over 10 – 20 minutes, with ECG monitoring.

Hyperphosphataemia

- Phosphate binders e.g. calcium carbonate or aluminium hydroxide orally with main meals.

Treatment of Hyperkalemia in AKI patients	
• Do a 12-lead ECG and look for hyperkalaemic changes • If ECG is abnormal or plasma $K^+ > 7$ mmol/l, connect patient to a cardiac monitor and give the following in sequence:	
1	IV 10% Calcium gluconate 0.5 - 1.0 ml/kg (1:1 dilution) over 5 -15 mins (Immediate onset of action)
2	IV Dextrose 0.5 g/kg (2 ml/kg of 25%) over 15 – 30 mins.
3	± IV Insulin 0.1 unit/kg (onset of action 30 mins).
4	IV 8.4% sodium bicarbonate 1 ml/kg (1:1 dilution) over 10 - 30 mins (Onset of action 15 - 30 mins)
5	Nebulized 0.5% salbutamol 2.5 - 5 mg (0.5 - 1 ml : 3 ml 0.9% Saline) (Onset of action 30 mins)
6	Calcium polystyrene sulphonate 0.25g/kg oral or rectally 4 times/day (Max 10g/dose) (Calcium Resonium / Kalimate) [Give rectally (NOT orally) in neonates 0.125 – 0.25g/kg 4 times/day]
OR	
6	Sodium polystyrene sulphonate 1g/kg oral or rectally 4 times/day (Max15g/dose) (Resonium)
• In patients with serum potassium between 5.5 - 7 mmol/L *without* ECG changes, give calcium or sodium polystyrene sulphonate • If insulin is given after dextrose, monitor RBS / Dextrostix for hypoglycaemia. • Dialyse if poor or no response to the above measures	

Nutrition

- Optimal intake in AKI is influenced by nature of disease causing it, extent of catabolism, modality and frequency of renal replacement therapy.
- Generally, the principles of nutritional requirement apply except for:
  - Avoiding excessive protein intake.
  - Minimizing phosphorus and potassium intake.
  - Avoiding excessive fluid intake (if applicable).
  - If the gastro-intestinal tract is intact and functional, start enteral feeds as soon as possible.
  - Total parenteral nutrition via central line if enteral feeding is not possible; use concentrated dextrose (25%), lipids (10-20%) and protein (1.0-2.0g/kg/day).
  - If oliguric and caloric intake is insufficient because of fluid restriction, start dialysis earlier.

Dialysis

Dialysis is indicated if there are life-threatening complications like:

- Fluid overload manifesting as
  - Pulmonary oedema.
  - Congestive cardiac failure, or
  - Refractory hypertension.
- Electrolyte / acid-base imbalances:
  - Hyperkalaemia ($K^+ > 7.0$).
  - Symptomatic hypo- or hypernatraemia, or
  - Refractory metabolic acidosis.
- Symptomatic uraemia.
- Oliguria preventing adequate nutrition.
- Oliguria following recent cardiac surgery.

The choice of dialysis modality depends on:

- Experience with the modality.
- Patient's haemodynamic stability.
- Contraindications to peritoneal dialysis e.g. recent abdominal surgery.

Medications

- Avoid nephrotoxic drugs if possible; if still needed, monitor drug levels and potential adverse effects.
- Check dosage adjustment for all drugs used.
- Concentrate drugs to the lowest volume of dilution if patient is oliguric.

Dosage adjustment in renal failure for some common antimicrobials			
Drug	Cr Clearance[1]	Dose	Dose Interval
Crystalline/ Benzylpenicillin	10 - 50	Nil	8 – 12
	< 10	Nil	12
Cloxacillin	< 10	Nil	8
Amoxicillin/clavulanic acid (Augmentin)	10 - 30	Normal dose initially then half-dose 12-hly	
	< 10	Normal dose initially then half-dose 24-hly	
Ampicillin/sulbactam (Unasyn)	15 - 29	Nil	12
	5 - 14	Nil	24
Cefotaxime	< 5	Normal dose initially, then 1/2 dose, same frequency	
Cefuroxime	> 20	Nil	8
	10 - 20	Nil	12
	< 10	Nil	24
Ceftriaxone	< 10	Dose not > 40mg/kg (maximum 2g)/day	
Ceftazidime	30 - 50	50-100%	12
	15 - 30	50-100%	24
	5 -15	25-50%	24
	< 5	25–50%	48
Cefepime	30 - 50	50mg/kg	12
	11 - 29	50mg/kg	24
	< 10	25mg/kg	24
Imipenem	40	75%	8
	10	25%	12
	Anuric	15%	24
Meropenem	25 - 50	100%	12
	10 - 25	50%	12
	< 10	50%	24
Ciprofloxacin	40	Nil	12
	10	50%	24
	anuric	33%	24

Dosage adjustment in renal failure for some common antimicrobials (cont).

Drug	Cr Clearance[1]	Dose	Dose Interval
Metronidazole	< 10	Nil	12
Acyclovir (IV infusion)	25 - 50	Nil	12
	10 - 25	Nil	24
Acyclovir (oral)	10 - 25	Nil	8
	< 10	Nil	12
Erythromycin	< 10	60%	Nil
Gentamicin	Avoid if possible. If needed, give 5mg/kg, check trough level 24 hours later, and peak 1 hour post-dose.		
Amikacin	Avoid if possible, If needed, give initial dose, take trough sample immediately before next dose, and peak 1 hour post-dose.		
Vancomycin	Give initial / loading dose, take trough sample immediately before next dose and peak, 1 hour after completion of infusion.		

Footnote:
1, Creatinine Clearance:
It is difficult to estimate GFR from the serum creatinine levels in AKI. A rough estimate can be calculated using the formula below once the serum creatinine level remains constant for at least 2 days.

$$\text{Calculated creatinine clearance } (ml/min/1.73m^2) = \frac{\text{Height (cm)} \times 40}{\text{Serum creatinine (micromol/l)}}$$

Assume creatinine clearance of < 10ml/min/1.73m² if patient is on dialysis or anuric.

Chapter 66: Acute Peritoneal Dialysis

Introduction

The purpose of dialysis is

- To remove endogenous and exogenous toxins and
- To maintain fluid, electrolyte and acid-base equilibrium until renal function returns.

Peritoneal dialysis (PD) is the simpler modality in infants and children as it is technically simpler and easily accessible even in centers without paediatric nephrologists.

Contraindications to Acute PD

- Abdominal wall defects or infection.
- Bowel distension, perforation, adhesion or resection.
- Communication between the chest and abdominal cavities.

Types of Catheter Access

- A *soft PD catheter* implanted percutaneously or surgically (preferred).
- A *straight rigid catheter* if a soft PD catheter is not available.

Indications for Dialysis

Acute renal failure

- Pulmonary oedema
- Refractory hypertension
- Oliguria following recent heart surgery
- Symptomatic electrolyte or acid-base imbalance
  - Hyperkalaemia ($K^+ > 7.0$)
  - Hypo- or hypernatraemia
  - Acidosis (pH<7.2, or <7.3 with hyperkalaemia)
- Uraemia

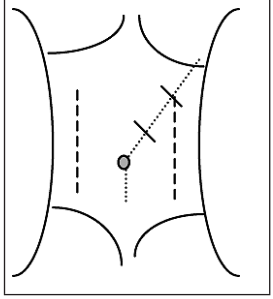
Inborn errors of metabolism

- Encephalopathy
- Hyperammonaemia
- Severe metabolic acidosis

Sites of insertion

- Commonest site is at the midline infra-umbilical position 1 inch below the umbilicus.
- In small children, where the space below the umbilicus is limited, alternative sites include insertion lateral to the inferior epigastric artery as shown in the dotted lines in the diagram, two-thirds of the distance from the umbilicus to the left last rib (just lateral to the border of rectus muscle).
- Ensure that the catheter is inserted way below any enlarged spleen or liver.

Site of Insertion and Direction of Catheter Introduction



Procedure of PD catheter insertion

1. Consent for peritoneal dialysis.
2. Bladder must be emptied; catheterise the bladder in unconscious, ill patients.
3. The procedure must be done under aseptic technique.
4. Prepare the set of PD lines and spike the PD fluids.
5. Clean the area with povidone iodine and drape the patient.
6. Infiltrate insertion site with lignocaine; additional IV sedation may be needed.
7. For small infants or patients with very scaphoid abdomen, infiltrating the abdominal cavity with 10 - 15 ml/kg PD fluid using 20G or larger branula prior to catheter insertion will help prevent traumatic puncture of underlying viscus.
8. For technique of catheter insertion - *see tables below*.
9. Connect the catheter to the PD line via the connector provided in the set.
10. Bleeding from the insertion site can be stopped by a purse-string suture. cover the site with dry gauze and secure with plaster.

Monitoring while on PD

- Oversee the first 3 cycles of dialysis to ensure good flow.
- Check for turbidity, leakage and ultrafiltration every two hours.
- Input / output chart, vital signs and PD chart should be kept up-to-date. Turbid effluent must be noted to the doctor.
- Send PD fluid for cell count and culture and sensitivity at start and end of PD and when the effluent is turbid.
- Blood urea, serum electrolytes and creatinine should be requested according to patients needs.
  In stable patients, once daily should be more than sufficient.
- Blood urea and electrolyte results to be reviewed by the doctor and Potassium chloride to be added into dialysate if necessary.
  (1 Gm of Potassium chloride in 10 ml ampoule is equivalent to 13.3 mmol of potassium. Hence adding 3 ml to 1 litre would result in dialysate with 4.0 mmol/l of potassium).

Technique of insertion of different PD catheters	
Acute stiff PD catheter	
1	Check catheter for any breakages (by withdrawing the stilette) before insertion.
2	Make a small skin incision (slightly smaller than the diameter of the catheter) using a sharp pointed blade. Do not cut the muscle layer.
3	Introduce the catheter with the stillete perpendicular to the abdominal wall while controlling the length with the dominant hand, until the peritoneum is pierced.
4	The stilette is then withdrawn and the catheter gently pushed in, directing it towards either iliac fossa until all the perforations are well within the peritoneal cavity.
Soft PD catheter (Seldinger technique)	
1	Cooke's set 15F.
2	Advance the needle provided in the set connected to a syringe perpendicularly until peritoneum is breached (a give is felt).
3	Thread and advance the guide wire through the needle aiming for either iliac fossa.
4	Remove the needle. Using the guide wire, introduce the dilator and sheath through a skin nick into the abdominal cavity.
5	Remove the dilator and guide wire while retaining the sheath in the abdomen.
6	Introduce the soft PD catheter through the sheath into the abdominal cavity directing it to either iliac fossa until the external cuff fits snugly at the skin.
7	Peel off the sheath and secure the catheter via taping or a skin stitch.

The PD Prescription

Exchange volume

- Start at 20 ml/kg and observe for discomfort, cardiorespiratory changes or leakage at catheter site.
- The volume can be increased to a maximum of 50ml/kg or 1000 -1200ml/m^2 body surface area.

Cycle Duration

- First 6 cycles are rapid cycles i.e. no dwell time. The cycle duration depends on needs of the patient. However, the standard prescription usually last an hour:
  - 5-10 minutes to instill (depending on exchange volume)
  - 30-40 minutes dwell
  - 10-15 minutes to drain (depending on exchange volume)
- The cycles can be done manually or with an automated cycler machine if available.

PD Fluids

- Type of PD fluids:
  - 1.5%, and 4.25% dextrose (standard commercially availabe)
  - Bicarbonate dialysate[1], useful if lactic acidosis is a significant problem
- PD is usually initiated with 1.5% - if more rapid ultrafiltration is required higher glucose concentration by mixing various combinations of 1.5 and 4.25% solutions can be used.
- Watch for hyperglycaemia.

Duration of PD

- The duration of PD depends on the needs of the patient
- The usual practice is 60 cycles but at times more cycles may be needed based on biochemical markers or clinical needs. Peritonitis is frequent when dialysis is prolonged or when acute catheters are used for more than 3 to 4 days.

[1]Note:

- *In centers with continuous renal replacement therapy, the bicarbonate solution used for CRRT (Continuous Renal Replacement Therapy) can be used.*
- *In centers where this is not available, the assistance of the pharmacist is required to constitute a physiological dialysis solution.*

The contents and concentrations are listed in the next page.

Pharmacy constituted PD-Bicarbonate solution 1.5% dextrose 3000ml / bag	
Content	Quantitiy (ml)
NaCl 0.9%	1374.00
NaCl 20%	13.23
Sodium Bicarbonate 8.4%	120.00
Magnesium Sulphate 49.3%	1.11
Dextrose 50%	90.00
Water for injection	1401.66

Common Complications

Poor drainage (omental obstruction, kinking)

- For temporary PD cannulas
  - Re-position.
  - Reinsert catheter if above unsuccessful.
- For surgically implanted catheters
  - Irrigation.
  - Add Heparin (500 units/ litre) into PD fluids.

Peritonitis

- Diagnostic criteria :
  - Abdominal pain, fever, cloudy PD effluent
  - PD effluent cell count > 100 WBC/mm^2.
- Treatment:
  - Intraperitoneal antibiotics (empirical Cloxacillin + Ceftazidime) for 7 - 14 days.
  - Adjust antibiotics once culture results known (dosage as given below).

Exit site infection

- Send swab for culture.
- Remove PD catheter that is not surgically implanted.
- Systemic antibiotics may be considered.

Leaking dialysate

- At exit site – resuture immediately.
- Leakage from tubings – change dialysis set, empiric intraperitoneal antibiotics for one to two days may be needed.

Blood stained effluent

- If mild, observe. It should clear with successive cycles.
- If heavy, but vital signs stable, run rapid cycles.
- Transfuse cryoprecipitate. Consider blood transfusion and DDAVP.
- If bleeding does not stop after the first few cycles, stop the dialysis.
- If heavy, patient in shock, resuscitate as for patient with hypovolaemic shock. **Stop dialysis and refer surgeon immediately.**

Paediatric Antibiotic Dosing Recommendations Administration should be via intraperitoneal route unless specified otherwise			
	Continuous therapy		Intermittent therapy
	Loading dose	Maintenance dose	
Glycopeptides			
Vancomycin	500 mg/L	30 mg/L	30 mg/kg q 5-7 days
Cephalosporins			
Cephazolin/ Cephalothin	250 mg/L	125 mg/L	15 mg/kg q 24 hrs
Cefuroxime	200 mg/L	125 mg/L	15 mg/kg q 24 hrs
Cefotaxime	500 mg/L	250 mg/L	30 mg/kg q 24 hrs
Ceftazidime	250 mg/L	125 mg/L	15 mg/kg q 24 hrs
Antifungals			
Amphotericin B	1 mg/kg IV	1 mg/kg/day IV	---
Fluconazole	---	---	3-6 mg/kg IP, IV, or PO q24-48 hrs (max 200 mg)
Aminoglycosides			
Amikacin	25 mg/L	12 mg/L	
Gentamicin	8 mg/L	4 mg/L	
Netilmycin	8 mg/L	4 mg/L	
Penicillins			
Amoxicillin	250-500 mg/L	50 mg/L	
Combinations			
Ampicillin/ Sulbactam	1000 mg/L	100 mg/L	
Imipenem/ Cilastin	500 mg/L	200 mg/L	

Chapter 67: Neurogenic Bladder

Introduction

- Neurogenic bladder can develop as a result of a lesion at any level in the nervous system, i.e. cerebral cortex, spinal cord, peripheral nervous system.
- The commonest cause of neurogenic bladder in children is congenital spinal dysraphism.

Multi-disciplinary approach

- Children with spinal dysraphism require care from a multidisciplinary team consisting of neurosurgeon, neurologist, orthopedic surgeon, rehabilitation specialist, neonatologist, nephrologists, urologist and other allied medical specialists.
- Long-term follow-up is necessary since renal or bladder function can still deteriorate after childhood.
- Children with the conditions listed in the table below can present with various patterns of detrusor sphincter dysfunction within a wide range of severity, often not predicted by the level of the spinal cord defect.

Causes of Neurogenic Bladder Dysfunction
Open spinal dysraphism
• Meningocele, myelomeningocele and lipomyelomeningocele
Occult spinal dysraphism
• Spinal bifida occulta
Anorectal agenesis, sacral agenesis
Spinal trauma
Spinal cord tumors
Transverse myelitis
Brain pathology
• Cerebral palsy
• Brain tumors

- The commonest type of spinal dysraphism is lumbosacral myelomeningocoele.
- At birth, the majority of patients with lumbosacral myelomeningocoele have normal upper urinary tracts, but 60% of them develop upper tract deterioration due to infections, bladder changes and reflux by 3 years of age.
- Progressive renal damage is due to high detrusor pressures both throughout the filling phase (poor compliance bladder) as well as superimposed detrusor contractions against a closed sphincter (detrusor sphincter dyssynergia).

Occult spinal dysraphism

- May present with cutaneous stigmata (hairy tufts, skin tags, lumbosacral subcutaneous masses and haemangiomas).
- Spinal ultrasound can be used in neonates and infants, optimally before 6 months of age, when ossification of posterior elements prevents an acoustic window.
- After 6 months of age, the imaging modality is MRI of spine.

Evaluation of Neurogenic Bladder Dysfunction

- Baseline Tests:
  - Urine- urinalysis, culture and sensitivity
  - Blood - renal function test
  - Ultrasound of bladder and kidneys
- Advanced Tests:
  - Urodynamics Studies

Urodynamic Studies

- It may consist of the following:
  - A bladder diary which should be recorded over at least 2-3 days.
  - In patients who are unable to void, catheterized volumes at regular intervals are measured.
  - Uroflowmetry and assessment of residual urine in patients who are able to void.
  - Video-urodynamics is recommended in children whenever available. However if video facilities are unavailable, a prior voiding cystourethrogram can be combined with a urodynamics study to improve interpretation.

Timing of urodynamic study

- A baseline urodynamic study is indicated in all children with neurogenic bladders. However because of limited availability of this procedure, children should be referred earlier for urodynamic studies when they have the following findings:
  - Recurrent UTI
  - Hydronephrosis
  - Incontinence despite clean intermittent catheterization (CIC).
  - Thickened bladder wall.
  - Raised serum creatinine
- In infants with any of the above conditions who have been started on CIC , anti-cholinergics may be started empirically while awaiting urodynamics studies.

Aims of management:

- Preserve upper renal tracts and renal function.
- Achieve urinary continence.
- Develop sense of autonomy and better self esteem.

MANAGEMENT OF BLADDER FUNCTION

Early management with clean intermittent catheterization (CIC)

- Aims to create a low pressure reservoir and prevent upper tract deterioration.
- Ensuring complete and safe bladder emptying with improvement of incontinence
- CIC should be started once a myelomeningocele is repaired.
- Starting CIC in early infancy has led to easier acceptance by parents and children.
- Children, as young as 5 years of age, have learnt to do self-catheterization.
- Patients are taught catheterization in hospital by a trained nurse/doctor.
- The rationale and benefits of intermittent catheterisation are explained, and the parent/patient is reassured that it should be neither painful nor dangerous.
- Patients are taught to catheterize themselves lying down, standing up, or sitting on a lavatory, chair or wheelchair.

Complications of CIC

- Urethral trauma with creation of false passages and strictures.
- Urinary tract infection
- Bleeding

Anti-cholinergics

- Anti-cholinergics are first-line therapy indicated to treat neurogenic detrusor overactivity and poor bladder compliance. These conditions are diagnosed on urodynamics assessment. However as mentioned above, anti-cholinergics may be started empirically in the specific conditions while awaiting definitive urodynamics assessment.
- The most commonly used anticholinergic is oxybutynin (0.3-0.5mg/kg/day) in 2 to 3 divided doses.
- Other anti-muscarinic drugs prescribed in combined urology/surgeon/ nephrology care are Trospium chloride, Tolterodine and Propiverine.

Intravesical Therapy

- Injection of botulinum toxin injection in the bladder in therapy-resistant bladders appears to be an effective and safe treatment alternative.

Surgical treatment

- Bladder augmentation is indicated whenever less invasive procedures have failed to improve compliance or reduce detrusor pressure.
- Additional surgical procedures may also be performed to improve continence.

Technique of Clean Intermittent Catheterisation (CIC)

Procedure

1. Assemble all equipment: catheter, ± lubricant, drainage receptacle, adjustable mirror.
2. Wash hands with soap and water.
3. Clean the urethral orifice with clean water.

In boys:

1. Lift penis with one hand to straighten out urethra.
2. Lubricate the catheter, with local anaesthetic gel (lignocaine)/K-Y jelly.
3. Use the other hand to insert the catheter into the urethra. There may be some resistance as the catheter tip reaches the bladder neck.
4. Continue to advance the catheter slowly using gentle, firm pressure until the sphincter relaxes.

In girls:

1. The labia are separated and the catheter inserted through the urethral meatus into the bladder.

For both males and females

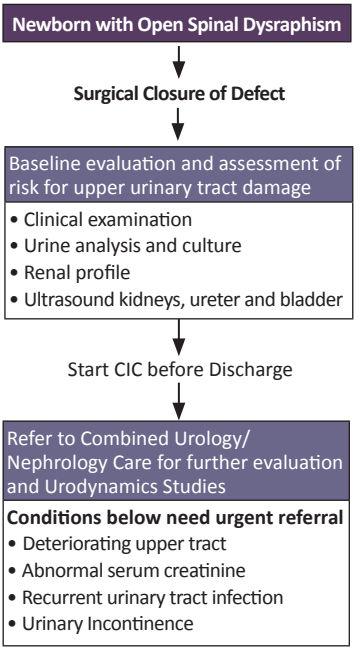
1. The catheter is inserted gently until the urine flows.
2. The urine is collected in a jug or bottle or is directed into the lavatory.
3. Once the urine has stopped flowing the catheter should be rotated and then, if no urine drains, slowly withdrawn.
4. Wash hands on completion of catheterisation.
5. Catheterise at the prescribed time with the best available measures.

Size of Catheters
Small babies: 6F
Children: 8-10F
Adolescents: 12-14F

How Often to Catheterise
Infants: 6 times a day
Children: 4-5 times a day, more frequently in patients with a high fluid intake, and in patients with a small capacity bladder.

Reuse of catheters

1. Catheters can be re-used for 2 to 4 weeks
2. After using the catheter, wash in soapy water, rinse well under running tap water, hang to air dry and store in clean container.


Newborn with Open Spinal Dysraphism
Surgical Closure of Defect
Baseline evaluation and assessment of risk for upper urinary tract damage
• Clinical examination
• Urine analysis and culture
• Renal profile
• Ultrasound kidneys, ureter and bladder
Start CIC before Discharge
Refer to Combined Urology/ Nephrology Care for further evaluation and Urodynamics Studies
Conditions below need urgent referral
• Deteriorating upper tract
• Abnormal serum creatinine
• Recurrent urinary tract infection
• Urinary Incontinence

Urinary tract infection (UTI) and antibiotics

- Prophylactic antibacterial therapy is not routinely recommended as therapy does not decrease the incidence of clinical infections.
- However, children with recurrent symptomatic UTI should be given prophylactic antibiotics and may benefit from circumcision.
- Asymptomatic bacteriuria is common especially in patients on CIC but does not require treatment.
- All febrile UTIs should be treated with antibiotics as soon as possible.

MANAGEMENT OF BOWEL FUNCTION

- Aim to achieve regular and efficient bowel emptying.
- Toilet Training – advise the children to sit on the toilet each day
- An effective bowel regimen consists of:
  - High fiber diet
  - Laxatives: Mineral oil, lactulose
  - Rectal wash out, enemas, manual disimpaction

Follow up assessments

- Voiding chart: timing of daytime and night-time voiding, volume of each void/CIC, incontinence and urge episodes.
- Constipation and fecal incontinence.
- Monitoring of blood pressure, growth, urinalysis, renal profile.
- Urine culture in suspected febrile or symptomatic UTI.
- Serial ultrasound imaging at regular intervals depending on the age and baseline ultrasound findings. Infants and younger children required more frequent ultrasound scans up to 3 to 6 monthly.
- Repeat urodynamic studies may be indicated for the following:
  - To assess response to treatment
  - Worsening hydronephrosis
  - Worsening renal function
  - Recurrent UTI/pyelonephritis
  - New onset of incontinence

Chapter 68: Urinary Tract Infection

Introduction

- Urinary tract infection (UTI) comprises 5% of febrile illnesses in early childhood; Before age 2 yrs, 2.1% of girls and 2.2% of boys will have had a UTI
- UTI is an important risk factor for the development of hypertension, renal failure and end stage renal disease.

Definition

- *Urinary tract infection* is growth of bacteria in the urinary tract *or* combination of clinical features and presence of bacteria in the urine
- *Significant bacteriuria* is defined as the presence of > 10^5 colony forming units (cfu) of a single organism per ml of freshly voided urine (Kass).
- *Acute pyelonephritis* is bacteriuria presenting clinically with fever > 38°C and/or loin pain and tenderness. It carries a higher risk of renal scarring
- *Acute cystitis* is infection limited to the lower urinary tract presenting clinically with acute voiding symptoms: dysuria, urgency, frequency, suprapubic pain or incontinence.
- *Asymptomatic bacteriuria* is presence of bacteriuria in the urine in an otherwise asymptomatic child.

Clinical Presentation

- Symptoms depend on the age of the child and the site of infection.
- In infants and toddlers: signs and symptoms are non-specific e.g. fever, irritability, jaundice and failure to thrive.
- UTI should be considered in children with unexplained fever.
- Symptoms of lower UTI such as pain with micturition and frequency are often not recognized before the age of two.

Physical Examination

- General examination, growth, blood pressure.
- Abdominal examination for distended bladder, ballotable kidneys, other masses, genitalia, and anal tone.
- Examine the back for any spinal lesion.
- Look for lower limb deformities or wasting (suggests a neurogenic bladder).

Diagnosis

- Accurate diagnosis is extremely important as false diagnosis of UTI would lead to unnecessary interventions that are costly and potentially harmful.
- The diagnosis is best made with a combination of culture and urinalysis
- **The quality of the urine sample is of crucial importance.**
- *Urine specimen transport*
  - If collected urine cannot be cultured within 4 hours; refrigerate specimen at 4 °C or add a bacteriostatic agent e.g. boric acid (1.8%)
  - Use container pre-filled with boric acid and fill urine to required level.

Urine testing

- Rapid diagnosis of UTI can be made by examining the fresh urine with urinary dipstick and microscopy. However, where possible, a fresh specimen of urine should be sent for culture and sensitivity.

Collection of Urine

Bag urine specimen

- High contamination rate of up to 70%.
- Negative culture excludes UTI in untreated children.
- Positive culture should be confirmed with a clean catch or suprapubic aspiration specimen (SPA).

Clean catch specimen

- Recommended in a child who is bladder trained.

Catheterisation

- Sensitivity 95%, specificity 99%, as compared to SPA.
- Low risk of introducing infection but have higher success rates and the procedure is less painful compared to SPA.

Suprapubic aspiration (SPA)

- Best technique ("gold standard") of obtaining an uncontaminated urine sample.
- Any gram-negative growth is significant.
- Technique:
  - Lie the child in a supine position.
  - Thin needle with syringe is inserted vertically in the midline, 1 - 2 cm above symphysis pubis.
  - Urine is obtained at a depth of 2 to 3 cm.
- Usually done in infants < 1 year; also applicable in children aged 4 - 5 years if bladder is palpable above the symphysis pubis.
- Success rate is 98% with ultrasound guidance.

Note: When it is not possible to collect urine by non-invasive methods, catheterization or SPA should be used.

Sensitivity and specificity of various tests for UTI

Test	Sensitivity % (range)	Specificity % (range)
Leucocyte esterase (LE)	78 (64-92)	83 (67-94)
Nitrite	98 (90-100)	53(15-82)
LE or nitrite positive	72 (58-91)	93 (90-100)
Pyuria	81 (45-98)	73 (32-100)
Bacteria	83 (11-100)	81(16-99)
Any positive test	70 (60-90)	99.8 (99-100)

Management

- All infants with febrile UTI should be admitted and intravenous antibiotics started as for acute pyelonephritis.
- In patients with high risk of serious illness, it is preferable that the urine sample should be obtained first; however treatment should be started if urine sample is unobtainable.

Antibiotic prophylaxis

- Antibiotic prophylaxis should not be routinely recommended for infants and children following a first episode of UTI except for certain indications as listed below
- Recent evidence has shown that antimicrobial prophylaxis does reduced the risk of febrile or symptomatic UTI in children with VUR III or IV but has no significant effect on the incidence of renal scarring
- Hence antibiotic prophylaxis should be considered in the following:
  - Infants and children with recurrent symptomatic UTI
  - Infants and children with VUR grade III and above

Measures to reduce risk of further infections

- *Dysfunctional elimination syndrome* (DES) or dysfunctional voiding is defined as an abnormal pattern of voiding of unknown aetiology characterised by faecal and/or urinary incontinence and withholding of both urine and faeces.
- Treatment of DES includes high fibre diet, use of laxatives, timed frequent voiding, and regular bowel movement.
- If condition persists, referral to a paediatric urologist/nephrologist is needed.

Antibiotic Treatment for UTI

UTI (Acute cystitis) with *E.coli., Proteus spp.*

Preferred Treatment
PO Trimethoprim 4mg/kg/dose bd (max 300mg daily) for 1 week

Alternative Treatment
PO Trimethoprim/Sulphamethazole 4mg/kg/dose (TMP) bd for 1 week

Note:
- Cephalexin, cefuroxime can also be used especially in children who had prior antibiotics.
- A single dose of antibiotic therapy is not recommended.

Upper Tract UTI (Acute pyelonephritis) with *E.coli., Proteus spp.*

Preferred Treatment
IV Cefotaxime 100mg/kg/day q8h for 10-14 days

Alternative Treatment
IV Cefuroxime 100mg/kg/day q8h or IV Gentamicin 5-7mg/kg/day daily

Note:
- Repeat culture within 48hours if poor response.
- Antibiotic may need to be changed according to sensitivity.
- Suggest to continue intravenous antibiotic until child is afebrile for 2-3 days and then switch to appropriate oral therapy after culture results e.g. Cefuroxime, for total of 10-14 days.

Asymptomatic bacteriuria

No treatment recommended

Antibiotic Prophylaxis for UTI

UTI Prophylaxis

Preferred Treatment
PO Trimethoprim 1-2mg/kg ON

Alternative Treatment
PO Nitrofurantoin 1-2mg/kg ON or PO Cephalexin 5mg/kg ON

Note:
- Antibiotic prophylaxis is not routinely recommended in children with UTI
- Prophylactic antibiotics should be given for 3 days with MCUG done on the second day.
- A child develops an infection while on prophylactic medication, treatment should be with a different antibiotic and not a higher dose of the same prophylactic antibiotic.

Recommendations for imaging

Previous guidelines have recommended routine radiological imaging for all children with UTI. Current evidence has narrowed the indications for imaging as summarized below:

Ultrasound

Recommended in

- All children less than 3 years of age
- Children above 3 years of age with poor urinary stream, seriously ill with UTI, palpable abdominal masses, raised serum creatinine, non E coli UTI, febrile after 48 hours of antibiotic treatment, or recurrent UTI.

DMSA scan

Recommended in infants and children with UTI with any of the following features:

- Seriously ill with UTI.
- Poor urine flow.
- Abdominal or bladder mass.
- Raised creatinine.
- Septicaemia.
- Failure to respond to treatment with suitable antibiotics within 48 hours.
- Infection with non *E. coli* organisms.

Micturating cystourethogram (MCUG)

Routine MCUG after a first UTI is not recommended but should be considered in a selected group of patients as listed below:

- Infants with recurrent UTI.
- Infants with UTI and the following features: poor urinary stream, seriously ill with UTI, palpable abdominal masses, raised serum creatinine, non *E. coli* UTI, febrile after 48 hours of antibiotic treatment.
- Children less than 3 years old with the following features:
  - Dilatation on ultrasound.
  - Poor urine flow.
  - Non *E. coli* infection.
  - Family history of Vesicoureteric Reflux (VUR).

Other radiological investigations e.g. DTPA scan, MCUG in older children would depend on the ultrasound findings.

Further Management
This depends upon the results of investigations, as below.

NORMAL RENAL TRACTS

- Prophylactic antibiotic not required.
- Urine culture during any febrile illness or if the child is unwell.

NO VESICOURETERIC REFLUX BUT RENAL SCARRING PRESENT.

- Repeat urine culture only if symptomatic.
- Assessment includes height, weight, blood pressure and routine tests for proteinuria.
- Children with a minor, unilateral renal scarring do not need long-term follow-up unless recurrent UTI or family history or lifestyle risk factors for hypertension.
- Children with bilateral renal abnormalities, impaired renal function, raised blood pressure and or proteinuria should be managed by a nephrologist.
- Close follow up during pregnancy.

VESICOURETERIC REFLUX

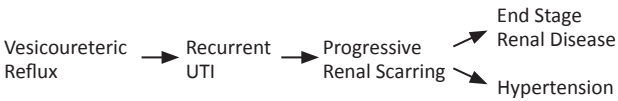
Definition

- Vesicoureteric reflux (VUR) is defined as the retrograde flow of urine from the bladder into the ureter and collecting system.
- In most individuals VUR results from a congenital anomaly of ureterovesical junction (primary VUR), whereas in others it results from high pressure voiding secondary to posterior urethral valve, neuropathic bladder or voiding dysfunction (secondary VUR).

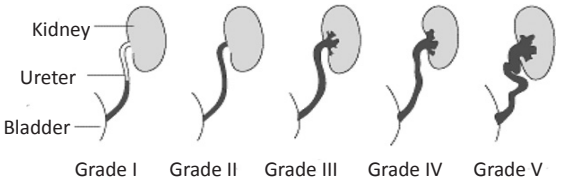
Significance of VUR

- Commonest radiological abnormality in children with UTI (30 – 40%).
- Children with VUR thought to be at risk for further episodes of pyelonephritis with potential for increasing renal scarring and renal impairment (reflux nephropathy).

NATURAL HISTORY OF VESICOURETERIC REFLUX



CLASSIFICATION OF VESICOURETERIC REFLUX ACCORDING TO THE INTERNATIONAL REFLUX STUDY COMMITTEE



Management

- *Antibiotic prophylaxis:* refer to antibiotic prophylaxis section above.
- *Surgical management or endoscopic treatment* is considered if the child has recurrent breakthrough febrile UTI.

POSTERIOR URETHRAL VALVE

- Refer to a Paediatric urologist/surgeon/nephrologist.

RENAL DYSPLASIA, HYPOPLASIA OR MODERATE TO SEVERE HYDRONEPHROSIS

- May need further imaging to evaluate function or drainage in the case of hydronephrosis.
- Refer surgeon if obstruction is confirmed.
- Monitor renal function, BP and growth parameters.

Summary

- All children less than 2 years of age with unexplained fever should have urine tested for UTI.
- Greater emphasis on earlier diagnosis & prompt treatment of UTI
- Diagnosis of UTI should be unequivocally established before a child is subjected to invasive and expensive radiological studies
- Antibiotic prophylaxis should not be routinely recommended following first-time UTI.

Chapter 69: Antenatal Hydronephrosis

Definition

- No consensus statement to date.
- Most studied parameter is the measurement of antero -posterior diameter (APD) of renal pelvis as visualized on transverse plane.
- Most agree that APD of renal pelvis of at least 5 mm on antenatal ultrasound of the fetus is abnormal.
- APD > 15mm represents severe or significant hydronephrosis.
- Fetal Hydronephrosis Index(HI): APD of renal pelvis divided by urinary bladder volume has been proposed as studied parameter but not uniformly accepted yet.

Advantages of prenatal detection

- May potentially be used for prenatal counseling and has allowed identification of conditions that require immediate treatment and which otherwise would go unrecognized until symptoms arose postnatally.
- Meta-analysis of 17 studies revealed that calculated risk of any postnatal pathology per degree of antenatal hydronephrosis was 11.9% for mild , 45.1% for moderate and 88.3% for severe.

Goals in evaluation of patients with antenatal hydronephrosis

- Prevent potential complications, e.g. urinary tract infection (UTI), renal stones and renal failure.
- Preserve renal function.
- Distinguish children who require follow up and intervention from those who do not.

Timing of detection

- 90% after eighteen weeks of gestation.
- 95% by 22 weeks.

The Society of Fetal Urology (SFU) Hydronephrosis Grading System	
Grades	**Pattern of renal sinus splitting**
SFU Grade 0	No splitting (renal pelvis)
SFU Grade I	Urine in pelvis barely splits sinus
SFU Grade II	Urine fills intrarenal pelvis
SFU Grade II	Urine fills extrarenal pelvis. Major calyces dilated
SFU Grade III	SFU Grade 2 and minor calyces uniformly dilated but renal parenchyma preserved.
SFU Grade IV	SFU Grade 3 and renal parenchyma thin

- Marked hydronephrosis is frequently seen in pelvic ureteric junction obstruction whereas the mild hydronephrosis is associated with vesicoureteric reflux.

Epidemiology

- 1-5% of all pregnancies
- Increased frequency of up to 8% with positive family history of renal agenesis, multicystic kidney, reflux nephropathy and polycystic kidneys.
- Male to female ratio is 2:1.
- Bilateral in 20 to 40 %.

Aetiology in Antenatal Hydronephrosis	
Abnormality	Frequency (%)
Transient	48
Physiologic	15
Pelvic ureteric junction obstruction	11
Vesicoureteric reflux	4
Megaureter,obstructed or non-obstructed	4
Multicystic kidneys	2
Ureterocoeles	2
Posterior urethral valves	1

Transient and physiologic hydronephrosis

- 60% of antenatal hydronephrosis is physiological. This will resolve before end of pregnancy or within first year of life.
- Fetal urine flow is 4-6 times greater than neonatal urine production.
- This is due to differences in renovascular resistances, GFR and concentrating ability before and after birth. These differences may contribute to ureteric dilatation in-utero in the absence of functionally significant obstruction.

Antenatal management

- In general antenatal interventions are not required except for watchful monitoring.
- Pregnancy should be allowed to proceed to term and normal delivery can be allowed in the absence of other complications like severe oligohydramnios or other fetal abnormalities.

Timing of postnatal evaluation

- Within first week of life: Neonates with unilateral hydronephrosis and normal contralateral kidney.
- Immediate evaluation before discharge: Bilateral hydronephrosis, hydronephrosis in solitary kidneys and bladder outlet obstruction.

Postnatal management

Physical examination

- Certain clinical features may suggest specific underlying causes:
  - Abdominal mass: Enlarged kidney due to pelvic-ureteric junction obstruction *or* multicystic dysplastic kidneys.
  - Poor stream and dribbling: Posterior urethral valves in a male infant.
  - Deficient abdominal wall with undescended testes: Prune Belly syndrome.
  - Abnormalities in the spine and lower limb with patulous anus: Neurogenic bladder.
- Examination for other anomalies should also be carried out.

Unilateral hydronephrosis

- In babies who are normal on physical examination, a repeat ultrasound should be done after birth; subsequent management will depend on the ultrasound findings.
- The ultrasound should be repeated one month later if initial postnatal US is normal or shows only mild hydronephrosis. The patient can be discharged if the repeat ultrasound is also normal.

Bilateral Hydronephrosis

- These babies need a full examination and investigation after birth.
  - Ultrasound of the kidneys and urinary tracts should be repeated.
  - Urine output should be monitored.
  - Renal profile should be done on day 2 of life.
  - The child should be monitored closely for UTI and a second-generation cephalosporin started if there is any suggestion of UTI.
- In boys, detailed ultrasound scan should be done by an experienced radiologist to detect thickened bladder wall and dilated posterior urethra suggestive of posterior urethral valves. Any suggestion of posterior urethral valve or renal failure warrants an urgent MCUG.

Urgent referral to a Paediatric nephrologist and/or Urologist is needed if the newborn has renal failure, or confirmed or suspected posterior urethral valves.

Other radiological investigations

99mDTPA/Mag 3 SCAN

- DTPA or MAG3 scans are required when there is moderate or gross hydronephrosis on prenatal ultrasound. These scans detect differential functions of both kidneys as well as presence of significant obstruction in the urinary tract. In Malaysia only DTPA scan is available in most radionuclide centers. It is best done after one month of life.
- DTPA relies principally on glomerular filtration; results may be suboptimal in infants with immature kidneys and low GFR. In such scenarios, MAG 3 scan is preferred.

Magnetic Resonance Urography

- Evidence for its use in evaluation of antenatal hydronephrosis is fairly poor.

Intravenous Urogram (IVU)

- With the availability of DTPA /Mag3 scan, IVU is no more indicated.

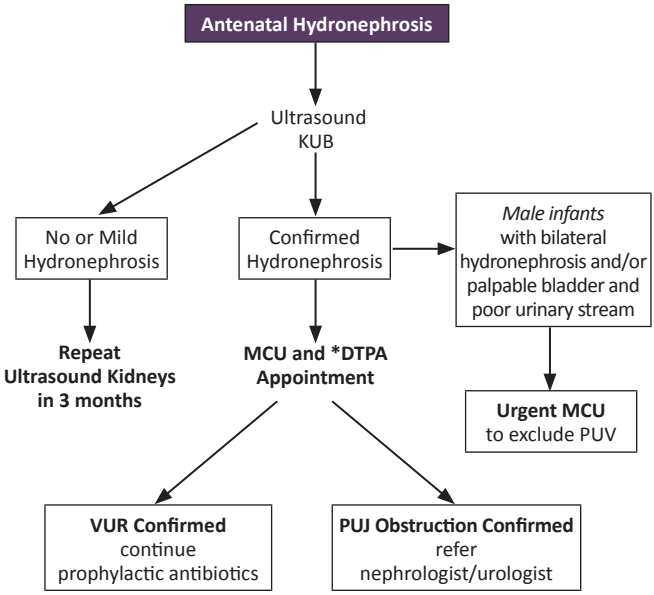
Antibiotics

- Efficacy of antibiotic prophylaxis has not been proven.
- Consider antibiotic prophylaxis in high risk population such as those with gross hydronephrosis and hydroureters.

Commonly used Oral Antibiotic Prophylaxis
Trimethoprim *Dose*: 1-2mg/kg at night
Cephalexin *Dose*: 5mg/kg at night

Follow up Care

- All children with significant hydronephrosis should be referred to paediatric nephrologists / urologist after relevant radiological investigations have been completed.


Antenatal Hydronephrosis
Ultrasound KUB
No or Mild Hydronephrosis
Confirmed Hydronephrosis
Male infants with bilateral hydronephrosis and/or palpable bladder and poor urinary stream
Repeat Ultrasound Kidneys in 3 months
MCU and *DTPA Appointment
Urgent MCU to exclude PUV
VUR Confirmed continue prophylactic antibiotics
PUJ Obstruction Confirmed refer nephrologist/urologist

Definition

Definitions of Blood Pressure (BP) Categories and Stages		
	Children aged 1-13 years	Children ≥ 13 years age
Normal BP	< 90th percentile	< 120/< 80mmHg
Elevated BP	≥ 90th percentile to <95th percentile or 120/80 mmHg to <95th percentile (whichever is lower)	120/<80 to 129/<80 mmHg
Stage 1 Hypertension	≥ 95th percentile to <95th percentile + 12mmHg or 130/80 to 139/89 mmHg (whichever is lower)	130/80 to 139/89 mmHg
Stage 2 Hypertension	≥ 95th percentile +12mmHg or ≥ 140/90 (whichever is lower)	

For Normative BP Tables (see **Chapter 1 on Normal Values in Children**)

BP Measurement: Who and When?

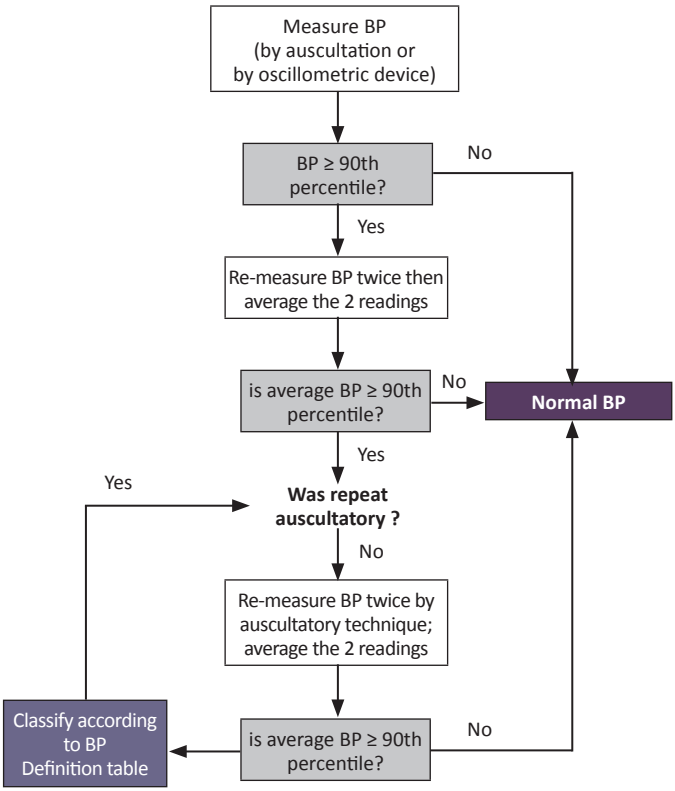
BP should be measured at all medical encounters in the following groups:

- All children and adolescents ≥ 7 years old.
  Although the latest guidelines from the US Task force recommends the age cut off to be 3 years, the Malaysian Hypertension guidelines recommends 7 years taking into consideration the current state of resources in primary health centres and the 2013 USPSTF recommendations which still did not recommend routine screening in young children because of inadequate evidence.
- Children < 7 years old and infants who at risk of developing hypertension:
  - History of neonatal complications requiring neonatal intensive care
  - Congenital heart disease
  - Recurrent urinary tract infection
  - Hematuria, proteinuria, known renal or urologic disease
  - Family history of congenital renal disease
  - Solid organ or bone marrow transplant
  - Malignancy
  - Treatment with drugs known to raise BP
  - Other systemic illness associated with hypertension
  - Evidence of raised intracranial pressure

BP Measurement Technique

- Choose an appropriately sized cuff. (Cuff width covers ≥ 40% of the upper arm and cuff length covers 80%-100% of the circumference of the arm.)
- Measure BP with the child in a seated position and their arm supported, after he or she has been sitting quietly for 3-5 minutes (for an infant, lying supine).
- Perform a manual BP reading using auscultation if any BP level >90 percentile on oscillometric devices.
- BP should be measured preferably 3 times at each visit and the average of measurement should be used.

MODIFIED BP MEASUREMENT ALGORITHM



Diagnosis

- A diagnosis of hypertension is made if a child or adolescent has auscultatory-confirmed BP readings ≥ 95th percentiles on 3 different visits.

White Coat Hypertension

- White coat hypertension is defined as office BP readings ≥ 95th percentile with normal values outside the office setting.
- Ambulatory blood pressure measurement (ABPM) is used to differentiate between ambulatory(sustained) hypertension and white coat hypertension wherever possible.
- White coat hypertension does not require treatment but may need repeat ABPM in one- to two- year intervals to detect development of sustained hypertension.

Primary Hypertension

- Children and adolescents ≥ 6 years of age do not require an extensive evaluation for secondary causes of hypertension if one or more of the following factors are present:
  - A positive family history of hypertension
  - Overweight or obese
  - Absence of history or physical findings suggestive of a secondary cause of hypertension

Secondary Hypertension

- It is vital to identify causes of secondary hypertension as resolution of hypertension may occur after adequate treatment of underlying disease(s), hence avoiding the need for prolonged drug therapy.

Causes of Secondary Hypertension in Children	
Parenchymal renal disease Glomerulonephritis • Post Infectious • Ig A nephropathy • Henoch-Schonlein purpura nephritis • Lupus nephritis • Others Pyelonephritis-related renal scarring Acute kidney injury Congenital anomaly of kidney and urinary tract (CAKUT) Polycystic kidney disease Obstructive Uropathy *Renovascular* Renal artery stenosis Thrombosis of renal artery and vein Acute and post haemolytic uraemic syndrome Trauma *Endocrine* Cortisol/glucocorticoid excess Aldosterone/mineralocorticoid excess Catecholamine excess Congenital adrenal hyperplasia Thyroid disease Hypercalcemia	*Cardiovascular* Coarctation of aorta Takayasu arteritis *Central nervous system* Pain Convulsions Increased intracranial pressure Guillain-Barre syndrome Dysautonomia *Malignancy* Wilms' tumour Neuroblastoma Pheochromocytoma *Pharmacology* Sympathomimetics Corticosteroids Stimulants Oral contraceptives Anabolic steroids Cocaine Phencyclidine (PCP) Nicotine Caffeine Acute Vitamin D intoxication *Others* Obstructive sleep apnoea Bronchopulmonary dysplasia Genetic defects (e.g. Liddle syndrome)

CLINICAL EVALUATION

History

- Antenatal history - antenatal imaging, maternal health, drugs in pregnancy
- Neonatal history- prematurity, birth weight, umbilical catheter insertion, bronchopulmonary dysplasia, medications
- History of renal disease and urinary tract infections
- Congenital heart defects
- Cardiovascular risk factors
- History of sleep disturbance and snoring in older children
- Review of symptoms
- Family history of hypertension, heart disease, renal disease and stroke
- Medications and drugs
- Diet and salt intake
- Level of physical activity

Examination

Systematic examination to look for physical findings of end organ dysfunction and of underlying diseases which include the following:

- Signs of heart failure - Tachycardia, displaced apex beat, gallop rhythm, hepatomegaly
- Absent or weak femoral pulses; if detected measure four limb blood pressure
- Neurological deficit
- Fundoscopy: Papilloedema and / or retinal haemorrhages
- Organomegaly and / or abdominal masses
- Signs of thyroid disease or Cushing's disease
- Carotid, abdominal, and femoral bruits
- Obesity

The presence of "Red flag" symptoms and signs as outlined in table below in a child with hypertension warrants early/urgent investigations and management

"Red flag" symptoms and signs	
Red Flags	End Organ Dysfunction
Nausea and/or vomiting Headache Visual disturbance Behavioural change Altered mental status Drowsiness Seizure	Hypertensive encephalopathy
Fundoscopy: Retinal haemorrhage, cotton wool lesions Papilloedema	Hypertensive vascular changes Increase intracranial pressure
Chest pain Breathlessness Edema Gallop rhythm Cardiomegaly Pulmonary edema	Cardiac failure

Investigations

- Routine investigations in all children with elevated BP/hypertension:
  - Urine dipstick for proteinuria and hematuria
  - Urine culture for infection
  - Full blood count
  - Blood urea, serum creatinine and electrolytes
  - Thyroid stimulating hormone
  - Abdominal, renal and urinary tract ultrasound
- Investigations to assess comorbidities:
  - Fasting lipid profile
  - Fasting blood sugar (+/- HbA1c)
- Further investigations as indicated: (At centres with specialists, often after consultation with relevant subspecialty experts)
  - Glomerulonephritis screen (e.g. C3, C4, anti-nuclear antibody (ANA), anti-neutrophil cyto-plasmic antibody (ANCA))
  - Plasma renin and aldosterone
  - Renal colour Doppler ultrasonography
  - Tc99 Dimercaptosuccinic acid scan (DMSA)
  - Urine and plasma cathecholamines or metanephrines
  - Urinary free cortisol and plasma cortisol
  - Sleep study
  - Genetic study
- Echocardiography: to be performed to assess for cardiac target organ damage at time of consideration of pharmacologic treatment of HTN.

When a child is diagnosed with hypertension, he or she should be referred to a paediatrician for further evaluation and management.

TREATMENT APPROACH

The treatment goal should be a reduction of SBP and DBP to <90th percentile and <130/80 mmHg in adolescents ≥13 years old.

A. Non-pharmacologic therapy or Therapeutic Lifestyle Changes

- Exercise
- Weight loss
- Low-salt or no-added-salt diet
- Cessation of smoking

B. Pharmacologic therapy

Initiate pharmacologic therapy in children and with one or more of the following conditions:

- Hypertension with failed lifestyle modifications.
- Symptomatic hypertension.
- Stage 2 hypertension without a clearly modifiable factor (e.g. obesity)
- Any stage of hypertension associated with chronic kidney disease or diabetes mellitus.
- Hypertensive end-organ damage, most often left ventricular hypertrophy (LVH).

Antihypertensive Medications			
Drug	Initial dose	Maximum dose	Dosing interval
ACE Inhibitor			
Captopril	Infants: 0.05 mg/kg/dose Children: 0.5 mg/kg/dose	6mg/kg/day 6mg/kg/day	Daily to 4 times/day 3 times/day
Enlapril	> 1month age: 0.08 mg/kg/dose (up to 5 mg/day)	0.6mg/kg/day (up to 40mg/day)	Daily to twice/day
Angiotensin receptor blockers (ARBs)			
Losartan	≥ 6 years: 0.7 mg/kg (up to 50mg)	1.4mg/kg (up to 100mg)	Daily
Irbesartan	6 - 12 years: 75mg once daily	150mg once daily	Daily
Thiazide diuretics			
Chloro-thiazide	10mg/kg/day	20mg/kg/ day (up to 375mg/day)	Daily to twice/day
Hydrochloro-thiazide	1mg/kg/day	2mg/kg/day (up to 37.5mg/day)	Daily to twice/day
Calcium channel blockers			
Amlodipine	1-5 years: 0.1 mg/kg ≥ 6 years: 2.5 mg	0.6mg/kg (up to 5mg/day) 10mg	Daily Daily
Nifedipine	0.25 mg/kg	0.5mg/kg/dose (up to 10mg)	3 to 4 times/day
Beta blockers			
Atenolol	0.5-1 mg/kg/day	2mg/kg (up to 100mg/day)	Daily or twice/ day
Metoprolol	0.5-1 mg/kg/day (up to 25mg)	6mg/kg/day (up to 200mg/day)	Daily or twice/ day
Propranolol	1mg/kg/dose	2mg/kg/dose (up to 640mg/day)	2-3 times/day

Hypertensive Emergencies

- Hypertensive emergency is defined as an acute severe symptomatic elevation in BP WITH evidence of potentially life-threatening symptoms or target organ damage. BP is elevated far above the level of stage 2 hypertension.
- Hypertensive urgency is defined as an acute severe elevation in BP WITHOUT severe, life-threatening symptoms or evidence of acute target organ damage.

Hypertensive Encephalopathy

- Characterised by severe BP elevation with cerebral edema and neurological symptoms of lethargy, coma, and/or seizures.
- Can be produced with no extreme BP elevations when the HTN appears as a sudden onset, since the autoregulation of cerebral flow is not able to control the rapid BP increment.

Evaluation of a child with a hypertensive emergency should include:

- History and physical examination
  - to look for signs of acute organ symptom and/or damage.
  - to identify the underlying aetiology once treatment has been initiated
- Fundoscopic examination: hemorrhages, exudates and papilloedema
- Neurologic clinical evaluation
  - In the case of hypertensive encephalopathy,
  - CT brain to exclude hemorrhage
  - MRI for edema of white matter in the parieto-occipital regions or posterior reversible encephalopathy syndrome (PRES).

Management Principles of Hypertensive Emergencies

- Admit patient to ICU or HDW to ensure close monitoring and support of the vital organs including neurologic status.
- Establish vascular access immediately.
- Cardiac and continuous BP monitoring, preferably by intra-arterial catheter.
- Urine output monitoring from the outset.
- Manage any serious complications before or as hypertension is being treated (e.g. anticonvulsants should be administered to a seizing patient along with antihypertensive medications)
- Treatment strategy is directed at lowering BP promptly but gradually.
  - A sudden decrease can lead to neurological complications (e.g. intracranial bleeding).
  - Avoid short acting Nifedipine as this may precipitate a sudden uncontrolled drop in BP
- The initial goal of therapy is to reduce mean arterial pressure by approximately 25% over the first 24 hours.
- Children with a hypertensive emergency should always be treated with intravenous drugs. Continuous infusion is safer than bolus.
- Hypertensive urgencies can be treated by oral drugs.

Antihypertensive Drugs for Hypertensive Emergencies and Urgencies					
Drug	Class	Route	Dose	Onset of action	Comment
Labetalol	α-/ β - adrenergic blocker	IV bolus IV infusion	0.2-1 mg/kg up to 40 mg/dose 0.25-3 mg/kg/hr	5- 10 mins	Contraindicated in asthma, heart failure, may cause bradycardia.
Nicardipine	Calcium channel blocker	IV infusion	1-3 mcg/kg/min	within mins	Reflex tachycardia
Hydralazine	Direct vasodilator	IV bolus IV infusion	Initial: 0.1- 0.2mg/kg/dose every 4 - 6 hrs; increase as required to 0.2-0.6 mg/kg/dose every 4 - 6 hrs as need Maximum single dose: 20 mg 12.5 - 50mcg/kg/hr (Max 3mg/kg in 24hrs for children > 1 nth)	10 mins	Tachycardia, vomiting, flushing.
Esmolol	Beta-blocker	IV infusion	100-500 mcg/kg loading dose then 100-500 mcg/kg/min	Immediate	Contraindicated in asthma, BPD, HF and may cause profound bradycardia
Furosemide	Loop diuretic	IV bolus	0.5-5mg/kg/dose	within mins	Hypokalemia. Useful in volume hypertension
Nifedipine	Calcium channel blocker	Oral	0.25mg/kg/dose	20-30 mins	May cause unpredictable hypotension, reflex tachycardia
Captopril	ACEI	Oral	0.1-0.2mg/kg/dose	10-20 mins	Contraindicated in suspected bilateral renal artery stenosis
Minoxidil	Direct vasodilator	Oral	0.1-0.2mg/kg/dose	5-10 mins	Fluid retention

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Variation in Red Blood Cell Indices with Age			
Age	Hb (g/dl)	RBC (x10 /l)	MCV (fl)
Birth	14.9 – 23.7	3.7-6.5	100-135
2 months	9.4-13.0	3.1-4.3	84-105
12 months	11.3-14.1	4.1-5.3	71-85
2-6 year	11.5-13.5	3.9-5.3	75-87
6-12 year	11.5-15.5	4.0-5.2	77-95
12-18 yr girls	12.0-16.0	4.1-5.1	78-95
12-18 yr boys	13.0-16.0	4.5-5.3	78-95

Hb, haemoglobin; RBC, red blood cell count; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin

IRON DEFICIENCY ANAEMIA

Laboratory findings

- Red cell indices : Low MCV, Low MCH values
- Low serum Iron, High TIBC
- Low serum ferritin

Causes of Iron Deficiency Anaemia

- Chronic blood loss
- Increase iron demand – prematurity , growth
- Malabsorption
- Worm infestation
- Inadequate dietary intake

Treatment

- Nutritional counselling
  - If breast fed, maintain breastfeeding
  - Use iron fortified cereals
- Oral iron medication
  - Give 6 mg/kg/day of elemental iron
  - Continue for 6-8 weeks after haemoglobin level is restored to normal
  - Dose calculation depends on the elemental iron in the preparation
- Syr FAC (Ferrous ammonium citrate): the content of elemental iron per ml depends on the preparation available, (usually 86 mg/5ml)
- Tab. Ferrous fumarate 200 mg has 65 mg of elemental iron per tablet

Consider the following if failure to response to oral iron:

- Non-compliance
- Inadequate iron dosage
- Unrecognized blood loss
- Impaired GI absorption
- Incorrect diagnosis
- Rare conditions e.g. IRIDA (Iron Resistant Iron Deficiency Anaemia- these patients are resistant to oral/im iron, may partially respond to parenteral iron)

Blood transfusion

- Generally NOT required in chronic Iron Deficiency Anaemia unless patient is
  - In overt cardiac decompensation
  - Severely symptomatic (e.g. FTT, poor weight gain).
- In patients with chronic anaemia, it is usually safe to plan the transfusion the next morning (during working hours) and take necessary blood investigations prior to transfusion (e.g. FBP, Hb analysis, HIV etc.)
- In severe anaemia (Hb < 4 g/dL) low volume RBC cells (< 5mls/kg) is preferred. It might be necessary to transfuse slowly over 4-6 hours with IV Frusemide (1mg/kg) midway.

HEREDITARY SPHEROCYTOSIS

Pathogenesis

- Due to the inheritance of a defective structural protein (spectrin) in the RBC membrane producing spheroidal and osmotically fragile RBCs
- These RBCs are trapped and destroyed in the spleen --> shortened RBC life span
- Degree of clinical severity is proportional to the severity of RBC membrane defect
- Inheritance: AD in 2/3; AR or *de novo* in 1/3

Clinical features – can be mild, moderate and severe

- Anaemia
- Intermittent jaundice
- Splenomegaly
- Haemolytic crises
- Pigment gallstones in adolescents and young adults
- Aplastic crises with Parvovirus B19 infections
- Megaloblastic crises (All patients should receive folate supplement)

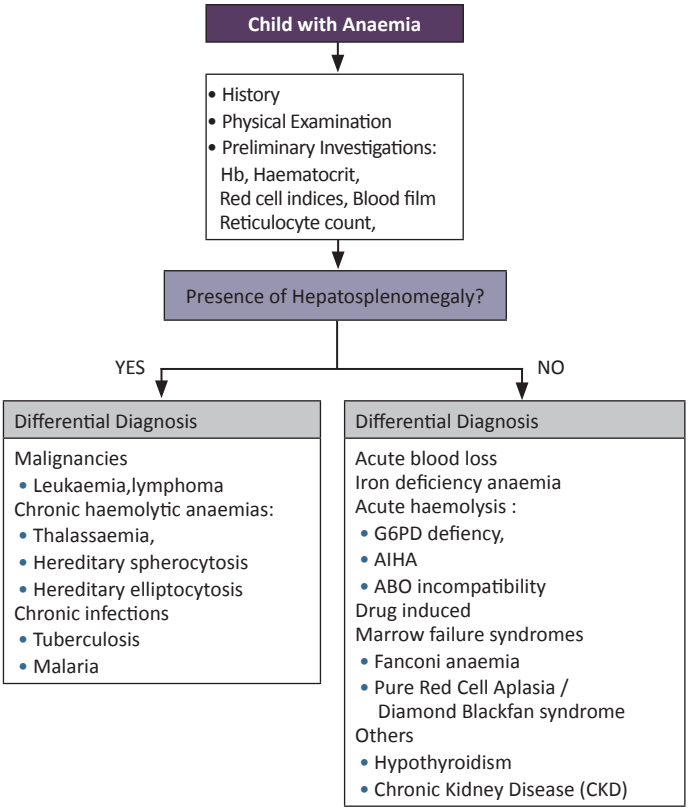
Rare manifestations

- Leg ulcers
- Spinocerebellar ataxia
- Myopathy
- Extramedullary haematopoietic tumours

Investigations in children with Suspected Spherocytosis
Reticulocytosis
Microspherocytes in peripheral blood film
Osmotic fragility is increased
Elevated MCHC
Normal direct antiglobulin test
Autohaemolysis is increased and corrected by glucose

Treatment

- Folic acid supplements
- Splenectomy
  - To be delayed as long as possible.
  - In mild cases, avoid splenectomy unless gallstones developed
- Splenectomy is avoided for patients < 5 years age because of the increased risk of post-splenectomy sepsis due to capsulated bacteria For patients planned for splenectomy, give pneumococcal, haemophilus and meningococcal vaccination 4-6 weeks prior to splenectomy and prophylactic oral penicillin given post-splenectomy for life.


Child with Anaemia
• History
• Physical Examination
• Preliminary Investigations:
Hb, Haematocrit,
Red cell indices, Blood film
Reticulocyte count,
Presence of Hepatosplenomegaly?
YES
NO
Differential Diagnosis
Malignancies
• Leukaemia,lymphoma
Chronic haemolytic anaemias:
• Thalassaemia,
• Hereditary spherocytosis
• Hereditary elliptocytosis
Chronic infections
• Tuberculosis
• Malaria
Differential Diagnosis
Acute blood loss
Iron deficiency anaemia
Acute haemolysis :
• G6PD defiency,
• AIHA
• ABO incompatibility
Drug induced
Marrow failure syndromes
• Fanconi anaemia
• Pure Red Cell Aplasia /
Diamond Blackfan syndrome
Others
• Hypothyroidism
• Chronic Kidney Disease (CKD)

Chapter 72: Thalassaemia

Introduction

- β-Thalassaemia major is an inherited blood disorder presenting with anaemia classically at 4 - 6 months of age. Common presenting symptoms are pallor, lethargy, failure to thrive and hepatosplenomegaly.
- Most of the population are unaware of their carrier status.
- Carrier rates of thalassaemia gene in Malaysia:
  - β-thalassaemia : 3 - 5%
  - α-thalassaemia : 1.8 - 7.5%
  - Haemoglobin E (HbE) : 5 - 46%
- HbE carriers are mainly in the northern peninsular states.
- Interaction between a β-thal carrier with an HbE carrier may result in the birth of a patient with HbE/β-thalassaemia or thalassaemia intermedia with variable clinical severity. The moderate to severe forms behave like β-thalassaemia major patients while the milder forms are asymptomatic.

Baseline investigations to be done for ALL new patients: -

- Full blood count (In typical cases, the Hb is usually below 7g/dl)
- Peripheral blood film
- *Mandatory:* Haemoglobin analysis by electrophoresis or HPLC (High-performance liquid chromatography)

Typical findings for β-thalassaemia major:
HbA decreased or absent, HbF increased, HbA2 variable

Other pointers

- Red cell phenotyping **(required)** before first transfusion. This test is not useful if the patient has been transfused in the last 3 months
- DNA analysis
- Mandatory in prenatal diagnosis
- Available upon request at tertiary centre labs in IMR, HKL, HUKM, UMMC and USM
- β gene analysis done in IMR and α gene analysis in HKL- these tests require a special form and consent
- Infection screen: HIV, Hepatitis B & C, VDRL screen (before first transfusion).
- All nuclear family members must be investigated by Hb Analysis for genetic counselling.
- 1st degree and 2nd degree relatives is encouraged to be screened and counselled (cascade screening).

Management

Regular blood transfusion and iron chelation therapy is the mainstay of treatment in patients with transfusion dependent thalassaemia.

Maintenance Blood Transfusion

BETA THALASSAEMIA MAJOR

When to start blood transfusion?

- ***After*** mandatory blood investigations has been taken for confirmation of diagnosis. Note that it is not necessary to wait for the confirmatory diagnosis result to be available before transfusing the patient in emergency situations, BUT blood investigations MUST be taken before transfusion.
- It is very important that Hb analysis, infection screen and RBC phenotype is done ***prior*** to first transfusion as failure to do so will affect the subsequent lab results and complicate the management of the patient later on.
- THAL MAJOR: Once diagnosis is confirmed or if Hb < 7g/dl on 2 occasions > 2 weeks apart (in absence other factors e.g. infection).
- THAL INTERMEDIA: Hb < 8g/dl if there is evidence of impaired growth attributed to anaemia after exclusion of other causes (dietary, constitutional).
- Bone changes (maxillary / mandibular prominence), enlarging liver and spleen, para spinal masses.

Transfusion targets

All thalassaemia major/severe E-β thal should be transfused so as to

- Maintain pre transfusion Hb level at approximately 9 -10 g/dl.
- Keep mean post-transfusion Hb at 13.5-15.5g/dl.
- Keep mean Hb 12 - 12.5 g/dl.
- The above targets allow for normal physical activity and growth, abolishes chronic hypoxaemia and reduces compensatory marrow hyperplasia which causes irreversible facial bone changes and para-spinal masses.

Transfusion interval

- Usually 4 weekly interval (usual rate of Hb decline is at 1g/dl/week).
- Interval varies depending on patients (range: 3 - 6 weekly).

Transfusion volume

- Volume: 15 – 20 mls/kg packed red cells (PRBC).
- Round-up the volume to the nearest unit of cross-matched blood provided, i.e. if calculated volume is just > 1 unit of blood, give 1 unit; or if calculated volume is just < 2 units, give 2 units.
- This strategy minimizes the number of exposure to immunological units of blood avoid wastage of donated blood.

Note:

- In the presence of cardiac failure or Hb < 5g/dl, use low volume PRBC (~ 5-10 ml/kg) at slow infusion rate over > 4 hours with IV Frusemide 1 mg/kg (20 mg maximum dose).
- It is recommended that thalassaemia patients receive leucodepleted (pre-storage, post storage or bedside leucocyte filters) PRBC of < 2 wks old.
- Leucodepletion minimizes non-haemolytic febrile reactions and alloimmunization by removing white cells in the PRBC.

Thalassaemia intermedia

- A clinical diagnosis where patients presents with less severe anaemia at > 2 years of age.
- Severity varies from being symptomatic at presentation to being asymptomatic until later adult life.
- Assessment and decision to start regular transfusion is best left to the specialist.
- All the mandatory bloods pre transfusion investigation is required as per transfusion dependent thalassaemia (refer above).

ALPHA THALASSAEMIA (HB H DISEASE)

Transfuse only if Hb persistently < 7g/dl /or symptomatic of chronic anaemia.

IRON CHELATION THERAPY

- Essential to prevent iron overload in transfusion dependent thalassaemia
- Compliance to optimal treatment is directly related to superior survival outcome, possible beyond the 6th decade.
- Currently 3 approved iron chelators are available:
  - Desferrioxamine (DFO)
  - Deferiprone (DFP)
  - Deferasirox (DFX)

Desferrioxamine (Desferal®)

- When to start
  - Age > 3 years old.
  - Serum ferritin reaches 1000 µg/L.
  - Usually this is after 10 – 20 blood transfusions.
- Dosage and route
  - Average daily dose is 20 – 40mg/kg/day.
  - By subcutaneous (SC) continuous infusion using a portable pump over 8-10 hours daily, 5 - 7 nights a week.
- Aim to maintain serum ferritin level below 1000 µg/L.
- Is given together with Vitamin C, which augments iron excretion with Desferal®.
- Severely iron overloaded patients require longer or continuous SC or IV infusion of Desferal® (via central line if necessary).

Complications of Desferal®

- Local skin reactions usually due to inadequately diluted Desferal® or infection
- Yersinia infection: presents with fever, abdominal pain and diarrhoea.
- Treatment:
  - Withold Desferal®
  - Treat with cotrimoxazole, aminoglycoside or 3rd generation cephalosporin.
- Desferal® toxicity (if using high doses > 50mg/kg/day in the presence of low serum ferritin in children):
  - Ocular toxicity: reduced vision, visual field defects, night blindness; reversible
  - Auditory toxicity: high tone deafness. Not usually reversible
  - Skeletal lesions: pseudo rickets, metaphyseal changes, vertebral growth retardation.

Oral iron chelators

Deferiprone / L1 (Ferriprox®/Kelfer®)

- Is an alternative if iron chelation is ineffective/inadequate despite optimal Desferal® use, or if Desferal® use is contraindicated.
- No formal evaluation in children < 10 years of age.
- Deferiprone is given 75 – 100 mg/kg/day in 3 divided doses.
- It can also be used in combination with Desferal®, using a lower dose of 50mg/kg/day.
- There are risks of GI disturbance, arthritis and rare occurrence of idiopathic agranulocytosis. Weekly full blood count monitoring is recommended. Stop if neutropenic (<1,500/mm^3).

Deferasirox (Exjade®)

- Can be used for transfusional iron overload in patients 2 years or older.
- Dose: 20-30 mg/kg/day in liquid dispersible tablet, taken once daily.
- Adverse effects: transient skin rash, GI disturbance and a reversible rise in serum creatinine. Monthly monitoring of renal function is required.

Complications of chronic iron overload

- Endocrine: growth retardation, impaired glucose tolerance, pubertal delay, hypothyroidism, hypoparathyroidism and diabetes mellitus.
- Cardiac: arrhythmias, pericarditis, cardiac failure.
- Hepatic: liver cirrhosis (especially if with Hepatitis B/C infection).

MONITORING OF PATIENTS

- During each admission for blood transfusion, the following should be done
  - Clinical assessment: height, weight, liver & spleen size, any adverse side effects of chelation therapy.
  - Pre-transfusion Hb, platelet count and WBC (if on Deferiprone).
- Every year or more frequent if indicated
  - Evaluate growth and development.
  - Endocrine assessment – modified GTT, T4/TSH, Ca, PO_4 (If Ca low - check PTH and Vit D).
- Pubertal and sexual development from 10 years onwards.
  - Tanner stage of breast and genitalia.
  - FSH,LH, oestradiol or testosterone levels.
- Bone: osteoporosis and skeletal abnormalities.
- Infection screen (6 monthly) – Hepatitis B and C, HIV, VDRL.
- Calculate the volume of pure RBC transfused based on the haematocrit (HCT) of packed red blood cells (PRBC) given
  - usually HCT of PRBC from blood bank is ~ 50 - 55%.
- Volume of pure RBC transfused = (volume of blood) x (HCT of PRBC) (e.g. 600 mls x 0.55 = 330 mls).
- Annual volume of pure RBC transfused per kg body weight (use median body weight).
- Evaluate iron balance and overload status.
- Cardiac assessment at variable intervals and especially after 10 yrs of age
  - Annual cardiac echocardiography.
  - Yearly ECG or Holter monitoring for arrhythmias.
  - Cardiac T2* MRI.
  - Liver iron assessment
  - Liver T2* MRI for non-invasive assessment of liver iron – done concurrently with cardiac T2* MRI.
  - Liver biopsy for liver iron concentration and the assessment of hepatitis, fibrosis or cirrhosis in selected cases or prior to bone marrow transplantation.

Splenectomy

- Indications
  - When there is evidence of hypersplenism .
  - Defined by blood consumption volume of RBC > 1.5X normal or >200-220 mls/kg/year in patients > 5 years of age to maintain average haemoglobin levels.
- Note:
  - Pneumococcal and HIB vaccinations 4-6 weeks prior to splenectomy.
  - Meningococcal vaccine required in endemic areas.
  - Penicillin prophylaxis for life after splenectomy.
- Low dose aspirin (75 mg daily) if thrombocytosis > 800,000/mm^3 after splenectomy.

Diet and supplements

- Oral folate at minimum 1 mg daily may benefit most patients.
- Low dose Vitamin C at 3 mg/kg augments iron excretion for those on Desferal only.
- Dose: <10 yrs, 50mg daily; >10yrs, 100mg daily
- Give only on Desferal days
- Avoid iron rich food such as red meat and iron fortified cereals or milk.
- Drinking tea is advised as it may help decrease intestinal iron absorption.
- Dairy products are recommended as they are rich in calcium.
- Vitamin E (antioxidant),Calcium and zinc supplement recommended

Bone marrow transplantation (BMT)

- Potential curative option when there is an HLA-compatible sibling marrow donor.
- Results from unrelated donor or cord blood transplant are inferior to matched sibling bone marrow transplant with higher morbidity, mortality and rejection rates.
- Classification of patients into Pesaro risk groups based on the presence of 3 risk factors: hepatomegaly > 2cm, irregular iron chelation and presence of liver fibrosis.
- Best results if performed at the earliest age possible in Class 1 patients.

Pesaro Risk Groups and Outcome following BMT

Class	No. of risk factors	Event Free Survival %	Mortality %	Rejection %
I	0	91	7	2
2	I-2	83	I3	3
3	3	58	21	28
Adults	-	62	34	-

Note:
In newly diagnosed transfusion dependent thalassaemics (β major / severe Eβ), the family should be informed of this option and referred early to a Paediatrician for counselling and HLA typing of patient and unaffected siblings to identify a potential donor.

Antenatal diagnosis

- Can be done by chorionic villous sampling at 9-11 weeks period of gestation.

Patient and parents support groups

- Most states in Malaysia have their own Thalassaemia Societies which
- Provide support and education for families.
- Organises thalassaemia related activities and awareness campaigns.

More information in www.moh.gov.my or www.mytalasemia.net.my.

Chapter 73: Immune Thrombocytopenic Purpura

Definition

- Acute childhood ITP is a benign self-limiting disorder, presenting with isolated thrombocytopenia (<100 X 10^9/L), in the absence of an underlying cause.
- 5% of patients with acute ITP may have recurrence of acute ITP.
- Persistent / chronic ITP develops in 10% of patients with acute ITP.

Pathogenesis

ITP is an autoimmune disorder characterized by autoantibody mediated immunologic destruction of normal platelets (mainly occurring in the spleen), in response to an unknown stimulus.

Clinical Manifestations

- Onset is usually abrupt / acute.
- Duration from onset of thrombocytopenia to normalisation of platelet counts can be a few days to 6 months (average 3 weeks).
- Majority will give a history of a viral infection in the preceding 2-4 weeks.
- Spectrum of bleeding severity ranges from cutaneous bleeding, i.e., petechiae --> mucosal bleeds (gum bleeds, epistaxis, gross haematuria) --> life threatening bleeds i.e. intracranial haemorrhage.

Diagnosis and Investigations

- Diagnosis is based on history, PE, blood counts, and PBF.
- Physical examinaton: absence of hepatosplenomegaly or lymphadenopathy.
- Blood counts: isolated thrombocytopenia, with normal haemoglobin and white cell count.
- PBF: normal apart from reduced, larger platelets, no abnormal cells.
- Other tests may be indicated when there is atypical presentation. The tests would depend on the differential diagnoses suspected in the thrombocytopaenic child.
- Bone marrow examination is not necessary to diagnose ITP if the treating physician is certain that the personal history, family history, physical examination, complete blood count, and peripheral blood smear are typical of ITP.
- Examples of abnormalities that might indicate an alternate diagnosis rather than ITP are:-
  - Fever or bone or joint pain
  - A family history of low platelets or easy bruising
  - Risk factors for HIV
  - Skeletal or soft-tissue morphologic abnormalities
  - Non-petechial rash
  - Lymphadenopathy
  - Abnormal Hb, WBC count, or morphology not typical of ITP

Management

- Most children remit spontaneously. Not all children with acute ITP need hospitalization.
- The platelet count is usually < 20 x 10^9/L at diagnosis.
- 70% achieve a platelet count > 50 x 10^9/L by the end of the 3rd week without treatment
- Consider hospitalization in:
  - Severe life-threatening bleeding (e.g. ICH) regardless of platelet count.
  - Platelet count < 20 x 10^9/L with evidence of bleeding.
  - Platelet count < 20 x 10^9/L without bleeding but inaccessible to health care.
  - Lack of confidence in homecare.
- Advise:
  - Precaution with physical activities especially small children.
  - Avoid contact sports.
  - Seek immediate medical attention if significant bleed.
  - Avoid aspirin /NSAIDs.
- Observation and monitoring of platelet count, without specific treatment, is appropriate for patients with:
  - Platelet count > 20 x 10^9/L without bleeding.
  - Platelet count > 30 x 10^9/L with only cutaneous purpura.
  - Repeat FBC within the first 7-10 days to ensure there is no evidence of evolving marrow disorder.
- Treatment is generally indicated if there is:
  - Life threatening bleeding episode (e.g. ICH) regardless of platelet count.
  - Platelet count < 20 x 10^9/L with mucosal bleeding.
  - Platelet count < 10 x 10^9/L with any bleeding.
- Choice of treatment includes:
  - Oral Prednisolone 2 mg/kg/day for 14 days then taper off over 5 days (regardless of response)
  - Oral Prednisolone 4 mg/kg/day for 3 - 4 days
  - IV Immunoglobulin (IVIG) 0.8 g/kg/dose for a single dose, round up to the nearest bottle to avoid wastage

Notes regarding treatment:

- Treatment do not resolve the condition faster, but can temporarily raise the platelet count much quicker compared to no treatment. There is no evidence that these treatment reduce bleeding complications/mortality / influence progression to chronic ITP.
- Side effects of IVIG are:-common (15 - 75%): fever, flushing, headache, nausea, aseptic meningitis and possible transmission of blood borne infections e.g. Hepatitis C (older preparations).
- Steroids should not be continued if there is no response or if there is a rapid relapse after withdrawal. The long-term side-effects in a child outweigh the benefits.
- Treatment is directed at the clinical status of the patient i.e. treat the child, not the platelet count.

Intracranial Haemorrhage (ICH)

- Is the most feared complication of ITP.
- Incidence in a child with ITP is between 0.1 - 0.5%.
- The risk is highest with platelet count < 20 x 10^9/L, history of head trauma, aspirin use and presence of cerebral arteriovenous malformation.
- 50% of all ICH occurs after 1 month of presentation, 30% after 6 months.
- Early treatment with steroid or IVIG may not prevent late onset ICH.

Emergency treatment

- Emergency treatment of ITP with severe bleeding, i.e. severe epistaxis or gastrointestinal bleed causing drop in Hb or ICH includes:
  - IV Methylprednisolone 30 mg/kg/day for 3 days.
  - IVIG 0.8g - 1g/kg as a single dose – calculated to nearest bottle of IVIG. (usually 3 grams/bottle)
  - Combination of IVIG and methylprednisolone in life threatening conditions.
  - Platelet transfusion in life threatening haemorrhage: 8 - 12 units/m^2 BSA (2 to 3 folds more than usual units) as the platelets will be consumed by the haemorrhage to form blood clots and will reduce further circulating platelets.
  - Consider emergency splenectomy if other modalities fail.
  - Neurosurgical intervention maybe indicated in ICH.

CHRONIC ITP

Definition

- Persistent thrombocytopenia after 6 months of onset * (occurs in 20%)
- Wide spectrum of manifestations: mild asymptomatic low platelet counts to intermittent relapsing symptomatic thrombocytopenia to rare persistent symptomatic and haemorrhagic disease.

Management

- Counselling and education of patient and caretakers regarding natural history of disease and how to detect problems and possible complications early are important. Parents should be comfortable of taking care of patients with persistent low platelet counts at home. At the same time they must be made aware of when and how to seek early medical attention when the need arises.
- Every opportunity should be given for disease to remit spontaneously as the majority will do so if given enough time.
- Asymptomatic children can be left without therapy and kept under observation with continued precautions during physical activity.
- Symptomatic children may need short course of treatments as for acute ITP to tide them over the "relapse" period or during surgical procedures.
- Revisit diagnosis to exclude other causes of thrombocytopenia (Immunodeficiency, lymphoproliferative, collagen disorders, HIV infection).
- 2nd line therapies
  - Steroid pulses: oral Dexamethasone 1 mg/kg given on 4 consecutive days every 4 weeks for 4 months.
  - Intermittent anti-Rh (D) Immunoglobulin treatment for those who are Rh D positive: 45 - 50 ug/kg. May cause drop in Hb levels.

Note:

- Care must be taken with any pulse steroid strategy to avoid treatment- related steroid side effects.
- Family and patient must be aware of immunosuppressive complications, e.g. risk of severe varicella.
- There is no justification for long-term continuous steroids.
- Rituximab and Cyclosporine may be considered in refractory disease.

Splenectomy

- Rarely indicated in children as spontaneous remissions may still occur up to 15 years from diagnosis.
- The risk of dying from ITP is 0.002% whilst the mortality associated with post-splenectomy sepsis is 1.4 - 2.7 %.
- May be considered if:
  - Life-threatening bleeding event
  - Severe life-style restriction with no or transient success with intermittent IVIG, pulsed steroids or anti-D immunoglobulin.
- Laparoscopic method may be better if available.
- *Pre - splenectomy*: immunize against pneumococcus, haemophilus and meningococcus
- *Post – splenectomy*: lifelong penicillin prophylaxis (oral / intramuscular).
- Pneumococcal booster should be given every 5 years.
- Up to 70% of patients may achieve complete remission post-splenectomy.

From Blood 2009;113:2386-2393

IWG (International Working Group) PROPOSAL ON CLASSIFICATION OF IMMUNE THROMBOCYTOPENIC PURPURA

Phases of the Disease	
Newly Diagnosed ITP	Within 3 months from diagnosis.
Persistent ITP	Between 3 to 12 months from diagnosis. Includes patients not reaching spontaneous remission or not maintaining complete response off therapy.
Chronic ITP	Lasting for more than 12 months.
Severe ITP	Presence of bleeding symptoms at presentation sufficient to mandate treatment, or occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose.

Chapter 74: Haemophilia

Definition

- A group of blood disorders in which there is a defect in the clotting mechanism.
- Of X-linked recessive inheritance, but in 30% there is no family history as it is a spontaneous new mutation.
- The most common haemophilias are:
  - Haemophilia A – Deficiency of factor VIII (85% cases)
  - Haemophilia B – Deficiency of factor IX (15% cases)

Clinical Manifestation

- Bleeding in the neonatal period is unusual.
- Usually presents with easy bruising when crawling and walking (9-12 months age).
- Haemarthrosis is characteristic of haemophilia. Large joints are usually affected (knee, ankle, elbow); swollen, painful joints are common.
- Epistaxis, gum bleeding, haematuria also occur.
- Intracranial haemorrhages can be life threatening.
- Bleeding may also occur spontaneously or after trauma, operation or dental procedures.

Diagnostic Investigations

- Full blood count
- Coagulation screen: PT, APTT
- Specific factor assay: FVIII level (low in Haemophilia A).
- Specific factor assay: FIX level (low in Haemophilia B).
- Bleeding time if applicable.
- Von Willebrand screen even if APTT normal.
- In haemophilia, the activated partial thromboplastin time (APTT) is prolonged in moderate and severe haemophilia but may not show prolongation in mild haemophilia. The platelet count and prothrombin time (PT) are normal. When the APTT is prolonged, then the lab will proceed to do the factor VIII antigen level. If this is normal, only then will they proceed to assay the Factor IX level. Once the level has been measured, then the haemophilia can be classified as below.

Classification of haemophilia and clinical presentation		
Factor level	Classification	Clinical presentation
< 1 %	Severe	Spontaneous bleeding, risk of intracranial haemorrhage
1-5 %	Moderate	Bleeding may only occur with trauma, surgery or dental procedures
5-25 %	Mild	

Further Investigations

- Hepatitis B surface antigen, anti HBS antibody
- Hepatitis C antibody
- HIV serology
- Renal profile and Liver function test.
- Platelet aggregation if high suspicion of platelet defect.
- Diagnosis of carrier status for genetic counseling.
  - Mother of a newly diagnosed son with haemophilia.
  - Female siblings of boys with haemophilia.
  - Daughter of a man with haemophilia.

Once a child is diagnosed to have haemophilia, check the viral status at diagnosis and then yearly. This is because treatment carries the risk of acquiring viruses. All haemophiliacs should be immunized against Hepatitis B.

Treatment

- Ideally, treatment of severe haemophilia should be prophylactic to prevent arthropathy and ensure the best quality of life possible.The dosage of prophylaxis is usually 25-35 U/kg of Factor VIII concentrate, given every other day or 3 times a week. For Factor IX, the dosage is 40-60 U/kg, given every 2-3 days. However, this form of management is costly and requires central venous access.
- On demand treatment is another treatment option when clotting factors are inadequate. It consists of replacing the missing factor: Factor VIII concentrates are used in haemophilia A, Factor IX concentrates in Haemophilia B. Fresh frozen plasma and cryoprecipitate ideally SHOULD NOT be used as there is a high risk of viral transmission.
- The dose of factor replacement depends on the type and severity of bleed.

Suggested Replacement Doses of Factor VIII and XI Concentrate		
Type of bleed	Factor VIII dose	Factor XI dose
Haemarthrosis	20 U/kg	40 U/kg
Soft tissue or muscle bleeds	30-40 U /kg	60-80 U/kg
Intracranial haemorrhage or surgery	50 U/kg	100 U/kg

- Dose of factor required can also be calculated using the formulas below
  - Units of Factor VIII: (% rise required) x (weight in kg) x 0.5.
  - Units of Factor IX: (% rise required) x (weight in kg) x 1.4.
- The percentage of factor aimed for depends on the type of bleed.
  - For haemarthroses, 30-40 % is adequate.
  - For soft tissue or muscle bleed aim for 40- 50 % level.
    (there is potential to track and cause compression/compartment syndrome)
- For intracranial bleeds or patients going for surgery, aim for 100%.
- Infuse Factor VIII by slow IV push at a rate not exceeding 100 units per minute in young children.

- Factor VIII is given every 8 - 12 hours. Factor IX is given every 12 - 24 hours.
- Duration of treatment depends on type of bleed:
  - Haemarthroses 2-3 days.
  - Soft tissue bleeds 4-5 days.
  - Intracranial bleeds or surgery 7-10 days.
- Veins must be handled with care. Never perform cut-down unless in an emergency as it destroys the vein.

Complications

Joint destruction

- Recurrent haemarthroses into the same joint will eventually destroy the joint causing osteoarthritis and deformity.
- This can be prevented by prompt and adequate factor replacement.

Acquisition of viruses

- Hepatitis B, C or HIV: immunisation and regular screening recommended.

Inhibitors

- These are antibodies directed against the exogenous factor VIII or IX neutralizing the clotting activity.
- Overall incidence is 15-25% in haemophilia A and 1-3% in haemophilia B.
- Can develop at any age but usually after 10 – 20 exposure days. It is suspected when there is lack of response to replacement therapy despite high doses.
- Treatment requires "bypassing" the deficient clotting factor. Currently 2 agents are available - Recombinant activated Factor VII (rfVIIa or Novoseven) and FEIBA (factor eight inhibitor bypass activity). Immune tolerance induction is also another option.
- Management of inhibitors are difficult and requires consultation with the haematologist in specialized centres.

Supportive Treatment

Analgesia

- There is rapid pain relief in haemarthroses once missing factor concentrate is infused.
- If analgesia is required, avoid intramuscular injections.
- Do not use aspirin or the non-steroidal anti-inflammatory drugs (NSAIDS) as they will affect platelet function.
- Paracetamol with or without opioids can provide adequate pain control.

Dental care

- Good dental hygiene is important as dental caries are a regular source of bleeding.
- Dental clearance with factor replacement will be required in severe cases.

Immunisations

- This is important and must be given: The subcutaneous route is preferred.
- Give under factor cover if haematomas are a problem.

Haemophilia Society

- All haemophiliacs should be registered with a patient support group e.g. Haemophilia Society.
- They should have a medic-alert bracelet/chain which identifies them as haemophiliacs and carry a book in which the diagnosis, classification of severity, types of bleeds and admissions can be recorded

SPECIFIC GUIDELINES FOR MANAGEMENT

Intracranial haemorrhage (ICH)

- Give factor replacement before suspected bleed is confirmed by CT scan
- Aim to increase Factor VIII level to 100%.
- For haemophilia B if monoclonal factor IX is used a level of 80% is adequate and if prothrombin complex concentrate (PCC) is used 50% level is recommended.
- Urgent CT scan:
  - If CT scan confirms ICH : maintain factor level 80%–100% for Day 1 to Day 7 and 50% for Day 8 to Day 21.
  - If CT scan show no evidence of ICH, admit 1 day for observation.
- Follow up for long term sequelae.
- Lab investigations:
  - Pre-treatment factor assay level and inhibitor level before starting treatment and to repeat after 3 days of treatment to ensure adequate levels have been achieved and no inhibitor has developed.
  - Post treatment factor assay level (½ hour after infusion) to ensure required factor level is achieved (if the level is not achieved , consider development of inhibitors) and should be repeated after 3 – 5 days.
- Follow up CT scan after 2 weeks

Surgery

- Pre-op investigations
  - Full coagulation profile – PT, PTT
  - Pre-factor assay level and inhibitor level
  - Blood grouping, full antibody screening and full cross matching if required.
- Calculate dose
  - ½ hour before operation, infuse patient with appropriate factors.
  - Preferable level:
    - 80-100% for factor VIII
    - 70% for monoclonal factor IX
    - 50% if prothrombin complex concentrate (PCC) used
- Check post transfusion specific factor level ½ hour later if necessary or after surgery to ensure correct factor level is achieved.

- Clotting factor level should be maintained above 50% during the operation and 24 hours after surgery.
- Maintain adequate factor levels -
  - Days 1-3 60-80%
    4-7 40-60%
    8-14 30-50%
- Repeat factor assay and check inhibitor level on day 3 to ensure adequate. levels. Post operatively a minimum of 10 to 14 days replacement therapy is recommended.

Iliopsoas bleed

- *Symptoms*: Pain/discomfort in the lower abdomen/upper thighs
- *Signs*: Hip flexed, internally-rotated, unable to extend
- *Danger*: Hypovolaemia, large volumes of blood may be lost in the retroperitoneal space.

Management:

- Factor replacement: 50U/kg stat, followed by 25U/kg bd till asymptomatic, then 20U /kg every other day for 10-14 days.
- Ultrasound / CT scan to diagnose.
- Physiotherapy - when pain subsides.
- Repeat U/S to assess progress.

Haematuria

Management

- Bed rest.
- Hydration (1.5 x maintenance).
- Monitor for first 24 hours: UFEME & Urine C&S.
- If bleeding persists for > 24 hours, start factor concentrate infusion.
- Perform KUB & Ultrasound of the kidneys.

DO NOT give anti-fibrinolytic drugs (tranexamic acid) because this may cause formation of clots in the tubules which may not recanalize.

Haemarthroses (Joint haemorrhages)

- Most spontaneous haemarthroses respond to a single infusion of factor concentrate. Aim for a level of 30 % to 40%.
- If swelling or spasm is present, treatment to level of 50% is required and infusion may have to be repeated at 12-24 hours interval until pain subsides.
- Minor haemarthroses may not require immobilization, elastic bandage or slings and ice may help in pain relief.
- In severe haemarthroses
  - Splint in position of comfort.
  - Rest.
  - Early physiotherapy.

METABOLIC EMERGENCIES

Tumour Lysis Syndrome

Tumour lysis syndrome
Characterised by: Hyperuricemia Hyperkalemia Hyperphosphatemia Hypocalcemia

Introduction

- Pathophysiology:
  Massive tumour cell death
  --> rapid release of intracellular metabolites
  --> exceeds excretory capacity of the kidneys
  --> acute kidney injury (AKI)
- More common in lymphoproliferative tumours with abdominal involvement (e.g. lymphoma, leukaemia)
- Beware of giving steroids in any patients with suspected leukaemia!!!
- Can occur spontaneously even before any chemotherapy is started

Characterised by:

- Hyperuricemia: Breakdown of intracellular purines in DNA increase uric aci.d
- Hyperkalaemia can occur secondary to
  - Tumour cell lysis
  - Renal failure from uric acid nephropathy or hyperphosphatemia
- Hyperphosphatemia with associated hypocalcaemia.
- Most commonly occurs in lymphoproliferative disorders as phosphate content in lymphoblasts are 4 X higher than in normal lymphocytes
- Tissue damage from $CaPO_4$ precipitation (When Ca X PO_4 > 60mg/dl)
- Hypocalcaemia leads to altered sensorium, photophobia, neuromuscular irritability, seizures, carpopedal spasm and GIT symptoms

Risk factors for Tumour lysis syndrome	
Patient Factors Hyperuricaemia Dehydration Reduced urine output Acute kidney injury Acidic urine Rarely: underlying disease e.g. HPT (Hypertension), CKD (Chronic Kidney Disease)	*Tumour Factors* Bulky disease, i.e. ALL, Lymphoma Exquisitively chemosensitive tumours

Renal failure - cause of renal failure in the patient with TLS is multifactorial:-

- Uric acid, phosphorus and potassium are excreted by kidneys
- Lactic acidosis will facilitate uric acid crystallization and uric acid obstructive nephropathy.
- Increased phosphorus excretion causes calcium phosphate precipitation in microvasculature and tubules.
- Risk increases if renal parenchyma is infiltrated by tumour, e.g. in abdominal or renal lymphoma or ureteric obstruction from tumour compression/lymph nodes.

Management (Prevention):

- To be instituted in every case of acute leukaemia or lymphoma prior to induction chemotherapy.
- Hydration: Ensure adequate hydration in all patients.
- In high risk patients, hyper hydration of 125ml/m²/hr or 3000ml/m²/day .
- NO ADDED POTASSIUM in drip.
- Allopurinol 10mg/kg/day, max 300mg/day.
- Rasburicase in patients with high risk of developing TLS. (No allopurinol in these patients).
- Alkalization of urine with sodium bicarbonate is no longer advocated.
  - HCO_3 makes uric acid more soluble.
  - However,
    - Calcium phosphate precipitates in alkaline urine (esp. if pH >8).
    - Alkalinisation may aggravate hypocalcaemia.
  - Xanthine, hypoxanthine and allantoin precipitation is not affected by pH.
- May have to delay chemotherapy until metabolic status stabilizes
- Close electrolyte monitoring: BUSE, Ca^{2+}, PO_4, uric acid, creatinine, HCO_3
- Strict I/O charting. Ensure adequate urine flow once hydrated. May require frusemide.

Management (Treatment)

- Treat hyperkalaemia as per institution protocol– kalimate/ resonium/ lytic cocktail.
- Diuretics as required.
- Treatment of hypocalcaemia depends on the phosphate level:
  - If phosphate is raised, correct the high phosphate.
  - If phosphate is normal /symptoms of hypokalaemia, give IV calcium correction.
  - If hypocalcaemia is refractory to treatment, exclude associated hypomagnesaemia.
- Definitive treatment of established TLS is dialysis
  - Haemodialysis most efficient at correcting electrolyte abnormalities.
  - Peritoneal dialysis is not effective in removing phosphates.

OTHER METABOLIC EMERGENCIES:

Hyponatraemia

- May occur in acute myeloid leukaemia (AML)
- Can occur as part of SIADH

Hypernatremia

- May occur in patients with Diabetes Insipidus due to brain tumours, LCH, etc.

Hypokalaemia

- Common in AML
- Due to rapid cellular generation which leads to uptake of potassium into cells
- Intracellular K+ 30-40 X higher than extracellular K+
- Therefore hypokalaemia may develop after chemotherapy

Hypercalcaemia

- Associated with NHL (Non Hodgkin Lymphoma), Hodgkin lymphoma, rhabdoid tumours, alveolar rhabdomyosarcoma, etc.
- Treatment:
  - Ensure adequate hydration
  - IV Frusemide (which increases calcium excretion)

HAEMATOLOGICAL EMERGENCIES

Hyperleukocytosis

- Defined as TWBC > 100,000/mm³ in patients with acute leukaemia.
- Symptoms are related to leukostasis, especially in acute monocytic leukaemia.
  - LUNGS: Pulmonary infiltrates causing dyspnoea, hypoxaemia and right ventricular failure
  - CNS: causing headache, papilledema, seizures, haemorrhage or infarct.
  - Other complications: renal failure, priapism, dactylitis.
- Mechanism:
  - Excessive leukocytes form aggregates and thrombi in small veins causing obstruction.
  - Worsens when blood is viscous.
  - Excessive leukocytes competes for oxygen; damages vessel wall causing bleeding.

Management

- Adequate hydration/ hyper hydration at 125mls/m²/hour
  - Facilitate excretion of toxic metabolites.
  - Reduce blood viscosity.
- Avoid increasing blood viscosity
  - Exercise caution in use of packed cell transfusion and diuretics.
- During induction in patients with hyperleukocytosis, keep platelet count >20 000/mm³ and coagulation profile near normal.
- Exchange transfusions and leukopheresis should not be used alone as rapid rebound usually occurs. Concurrent chemotherapy should therefore be initiated soonest possible.

Coagulopathy

- AML (especially AML M3) is associated with an initial bleeding diathesis
- Consumptive coagulopathy is due to release of a tissue factor with pro-coagulant activity from cells
- The use of all-trans retinoic acid (ATRA) has circumvented this complication
- Management
  - Platelet transfusions: 6 units/m² should increase platelets by 50,000/mm³
  - Fresh frozen plasma (FFP) or cryoprecipitate
  - Vitamin K

Other haematological emergencies

- Thrombocytopenia
- Severe anaemia

SUPERIOR VENA CAVA OBSTRUCTION

- Especially in newly diagnosed NHL/Hodgkin Lymphoma/acute leukaemia.
- Rarely, malignant teratoma, thymoma, neuroblastoma, rhabdomyosarcoma or Ewing's sarcoma may present with anterior or middle mediastinal mass and obstruction.
- 50% associated with thrombosis.
- Presentation: shortness of breath, facial swelling, syncope.

Management

- Recognition of symptoms and signs of SVC obstruction.
- Avoid sedation and general anaesthesia --> significant risk of circulatory collapse or respiratory failure with general anaesthesia or sedation.
- Avoid upper limb venepunctures as may cause bleeding due to increased intravascular pressure / aggravate SVC obstruction.
- Tissue diagnosis should be established by the least invasive method possible.
- Consider obtaining diagnosis by BMA, biopsy of superficial lymph node under LA or measurement of serum marker,s e.g. alpha-fetoprotein.
- If tissue diagnosis impossible, treat empirically based on the most likely diagnosis.
- Chemotherapy and radiotherapy may make histologic diagnosis difficult (as early as 48 hours) --> biopsy as soon as patient is fit / safe.
- NHL - Primary mode of treatment is with steroids and chemotherapy.
- Consider radiotherapy for symptomatic treatment in severe cases.

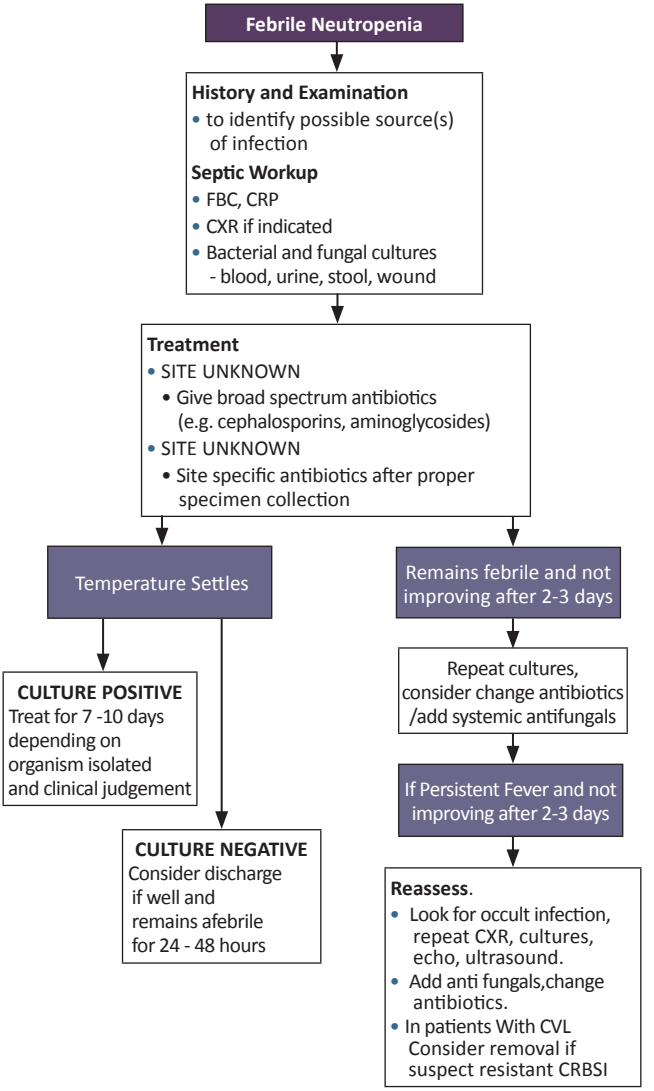
INFECTION

Febrile neutropenia

- Febrile episodes in oncology patients must be treated with urgency especially if associated with neutropenia. Usually bacteraemia or disseminated fungal infections occur when the absolute neutrophil count (ANC) <500 /mm³.
- Risk increases maximally if ANC < 100 /mm³ and greatly reduced if the ANC > 1000 /mm³.

Management (Refer Algorithm on next page)

APPROACH TO CHILD WITH FEBRILE NEUTROPENIA



Other considerations:

- If central venous line (CVL) is present, culture from both lumens; add anti-*Staph* cover e.g. Cloxacillin.
- Repeated physical examination to look for new signs and symptoms or clues to possible sources.
- Close monitoring of patient's well-being --> vital signs, perfusion, BP, I/O.
- Repeat cultures if indicated.
- Investigative parameters, FBC, CRP, BUSE as necessary.
- In presence of oral thrush or other evidence of fungal infection, start antifungals.
- Monitor renal function closely as some patients may have recently been given potentially nephrotoxic chemotherapy, e.g. cisplatin.

Typhlitis

- A necrotizing colitis localised to the caecum occurring in neutropenic patients.
- Bacterial invasion of mucosa causing inflammation --> full thickness infarction and perforation.
- Usual organisms are *Clostridium* and *Pseudomonas*.
- X-ray shows nonspecific thickening of gut wall --> pneumatosis intestinalis +/- evidence of free gas in abdomen.

Management

- Usually conservative with broad spectrum antibiotics covering gram -ve organisms and anaerobes (use metronidazole).
- Mortality 20-100%.
- Criteria for surgical intervention:
  - Persistent gastrointestinal bleeding despite resolution of neutropenia and thrombocytopenia and correction of coagulation abnormalities.
  - Evidence of perforation.
  - Clinical deterioration suggesting uncontrolled sepsis (controversial).

NEUROLOGICAL COMPLICATIONS

Spinal Cord Compression

Prolonged compression leads to permanent neurologic sequelae

- Epidural extension: Lymphoma, neuroblastoma and soft tissue sarcoma.
- Intradural: Spinal cord tumour.

Presentation

- Back pain: localized or radicular, aggravated by movement, straight leg raising, and neck flexion.
- Later: weakness, sensory loss, loss of bladder and bowel continence
- Diagnosed by MRI or CT.

Management

- Urgent laminectomy (if deterioration within 72 hours)
- If paralysis present > 72 hours, chemotherapy is the better option if tumour is chemo sensitive, e.g. lymphoma, neuroblastoma and Ewing's tumour. This avoids vertebral damage. Onset of action of chemotherapy is similar to radiotherapy.
- Prior IV Dexamethasone 0.5mg/kg 6 hourly to reduce oedema. Caution when dealing with possible lymphoma.
- +/- Radiotherapy.

Increased Intracranial Pressure (ICP) and brain herniation

- Cause: Infratentorial tumours causing blockage of the 3rd or 4th ventricles such as medulloblastomas, astrocytomas and ependymomas
- Signs and symptoms vary according to age/site
  - Infant - vomiting, lethargy, seizures, symptoms of obstructive hydrocephalus and increased head circumference.
  - Older children - early morning headaches +/- vomiting, poor school performance.
  - Cerebellum: ipsilateral hypotonia and ataxia.
  - Herniation of cerebellar tonsil: head tilt and neck stiffness.
  - Tumours near 3rd ventricle: craniopharyngioma, germinoma, optic glioma, hypothalamic and pituitary tumours --> visual loss, increased ICP (intracranial pressure) and hydrocephalus.
  - Aqueduct of Sylvius obstruction due to pineal tumour: raised ICP, Parinaud's syndrome (impaired upward gaze, convergence nystagmus, altered pupillary response).

Management

- Assessment of vital signs, look for focal neurological deficit.
- Look for evidence of raised ICP (bradycardia, hypertension and apnoea).
- Look for evidence of herniation (respiratory pattern, pupil size and reactivity).
- Dexamethasone 0.5 mg/kg QID to reduce oedema.
- Urgent CT to determine cause.
- Prophylactic antiepileptic agents.
- **LUMBAR PUNCTURE IS CONTRAINDICATED**
- Decompression – i.e. shunting +/- surgery.

Cerebrovascular accident (CVA)

- Can result from direct or metastatic spread of tumour, antineoplastic agent or haematological abnormality.
- L-Asparaginase is associated with venous or lateral and sagittal sinus thrombosis caused by rebound hypercoagulable state.
- AML especially APML (acute promyelocytic leukaemia) associated with DIVC (disseminated intravascular coagulation) and CVA, due to the release of procoagulants.

Management

- Supportive.

Use of anticoagulant potentially detrimental.

MISCELLANOUS EMERGENCIES

Acute Pancreatitis

- Should be considered in patients on L-Asparaginase and steroids and complaining of abdominal pain.
- Careful examination plus measurement of serum amylase and ultrasound abdomen.

ATRA (all-trans retinoic acid) syndrome

- Characterised by: fever, respiratory distress, oedema, pleural/pericardial effusion, and hypotension.
- Pathophysiology: due to leukostasis associated with ATRA induced multiplication and differentiation of leukaemic promyelocytes.
- Treatment: Dexamethasone 0.5-1mg/kg/dose bd, maximum dose 20 mg bd.

Chapter 76: Acute Lymphoblastic Leukaemia

Acute lymphoblastic leukaemia (ALL) is the most common childhood malignancy, representing nearly one third of all paediatric cancers.

- Peak age: 2 – 5 years old; Male: Female ratio of 1.2:1

Presentation

- Signs and symptoms which reflect bone marrow infiltration by malignant cells causing anaemia, neutropenia, thrombocytopenia and extra-medullary disease.
- Common:
  - Pallor
  - Bleeding/ bruising
  - Non remitting fever
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Bone pains - not to be misdiagnosed as Juvenile Idiopathic Arthritis
  - Persistent back pain may be due to infiltration of vertebra
- Less common:
  - CNS involvement: headache, nausea, vomiting, lethargy, irritability, seizures, symptoms of spinal cord compression due to spinal mass.
  - Testicular involvement, usually a unilateral painless testicular enlargement.
  - Skin manifestations e.g. skin nodules

Initial investigations

Diagnosis

- Full Blood Count (FBC) and Peripheral Blood Film (PBF)
  - May have anaemia /thrombocytopenia
  - Total White Count (TWC) can be normal, low or high
  - PBF usually shows blast cells but may not always do so.
- Bone marrow examination
  - Aspirate (BMA – Bone Marrow Aspiration) and trephine biopsy
  - Immunophenotyping
  - Cytogenetics
  - Molecular studies
    - HKL (Haematology unit) or IMR Haematology Lab (3mls in EDTA bottle)
    - Other University/Private laboratories
- Cerebral Spinal Fluid (CSF) examination for blast cells

For assessment and monitoring

- CXR to look for mediastinal masses
- BUSE especially serum K^+ ,Serum Creatinine, Uric Acid, PO_4, Ca^{2+}, HCO_3
- Lactate dehydrogenase (LDH) – assess degree of leukaemic cell burden and risk of tumour lysis.
- Coagulation studies in APML (acute promyelocytic leukemiamia) or if the child is toxic or bleeding.
- Blood cultures and septic workup if febrile.
- Hepatitis B/C, HIV and VZ IgG screen pre transfusion and pre treatment.
- Will require repeat BMA and CSF examinations at protocol defined intervals.

Prognosis

- Overall cure rates for childhood ALL are over 80%
- Generally depends on:-
  - Prognostic groups, based on clinical and laboratory features
  - Patient receiving treatment in centres with paediatric oncologists
  - Availability of other special diagnostic tests
  - Use of standard treatment protocols
  - Level of supportive care available
- Unfavourable if there are clinical features indicating high risk
  - Age > 10 years old and infants
  - Very high WBC count at diagnosis
  - Molecular characteristics of the leukaemic blasts, e.g. Philadelphia chromosome t (9; 22) (q34; q11); BCR-ABL; P185BCR-ABL tyrosine kinase.
  - Day 8 peripheral blast cell count > 1000 x 109/L.
  - Poor response to induction chemotherapy based on subsequent BMA/ MRD (Minimal Residual Disease) reassessment where available.

Treatment

- The regimes or treatment protocols used vary according to treatment institutions:
  - BFM – Germany, MRC – UK, CCG/COG – USA
- Generally consists of
  - Induction
  - CNS treatment/ prophylaxis
  - Consolidation/intensification
  - Maintenance
- Complications such as oncologic emergencies can be seen before, during and after treatment. (see **Chapter on Oncologic Emergencies**)
- Once discharged, care givers must be able to recognise signs and symptoms that require urgent medical attention, especially infections as they can be life threatening.
- Infections must be taken seriously (even while on maintenance therapy) as evidence suggests that patients are still immunocompromised up to 3 months after discontinuing chemotherapy.

Maintenance therapy

- Duration is for a total of 2 years for girls and 2.5 years for boys. (BFM 2009 is 2 years for both)
- General guidelines for children with ALL on maintenance chemotherapy
  - Check height, weight and calculate surface area (BSA/m^2) every visit and adjust drug dosages accordingly.
  - To calculate BSA = √ [Height (cm) x Weight (kg) / 3600]
  - Check FBC fortnightly for the first 1-2 months after starting maintenance chemotherapy, and monthly after that if stable

- Consider doing BMA if counts are repeatedly low or relapse suspected.

2/3 of relapses occur within the first year of stopping treatment. CNS relapse usually manifests as headache, vomiting, abnormal sensorium or hypothalamic symptoms (hyperphagia and abnormal weight gain). Testicular relapse presents as painless testicular swelling, usually unilateral.

Cotrimoxazole

- Routinely used as prophylaxis for PJP (Pseudomonas jiroveci) except 1 week prior to and during high dose methotrexate therapy
- In the event of chronic cough or unexplained tachypnoea, consider PJP
- If CXR shows interstitial pneumonitis:- send nasopharyngeal secretions for PCP (Pneumocystis pneumonia) Antigen detection
  - e.g. Immunofluorescent test (IFT) or PJP PCR detection
- Treat empirically with Cotrimoxazole (20 mg/kg/day in divided doses) PJP should be treated for a total of 2 weeks

Different institutions and protocols have different regimes for maintenance chemotherapy.
So it is important to know the requirements of the various protocols:

As a general rule, chemotherapy is adjusted to maintain

- TWC at 2 - 3 $X10^9$/L
- ANC (Absolute Neutrophil Count) at or more than 0.75 X 10^9/L

If TWC is 1-2 x 10^9/L and ANC 0.5 - 0.75 x 10^9/L or platelets 50-100 x 10^9/L ,

- Reduce tablet 6-mercaptopurine (6MP) and oral methotrexate (MTX) dose by 50%
- Once counts are above those levels, increase 6MP and MTX back to 75% of normal dose.
- Review the patient in 1 week and if counts are acceptable, increase back to 100% of normal dose.

If TWC is < 1 x 10^9/L and ANC < 0.5 x 10^9/L or platelets < 50 x 10^9/L ,

- Stop both drugs
- Restart drugs at 50% dose once neutrophil count have recovered > 0.75 x 10^9/L
- Increase back gradually to 75% and later 100% if counts are acceptable

Hb is usually stable during maintenance chemotherapy, although repeatedly low Hb alone may be due to 6MP intolerance. Some patients may require transfusion if anaemia occurs early in the course of maintenance therapy. The standard doses of 6MP and MTX are to be maintained as much as possible.

- If persistent anaemia (i.e. Hb< 8 gm/dl), reduce 6MP dose first and maintain the MTX.
- If anaemia persists despite reducing dose of 6MP, reduce MTX dose appropriately.
- If counts are persistently low and doses of 6MP/MTX are already suboptimal, consider ceasing /withholding Cotrimoxazole.
- Re-introduce Cotrimoxazole once 6MP or MTX are at > 75% of standard protocol dosage.

Maintenance of adequate chemotherapy should take priority over continuing Cotrimoxazole. If neutropaenia recurs or if child cannot tolerate at least 75% drug of dosages, Cotrimoxazole should be stopped.

- Remember that the child is at increased risk of PJP.
- Relatively low threshold for treatment of suspected interstitial pneumonitis.

If counts take a long time to recover, consider performing BMA after 2-3 weeks to rule out sub-clinical relapse.
Consider sending blood for Thiopurine Methyltransferase (TPMT) enzyme deficiency screening if available. Children with homozygous TMPT deficiency can have profound myelosuppression due to 6-MP.

- In severe diarrhoea and vomiting, stop both drugs.
  - Restart at 50% dose when better and return to full dose when tolerated
- If patient develops severe MTX mucositis;
  - Withhold MTX until improvement and restart at full dose
  - Initiate supportive treatment with mouthwash and antifungal treatment
- In clinically significant liver dysfunction;
  - Oral MTX should be stopped
  - Restart at reduced dose and increase as tolerated
  - Investigate for causes of liver dysfunction and monitor LFT

Infections

refer also **Chapter on Oncologic Emergencies** – febrile neutropenia

- If there is significant fever (Temperature ≥ 38.5°C x 1 or ≤ 38°C x2, one hour apart) and neutropenia, stop all chemotherapy drugs and admit for IV antibiotics. Take appropriate cultures and CXR if indicated and give IV antibiotics immediately without waiting for specific bacteriological confirmation. Use a combination of aminoglycosides and cephalosporins to cover both gram negative and gram positive organisms. If nosocomial infection is suspected, use the appropriate antibiotics according to your hospital's culture sensitivity pattern.
- Any fever developing within 24 hours of central venous line access should be treated as CRBSI (Catheter-related bloodstream infection).
- Common organisms are the gram positive cocci. Consider adding cloxacillin to the antibiotic regime.
- Assume multiresistant bacterial sepsis when dealing with patients presenting with septic shock, especially if recently discharged from hospital.
- Vancomycin is indicated if there is a long line (Hickman) or chemoport *in-situ* or if MRSA or coagulase negative *Staphylococcus* infections are suspected.
- Antifungal therapy may be indicated in prolonged neutropenia or if there is no response to antibiotics or if fungal infection is suspected.
- Early and aggressive empirical therapy without waiting for blood culture results will save lives.

Varicella and Measles

- Are life-threatening infections in the immunocompromised children.
- Reinforce this information on parents when they come for follow-up.
- If a patient is significantly/directly exposed (e.g. in the same room > 1 hr with an index case of varicella/measles including 3 days prior to clinical presentation) they are at increased risk of developing these infections.
- MEASLES:
  - Give Measles Human broad-spectrum immune globulin IM 0.5ml/kg (may be divided into 2 separate injection sites) on the same day.
- VARICELLA / Chickenpox:
  - Chemotherapy must be stopped on suspicion of exposure
  - If patient develops varicella, chemotherapy should be withheld and recommenced 2 weeks after the last vesicle has dried
  - For exposed patients: who are VZ IgG – ve at diagnosis, on chemotherapy or within 6 months of stopping chemotherapy:-
  - If VZIG available (should be given within 7 days of contact)
    DOSE: < 5yrs: 250 mg; 5 – 7 yrs: 500 mg; 7 – 12 yrs: 750 mg.
  - If VZIG not available,
    DOSE: oral acyclovir 200mg tds if < 6 years old; 400 mg tds if > 6 years old
    DURATION: 5 days
    Monitor for signs of overt varicella infection
- For patients who develop varicella
  - Admit, isolate and treat immediately with IV acyclovir .
  - DOSE: 500 mg/m^2/dose 8 hourly or 10mg/kg 8 hourly until no new lesions are noted.
  - Switch to oral acyclovir 400mg 5x daily if <6 years old; 800mg 5x daily if >6 years until the lesions are healed.
  - Usual treatment duration is about 10 days.

Vaccinations

- Children on chemotherapy should not receive any vaccinations.
- Continue their immunisation programme from where they left off after 6 months off chemotherapy.

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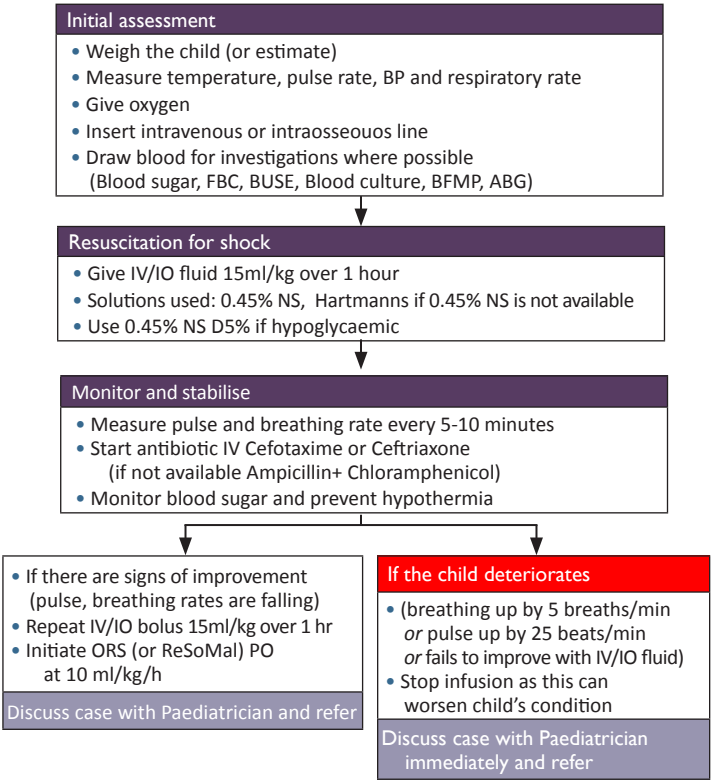
RESUSCITATION PROTOCOL FOR CHILDREN WITH SEVERE MALNUTRITION

This guideline is intended for *Orang Asli and indigenous children* who present to District Hospitals and Health Centres with a history of being unwell with fever, diarrhoea, vomiting and poor feeding.

Important: This protocol is not to be used for a child who does not have severe malnutrition.

This guideline is only recommended for those who fulfill the following criteria:

- Orang Asli or other indigenous ethnic group.
- Severe malnutrition.
- Lethargic or has lost consciousness.
- Ill or in Shock.



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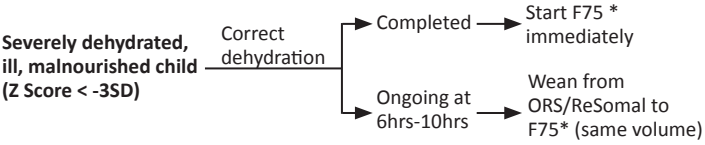
Re-feeding severely malnoursihed children

This protocol is based on the protocol for Management of the child with a serious infection or severe malnutrition (IMCI), Unicef WHO 2000 and Updates On The Management Of Severe Acute Malnutrition In Infants And Children WHO 2013

RE-FEEDING PLAN



Starter feed with F75 based on IMCI protocol

- Feeds at 75-100kcal/kg/day (< 100kcal/kg/day in the initial phase).
- Protein at 1-1.5 g/kg/day.
- Total volume 130mls/kg/day (if severe oedema, reduce to 100mls/kg/day).

How to increase feeds?

- Increase F75 gradually in volume, e.g. 10 ml/kg/day in first 3-4 days
- Gradual decrease in feeding frequency: 2, then 3 and 4 hourly when improves.
- Calculate calorie and protein content daily
- Consider F100 catch up formula when
  - Calories 130/kCal-kg/day-140kCal/kg/day.
  - Child can tolerate orally well, gains weight, without signs of heart failure.

Note:

1. *In a severely oedematous child this process might take about a week.*
2. *If you do not increase calories and proteins the child is not going to gain weight and ward stay will be prolonged.*

Monitoring

- *Avoid causing heart failure*
  - Suspect if: sustained increase (> 2 hrs) of respiratory rate (increases by 5/min), and / or heart rate by 25/min from baseline.
  - If present: reduce feed to 100ml/kg/day for 24 hr then slowly increase as follows:
    - 115ml/kg/day for next 24 hrs; then 130ml/kg/day for next 48 hrs.
    - Then increase each day by 10 mls.
- *Ensure adequate weight gain*
  - Weigh child every morning before feeds; ideal weight gain is > 10g/kg/day.
- If poor weight gain < 5g/kg/day do a full reassessment.
- If moderate weight gain (5-10g/kg/day) check intake or check for infection.
- Watch for secondary infection.
- Watch for hypokalemia and hypophosphatemia.

Introducing Catch up Growth formula (F100)

- Gradual transition from F75 to F100 (usually over 48-72 hrs).
- Increase successive feed by 10mls till some feeds remains uneaten.
- Modified porridge or complementary food can be used, provided they have comparable energy and protein levels.
- Gradually wean to normal diet with unlimited frequent feeds at 150-220 kCal/kg/day.
- Offer protein at 4-6 g/kg/day.
- Continue breast feeding if child is breastfed.

Note: If child refuses F75/F100 and is too vigorous for forced RT feeding, then give normal diet. However must calculate calories and protein (as above).

Vitamin A supplements

- Children with severe acute malnutrition should be provided with about 5000 IU daily intake of vitamin A throughout the treatment period.
- High dose of vitamin A (100 000 - 200 000 IU) is not required if supplement they are receiving is F-75, F-100 or ready to use therapeutic food that comply with WHO specifications.

Discharge criteria

- Not oedematous.
- Gaining weight well.
- Afebrile.
- Has completed antibiotics.
- Aged ≥ 12 mths (caution < 12 mths: A Specialist opinion is required before discharge).

In situation where patient need to be transferred to district facilities, make sure:

- Provide a clear plan on how to feed and how to monitor progress.
- Provide a dietary plan with adequate calorie and protein requirements.
- A follow up appointment with a Paediatrician.

Recipes for starter and catch-up formulas			
	F-75 (starter)	F-100 (catch-up)	F-135 (catch-up)
Dried skimmed milk (g)*	25	80	90
Sugar (g)	100	50	65
Vegetable oil (g)	30 (or 35 ml)	60 (or 70 ml)	85 (or 95 ml)
Electrolyte/mineral solution (ml)	20	20	20
Water: make up to	1000 ml	1000 ml	1000 ml
Contents per 100ml			
Energy (kcal)	75	100	135
Protein (g)	0.9	2.9	3.3
Lactose (g)	1.3	4.2	4.8
Potassium (mmol)	4.0	6.3	7.7
Sodium (mmol)	0.6	1.9	2.2
Magnesium (mmol)	0.43	0.73	0.8
Zinc (mg)	2.0	2.3	3.0
Copper (mg)	0.25	0.25	0.34
% energy from protein	5	12	10
% energy from fat	36	53	57
Osmolarity (mOsmol/L)	413	419	508

Preparation

- Using an electric blender: place some of the warm boiled water in the blender, add the milk powder, sugar, oil and electrolyte/mineral solution. Make up to 1000 ml, and blend at high speed.
- If no blender is available, mix milk, sugar, oil and electrolyte/ mineral solution to a paste, and then slowly add the rest of the warm boiled water and whisk vigorously with a manual whisk.
- Store made-up formula in refrigerator.

***Alternative recipes: (other milk sources)**

F-75 starter formulas (make up to 100 ml)

- Full-cream dried milk 35 g, 100 g sugar, 20 g (or ml) oil, 20 ml electrolyte/ mineral solution.
- Full-cream milk (fresh/ long life) 300 ml, 100 g sugar, 20 g (or ml) oil, 20 ml electrolyte/mineral solution.

F-100 catch-up formulas (make up to 100 ml)

- Full-cream dried milk 110 g, 50 g sugar, 30 g (or ml) oil, 20 ml electrolyte/ mineral solution.
- Full-cream milk (fresh / long life) 880 ml, 75 g sugar, 20 g (or ml) oil, 20 ml electrolyte/mineral solution.

Introduction

- Acute gastroenteritis (AGE) is a leading cause of childhood morbidity and mortality and an important cause of malnutrition.
- Many diarrhoeal deaths are caused by dehydration and electrolytes loss.
- Dehydration can be safely and effectively treated with Oral Rehydration Solution (ORS) but severe dehydration may require intravenous fluid therapy.

First assess the state of perfusion of the child.

Is the child in shock?

- Signs of shock (haemodynamic instability) include tachycardia, weak peripheral pulses, delayed capillary refill time > 2 seconds, cold peripheries, depressed mental state with or without hypotension.

Any child with shock go straight to treatment Plan C.

You can also use the WHO chart below to assess the degree of dehydration and then choose the treatment plan A, B or C, as needed.

Assess:			
Look at child's general condition	Well, alert	Restless or irritable	Lethargic or unconscious
Look for sunken eyes	No sunken eyes	Sunken eyes	Sunken eyes
Offer the child fluid	Drinks normally	Drinks eagerly, thirsty	Not able to drink or drinks poorly
Pinch skin of abdomen	Skin goes back immediately	Skin goes back slowly	Skin goes back very slowly (> 2 secs)
Classify	**Mild Dehydration** <5% Dehydrated* *IMCI: No signs of Dehydration*	≥ 2 above signs: **Moderate Dehydration** 5-10% Dehydrated *IMCI: Some signs of Dehydration*	≥ 2 above signs: **Severe Dehydration** > 10% Dehydrated
Treat	**Plan A** Give fluid and food to treat diarrhoea at home	**Plan B** Give fluid and food for some dehydration	**Plan C** Give fluid for severe dehydration. Provide food as soon as child tolerates.

**% of body weight (in g) loss in fluid (Fluid Deficit) e.g. a 10 kg child with 5% dehydration has loss 5/100 x 10000g = 500 mls of fluid deficit.*

PLAN A: TREAT DIARRHOEA AT HOME

Counsel the mother on the 3 rules of home treatment:
Give Extra Fluid, Continue Feeding, When to return

1. Give Extra Fluids (as much as the child will take)

- Tell the mother:
  - Breastfeed frequently and for longer at each feed.
  - If exclusively breastfed, give Oral Rehydration Solution (ORS) or cooled boiled water in addition to breastmilk.
  - If the child is not exclusively breastfed, give one or more of the following: ORS, food-based fluids (soup and rice water) or cooled boiled water.
- It is especially important to give ORS at home when:
  - The child has been treated with Plan B or Plan C during this visit.
- Teach the mother how to mix and give ORS. Give her 8 sachets to use at home.
- Show mother how much ORS to give in addition to the usual fluid intake:

  Up to 2 years : 50 to 100ml after each loose stool
  2 years or more : 100 to 200ml after each loose stool
  (If weight is available, give 10ml/kg of ORS after each loose stool)
- Tell mother to
  - Give frequent small sips from a cup or spoon.
  - If child vomits, wait 10 minutes, then continue but more slowly.
  - Continue giving extra fluid until diarrhoea stops.

2. Continue Feeding

- Breastfed infants should continue nursing on demand.
- Formula fed infants should continue their usual formula immediately on rehydration.
- Lactose-free or lactose-reduced formula usually are unnecessary.
- Children receiving semi-solid or solid foods should continue to receive their usual food during the illness.
- Foods high in simple sugar should be avoided as osmotic load may worsen the diarrhoea.

3. When to Return (to clinic/hospital)

- When the child:
  - Is not able to drink or breastfeed or drinking poorly.
  - Becomes sicker.
  - Develops a fever.
  - Has blood in stool.

PLAN B: TREAT SOME DEHYDRATION WITH ORS

Give the recommended amount of ORS over 4-hour period:

Determine the amount of ORS to be given in the first 4 hours.				
Age	Up to 4 months	4 - 12 mths	12 mths - 2 yrs	2 - 5 yrs
Weight	Less than 6 kgs	6 to 10 kgs	10-12 kgs	12 to 19 kgs
Volume	200-400 mls	400-700 mls	700-900 mls	900-1400 mls

1. Use the child's age only when you do not know the weight. The approximate amount of ORS required (in ml) can be calculated by multiplying the child's weight (in kg) x 75.
2. If the patient wants more ORS than shown, give more.

Show the mother how to give ORS solution

- Give frequent small sips from cup or spoon.
- If the child vomits, wait 10 minutes, then continue but more slowly (i.e. 1 spoonful every 2 - 3 minutes).
- Continue breastfeeding whenever the child wants.

After 4 hours

Reassess the child and classify the child for dehydration.
Select the appropriate plan to continue treatment (Plan A, B or C).
Begin feeding the child.

If the mother must leave before completing treatment

- Show her how to prepare ORS solution at home.
- Show her how much ORS to give to finish the 4-hour treatment at home.
- Give her enough ORS packets to complete rehydration. Also give her 8 packets as recommended in Plan A.
- Explain the 3 Rules of Home Treatment (Plan A):
  1. GIVE EXTRA FLUID
  2. CONTINUE FEEDING
  3. WHEN TO RETURN

Important!

- If possible, observe the child at least 6 hours after re-hydration to be sure the mother can maintain hydration giving the child ORS solution by mouth.
- If there is an outbreak of cholera in your area, give an appropriate oral antibiotic after the patient is alert.

PLAN C: TREAT SEVERE DEHYDRATION QUICKLY

- Airway, Breathing and Circulation (ABCs) should be assessed and established quickly.
- Start intravenous (IV) or intraosseous (IO) fluid immediately. If patient can drink, give ORS by mouth while the drip is being set up.
- Initial fluids for resuscitation of shock: 20 ml/kg of 0.9% Normal Saline (NS) or Hartmann's solution as a rapid IV bolus.
- Repeated if necessary until patient is out of shock or if fluid overload is suspected. Review patient after each bolus and consider other causes of shock if child is not responsive to fluid bolus, e.g. septicaemia.
- Once circulation restores, commence rehydration, provide maintenance and replace ongoing losses.
  - For rehydration use isotonic solution: 0.9% NS or Hartmann's solution (0.45% NS in neonates).

    Fluid deficit: Percentage dehydration X body weight in grams (to be given over 4-6 hours).

    Maintenance fluid (See **Chapter 3 Fluid And Electrolyte Guidelines**)

Example:

A 12-kg child is clinically shocked and 10% dehydrated as a result of gastroenteritis.

Initial therapy: To establish ABCs

- 20 ml/kg for shock = 12× 20 = 120 ml of 0.9% NS given as a rapid intravenous bolus. Repeat if necessary.
- Fluid for Rehydration/Fluid deficit: 10/100 x 12000 = 1200 ml
- Daily maintenance fluid = 1st 10 kg 100 × 10 = 1000 ml
  Subsequent 2 kg 2 x 50 = 100 ml
  Total = 1100 ml/day
- To rehydrate (1200 ml over 6 hours) 0.9%NS or Hartmann's solution + maintenance (1100 ml over 24 hours) with 0.9%NS D5%.
- Replace on going diarrhoea/vomiting lossess orally whenever possible: 5- 10ml/kg for each episode.

The cornerstone of management is to reassess the hydration status frequently (e.g. at 1-2 hourly), and adjust the infusion as necessary.

- Caution - more judicious fluid administration rate will be required in certain situations:
  - Children less than 6 months age.
  - Children with co-morbidities.
  - Children that need careful fluid balance, i.e.: heart or kidney problems, severe malnutrition (See **Chapter Approach To Severly Malnourished Chidren**).
  - Children with severe hyponatraemia/ hypernatraemia (See **Chapter 3 Paediatric Fluids and Electrolyte Guidelines**).
- Start giving more of the maintenance fluid as oral feeds e.g. ORS (about 5ml/kg/hour) as soon as the child can drink, usually after 3 to 4 hours for infants, and 1 to 2 hours for older children. This fluid should be administered frequently in small volumes (cup and spoon works very well for this process).

- Generally normal feeds should be administered in addition to the rehydration fluid, particularly if the infant is breastfed.
- Once a child is able to feed and not vomiting, oral rehydration according to Plan A or B can be used and the IV drip reduced gradually and taken off.
- If you cannot or fail to set up IV or 10 line, arrange for the child to be sent to the nearest centre that can do so immediately.
- Meanwhile as arrangements are made to send the child (or as you make further attempts to establish IV or 10 access),
  - Try to rehydrate the child with ORS orally (if the child can drink) or by nasogastric or orogastric tube. Give ORS 20 ml/kg/hour over 6 hours. Continue to give the ORS along the journey.
  - Reassess the child every 1-2 hours.
  - If there is repeated vomiting or increasing abdominal distension, give the fluid more slowly.
  - Reassess the child after six hours, classify dehydration
  - Then choose the most appropriate plan (A, B or C) to continue treatment.
- ***If there is an outbreak of cholera in your area, give an appropriate oral antibiotic after the patient is alert.***

Other indications for intravenous therapy

- Unconscious child.
- Failed ORS treatment due to continuing rapid stool loss (>15-20ml/kg/hr).
- Failed ORS treatment due to frequent, severe vomiting, drinking poorly.
- Abdominal distension with paralytic ileus, usually caused by some antidiarrhoeal drugs (e.g. codeine, loperamide) and hypokalaemia
- Glucose malabsorption, indicated by marked increase in stool output and large amount of glucose in the stool when ORS solution is given (uncommon).

Indications for admission to Hospital

- Shock or severe dehydration.
- Failed ORS treatment and need for intravenous therapy.
- Concern for other possible illness or uncertainty of diagnosis.
- Patient factors, e.g. young age, unusual irritability/drowsiness, worsening symptoms.
- Caregivers not able to provide adequate care at home.
- Social or logistical concerns that may prevent return evaluation if necessary.

* *Lower threshold for children with obesity/undernutrition due to possibility of underestimating degree of dehydration.*

Other problems associated with diarrhoea

- Fever
  - May be due to another infection or dehydration.
  - Always search for the source of infection if there is fever, especially if it persists after the child is rehydrated.
- Seizures
  - Consider:
    - Febrile convulsion (assess for possible meningitis)
    - Hypoglycaemia
    - Hyper/hyponatraemia
- Lactose intolerance
  - Usually in formula-fed babies less than 6 months old with infectious diarrhoea.
  - Clinical features:
    - Persistent loose/watery stool
    - Abdominal distension
    - Increased flatus
    - Perianal excoriation
  - Making the diagnosis: compatible history; check stool for reducing sugar (sensitivity of the test can be greatly increased by sending the liquid portion of the stool for analysis simply by inverting the diaper).
  - Treatment: If diarrhoea is persistent and watery (over 7-10 days) and there is evidence of lactose intolerance, a lactose free formula (preferably cow's milk based) may be given.
  - Normal formula can usually be reintroduced after 3-4 weeks.
- Cow's Milk Protein Allergy
  - A known potentially serious complication following acute gastroenteritis.
  - To be suspected when trial of lactose free formula fails in patients with protracted course of diarrhoea.
  - Children suspected with this condition should be referred to a paediatric gastroenterologist for further assessment.

Nutritional Strategies

- Usually no necessity to withold feeding.
- Undiluted vs diluted formula
  - No dilution of formula is needed for children taking milk formula.
- Lactose free formula (cow's milk-based or soy based)
  - Not recommended routinely. Indicated only in children with lactose intolerance.
  - Cow's milk based lactose free formula is preferred.

PHARMACOLOGICAL AGENTS

Antimicrobials

- Antibiotics should not be used routinely.
- They are reliably helpful only in children with bloody diarrhoea, probable shigellosis, and suspected cholera with severe dehydration.

Antidiarrhoeal medications

- Diosmectite (Smecta®) has been shown to be safe and effective in reducing stool output and duration of diarrhoea. It can be used as an adjunct in the management of AGE. It acts by restoring integrity of damaged intestinal epithelium, also capable to bind to selected bacterial pathogens and rotavirus.
- Other anti diarrhoeal agents like kaolin (silicates), loperamide (anti-motility) and diphenoxylate (anti motility) are not recommended.

Antiemetic medication

- Not recommended, potentially harmful.

Probiotics

- Probiotics has been shown to reduce duration of diarrhoea in several randomized controlled trials. However, the effectiveness is very strain and dose specific. Therefore, only probiotic strain or strains with proven efficacy in appropriate doses can be used as an adjunct to standard therapy.

Zinc supplements

- It was found that zinc supplements during an acute episode of diarrhoea may be of benefit in children aged 6 months or more in areas where the prevalence of zinc deficiency or the prevalence of malnutrition is high.
- WHO recommends zinc supplements as soon as possible after diarrhoea has started.
- Dosage for age 6 months and above 20mg/day, for 10-14 days.

Prebiotics

- Not recommended.

Chapter 79: Chronic Diarrhoea

Introduction

WHO defines persistent or chronic diarrhoea as an episode of diarrhoea that begins acutely and lasts for 14 days or more. The main complication results from chronic diarrhoea is malnutrition.

Mechanisms of diarrhoea

- Osmotic e.g.Lactose intolerance.
- Secretory e.g. Cholera.
- Mixed secretory-osmotic e.g. Rotavirus.
- Mucosal inflammation e.g. Invasive bacteria, Inflammatory Bowel Disease.
- Motility disturbance.

Parameter	Osmotic diarrhoea	Secretory diarrhoea	Mixed
	Carbohydrate load retains water in gut lumen	Gut mucosa secretes water into gut lumen	
Stool volume	10-20 ml/kg/day (max. 200ml/day)	20 ml/kg/day (>200ml/days)	
Stool Osmolality	> 400	Up to 300	
Stool Sodium	30 – 70 mmol/l	95 – 120 mmol/l	
Stool Potassium	<30mmol/l	>40mmol/l	
Osmotic Gap	>135mOsm/l	<50mOsm/l	
Stool pH	<5.5	>6.0	
Stool reducing substance	Positive	Negative	
Response to fasting	Diarrhoea stops	Diarrhoea continues	
Severe metabolic acidosis			If positive suggests structural defect

Adapted from MKH, et al., Investigation of chronic diarrhoea. Paediatrics and Child Health (2016)

Causes of chronic diarrhoea beyond infancy

Infection
- Bacteria: *Shigella, Salmonella*, C. jejuni, E. coli, C. difficile, Aeromonas, Yersinia, Mycobacterium tuberculosis*
- Virus: Rotavirus, Adenovirus, cytomegalovirus, HIV
- Parasites: *Crytosporidium, Giardia, Entamoeba histolytica, Isospora*
- Small bowel bacterial overgrowth
- Post enteritis syndrome*
- Tropical sprue

Food-sensitive diseases
- Coeliac disease
- Allergic and eosinophilic enteropathies
- Chronic non-specific diarrhoea (toddler's diarrhoea)*
- Lactose intolerance, Sucrose-isomaltase deficiency

Immune-mediated disorders
- Inflammatory bowel disease* (IBD)
- Coeliac disease
- Primary immunodeficiency: common variable immunodeficiency, severe combined immunodeficiency, IgA deficiency
- AIDS enteropathy
- Autoimmune enteropathy, e.g.IPEX (immunodysregulation polyendocrinopathy enteropathy X- linked syndrome) and APECED (autoimmune phenomena, polyendocrinopathy, candidiasis, and ectodermal dystrophy)

Anatomical abnormalities
- Malrotation
- Short gut syndrome
- Intestinal lymphangiectasia

Pancreatic insufficiency
- Cystic fibrosis
- Shwachman-diamond syndrome

Primary metabolic diseases
- Mitochondrial cytopathies
- Mucopolysaccharidosis syndromes
- Congenital disorders of glycosylation

Malignancy
- Gastrinoma (Zollinger-Ellison syndrome), VIPoma, Carcinoid syndrome
- Small bowel lymphoma
- Multiple endocrine neoplasia (MEN)

Others
- Irritable bowel syndrome* (IBS)
- Factitious diarrhoea or Munchausen's syndrome, Laxative abuse
- Non-absorbable dietary substitutes: sorbitol, Olestra
- Polypopsis syndromes
- Hirchsprung's disease
- Constipation with overflow incontinence*
- Hyperthyroidism

* Common causes of chronic diarrhoea

Causes of chronic diarrhoea in infancy	
Normal Villous-Crypt Architecture	**Villous-Crypt Structural Abnormality**
Ion transport defects • Congenital chloride-losing diarrhoea • Congenital sodium diarrhoea *Other transporter defect* • Ileal bile salt receptor defect • Acrodermatitis enteropathica *Carbohydrate* • Glucose-galactose malabsorption • Congenital sucrose-isomaltase deficiency *Protein* • Cow's milk protein allergy* • Enterokinase deficiency • Lysinuric protein intolerance *Pancreas* • Exocrine pancreatic insufficiency • Congenital lipase deficiency • Congenital amylase deficiency *Anatomic* • Congenital short bowel syndrome • Hisrchsprung'senterocolitis • Enteric endocrine dysgenesis	• Microvillous inclusion disease • Tufting enteropathy • Abetalipoproteinemia • Hypobetalipoproteinemia • Chylomicron retention disease • Autoimmune enteropathy/IPEX • Primary lymphagiectasia • Congenital enterocyte heparin sulfate deficiency • Allergic enteropathy • Primary immunodeficiency • Syndromic diarrhea
* Common causes of chronic diarrhoea	

Clinical Assessment

Implications of some aspects of the medical history in children with chronic diarrhoea.

- Onset
  - Congenital: Chloridorrhea, Sodium malabsorption
  - Abrupt: Infections
  - Gradual: Everything else
  - With introduction of wheat cereals: Coeliac disease
- Stool Characteristics
  - Day time only: Functional diarrhoea (chronic non-specific diarrhoea of childhood)
  - Nocturnal: Organic aetiology
  - Blood: Dietary protein intolerance (eg. milk), inflammatory bowel disease,
  - White/light, tan colour: Absence of bile; Coeliac disease
  - Family history: Congenital absorptive defects, inflammatory bowel disease, coeliac disease, multiple endocrine neoplasia
- Dietary History
  - "Sugar-free" foods: Fructose, sorbitol or mannitol ingestion
  - Excessive juice: Osmotic diarrhoea/chronic non specific diarrhoea
  - Raw milk: Brainerd diarrhoea
  - Exposure to potentially impure water source: Chronic bacterial infections (e.g. *Aeromonas*), giardiasis, cryptosporidiosis, Brainerd diarrhoea.
- Travel history: Infectious diarrhoea, chronic idiopathic secretory diarrhoea.
- Failure to thrive/weight loss: Malabsorption, pancreatic exocrine insufficiency,anorexia nervosa.
- Previous therapeutic interventions (drugs, radiation, surgery, antibiotics): Drug side effects, radiation enteritis, post surgical status, pseudomembranous colitis (*C. difficile*),post-cholecystectomy diarrhoea
- Secondary gain from illness: Laxative abuse
- Systemic illness symptoms: Hyperthyroidism, diabetes, inflammatory bowel disease, tuberculosis, mastocytosis.
- Intravenous drug abuse, sexual promiscuity (in adolescent/child's parent: HIV disease
- Immune problems: HIV disease, immunoglobulin deficiencies
- Abdominal pain: Obstruction, irritable bowel syndrome, IBD
- Excessive flatus: Carbohydrate malabsorption
- Leakage of stool: Faecal incontinence (consider occult constipation)

Physical examination

- Growth chart, muscle bulk (mid-arm circumference), subcutaneous fat (triceps skin-fold thickness)
- Vital signs
- Pubertal stage, psychomotor development
- Hydration status - -mucous membrane
- Signs of nutrient deficiencies
- Abdominal distension in malabsorption syndromes or small bowel bacterial overgrowth
- Abdominal tenderness in an inflammatory state
- Faecal mass in constipation, Bowel mass in IBD
- Perianal disease in inflammatory bowel disease
- Extra intestinal signs

Investigations

Stools

- Culture for bacteria
- Viral study
- *Clostridium difficile* toxin
- Microscopy for parasitic ova and cyst
- Electrolyte content and osmolarity
- Reducing substances
- Fat globules
- Elastase
- Calprotectin
- Lactoferrin

Bloods

- FBC: anaemia and thrombocytosis
- RBC characteristics: iron, vitamin B12 or folate deficiency in malabsorption/ malnutrition
- TWC and differential
- Immunoglobulin and lymphocyte and neutrophil function analysis: immune disorders
- Urea and Electrolytes
- Liver function test including albumin and prealbumin: low dietary protein intake, protein-losing enteropathy
- ESR, CRP, Ferritin: inflammation
- Coagulation screen, Vitamins A,D,E,K : fat malabsorption
- Lipid profile
- Tissue transglutaminase immune globulin A antibody: coeliac disease (low total IgA level may result in a false-negative test)
- Isoelectric focussing of transferrin

Imaging

- Contrast studies (Upper GI barium contrast studies to study gross anatomy of upper GI tract)
- CT scan abdomen, MRI

Others

- Sweat test
- Upper GI endoscopy and small bowel biopsy for histology, culture and electron microscopy
- Colonoscopy and biopsy for histology, culture
- Rectal biopsy

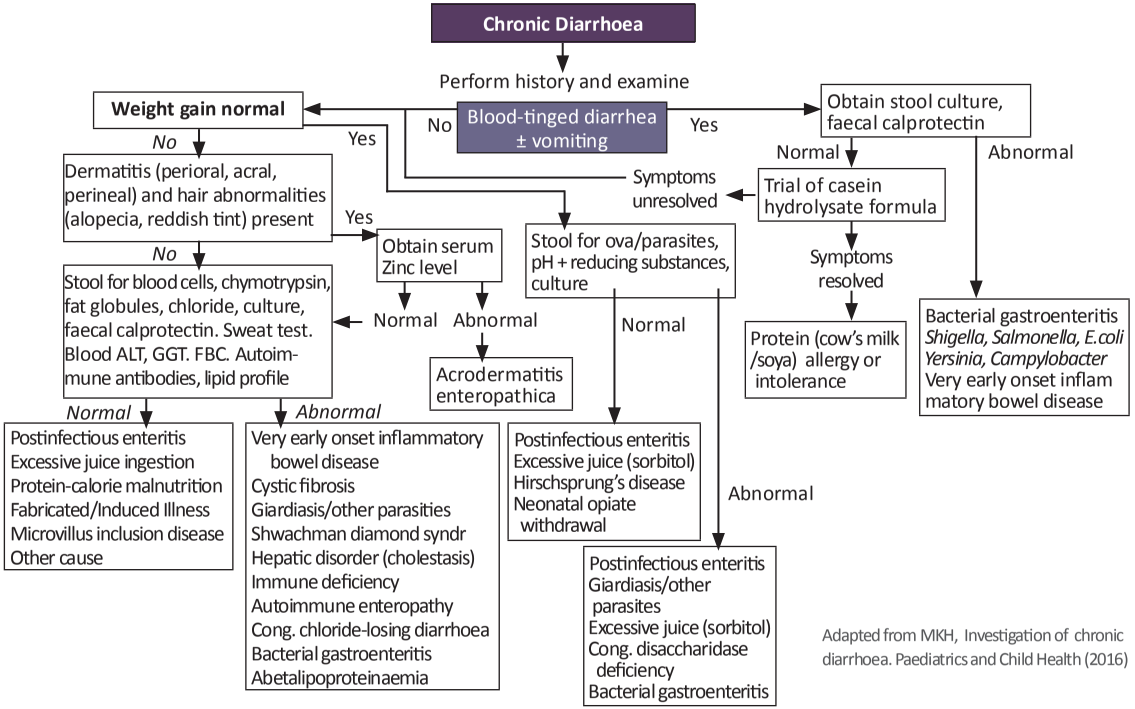
Management of chronic diarrhoea

- Initial resuscitation, correct any fluid and electrolyte abnormalities, hypoglycaemia and prevent hypothermia.
- Identify and treat the underlying cause (e.g. antibiotics, anti-parasitic). Specialist referral if necessary.
- Nutritional assessment and rehabilitation.
- Consider treatment with protein hydrolysate in post-enteritis syndrome.
- Consider micronutrient supplementations in children with chronic diarrhoea and malnourishment, e.g. iron, vitamin A, thiamine etc.
- In cases of lactose intolerance, breastfeeding should be continued unless there are persistent symptoms with perianal excoriation and failure of adequate weight gain. Formula-fed infants should be placed on lactose-free formula (preferably cow's milk based) for 3-4 weeks.
- Suspect monosaccharide intolerance if diarrhea continues even with lactose-free formula or with glucose-containing oral rehydration solution. Treatment includes bowel rest, parenteral nutrition and gradual introduction of feed.
- Beware of refeeding syndrome in those with severe weight loss and those with prolonged IV hydration. Serial monitoring of serum electrolytes is required in the early stages of nutritional recovery. Supplementation should betitrated base on the monitoring. Phosphate supplementation is usually recommended.

Conclusion

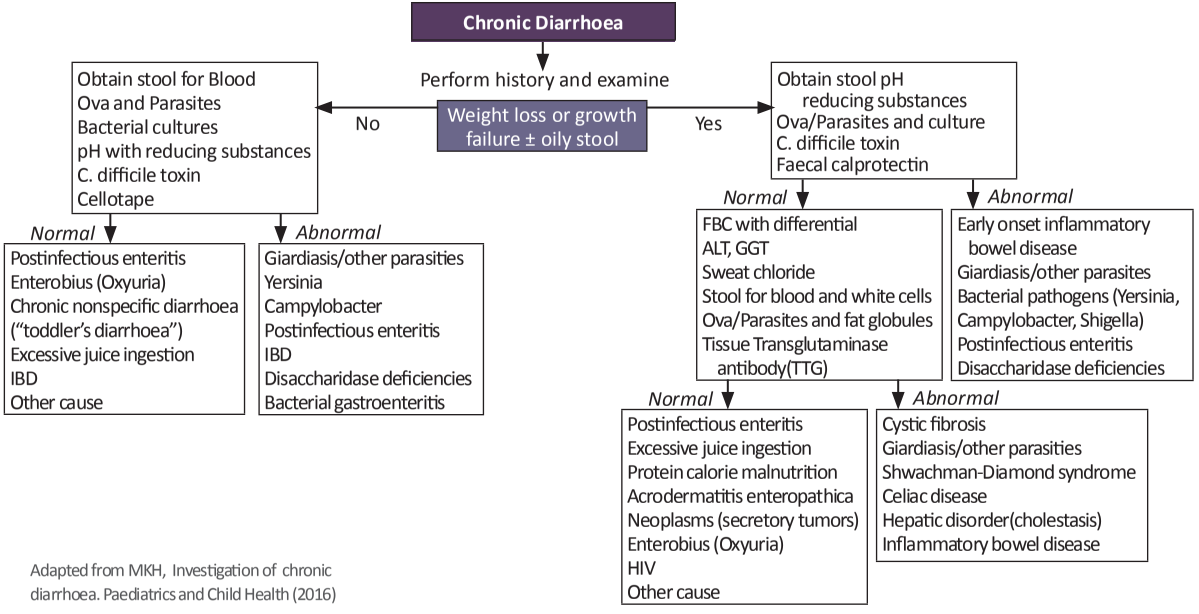
- Despite being a complex condition which frequently requires tertiary gastroenterology unit input, a complete history, physical examination and logical stepwise investigations would usually yield significant clues on the diagnosis.
- The type of diarrhoea ie. secretory vs osmotic type should be determine early in the course of investigations.
- It helps to narrow down the differential diagnosis and assists in planning the therapeutic strategies.
- The nutritional status should not be ignored. It should be ascertained on initial assessment and appropriate nutritional rehabilitation strategies (parenteral or enteral nutrition) should be employed whilst investigating the aetiology.

ALGORITHM FOR WORKUP OF CHRONIC DIARRHOEA IN INFANTS YOUNGER THAN 6 MONTHS



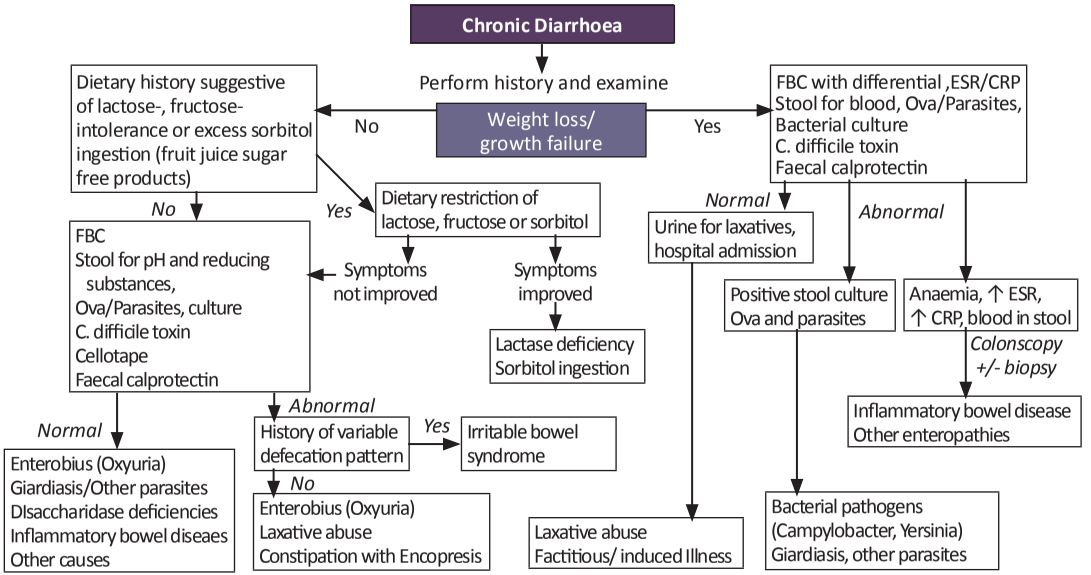
Adapted from MKH, Investigation of chronic diarrhoea. Paediatrics and Child Health (2016)

ALGORITHM FOR WORKUP OF CHRONIC DIARRHOEA IN INFANTS AND TODDLERS



Adapted from MKH, Investigation of chronic diarrhoea. Paediatrics and Child Health (2016)

ALGORITHM FOR WORKUP OF CHRONIC DIARRHOEA IN SCHOOL CHILDREN AND ADOLESCENTS



Adapted from MKH, Investigation of chronic diarrhoea. Paediatrics and Child Health (2016)

Chapter 80: Gastro-oesophageal Reflux

Introduction

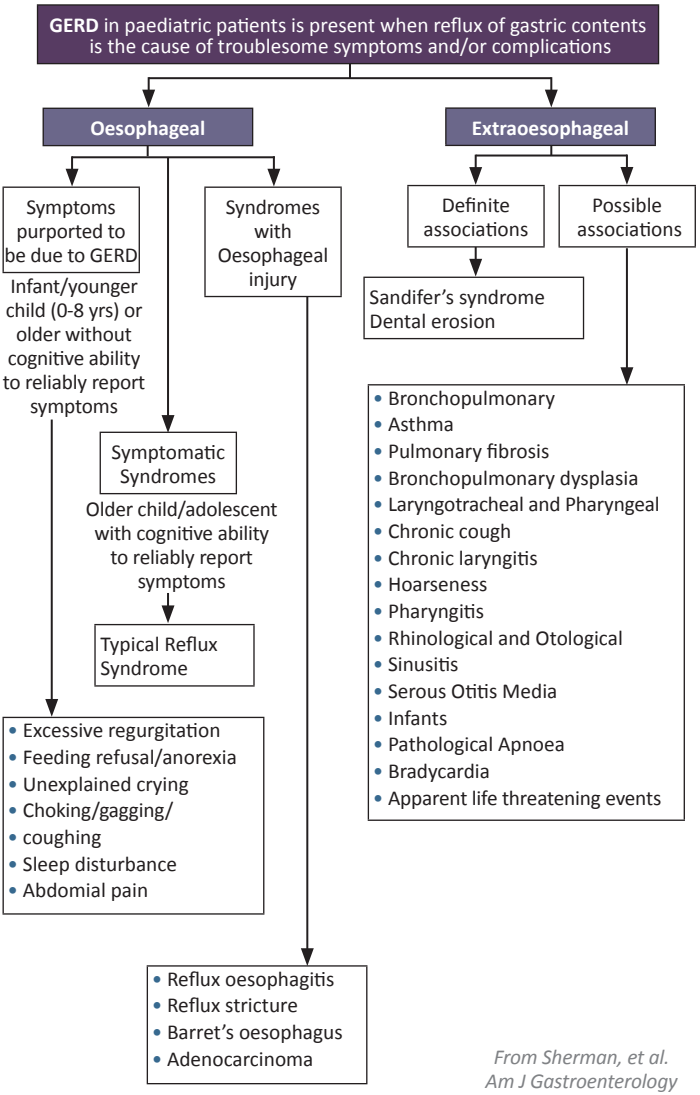
- Gastro-oesophageal reflux (GER) is the passage of gastric contents into the oesophagus with/without regurgitation and vomiting. This is a normal physiological process occurring several times per day in healthy children.
- Gastro-oesophageal reflux disease (GERD) in paediatric patients is present when reflux of gastric contents is the cause of troublesome symptoms and/or complications.

Symptoms and Signs:

- Symptoms and signs associated with reflux vary by age and are nonspecific.

Warning signals requiring investigation in infants with recurrent regurgitation or vomiting:

- Symptoms of gastrointestinal obstruction or disease
  - Bilious vomiting.
  - GI bleeding: hematemesis, hematochezia.
  - Consistently forceful vomiting.
  - Onset of vomiting after six months of life.
  - Constipation.
  - Diarrhea.
  - Abdominal tenderness, distension.
- Symptoms suggesting systemic or neurologic disease
  - Hepatosplenomegaly.
  - Bulging fontanelle.
  - Macro/microcephaly.
  - Seizures.
  - Genetic disorders (e.g., Trisomy 21).
  - Other chronic disorders (e.g., HIV).
- Nonspecific symptoms
  - Fever.
  - Lethargy.
  - Failure to thrive.



From Sherman, et al. Am J Gastroenterology 2009; 104: 1278-1295

Investigations

GERD is often diagnosed clinically and does not require investigations

- Indicated:
  - If its information is helpful to define difficult or unusual cases.
  - If of value in making treatment decisions.
  - When secondary causes of GERD need to be excluded especially in severely affected patients.
- Oesophageal pH Monitoring
  - The severity of pathologic acid reflux does not correlate consistently with symptom severity or demonstrable complications
  - For evaluation of the efficacy of antisecretory therapy
  - To correlate symptoms (e.g., cough, chest pain) with acid reflux episodes, and to select those infants and children with wheezing or respiratory symptoms in whom GER is an aggravating factor.
  - Sensitivity, specificity, and clinical utility of pH monitoring for diagnosis and management of extraesophageal complications of GER is uncertain.
- Barium Contrast Radiography
  - Not useful for the diagnosis of GERD as it has poor sensitivity and specificity but is useful to confirm or rule out anatomic abnormalities of the upper gastrointestinal (GI) tract.
- Nuclear Scintigraphy
  - May have a role in the diagnosis of pulmonary aspiration in patients with chronic and refractory respiratory symptoms. A negative test does not rule out possible pulmonary aspiration of refluxed material.
  - Not recommended for the routine evaluation of GERD in children.
- Oesophageal manometry
  - Not sufficiently sensitive or specific to diagnose GERD.
  - To diagnose motility disorder e.g. achalasia or other motor disorders of the esophagus that may mimic GERD.
- Endoscopy and Biopsy
  - Endoscopically visible breaks in the distal esophageal mucosa are the most reliable evidence of reflux oesophagitis.
  - To identify or rule out other causes of oesophagitis including eosinophilic oesophagitis which do not respond to conventional anti reflux therapy.
  - To diagnose and monitor Barrett's oesophagus and its complications.
- Empiric Trial of Acid Suppression as a Diagnostic Test
  - Expert opinion suggests that in an older child or adolescent with typical symptoms of GERD, an empiric trial of PPI is justified for up to 4 weeks.
  - However, improvement of heartburn, following treatment, does not confirm a diagnosis of GERD because symptoms may improve spontaneously or respond by a placebo effect
  - No evidence to support an empiric trial of acid suppression as a diagnostic test in infants/young children where symptoms of GERD are less specific.
  - Exposing them to the potential adverse events of PPI is not the best practice. Look for causes other than GERD before making such a move.

Treatment

- Physiologic GER does not need medical treatment.
- Symptoms are often non specific especially during infancy; many are exposed to anti-reflux treatment without any sufficient evidence.
- Should always be balance between intended improvement of symptoms with risk of side-effects.

Suggested Schematic Therapeutic Approach

- Parental reassurance & observe. Avoid overeating
- Lifestyle changes.
  - Dietary treatment
    - Use of a thickened formula (or commercial anti regurgitation formulae) may decrease visible regurgitation but does not reduce in the frequency of oesophageal reflux episodes.
    - There may be association between cow's milk protein allergy and GERD.
    - Therefore infants with GERD that are refractory to conventional anti reflux therapy may benefit from a 2- to 4-week trial of elimination of cow's milk in diet with an extensively hydrolyzed protein formula that has been evaluated in controlled trials. Locally available formulas are Alimentum, Pepti and Pregestimil. Usually there will be strong family history of atopy in these patients.
    - No evidence to support the routine elimination of any specific food in older children with GERD.
  - Position during sleep
    - Prone positioning decreases the amount of acid oesophageal exposure measured by pH probe compared with that measured in the supine position. However, prone and lateral positions are associated with an increased incidence of sudden infant death syndrome (SIDS). Therefore, in most infants from birth to 12months of age, supine positioning during sleep is recommended.
    - Prone or left-side sleeping position and/or elevation of the head of the bed for adolescents with GERD may be of benefit in select cases.
- Buffering agents (some efficacy in moderate GERD, relatively safe). Antacids only in older children.
  - Buffering agents e.g. alginate and sucralfate are useful on demand for occasional heartburn.
  - Chronic use of buffering agents is not recommended for GERD because some have absorbable components that may have adverse effects with long-term use.
- Prokinetics .
  - Treat pathophysiologic mechanism of GERD.
  - There is insufficient evidence of clinical efficacy to justify the routine use of metoclopramide, erythromycin, or domperidone for GERD.

- Proton Pump Inhibitors (PPI) (drug of choice in severe GERD). Histamine-2 receptor antagonists less effective than PPI.
  - Histamine-2 Receptor Antagonists (H2RAs).
    - Exhibit tachyphylaxis or tolerance (but PPIs do not)
    - Useful for on-demand treatment
  - Proton Pump Inhibitors
    - Administration of long-term acid suppression without a diagnosis is inadvisable.
    - When acid suppression is required, the smallest effective dose should be used.
    - Most patients require only once-daily PPI; routine use of twice-daily dose is not indicated.
    - No PPI has been officially approved for use in infants <1 year of age.
    - The potential adverse effects of acid suppression, including increased risk of community-acquired pneumonias and GI infections, need to be balanced against the benefits of therapy.
  - Antireflux surgery (either open or laparoscopic surgery).
    - May be of benefit in selected children with chronic-relapsing GERD.
    - Indications include: failure of optimized medical therapy, dependence on long-term medical therapy, significant non adherence with medical therapy, or pulmonary aspiration of refluxate.
    - Children with underlying disorders predisposing to the most severe GERD e.g. neurological impairment are at the highest risk for operative morbidity and postoperative failure.
    - It is essential therefore to rule out all non-GERD causes of the child's symptoms, confirm the diagnosis of chronic relapsing GERD, discuss with the parents the pros and cons of surgery and to assure that the caregivers understand the potential complications, symptom recurrence and sometimes the need to be back on medical therapy.

Definitions

Pediatric Acute Liver Failure (PALF) Study Group:

- Evidence of acute liver injury with no known evidence of chronic liver disease, and
- Biochemical and or clinical evidence of severe liver dysfunction as follows:
  - Hepatic based with a prothrombin time (PT) ≥ 20s or international normalised ratio (INR) ≥ 2.0, that is not corrected by parenteral vitamin K.
  - And/or hepatic encephalopathy(HE) (must be present if the PT is 15.0-19.9s or INR 1.5-1.9, but not if PT≥ 2.0 or INR ≥2.0).

Salient features

- Persistent jaundice with impalpable liver or a liver of reducing size, with progressive decline in serum aminotransferase levels
- Encephalopathy, may worsen quickly (needs frequent review).
  - Increasing lethargy or occasional hallucinations.
  - Symptoms may be subtle and not detectable by clinical assessment but are apparent to family members:
    - Personality changes: e.g. irritable /apathetic (young children), aggression, irritability, euphoria, apathy (older).
    - Intellectual deterioration, insomnia, sleep inversion.
- Bruising, petechiae or bleeding from deranged clotting unresponsive to intravenous vitamin K.
- Failure to maintain normoglycaemia (which aggravates encephalopathy) or presence of hyperammonaemia.
- Increased intracranial pressure (fixed dilated pupils, bradycardia, hypertension or papilloedema).

Grading of Liver Failure

Stage	Asterixis	EEG changes	Clinical manifestations
I *Prodrome*	Slight	Minimal	Mild intellectual impairment, disturbed sleep-wake cycle
II *Impending*	Easily elicited	Usually generalised slowing of rhythm	Drowsiness, confusion, coma, inappropriate behaviour, disorientation, mood swings
III *Stupor*	Present if patient cooperative	Grossly abnormal slowing	Drowsy, unresponsive to verbal commands, markedly confused, delirious, hyperreflexia, positive Babinski sign
IV *Coma*	Usually absent	Appearance of delta waves, decreased amplitudes	Unconscious, decerebrate or decorticate; Response to pain, - present (IV A) - absent (IV B)

Adapted from Diseases of the Liver and Biliary System in Children Fourth Edition, edited by Deirdre A. Kelly, published 2017 by Wiley & Sons Ltd

Aetiology of Hepatic Failure
Causes at different age group (45% remained indeterminate)

Metabolic syndromes (10% of PALF)

Neonate

Galactosaemia, tyrosinaemia, hereditary fructose intolerance, urea cycle defects, neonatal hemochromatosis, mitochondrial disorders, bile acid synthesis defects, Nieman-Pick type C

Infants

Hereditary fructose intolerance, fatty acid oxidation defect, bile acid synthesis defects, mitochondrial disorders, perinatal hemochromatosis, Nieman-Pick Type C

Toddler/Child

Wilson disease, mitochondrial disorders, Alpha 1 Anti Trypsin deficiency, Reye Syndrome, Nieman-Pick Type C

Adolescent

Wilson disease, fatty liver of pregnancy, Nieman-Pick type C

Infections (8% of PALF)

Neonate

HSV, Adenovirus, coxsackie virus, HBV, parvovirus B19, VZV, CMV,EBV, Measles

Infants

Hepatitis A virus, Hepatitis B virus, Non A Non B hepatitis, adenovirus, EBV, echovirus, coxsackie virus

Toddler/Child, Adolescent

Adenovirus, Varicella Zoster virus, Epstein Barr virus, Cytomegalovirus, paramyxovirus, influenza virus, Hepatitis A virus, Hepatitis B virus, Non A Non B hepatitis

Vascular/Ischemic

Neonate

Severe asphyxia, congenital heart disease, cardiac surgery

Infants

Myocarditis, severe asphyxia, cardiac surgery, congenital heart disease

Toddler/Child, Adolescent

Budd- Chiari syndrome, myocarditis, post-operatively, cardiomyopathy

Drugs/toxins (12% of PALF)

Infants

Paracetamol, valproate, trimethoprin/sulfamethoxazole

Toddler/Child, Adolescent

Paracetamol, valproate, antibiotics (trimethoprin/sulfamethoxazole, rifampicin, lisinopril, heliotrope, mushrooms, senecio

Autoimmunity (7% of PALF)

Toddler/Child, Adolescent

Autoimmune hepatitis

Malignancy

Neonate

Neonatal leukaemia, Haemophagocytic Lympho Histiocytosis

Infants, Toddler/Child, Adolescent

Haemophagocytic Lympho Histiocytosis

Adapted from Acute Liver Failure in Children, Mouzaki, Ng. VoL. 11, No. 3 p198-206

Causes of Liver failure	Disease specific investigations
Infections	
Viral hepatitis A, B, B+D, E	Hepatitis A: Anti HAV IgM Hepatitis B: HBsAg, Anti HBc IgM, HBcAg(? core or e Ag) Hepatitis C : Anti HCV antibody, Hep C PCR Hepatitis D: Anti Hep D antibody Hepatitis E: Anti Hep E antibody (IgM) Human Immunodeficiency Virus
Herpes simplex virus	Herpes Simplex Virus (I,II) IgM (neonates)
Epstein Barr, Cytomegalovirus	Cytomegalovirus, Epstein-Barr virus IgM
Measles, adenovirus, Echovirus, Varicella, Dengue, Malaria, tuberculosis, septicaemia	Measles, adenovirus, varicella, echo-virus, dengue, Leptospirosis
Leptospirosis, salmonellosis	Cultures: Blood, urine, sputum, stool, throat swab, skin lesion (if present), ascitic fluid (if present) Viral Culture: urine or skin lesions (if present)
Drugs/Toxins	
Hepatotoxic agent Paracetamol overdose Chlorinated hydrocarbons Amanita spp Salicylate (overdose) Iron overdose 2-nitropropane Yellow phosphorus Solvents Drugs associated idiosyncratic reaction Isoniazid, Erythromycin, quinolones, tetracyline Propylthiouracil Sodium valproate, carbamazepine, phenytoin, lamotrigine Halothane Amiodarone NSAIDS Recreational drugs associated with hepatic injury Cocaine, Ecstasy	History: herbal medication/ indig-enous Drug levels in serum/urine Paracetamol levels Salicylate levels

Causes of Liver failure	Disease specific investigations
Metabolics	
Urea cycle defects	Serum amino acid Urine organic acid
Galactosaemia,	Urine reducing sugar Galactose 1-phosphate uridyltransferase
Tyrosinaemia,	Urine for succinylacetone
MCAD	Plasma acylcarnitines
Congenital disorder of glycosylation	Transferin isoelectrophorosis
Mitochondrial disorders	Quantitative mitochondrial DNA assay, mutation analysis
Hereditary fructose intolerance	Quantitative enzyme assay, q22.3 band mutation in chr 9
Wilson's disease	Serum copper, ceruloplasmin 24-hour urine copper (pre &post penicillamine), Coomb's test
Neonatal hemochromatosis	Serum ferritin, Lip biopsy
Bile acid synthesis defects	Serum bile acids
Nieman-Pick type C	Liver biopsy
Autoimmune	
Autoimmune hepatitis Giant cell hepatitis with Coomb's positive haemolysis	Immunoglobulin IgG Antinuclear Antibodies, Smooth muscle antibody, Liver cytosol antibody, Soluble liver antigen, Liver kidney microsomal antibody, Anti-neutrophil cytoplasmic antibodies, Coomb's test
Lymphoproliferative	
Leukaemia Lymphoma	Full blood picture Bone marrow examination Ascitic fluid/ cerebral spinal fluid cytospin
Haemophagocytic Lympho Histiocytosis (HLH)	Genetics for HLH, ferritin, serum triglyceride, fibrinogen
Vascular/Ischemia	
Severe asphyxia, congenital heart disease, Cardiac surgery, post-operatively Budd- Chiari syndrome, myocarditis, cardiomyopathy	Ultrasound with doppler CT abdomen Echocardiography
Indeterminate	

Adapted Dhawan A (ed): Concise Pediatric and Adolescent Hepatology. Pediatr Adolesc Med. Basel, Karger, 2012, vol 16, pp 14–29

Investigations to consider

- Full Blood Count: Thrombocytopenia - consumptive/ reduced production; High WBC - stress response/ infections; Low WBC - Aplastic
- Coagulation screen (PT, APTT, INR): Coagulopathy (deficiencies of clotting factors/ consumptive)
- Blood Group Cross Match
- Bilirubin, transaminases (ALT, AST)
  - Bilirubin – marked conjugated hyperbilirubinemia (exception drug induced, fulminant hepatitis B, idiopathic anicteric fulminant failure)
  - Aminotransferases – ALT, AST high (>1000 IU/L) or may be low (fallen)
- Alanine phosphatase (ALP), Gamma glutamyl transpeptidase (GGT)
- Albumin
- Urea, electrolytes, creatinine:
  - High urea: dehydration, UGIB (Upper Gastrointestinal Bleed); Low urea: failure of hepatic synthesis; High creatinine: renal impairment.
  - Electrolytes abnormalities – dehydration/losses e.g. vomiting
- Calcium, phosphate
- Ammonia: Plasma ammonia – 2-8 times elevation (>100µmol/l)
- Lactate (random)
- Acid-base: Arterial blood gas – respiratory alkalosis to respiratory or metabolic acidosis
- Glucose: Hypoglycaemia
- Septic screen (Omit lumbar puncture)
- Chest radiograph
- Abdominal ultrasound + doppler
- +/- EEG (EEG changes on brain stem dysfunction and HE (especially grade 4) may vary and thus may require a neurology consult)

PRINCIPLES OF MANAGEMENT

General measures

- Closely monitored in quiet darkened room with head end elevated at 20° with no neck flexion (to decrease ICP and minimise cerebral irritability)
- DO NOT sedate unless already ventilated because it may precipitate respiratory failure and death
- Maintain oxygenation;
- Frequent neurological observations (1-4hourly)
- Give Vitamin K to correct prolong PT. If frank bleeding (GIT/Oral) occurs, consider prudent use of FFP 10ml/kg and cryoprecipitate 5ml/kg. Platelet count should be maintained ≥ 50 $x10^9$/dl.
- Prophylactic H2 agonist or proton pump inhibitor or oral antacid to prevent gastric/duodenal ulceration
- Full septic screen (excluding LP), CXR. Treat sepsis aggressively, monitoring level of aminoglycosides accordingly

Fluids

- Maintain blood glucose ≥ 4mmol/l using minimal fluid volume (Aim to maintain hydration & renal function while reducing risk of cerebral oedema).
- 80% of normal maintenance.
- Maintenance fluids consist of Dextrose 10% in 0.45% or 0.90% Normal saline.
- A central vein catheterisation is necessary for high glucose concentration delivery.
- Check capillary blood sugar every 2-4 hourly (maintain ≥ 4mmol/l).
- Strict monitoring of urine output & fluid balance (catheterisation if necessary).
- Aim urine output > 0.5ml/kg/hour.
- Check urinary electrolytes; serum urea, creatinine, electrolytes, osmolarity.
- Renal dysfunction: Possible causes: hepatorenal syndrome, dehydration, low CVP, low cardiac output. Consider haemofiltration or dialysis (discuss with nephrologist/intensivist) if supportive measures like fluid challenge, renal dose dopamine and frusemide infusion fail – to avoid acidosis and fluid overload.
- In the presence of persistent hypotension (decreased SVR) – might consider IV noradrenaline infusion followed by vasopressin analogues.

Ammonia lowering measures

- Stop oral protein initially. Gradually reintroduce at 0.5-1g/kg/day, then 1-2g/kg/day either enterally or parenterally.
- Provide adequate energy intake to avoid catabolism.
- Bowel decontamination: Lactulose to produce 3-4 loose stools per day (Syrup lactulose 1-2ml/kg every 4-6hourly).
- Enteral antibiotics (e.g. Neomycin 50-100mg/kg/day).
- IV N-acetylcysteine(NAC) SHOULD ONLY BE USED if paracetamol poisoning (history and high index of suspicion are very important as most of the time blood paracetamol levels are already normal by the time the patient presents to hospital with liver failure).
- NAC did not improve 1-year survival in non-paracetamol PALF. 1-year liver transplant free survival was significantly lower with NAC, particularly among those < 2 years old. (Squires RH, Dhawan A, Alonso E, et al. Hepatology 2013 April; 57(4):1542–1549.)
- Antibiotics: Combination that provides a good cover against gram negative organisms and anaerobes e.g. cefotaxime and metronidazole if no specific infective agent suspected (e.g. Leptospira. Mycoplasma).
- Antiviral: Acyclovir is recommended in neonates and small infants with ALF due to possibility of HSV infection.

Clinical pearls in comatose patient

- In the presence of sudden coma, consider intracranial bleed: request a CT brain.
- Patients with grade 3 or 4 encephalopathy require mechanical ventilation to maintain normal cerebral perfusion pressure. Sedation may use a combination of opiod (morphine or fentanyl) and benzodiazepines (midazolam).
- Try to avoid peak end-expiratory pressure of >8cm H_2O (may increase ICP); $PaCO_2$ should be kept within 4-4.5 kPa.(30-35mmHg).
- Raised ICP: consider mannitol (rapid bolus 0.5g/kg as a 20% solution over 15 minutes; can be repeated if serum osmolality is <320 mOsm/l), induction hypernatremia (Sodium ≥145mmol/l) and mild cerebral hypothermia (32-35°C).

King's College Hospital Criteria for Liver Transplantation

Non paracetamol ALF

- INR >6.5 or:
- 3 of the following 5 criteria:
  - Patient age <10 or >40
  - Serum bilirubin > 300 µmol/l
  - Time from onset of jaundice to the development of coma >7 days
  - INR >3.5
  - NANB hepatitis, Drug toxicity

Paracetamol induced ALF

- Arterial pH < 7.3 (after fluid resuscitation) OR
- All 3 of the following criteria:
  - INR >6.5
  - Serum creatinine > 300µmol/l
  - Encephalopathy (grade III or IV)

Contraindication for liver transplantation

Absolute

- Fixed and dilated pupils
- Uncontrolled sepsis
- Systemic mitochondrial/metabolic disorders
- Severe respiratory failure
- Hepatocellular carcinoma (HCC) with extrahepatic disease and rapid progression
- Nieman Pick Disease Type- C
- Severe portopulmonary hypertension not responsive to medical therapy

Relative

- Increasing inotropic requirements
- Infection under treatment
- Cerebral perfusion pressure <40mmHg > than 2 hours
- History of progressive or severe neurologic disorder
- Hemaphagocytic Lymphohistiocytosis
- HCC with venous invasion, rapid disease

Chapter 82: Approach to Gastrointestinal Bleeding

Determine type of Gastrointestinal (GI) Bleeding

Upper GI bleed

- Haemetemesis - vomiting out blood whether fresh or stale.
- Maelaena - passing out tarry black stools per rectum.

Lower GI bleed

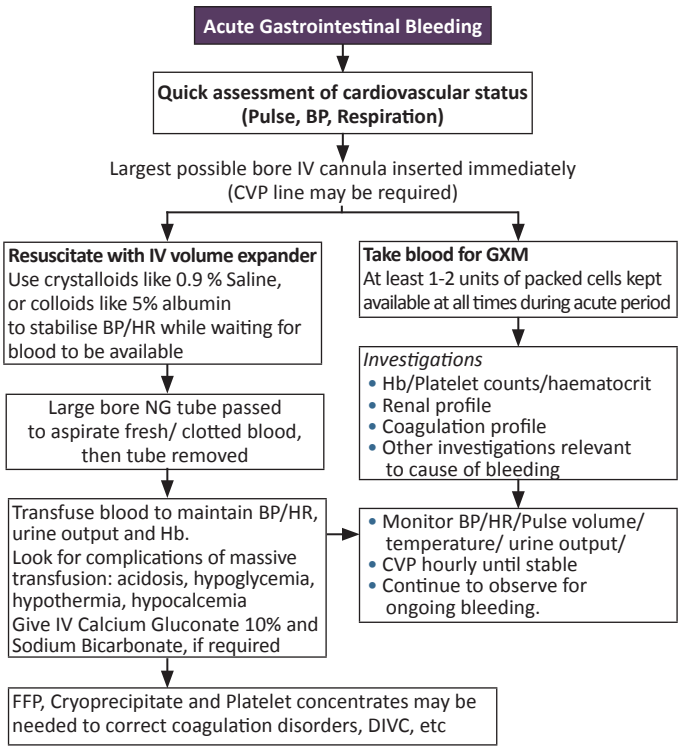
- Haematochezia – passing out bright red blood per rectum.
- Melaena

Sometimes, these are medical emergencies that carry significant mortality.

Salient features

- Duration and severity of haemetemesis, maelaena and/or haematochezia.
- Evidence of hypovolaemic shock.
- Rule out bleeding diathesis.
- Look out for non GI mimics of GI blood loss. such as epistaxis, maternal blood, dental issues, haemoptysis and medications such as iron that can mimic melaena.

ACUTE RESUSCITATION IN A CHILD WITH GASTROINTESTINAL BLEEDING



One of the most helpful factors in narrowing the cause of GI bleeding is the patient's age:

Differential Diagnosis of Gastrointestinal Bleeding		
	Upper GI Bleeding	Lower GI bleeding
Infant	*Mucosal* Oesophagitis, e.g. reflux, allergic Gastritis Mallory-Weiss tear Gastric heterotopia *Structural* Gastric or intestinal duplication *Other* Haemorrhagic disease of the newborn Vascular anomalies Swallowed maternal blood	*Mucosal* Necrotizing enterocolitis Infectious colitis Eosinophilic/allergic colitis Hirschsprung's enterocolitis *Structural* Intestinal duplication Meckel's diverticulum Intussusception
Child	*Mucosal* Oesophagitis Gastritis Peptic ulcer disease Mallory-Weiss tear *Other* Oesophageal varices Hereditary telangiectasia Vascular anomalies Foreign body	*Mucosal* Anal fissure Peptic ulcer disease Infectious colitis Ulcerative colitis/Crohn's disease Juvenile polyp Solitary rectal ulcer Hemorrhoid Lymphonodular hyperplasia *Structural* Intestinal duplication Meckel's diverticulum Intussusception Volvulus Visceral artery aneurysm *Other* Hemolytic-uremic syndrome Henoch-Schönlein purpura Dieulafoy's malformation Munchausen syndrome by proxy Arteriovenous malformation
Adapted from Pediatric Gastroenterology: The requisites in Pediatrics; Eds Chris Liacouras, David Piccoli		

Decision making after acute resuscitation

Reassessment of patients

When patient's condition is stable and resuscitative measures have been instituted,

Assess patient for cause of bleeding and the need for surgery.

History is reviewed.
Ask for history of chronic liver disease, dyspepsia, chronic or intermittent gastrointestinal bleeding (e.g. polyps), drug ingestion (anticoagulants, aspirin), or acute fever (dengue haemorrhagic fever), easy bleeding tendencies, constipation, haematological disorders, antibiotics treatment (pseudomembranous colitis).

Physical examination should be directed towards looking for signs of chronic liver disease (spider angiomata, palmar erythema, portal hypertension or splenomegaly) or telengiectasia / angiomata / purpura / pigmentation in mouth, trunk and extremities, etc.
perianal exam – fissures, fistula etc.

Diagnostic measures to localise source of bleeding

- Oesophagogastro-duodenoscopy (OGDS) or colonoscopy can be performed when patient's condition is stable.
- Double contrast barium study less useful than endoscopy but may be indicated in patients when endoscopy cannot precisely locate the source of bleeding (e.g. in intussusception).
- Ultrasound abdomen should be requested if there is evidence of liver disease, splenomegaly or intussusception is suspected.
- Nuclear scintigraphy eg Meckel's scan can be useful in detecting Meckel's diverticulum
- Visceral angiography can precisely locate the source of bleeding. But is only reserved for patients with a difficult bleeding problem.

Definitive measures to management of gastrointestinal bleeding

Medical Cause

Bleeding peptic ulcer

- Start H2 receptor antagonist (e.g. cimetidine or ranitidine).
- Proton pump inhibitor (omeprazole) should be considered when available as it has higher acid suppressant activity.
- Proton pump inhibitor (e.g. Pantoprazole etc) infusion has been increasingly used "off label" (discuss with Paediatric Gastroenterologist).
- If biopsy shows presence of *Helicobacter pylori* infection, treat accordingly.
- Stop all incriminating drugs e.g. aspirin, steroids and anticoagulant drugs if possible.

Bleeding oesophageal varices or ulcer

- Do not transfuse blood too rapidly as this will lead to increase in Central Venous Pressure (CVP) and a rapid increase in portal pressure may precipitate further bleeding.
- Aim to maintain Hb at 10 g/dL.
- Refer Paediatric Surgeon and Paediatric Gastroenterologist to consider use of octreotide.

Pseudomembranous colitis

- Stop all antibiotics – usually this measure will heal most mild pseudomembranous colitis.
- Consider oral metronidazole or oral vancomycin in moderate to severe pseudomembranous colitis

Surgical Cause

When surgical cause is suspected, early referral to the surgeon is important so that a team approach to the problem can be adopted.

- Intussusception requires immediate surgical referral and intervention may be attempted by the radiologist and proceed with surgical intervention if failed radiological reduction.
- Meckel's diverticulum.
- Malrotation with volvulus.

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Chapter 83: Sepsis and Septic Shock

Sepsis is a life-threatening organ dysfunction caused by dysregulated host responds to infection.
If a child with suspected or proven infection has any 2 of these clinical signs:

- Core temperature < 36°C or > 38.5°C (38.0 if immunocompromised)
- Inappropriate tachycardia and tachypnoea
- Altered mental state (e.g. irritability / lethargy / floppiness)
- Reduced peripheral perfusion / prolonged capillary refill

Then he should be treated as having sepsis or septic shock.

Key Points

- Sepsis and septic shock are medical emergencies hence early recognition by clinician is paramount. It is important to understand that vital signs are dynamic and prone to be confounding. Hypotension is a late sign.
- Septic children can present with:
  - Cold shock; narrow pulse pressure and prolonged capillary refill time (the hemodynamic abnormality is septic myocardial dysfunction and more common in infants and neonate)
  - Warm shock; wide pulse pressure and rapid capillary refill (haemodynamic abnormality is vasoplegia and more common in older children and adolescents)

Features of *Warm* and *Cold* shock

	WARM shock	COLD shock
Peripheries	Warm, flushed	Cold, clammy, cyanotic
Capillary refill	< 2 sec	> 2 sec
Pulse	Bounding	Weak, feeble
Heart rate	Tachycardia	Tachycardia or bradycardia
Blood pressure	Relatively maintained	Hypotension
Pulse pressure	Widened	Narrowed

- Initial management includes securing intravenous access, obtaining blood culture and venous blood gas, and early administration of empiric intravenous antibiotics.
- Titration of fluid resuscitation should be done carefully to prevent harm associated with inadequate or excessive administration. Any persistent cardiovascular failure after the administration of fluid more than 40mls/kg warrants reassessment of diagnosis and ongoing treatment options.
- It is safe to use peripheral intravenous line for administration of inotropes and vasopressors during initial phase of resuscitation.
- Fluid resuscitation and antibiotics should not be delayed by procedures such as lumbar puncture or blood culture.

Other considerations:

Empirical Antibiotics: initiate broad spectrum antibiotics as soon as possible and within 1 hour for both sepsis and septic shock

- Age < 3months: Cefotaxime 50mg/kg and C-Penicillin 50 000u/kg
- Age > 3months: Ceftriaxone 50mg/kg or Cefotaxime 50mg/kg
- Oncology patients: please follow local hospital protocol
- To tailor/ de-escalate antibiotics accordingly once organism identified
- Identify and control source of infection i.e. drainage of abscess

Inotropes/ vasopressors

- For peripheral administration; adrenaline and noradrenaline should be in a diluted concentration (i.e. 1ml/hr = 0.01mcg/kg/min).
- However, it is preferably to infuse via central line and avoid concurrent use with other IV fluid or medications whenever possible.
- Preferably to have invasive BP monitoring
- Dopamine as an alternative to noradrenaline in highly selected patients only (patients with low risk of tachyarrhythmia and absolute or relative bradycardia) or if noradrenaline not available.
- Dobutamine is useful in patients with evidence of persistent hypoperfusion despite adequate intravascular volume.
- Consider vasopressin if patient is refractory to noradrenaline and adrenaline (please consult Intensivist for advise)

Respiratory support depends on the conscious state of the patient

- If normal: consider non invasive ventilation (HFNC, CPAP, BIPAP)
- If abnormal conscious level: consider intubation.
- Intubation: Caution during induction and to consider Ketamine for sedation (as sedation may result in crash of blood pressure). Consider starting inotropic support early prior to intubation.
- Use PEEP and FiO2 to keep SpO2 92-94% and PaO2>80mmHg. Caution when using high PEEP as it can impede venous return and cause hypotension

Further management

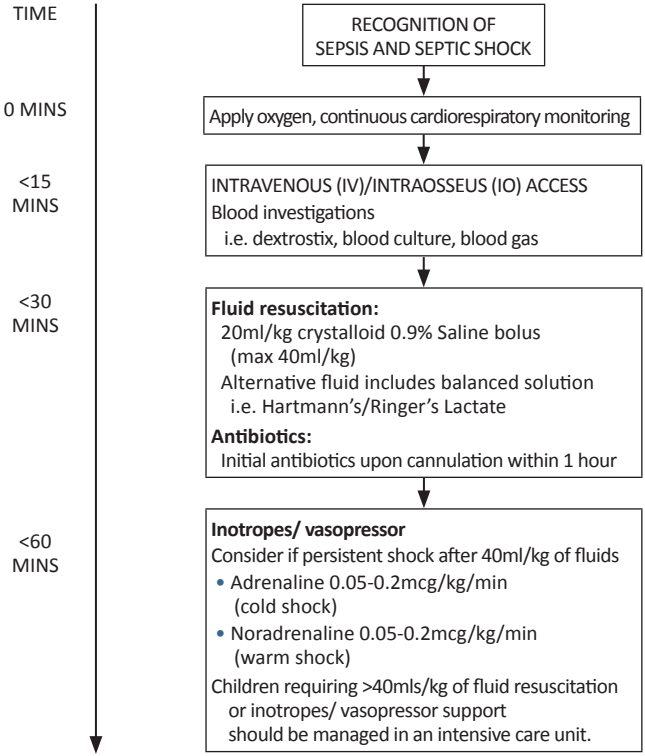
- Lactate level may be used as a surrogate for tissue hypoperfusion. In patients with elevated level lactate >4mmol/dL, frequent sampling is useful to guide resuscitation
- Consider second lines inotropes/vasopressor i.e. vasopressin to improve blood pressure
- Maintain blood glucose between 4-8mmol/L
- Fluids and inotropes to be titrated to optimise vital signs, urine output and conscious level
- The use of echocardiography may help in determining the fluid status and cardiac function

System	Features of compromised end organ perfusion	Therapeutic end point
Cardiovascular	Tachycardia Poor perfusion Hypotension	Heart Rate normalized for age Capillary refill < 2sec Normal pulse quality No difference in central and peripheral pulses Warm extremities Blood pressure normal for age
Neurology	Altered sensorium, irritability, confusion, agitation	Normal mental status
Respiratory	Tachypnoea, increase work of breathing, apnoea, cyanosis (late sign)	Improvement of work of breathing and respiratory rate
Renal	Oliguria: urine <0.5ml/kg/hr Anuria (late sign)	Urine >1ml/kg/hr

Supportive therapy

- *Steroid* to be used in refractory shock with suspected or definite adrenal insufficiency.
  Dosing depends on local protocol (IV hydrocortisone 1-2mg/kg qid)
- Intravenous immunoglobulin is recommended for toxic shock syndrome
- Bicarbonate therapy is not recommended for hypoperfusion induced lactic acidaemia with pH ≥ 7.15
- Venous thromboembolism prophylaxis is useful in high risk group in the absence of contraindications
- Packed cell transfusion is recommended if Hb ≤ 8g/dL or if patients are symptomatic
- Continuous Renal Replacement Therapy (CRRT) is recommended for haemodynamically unstable patients with Acute Kidney Injury (AKI) with indication for dialysis
- Stress ulcer prophylaxis is recommended for patients with high risk for gastrointestinal bleeding (proton-pump inhibitors or histamine-2 receptor antagonist)
- Enteral nutrition is recommended for patients without feeding intolerance
- Family conference is required to update family members on patient's condition and progress, as well as to set the goal of care

INITIAL MANAGEMENT OF SEPSIS AND SEPTIC SHOCK



Screening of children for HIV status

- Babies of HIV positive mothers
- Abandoned babies / street children.
- Babies of mothers with high risk behaviour (e.g. drug addicts, prostitutes, multiple sex partners / single-teenage or underage).
- Sexually abused children and children with sexually transmitted disease.
- Children receiving regular blood transfusions or blood products e.g. Thalassaemics.

Deliveries and infant nursing

- Standard precautions must be observed at all times. It is vital to use protective barriers such as arm length gloves, mask, goggles and gown with waterproof sleeves. Boots are to be used for institutional deliveries:
  - During deliveries.
  - During handling of placenta tissue.
  - During handling of babies such as wiping liquor off babies.
- All equipment, including resuscitation equipment should be cleaned and sterilised.
- For home deliveries, battery operated suction device should be used.
- Standard precautions are to be observed in caring for the babies.
- For parents or relatives, gloves are given for use when handling the placenta after discharge, or during burial of stillbirth or dead babies at home. The placenta from HIV positive mothers should be soaked in formalin solution before disposal. Alternatively, the placenta can be sealed in a plastic bag or other leak-proof container with clear instructions to parents not to remove it from the container.

Immunisation

- Vaccines protect HIV-infected children from getting severe vaccine-preventable diseases, and are generally well tolerated.
- All routine vaccinations can be given according to schedule, with special precautions for live vaccines i.e. BCG and MMR:
  - BCG : safe if child is asymptomatic and not immunosuppressed (e.g. at birth); omit if symptomatic or immunosuppressed.
  - MMR : safe, omit in children with severe immunosuppression (CD4<15%)
- Other recommended vaccines:
  - Pneumococcal polysaccharide vaccine when > 2 years of age; booster 3-5 years later. Where available, use Pneumococcal conjugate vaccine (more immunogenic).
  - Varicella-zoster vaccine, where available. 2 doses with 2 months interval. Omit in those with severe immunosuppression (CD4 < 15%).

Despite vaccination, remember that long term protection may not be achieved in severe immune suppression i.e. they may still be at risk of acquiring the infections!

Interventions to limit perinatal transmission

- Vertical transmission of HIV may occur while in utero, during the birth process or through breast-feeding. The rates vary from 25 - 30%.
- Breastfeeding confers an additional 14% risk of transmission, and is therefore contraindicated.
- Blood and blood products should be used judiciously even though the risk of transmission of HIV infection from blood transfusion is very small.

Several interventions have proven effective in reducing vertical transmission:

- Total substitution of breastfeeding with infant formula.
- Elective Caesarean section.
- Antiretroviral (ARV) prophylaxis.

Factors associated with higher transmission rate
Maternal • Low CD 4 counts • High viral load • Advanced disease • Seroconversion during pregnancy *Foetal* • Premature delivery of the baby • Delivery and procedures • Invasive procedures such as episiotomy • Foetal scalp electrodes • Foetal blood sampling and amniocentesis • Vaginal delivery • Rupture of membranes > 4 hours • Chorioamnionitis **Transmission rate not increased if maternal viral load fully suppressed*

Management of Babies Born to HIV Infected Mothers

Children born to HIV positive mothers are usually asymptomatic at birth. However, all will have acquired maternal antibodies. In uninfected children, antibody testing becomes negative by 10-18 months of age.

During pregnancy

Counsel mother regarding:

- Transmission rate (without intervention) –25 to 30%.
- ARV prophylaxis +/- elective LSCS reduces transmission to ~2%
- Feed with infant formula as breast feeding doubles the risk of transmission
- Difficulty in making early diagnosis because of presence of maternal antibody in babies. Stress importance of regular blood tests and follow-up.

Neonatal period

- Admit to ward or early review by paediatric team (if not admitted).
- Examine baby for
  - Evidence of other congenital infections.
  - Symptoms of drug withdrawal (reviewing maternal history is helpful).
- Most babies are asymptomatic and only require routine perinatal care.
- Start on prophylaxis ARV as soon as possible.
- Sample blood for:
  - HIV DNA/RNA PCR (done in IMR, do not use cord blood; sensitivity 90% by 1 month age).
  - FBC
  - Other tests as indicated: LFT, RFT, HbsAg, Hepatitis C, CMV, syphilis serology.

MANAGEMENT OF HIV IN CHILDREN

Clinical Features

Common presenting features are:

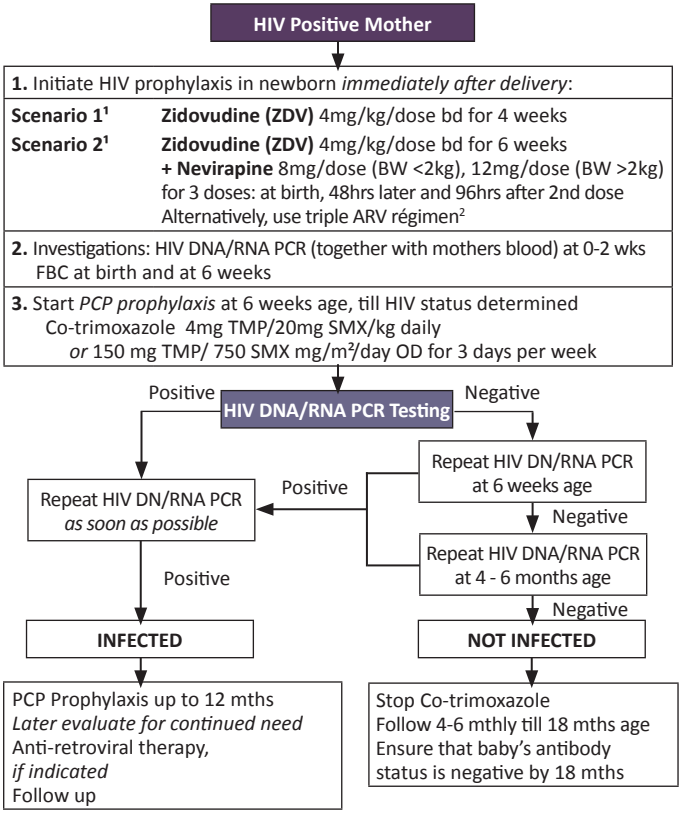
- Persistent lymphadenopathy
- Hepatosplenomegaly
- Failure to thrive
- Recurrent infections (respiratory, skin, gastrointestinal)
- Developmental delay, regression

Diagnosis of HIV infection

- In children > 18 months age: 2 consecutive positive HIV antibody tests.
- In children < 18 months age: 2 positive HIV DNA/RNA PCR tests.

Monitoring

- Monitor disease progression through clinical, immunological (CD4+ count or %) and viral load status.
- CD4+ count and viral load assay are done at diagnosis, 2-3 months after initiation or change of combination antiretroviral therapy (ART) and every 3-4 months thereafter (more frequently if change of therapy is made or progression of disease occurs).



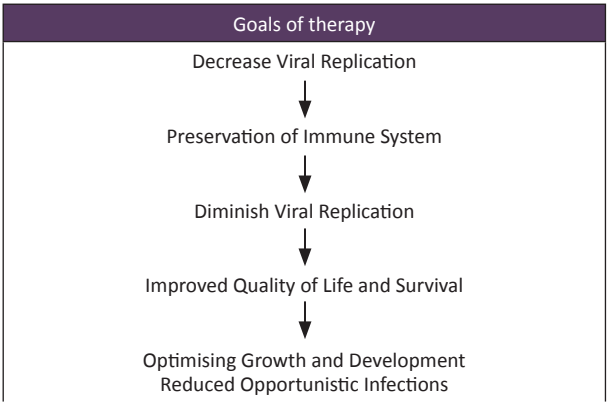
Footnote:

1. Scenario 1- Infant of HIV –infected pregnant mother who is on ART and has sustained viral suppression
   Scenario 2- Infant at higher risk of HIV acquisition e.g. infant born to HIV negative infected mother who:
   - Has not received intrapartum/antepartum ARV
   - Has received only intrapartum ARV
   - Has received antepartum ARV but does not have viral suppression near delivery
2. Triple ARV regimen (ZDV/Lamivudine/Nevirapine) is used in clinical practice by some experts

- ARV should be served as soon as possible (preferably within 6-12 hours of life) and certainly no later than 48 hours.
- Dose of Sy ZDV for premature baby < 30 weeks: 2mg/kg 12 hourly from birth to 4 weeks, then 3mg/kg 12hourly age 4-6 weeks
  >30 weeks: 2mg/kg 12hourly from birth to 2 wks, then 3mg/kg 12hourly age 2-6 wks.
- If oral feeding is contraindicated, then use IV ZDV at 1.5mg/kg/dose.

Antiretroviral Therapy

Clinical outcome following the introduction of ART in children is excellent, with reduced mortality and morbidity reported from various cohorts. However, this needs to be balanced with: the failure of current drugs to eradicate infection, long-term medication side effects and compliance-adherence issues.



When to start?

- ART is now recommended to be started in all children and adolescents living with HIV. Early initiation of ART reduces mortality, improves neurodevelopmental, growth and pubertal outcomes, improves immune reconstitution and reduces inflammation.
- Priority should be given to infants and children under 3 years of age, and to children with symptoms and/or low age-specific CD4 counts. Recommendation for when to start ART is shown in Table.¬
- Before starting ART, intensive education to parents, care-givers and older children-patients need to be stressed. Do not start in haste as we may repent at leisure!
- Assess family's capacity to comply with often difficult & rigid regimens. Stress that non-adherence to medications allows continuous viral replication and encourages the emergence of drug resistance and subsequent treatment failure.
- Please consult a specialist/consultant before starting treatment.

WHO classification of HIV-associated immunodeficiency using CD4 count				
Classification of HIV-associated Immunodeficiency	Age related CD4 values			
	< 11 mths (CD4 %)	12-35 mths (CD4 %)	36-59 mths (CD4 %)	≥5 years (cells/mm^3 or CD4 %)
Not significant	>35	>30	>25	>500
Mild	30–35	25–30	20–25	350–499
Advanced	25–29	20–24	15–19	200–349
Severe	<25	<20	<15	<200 or <15%

Clinical categories

There are 2 widely used clinical classification systems i.e CDC's 1994 Revised Paediatric Classification and the more recently updated WHO Clinical Classification system. Both classification systems are quite similar with only minor differences.

WHO Clinical Staging Of HIV for Infants and Children With Established HIV infection (Adapted from WHO 2007)

Clinical stage 1 (Asymptomatic)

- Asymptomatic
- Persistent generalized lymphadenopathy

Clinical stage 2 (Mild) *

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Lineal gingival erythema
- Herpes zoster
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
- Fungal nail infections

(*) Unexplained refers to where the condition is not explained by other causes.

WHO Clinical Classification system (continued)

Clinical stage 3 (Advanced) *

- Unexplained moderate malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (above 37.5 ºC, intermittent or constant, for longer than one month)
- Persistent oral candidiasis (after first 6 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis/periodontitis
- Lymph node TB
- Pulmonary TB
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease including bronchiectasis
- Unexplained anaemia (<8.0 g/dl), neutropenia (<0.5 x 10^9/L) or chronic thrombocytopenia (<50 x 10^9/ L)

Clinical stage 4 (Severe) *

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
- Chronic herpes simplex infection; (orolabial or cutaneous of more than one month'sduration, or visceral at any site)
- Extrapulmonary TB
- Kaposi sarcoma
- Oesophageal candidiasis (or Candida of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (after the neonatal period)
- HIV encephalopathy
- Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over 1 month
- Extrapulmonary cryptococcosis (including meningitis)
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
- Chronic cryptosporidiosis (with diarrhoea)
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacteria infection
- Cerebral or B cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- HIV-associated cardiomyopathy or nephropathy

(*) Unexplained refers to where the condition is not explained by other causes.

When to start ART?

Age	Initiate Treatment*	Priority
< 3 years	All	ALL infants regardless of clinical symptoms, immune status and viral load
3 - < 5 years	All	WHO Clinical Stage 3 or 4** or CD4 < 750 cells/mm^3 (< 25%)
> 5 years	All	WHO Clinical Stage 3 or 4** or CD4 < 350 cells/mm^3

* Before making the decision to initiate therapy, the provider should fully assess, discuss, and address issues associated with adherence with the child and caregiver.
** Stabilize any opportunistic infection (OI) before initiating ART.

Which drugs to use?

Always use combination of at least 3 drugs (see Table next page)

Either

- 2 NRTI + 1 NNRTI [Efavirenz (age > 3 years) or Nevirapine (age < 3 years)] or
- 2 NRTI + 1 PI (Lopinavir/r)
  - Recommended 2 NRTI combinations: ZDV + 3TC; ABC + 3TC; TDF + FTC (> 12 years)
  - Alternative 2 NRTI combinations : ZDV + ddI; ZDV + ABC
  - For infants exposed to maternal or infant NVP or other NNRTIs used for maternal treatment or Prevention of mother-to-child transmission (PMTCT), start ART with PI (Lopinavir/r) + 2 NRTIs.

Not Recommended

- Mono or dual therapy (except mother-to-child transmission prophylaxis during neonatal period)
- d4T + ZD : pharmacologic and antiviral antagonism
- d4T + dd : higher risk of lipodystrophy, peripheral neuropathies
- 3TC + FTC : similar resistance patterns and no additive benefit.

When to change?

- Treatment failure based on clinical, virologic and immunological parameters e.g. deterioration of condition, unsupressed / rebound viral load or dropping of CD4 count/%.
- Toxicity or intolerance of the current regimen
- If due to toxicity or intolerance:
  - Choose drugs with toxicity profiles different from the current regimen
  - Changing a single drug is permissible
  - Avoid reducing dose below lower end of therapeutic range for that drug.

- If due to treatment failure:
  - Assess and review adherence.
  - Perform genotypic resistant testing to help choose appropriate ARV.
  - If genotypic resistant testing not available, preferable to change all ARV (or at least 2) to drugs that the patient had not been exposed to befor
  - Choices are very limited! Do not add a drug to a failing regime.
  - Consider potential drug interactions with other medications.
  - When changing therapy because of disease progression in a patient with advanced disease, the patient's quality of life must be considered.
- Consult infectious diseases specialist before switching.

Follow up

- The aim of ART is to achieve an undetectable VL (< 50copies/ml) and CD4 reconstitution.
- Follow up usually every 3 – 4 months. However, if just commencing/ switching ART, then every 2-4 weeks.
- Ask about medication:
  - Adherence (who, what, how and when of taking medications)
  - Side effects e.g. vomiting, abdominal pain, jaundice
- Examine: Growth, head circumference, pallor, jaundice, oral thrush, lipodystrophy syndrome (especially if on stavudine &/or PI)
- FBC, CD4 count, viral load 3-4 monthly, RFT, LFT, Ca/PO4 (amylase if on ddI) every 6 months. If on PI also do fasting lipid profiles and blood sugar yearly.
- Explore social, psychological and financial issues e.g. school, home environment etc. Many children are orphans, live with relatives, adopted or under NGO's care. Referral to social welfare often required. Compliance-adherence to therapy strongly linked to these issues.

Other issues

- HIV / AIDS is a notifiable disease. Notify health office within 1 week of diagnosis.
- Screen other family members for HIV.
- Refer parents to Physician Clinic if they have HIV and are not on follow up.
- Disclosure of diagnosis to the child (would-be teenager, issues on sexual rights)
- Be aware of Immune Reconstitution Inflammatory Syndrome (IRIS)
  - In this condition there is a paradoxical worsening of a known condition (e.g. pulmonary TB or lymphadenitis) or the appearance of a new condition after initiating ARV.
  - This is due to restored immunity to specific infectious or non-infectious antigens.
- Address adolescent's issues
  - Common issues include peer pressure, sexual health, pregnancy, substance use/abuse.
  - Plan a transition program to adult care services.

Categories of antiretroviral drugs available in Malaysia					
Nucleoside / Nucleotide reverse transcriptase inhibitors (NRTI)	Non nucleoside reverse transcriptase inhibitor (NNRTI)	Protease inhibitors (PI)	Integrase inhibitors	CCR5 antagonists	Fusion inhibitors
Zidovudine (ZDV) Stavudine(d4T) Lamivudine (3TC) Didanosine (ddI) Abacavir (ABC) Tenofovir (TDF) Emtricitabine (FTC)	Nevirapine (NVP) Efavirenz (EFZ) Etravirine (ETV) Rilpivirine (RPV)	Ritonavir Lopinavir/Ritonavir (Kaletra) Atazanavir (ATV) Darunavir	Raltegravir	Maraviroc	Enfurvitide

Fixed-dose combination tablets (FDC)
ZDV + 3TC combined tablet (Combivir / Zovilam)
d4T + 3TC +NVP combined tablet (SLN 30)
TDF + FTC combined tablet (Truvada / Tenvir-EM)
ABC + 3TC combined tablet (Kivexa)
ABC + 3TC + ZDV combined tablet (Trizivir)

Footnote:
Not all ARVs are suitable for use in children
Stavudine (d4T) is currently being phased out from market, so do not start on SLN
* Maraviroc and Enfuvirtide not registered yet in Malaysia

Antiretroviral drugs dosages and common side effects			
Drug	Dosage	Side effects	Comments
Zidovudine (ZDV)	180-240mg/m^2/dose, bd Neonate: 4mg/kg bd (max. dose 300mg bd)	Anaemia, neutropenia, headache	Large volume of syrup not well tolerated in older children
Didanosine (ddI)	90-120mg/m^2/dose, bd (max. dose 200mg bd)	Diarrhoea, abdo pain, peripheral neuropathy	Ideally taken on empty stomach (1hr before or 2h after food)
Lamivudine (3TC)	4mg/kg/dose, bd (max. dose 150mg bd)	Diarrhoea, abdo pain; pancreatitis (rare)	Well tolerated Use oral solution within 1 month of opening
Stavudine (d4T)	1mg/kg/dose, bd (max. dose 40mg bd)	Headache, peripheral neuropathy, pancreatitis (rare)	Capsule may be opened and sprinkle on food or drinks. The drug is being phased out from the market
Abacavir (ABC)	8 mg/kg/dose bd (max. dose 300 mg bd)	Diarrhoea, nausea , rash, headache; Hypersensitivity, Steven-Johnson (rare)	NEVER restart ABC after hypersensitivity reaction (may cause death) occur in HLA B*5701 positive
Tenofovir (TDF)	> 2yr: 8mg/kg/dose, od (max. dose 300mg od) TDF + FTC combo > 12yr: 1 tab od	Renal insufficiency, decreased bone density (especially in young children)	Should be taken with food. Can be crushed and added to liquid
Emtricitabine (FTC)	< 3 mth: 3mg/kg/dose, od > 3 mth: 6mg/kg/dose, od (max. dose 200mg od)	Headache, insomnia, diarrhea, skin discoloration	Only available in combination with Tenofovir

Antiretroviral drugs dosages and common side effects			
Drug	Dosage	Side effects	Comments
Efavirenz (EFZ)	350mg/m^2 od 13-15kg 200mg 15-20kg 250mg 20-25kg 300mg 25-32kg 350mg 33 –40kg 400mg > 40kg 600mg od	Rash, headache, insomnia	Inducer of CYP3A4 hepatic enzyme; so has many drug interactions Capsules may be opened and added to food
Nevirapine (NVP)	150-200mg/m^2/day od for 14 days, then increase to 300-400mg/m^2/day, bd (max. dose 200mg bd)	Severe skin rash, headache, diarrhea, nausea	Few data on use with PI. Practice is to increase PI dose by about 30%
Ritonavir (RTV)	For boosting other PIs. See specific drug. Not recommended as a single PI.	Vomiting, nausea, headache, diarrhoea; hepatitis (rare)	Take with food to increase absorption and reduce GI side effects. Solution contains 43% alcohol and is very bitter!
Kaletra (Lopinavir/ ritonavir)	230/57.5mg/m^2/ dose, bd *7 -14kg* 12/3 mg/kg, bd *15-40kg* 10/2.5mg/kg, bd *> 40kg* 400/100mg, bd	Diarrhea, asthenia	Low volume, but a bitter taste. Higher dose used with NNRTI
Darunavir	> 3 yr 15-30kg: 375mg bd+50mg RTV bd, 30-40kg: 450mg bd+RTV 60mg bd, ≥40kg: 600mg bd+100mg RTV bd	Skin rash, hepatotoxicity	Contains sulphonamide moiety – check allergies especially Co-trimoxazole.
Raltegravir	> 2 yr: 6mg/kg/dose, bd > 12 yr: 400mg bd	Nausea, headache, dizziness, skin rash	Not recommended to cut film-coated tablet.

Horizontal Transmission Within Families

- Despite sharing of household utensils, linen, clothes, personal hygiene products; and daily interactions e.g. biting, kissing and other close contact, repeated studies have failed to show transmission through contact with saliva, sweat, tears and urine (except with exposure to well defined body fluids i.e. blood, semen, vaginal fluids).
- It is important to stress that the following has not transmitted infection:
  - Casual contact with an infected person
  - Swimming pools
  - Droplets coughed or sneezed into the air
  - Toilet seats
  - Sharing of utensils such as cups and plates
  - Insects

Note: It is difficult to isolate the virus from urine and saliva of seropositive children. So, day care settings are not a risk. However, due to a theoretical risk of direct inoculation by biting, aggressive children should not be send to day care. Teachers should be taught to handle cuts/grazes with care.

Guidelines for post exposure prophylaxis

- Goal is to prevent HIV infection among those sustaining exposure, and provide information and support during the follow up interval until infection is diagnosed or excluded with certainty.
- Risk for occupational transmission of HIV to Health Care Workers (HCW).
- Risk for HIV transmission after a percutaneous exposure to HIV infected blood is 0.3%; risk after mucous membrane exposure is 0.1%.
- Risk is dependent on:
  - Type, volume of body fluid involved
  - Type of exposure that has occurred
  - Viral load of the source patient
  - Disease stage

Treatment of an Exposure Site

- Wash wounds, skin exposure sites with soap, water; flush mucous membranes with water.
- Notify supervisor; refer HCW to designated doctor as in hospital needlestick injury protocol.

Uncomplicated Malaria

Symptoms of malaria infection and a positive parasitological test (microscopy or rapid diagnostic test (RDT)) but with no features of severe malaria (clinical or laboratory).

Treatment

UNCOMPLICATED PLASMODIUM FALCIPARUM

First Line Treatment	
Preferred Treatment	**Alternative Treatment**
Artemether / lumefantrine (Riamet) *Dosage according to body wt* 5-14 kg D1: 1 tab stat then 1 tab again after 8 hrs D2-3: 1 tab BD 15-24 kg D1: 2 tabs stat then 2 tabs again after 8 hrs D2-3: 2 tablets BD 25 – 35 kg D1: 3 tabs stat then 3 tabs again after 8 hrs D2-3: 3 tablets BD >35 kg D1: 4 tabs stat then again 4 tabs after 8 hrs D2-3: 4 tabs BD	**Artesunate / mefloquine FDC(ASMQ) Available as FDC tablet 25/55mg and 100/220mg** *Dosage according to body wt* 5-8kg: 25/55 mg PO q24h X3d 9-17kg: 50/110 mg PO q24h X3d 18-29kg: 100/220 mg PO q24h X3d >30kg: 200/440 mg PO q24h X3d
- Avoid ASMQ in children with epilepsy. - Add primaquine 0.25mg base/kg single dose OD to all patients on D1. - G6PD testing is not required prior to administration with this dose. - Riamet should be administered with high fat diet preferable to be taken with milk to enhance absorption - Both ASMQ FDC and Riamet are Artemisinin-based Combination Treatment (ACT).	

Second-line treatment for treatment failure

(in uncomplicated *Plasmodium Falciparum*):

Recommended second-line treatment:

- An alternative ACT is used (if Riamet was used in the first regimen, use ASMQ for treatment failure and vice-versa).
- Artesunate 4mg/kg OD plus clindamycin 10mg/kg bd for a total of 7 days
- Quinine 10mg salt/kg 8 hrly plus clindamycin 10mg/kg bd for a total of 7 days.
- Add primaquine 0.25mg base/kg single dose OD to all patients on D1. G6PD testing is not required prior to administration.

Treatment for *Plasmodium knowlesi, P. vivax,* or *P. malariae*	
Preferred Treatment	**Alternative Treatment**
Use ACT such as Riamet or ASMQ as in Plasmodium falciparum PLUS Primaquine* 0.5 mg base/kg daily for 14 days for *Plasmodium vivax* (max 30 mg base)	Total chloroquine 25mg base/kg divided over 3 days D1: 10 mg base/kg stat then 5 mg base/kg 6 hours later D2: 5 mg base/kg OD D3: 5 mg base/kg OD PLUS Primaquine* 0.5 mg base/kg daily for 14 days for Plasmodium vivax
PLUS	
Primaquine* 0.5 mg base/kg daily for 14 days	
Chloroquine should be prescribed as mg base in the drug chart. *P. malariae* and *P. knowlesi* do not form hypnozoites, hence do not require radical cure with primaquine. G6PD testing is required prior to administration of 0.5mg base/kg primaquine.	

Treatment of chloroquine-resistant *P. vivax, knowlesi or malariae*

- ACT (Riamet or ASMQ) should be used for relapse or chloroquine resistant *P. vivax*. For radical cure in *P. vivax*, ACT must be combined with supervised 14-day primaquine therapy.
- Quinine 10mg salt/kg three times a day for 7 days is also effective for chloroquine resistant *P. vivax* and this must be combined with primaquine for antihypnozoite activity.
- Mefloquine 15mg/kg single dose combined with primaquine have been found to be effective. (except for *P. knowlesi*)

Primaquine (0.5mg/kg) may cause haemolysis in individuals with G6PD deficiency, hence G6PD testing is required before administration of primaquine >0.25mg/kg. For those found to have mild to moderate G6PD deficiency, an intermittent primaquine regimen of 0.75mg base/kg weekly for 8 weeks can be given under medical supervision.
In severe G6PD deficiency primaquine is contraindicated and should not be used.

Severe and complicated P. vivax, knowlesi or malariae should be managed as for severe falciparum malaria (see below).

Severe *P. falciparum* malaria

- All Plasmodium species can potentially cause severe malaria, the commonest being *P. falciparum*.
- Young children especially those aged below 5 years old are more prone to develop severe or complicated malaria.

Recognising Severe P. falciparum malaria
Clinical features • Impaired consciousness or unarousable coma. • Prostration. • Failure to feed. • Multiple convulsions (more than two episodes in 24 h). • Deep breathing, respiratory distress (acidotic breathing). • Circulatory collapse or shock. • Clinical jaundice plus evidence of other vital organ dysfunction. • Haemoglobinuria. • Abnormal spontaneous bleeding. • Pulmonary oedema (radiological). *Laboratory findings* • Hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl). • Metabolic acidosis (plasma bicarbonate < 15 mmol/l). • Severe anaemia (Hb < 5 g/dL, packed cell volume < 15%). • Haemoglobinuria. • Hyperparasitaemia (> 2%/100 000/µl in low intensity transmission areas or > 5% or 250 000/µl in areas of high stable malaria transmission intensity). • Hyperlactataemia (lactate > 5 mmol/l). • Renal impairment (serum creatinine > 265 µmol/l).

Severe Vivax and Knowlesi Malaria

- Severe Vivax malaria is defined as for falciparum malaria but with no parasite density thresholds.
- Severe knowlesi malaria is defined as for falciparum malaria but with two differences:
  - *P. knowlesi* hyperparasitaemia: parasite density > 100 000/ul .
  - Jaundice and parasite density > 20 000/ul.

First-line Treatment

- *Children > 20kg and adults*
  - D1: IV artesunate 2.4 mg/kg on admission, then repeat again at 12h.
  - D2-7: IV artesunate 2.4 mg/kg OD or switch to oral ACT.
- *Children < 20kg*
  - D1: IV artesunate 3.0 mg/kg on admission, then repeat again at 12h.
  - D2-7: IV artesunate 3.0 mg/kg OD or switch to oral ACT.
- Parenteral artesunate should be given for a minimum of 24h (3 doses) or until patient is able to tolerate orally and thereafter to complete treatment with a full course of 3 days ACT.
- Avoid using ASMQ (Artesunate + mefloquine) if patient had impaired conscious level at presentation as neuropsychiatric complications had been reported with mefloquine in cerebral malaria.
- Do not use IV artesunate as monotherapy. If IV artesunate needs to be continued indefinitely, clindamycin must be added to the regimen to complete total 7 days treatment.
- IM artesunate (same dose as IV) can be used in patients with difficult intravenous access.
- Children with severe malaria should be started immediately on antibiotic treatment concurrently to cover for sepsis.

Second-line Treatment

- Loading IV quinine 20mg salt/kg over 4 hours then IV 10mg salt/kg q8 hrly (Dilute quinine in 250ml of D5% over 4 hours and the maintenance dose of quinine 10mg salt/kg starts 8 hours after the loading dose)
- D2-7: IV Quinine 10mg/kg q8h
  AND
  Doxycycline (>8yrs) (2.2 mg/kg BD) OR Clindamycin (10 mg/kg/dose bd) given for 7 days
- Quinine infusion rate should not exceed 5 mg salt/kg body weight per hour.
- Change to Oral Quinine if able to tolerate orally. (Maximum Quinine per dose = 600mg.) Reduce IV quinine dose by one third of total dose (10mg/kg tds to 10mg/kg bd) if unable to change to Oral quinine after 48hours or in renal failure or liver impairment.

Congenital malaria

- Congenital malaria is uncommon. It can be acquired by transmission of parasites from mother to child during pregnancy or perinatally during labour.
- Incidence varying from 0.3 to 33% has been reported from both endemic and non-endemic countries.
- Congenital malaria from *P. vivax* is more commonly reported in Asia whereas infection from *P. falciparum* is mainly described in African countrie.s
- Most babies present with symptoms between 10 and 30 days of age (range: 14hr to several months of age).
- The clinical features of neonatal malaria include anaemia (77%), fever (74%), liver and spleen enlargement (68%), poor feeding/lethargy/ irritability, jaundice and severe thrombocytopaenia.
- Congenital malaria may mimic neonatal sepsis and should be considered in the differential diagnosis of neonatal sepsis.
- All newborn babies of mother with malaria should been screened for congenital malaria.
- Treatment for *P. vivax* infection: chloroquine, total dose of 25mg base/kg orally divided over 3 days

  D1: 10 mg base/kg stat then 5 mg base/kg 6 hours later
  D2: 5 mg base/kg OD
  D3: 5 mg base/kg OD

  Primaquine is not required for treatment as the tissue/ exo-erythrocytic phase is absent in congenital malaria
- Treatment for *P. falciparum* infection: quinine 10mg/kg q8 hrly for 1 week.

Mixed Malaria infections

- Mixed malaria infections are not uncommon. ACTs are effective against all malaria species and are the treatment of choice.
- Treatment with primaquine should be given to patients with confirmed *P. vivax* infection.

Malaria Chemoprophylaxis		
Prophylaxis	Duration of Prophylaxis	Dosage
Atovaquone/ Proguanil (Malarone)	Start 2 days before, continue daily during exposure and for 7 days thereafter	Pediatric tablet of 62.5 mg Atovaquone and 25 mg Proguanil: 5-8 kg: 1/2 tablet daily >8-10 kg: 3/4 tablet daily >10-20 kg: 1 tablet daily >20-30 kg: 2 tablets daily >30-40 kg: 3 tablets daily >40 kg: 1 adult tablet daily
Mefloquine (Tablet with 250mg base, 274mg salt)	Start 2-3 weeks before, continue weekly during exposure and for 4 weeks thereafter	<15 kg: 5mg of salt/kg; 15-19 kg: ¼ tab/wk; 20-30 kg: ½ tab/wk; 31-45 kg: ¾ tab/wk; >45 kg: 1 tab/wk
Doxycycline (tab 100mg)	Start 2 days before, continue daily during exposure and for 4 weeks thereafter	1.5mg base/kg once daily (max. 100 mg) <25kg or <8 yr: Do Not Use 25-35kg or 8-10 yr: 50mg 36-50kg or 11-13 yr: 75mg >50kg or >14 yr: 100mg

Definition

- The presence of symptoms, signs and /or radiographic findings caused by MTB complex (*M. tuberculosis* or *M. bovis*).
- Disease may be pulmonary or extrapulmonary, (i.e. central nervous system (CNS), disseminated (miliary), lymph node, bone & joint) or both.

Clinical features

- Pulmonary disease is commonest. Symptoms include fever, cough, weight loss, night sweats, respiratory distress.
- Extrapulmonary disease may manifest as prolonged fever, apathy, weight loss, enlarged lymph nodes (cervical, supraclavicular, axillary), headache, vomiting, increasing drowsiness, infants may stop vocalising. Swellings and loss of function may suggest bone, joint or spinal TB.
- Phlyctenular conjuctivitis, erythema nodosum and pleural effusions are considered hypersensitivity reactions of TB disease.

Diagnosis of TB disease

Diagnosis in children is usually difficult. Features suggestive of tuberculosis are:

- *Recent contact* with a person (usually adult) with active tuberculosis. This constitutes one of the strongest evidence of TB in a child who has symptoms and x ray abnormalities suggestive of TB.
- *Symptoms and signs suggestive of TB* are as listed above. Infants are more likely to have non specific symptoms like low-grade fever, cough, weight loss, failure to thrive, and signs like wheezing, reduced breath sounds, tachypnoea and occasionally frank respiratory distress.
- *Positive Mantoux test* (>10 mm induration at 72 hours; tuberculin strength of 10 IU PPD).
- *Suggestive chest X-ray:*
  - Enlarged hilar lymph nodes +/- localised obstructive emphysema
  - Persistent segmental collapse consolidation not responding to conventional antibiotics.
  - Pleural effusion.
  - Calcification in lymph nodes - usually develops > 6 mths after infection.
- Laboratory tests
  - Presence of AFB on smears of clinical specimens and positive histopathology or cytopathology on tissue specimens are highly suggestive of TB. Isolation of *M. tuberculosis* by culture from appropriate specimens is confirmatory.

Diagnostic Work-up

- Efforts should be made to collect clinical specimens for AFB smear, cytopathology or histopathology, special stains and AFB culture to assure confirmation of diagnosis and drug susceptibility.
- If the source case is known, it is important to utilize information from the source such as culture and susceptibility results to help guide therapy.
- The diagnostic work-up for TB disease is tailored to the organ system most likely affected.

The diagnostic work-up for TB disease is tailored to the organ system most likely affected. The tests to consider include but are not limited to the following:

Pulmonary TB
- Chest radiograph
- Early morning gastric aspirates[1]
- Sputum (if >12 years, able to expectorate sputum)[1]
- Pleural fluid[1] or biopsy[1]

Central Nervous System (CNS) TB
- Cerebrospinal fluid (CSF) for FEME, acid fast bacilli (AFB) smear, TB culture and molecular testing.
- Computed tomography scan (CT) head with contrast.
- TB adenitis
- Excisional biopsy or fine needle aspirate[1]

Abdominal TB
- CT abdomen with contrast
- Biopsy of mass / mesenteric lymph node[1]

TB osteomyelitis
- CT/MRI of affected limb
- Biopsy of affected site[1]

Miliary / Disseminated TB
- As for pulmonary TB
- Early morning urine[1]
- CSF[1]

[1]Note:
- These specimens should be sent for AFB smear and TB culture and susceptibility testing. Molecular testing may also be required.
- Cytopathology/histopathology should be carried out on appropriate specimens.
- All children evaluated require a chest x-ray to rule out pulmonary TB.

Treatment of TB disease
- Antimicrobial therapy for TB disease requires a multidrug treatment regimen.
- Drug selection is dependent on drug susceptibility seen in the area the
- TB is acquired, disease burden and exposure to previous TB medications, as well as HIV prevalence.
- Therapeutic choices are best made according to drug susceptibility of the organism cultured from the patient.
- Almost all recommended treatment regimens have 2 phases, an initial
- intensive phase and a second continuation phase.
- For any one patient, the treatment regimen would depend on the diagnosis (pulmonary or extrapulmonary), severity and history of previous treatment.
- Directly observed therapy is recommended for treatment of active disease.
- Drug resistant TB can be considered if the source has drug resistant TB or confirmed if investigations (GeneXpert and sensitivity) indicate resistance.
- Infants with TB should be referred to/discussed with Paediatric ID consultant.

Tuberculosis Chemotherapy in Children					
Drug		Daily Dose		Intermittent Dose (Thrice Weekly)	
		mg/kg/day	Max dose (mg)	mg/kg/day	Max dose (mg)
Isoniazid	H	10-15	300	10	900
Rifampicin	R	10-20	600	10	600
Pyrazinamide	Z	30-40	2000	-	-
Ethambutol	E	15-25	1000	30-50	2500
Note: Pyridoxine 5-10 mg daily needs to be added if isoniazid is prescribed. The higher end of the range for isoniazid dose applies to younger children.					

Short course therapy

- This consists of a 6 month regimen, an initial 2 month intensive and
- subsequent 4 month continuation phase. Short course therapy is suitable for pulmonary tuberculosis and non-severe extrapulmonary tuberculosis
- Children with tuberculous meningitis , miliary and osteoarticular tuberculosis should be treated for 12 months. It is not recommended for drug resistant TB.

The short course consists of:
Intensive Phase (2 months)

- Daily Isoniazid, Rifampicin and Pyrazinamide
  - A 4th drug (Ethambutol) is added when initial drug resistance may be present or for extensive disease eg. miliary TB or where prevalence of HIV is high.
- *Maintenance Phase* (4 months)
  - Isoniazid and rifampicin for the remaining 4 months.
  - This should be given daily (preferred).
  - WHO does not recommend intermittent regimens but a thrice weekly regimen can be given in certain cases.
- All intermittent dose regimens must be directly supervised.

Pulmonary TB and Less Severe Extrapulmonary TB

- Recommended regimen is short course therapy as above.
- Less severe extrapulmonary TB include lymph node disease, unilateral pleural effusion, bone / joint (single site) excluding spine, and skin.

WHO Recommendations

- Children living in settings where the prevalence of HIV is high or where resistance to isoniazid is high, or both, with suspected or confirmed pulmonary tuberculosis or peripheral lymphadenitis; or children with extensive pulmonary disease living in settings of low HIV prevalence or low isoniazid resistance, should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months.
- Children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence or low resistance to isoniazid and children who are HIV-negative can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months
- Children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis living in settings with a high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens.
- Thrice-weekly regimens can be considered during the continuation phase of treatment, for children known to be HIV-uninfected and living in settings with well-established directly-observed therapy (DOT).
- Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary tuberculosis or tuberculous peripheral lymphadenitis.
- Children with suspected or confirmed tuberculous meningitis as well as those with suspected or confirmed osteoarticular tuberculosis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months; the total duration of treatment being 12 months.

Latent TB

- Young children living in close contact with a case of smear-positive PTB are at risk of TB infection and disease.
- The risk of developing disease after infection is much greater for infants and young children under five years of age.
- Active TB usually develops within two years of infection but the time-lag can be as short as a few weeks in infants.

Regimens for Latent TB treatment		
Drug	Duration	Interval
Isoniazid	6 months	Daily
Isoniazid + Rifampicin	3 months	Daily

Corticosteroids

- Indicated for children with TB meningitis.
- May be considered for children with pleural and pericardial effusion (to hasten reabsorption of fluid), severe miliary disease (if hypoxic) and endobronchial disease.
- Steroids should be given only when accompanied by appropriate antituberculous therapy.
- Dosage: prednisolone 1-2mg/kg per day (max. 40 mg daily) for first 3-4 week, then taper over 3-4 weeks.

Monitoring of Drug Toxicity

- Indications for baseline and routine monitoring of serum transaminases and bilirubin are recommended for:
  - Severe TB disease.
  - Clinical symptoms of hepatotoxicity.
  - Underlying hepatic disease.
  - Use of other hepatotoxic drugs (especially anticonvulsants).
  - HIV infection.
- Routine testing of serum transaminases in healthy children with none of the above risk factors is not necessary.
- Children on Ethambutol should be monitored for visual acuity and colour discrimination.

Breast-feeding and the Mother with Pulmonary Tuberculosis

- Tuberculosis treatment in lactating mothers is safe as the amount of drug ingested by the baby is minimal. Hence if the mother is already on treatment and is non-infective, the baby can be breastfed.
- Women who are receiving isoniazid and are breastfeeding should receive pyridoxine.
- If the mother is diagnosed to have active pulmonary TB and is still infective:
  - The newborn should be separated from the mother for at least one week while the mother is being treated. Mother should wear a surgical mask subsequently while breast feeding until she is asymptomatic and her sputum is AFB-smear negative .
  - Breast feeding is best avoided during this period, however, expressed breast milk can be given .
  - The infant should be evaluated for congenital TB. If this is excluded, BCG is deferred and the baby should receive isoniazid for 3 months and then tuberculin tested. If tuberculin negative and mother has been adherent to treatment and non-infectious, isoniazid can be discontinued and BCG given. If tuberculin positive, the infant should be reassessed for TB disease and if disease is not present, isoniazid is continued for total of 6 months and BCG given at the end of treatment.
  - Other close household contacts should be evaluated for TB.
- Congenital TB is rare but should be suspected if the infant born to a tuberculous mother fails to thrive or is symptomatic.

WHEN A CHILD IS A CONTACT TO A TB PATIENT

Assess

- Degree of contagion of source
- Duration of contact
- Intimacy of contact

High	• Sputum smear + pulmonary, laryngeal or pleural TB • Cavitation on CXR • Evidence of transmission to other contacts
Medium	• Sputum smear negative, culture + pulmonary/pleural TB
Low	• Sputum smear and culture negative
Negligible	• Extrapulmonary TB (no associated pulmonary TB)

SIGNIFICANT Contact to a contagious case

NO

No evaluation
Revisit if symptoms arise

YES

< 5 yrs age OR Immunocompromised

- Focused history and physical examination
- Tuberculin skin test (TST)
- Chest X-Ray (CXR)

Symptomatic | CXR Abnormal | TST

Evaluate Fully for TB disease

TST < 10mm* no evidence of TB and CXR normal

Advice caregiver on signs/symptoms of TB. Followup for 2 years
Revisit if symptoms arise

TST ≥ 10mm no evidence of TB and CXR normal

Complete treatment for Latent TB infection

> 5 yrs age

- Focused history and physical examination
- Tuberculin skin test (TST)

Symptomatic | Asymptomatic

Evaluate Fully for TB disease

TST < 10mm* no evidence of TB

No evaluation
Revisit if symptoms arise

TST ≥ 10mm

Obtain CXR

No evidence of TB

Advice caregiver on signs/symptoms of TB.
Followup for 2 years
Revisit if symptoms arise

CXR Abnormal

Evaluate Fully for TB disease

Behavioural risks for Transmission
- Frequent coughing
- Sneezing
- Singing
- Close social network

Note: Immunocompromised children or very young infants closely exposed to highly infectious adult may require Latent TB treatment even if TST < 10mm

- Regional lymphadenopathy is one of the more common complications of BCG vaccination and arises as a result of enlargement of ipsilateral lymph nodes, principally involving the axillary node.
- Differential diagnoses to consider are:
  - Pyogenic lymphadenitis.
  - Tuberculous lymphadenitis.
  - Non-tuberculous lymphadenitis.
- The following are features suggestive of BCG lymphadenitis
  - History of BCG vaccination on the ipsilateral arm.
  - Onset usually 2 to 4 months after BCG vaccination, although it may range from 2 weeks to 6 months. Almost all cases occur within 24 months.
  - There is absence of fever or other constitutional symptoms.
  - Absent or minimal local tenderness over the lesion(s).
  - >95% of cases involve ipsilateral axillary lymph nodes, but supraclavicular or cervical glands may be involved in isolation or in association with axillary lymphadenopathy.
  - Only 1 to 2 discrete lymph nodes are enlarged (clinically palpable) in the majority of cases. Involved lymph nodes are rarely matted together.
- Two forms of lymphadenitis can be recognized, non-suppurative or simple which may resolve spontaneously within a few weeks, or suppurative which is marked by the appearance of fluctuation with erythema and oedema of the overlying skin and increased pigmentation.
- Once suppuration has occurred, the subsequent course is usually one of spontaneous perforation, discharge and sinus formation. Healing eventually takes place through cicatrization and closure of the sinus, the process taking several months with possible scarring.

Correct Technique to give BCG Vaccination

Needle
Short (10mm) 26-27 gauge needle with a short bevel using a BCG or insulin syringe

Site
Left arm at Deltoid insertion

Dose
- 0.05 mls for infants (< 1 year of age)
- 0.1 ml for children > 1 year.

Route
Intradermal

Do not give BCG at other sites where the lymphatic drainage makes subsequent lymphadenitis difficult to diagnose and dangerous (especially on buttock where lymphatic drains to inguinal and deep aortic nodes).

Assessment

Careful history and examination are important to diagnose BCG adenitis

- BCG lymphadenitis without suppuration (no fluctuation)
  - Drugs are not required.
  - Reassurance and follow-up Is advised.
  - Several controlled trials and a recent metaanalysis (Cochrane database) have suggested that drugs such as antibiotics (e.g. erythromycin) or antituberculous drugs neither hasten resolution nor prevent its progression into suppuration.
- BCG lymphadenitis with suppuration (fluctuation)
  - Needle aspiration is recommended. Usually one aspiration is effective, but repeated aspirations may be needed for some patients.
  - Surgical excision may be needed when needle aspiration has failed (as in the case of matted and multiloculated nodes) or when suppurative nodes have already drained with sinus formation.
- Surgical incision is not recommended.

Needle aspiration

- Prevents spontaneous perforation and associated complications.
- Shortens the duration of healing.
- Is safe.

Persistent Lymphadenitis/ disseminated disease

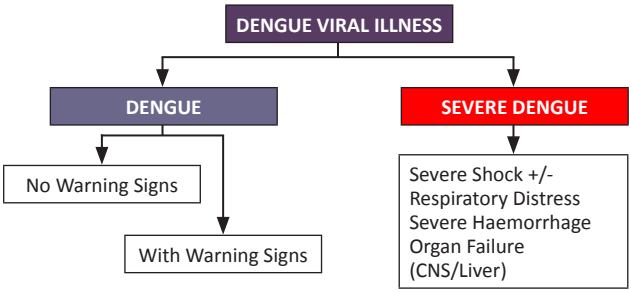
In patients with large and persistent or recurrent lymphadenopathy, constitutional symptoms, or failure to thrive, possibility of underlying immunodeficency should be considered and investigated. Thus all infants presenting with BCG lymphadenitis should be followed up till resolution.

Chapter 88: Dengue viral infections

Introduction

- Dengue virus infections affect all age groups and produce a spectrum of illness that ranges from asymptomatic to a mild or nonspecific viral illness to severe and occasionally fatal disease.
- The traditional 1997 World Health Organization classification of dengue was recently reviewed and changed. The new classification encompass various categories of dengue since dengue exists in continuum.
- The term DHF used in previous classification put too much emphasis on hemorrhage; However, ***the hallmark of severe dengue (and the manifestation that should be addressed early) IS NOT HEMORRHAGE but increased vascular permeability that lead to shock.***

CLASSIFICATION OF DENGUE VIRAL INFECTIONS, WHO 2009



This new system divides dengue into TWO major categories of severity:

- Dengue: with or without warning signs, and
- Severe dengue.

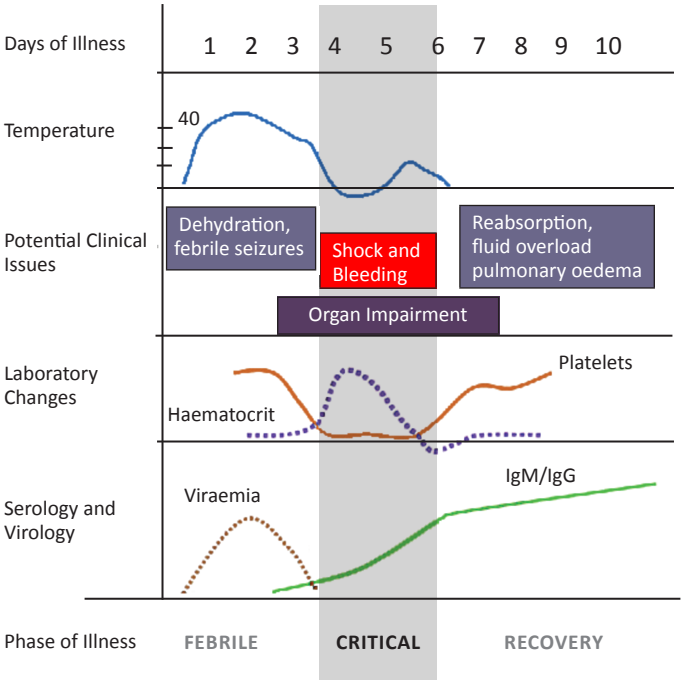
Probable Dengue	Warning Signs
• Lives in/travel to dengue endemic area • Fever and 2 of the following: • Nausea, vomiting • Rash • Aches and pains • Positive Tourniquet test • Leucopenia • Any warning sign • Laboratory-confirmed dengue (important when no sign of plasma leakage)	• Intense abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation. • Mucosal bleed • Lethargy, restlessness • Liver enlargement > 2cm • Laboratory: • Increase in hematocrit with concurrent rapid decrease in platelet count.

Criteria for Severe Dengue
Severe plasma leakage with rising hematocrit leading to: • Shock • Fluid accumulation (pleural,ascitic) • Respiratory distress • Severe bleeding • Severe organ involvement • Liver: Elevated transaminases (AST or ALT≥1000) • CNS: Impaired consciousness, seizures. • Heart and other organ involvement

Management of Patients with Dengue

- Dengue is a complex and unpredictable disease but success can be achieved with mortality rates of 1% when care is given in simple and inexpensive ways provided they are given appropriately at the right time.
- The timing of intervention starts at frontline healthcare personnel whether they are in A&E or OPD or even health clinics.
- Early recognition of disease and careful monitoring of IV fluid is important right from beginning.
- The healthcare personnel involved in managing dengue cases day to day need to familiarize themselves with the THREE main well demarcated phases of dengue: febrile, critical; and recovery. *(see next page)*
- To recognize dengue when child presents with fever;all we need is TO GO through the PROBABLE CASE DEFINITION OF DENGUE(previous page).You do not NEED rapid test always to diagnose dengue.
- In early phase of disease, it is difficult to differentiate dengue with other childhood illness; therefore performing a tourniquet test with FBC at first encounter would be useful to differentiate dengue from other illness.
- Temporal relationship of fever cessation (defervescence) is important as in DENGUE (unlike other viral illness) manifest its severity (leakage/ shock) when temperature seems to have declined.

PHASES OF DENGUE IN RELATION TO SYMPTOMS AND LABORATORY CHANGES



Adapted from World Health Organization: Dengue Hemorrhagic Fever: Diagnosis, Treatment, Prevention and Control. Third Edition. Geneva, WHO/TDR, 2009.

Note: During viraemic phase of dengue, viral study of PCR/culture (not offered) or NS1 Ag test will be positive.

Priorities during first encounter are:

1 - Establish whether patient has dengue

2 - Determine phase of illness

3 - Recognise warning signs and/or the presence of severe dengue if present.

- Most patients with Dengue Fever without warning signs can be managed without hospitalization provided they are alert, there are no warning signs or evidence of abnormal bleeding, their oral intake and urine output are satisfactory, and the caregiver is educated regarding fever control and avoiding non-steroidal anti-inflammatory agents and is familiar with the course of illness.
- A dengue information/home care card that emphasizes danger/warning signs is important. This should be given to parents/guardian if child is not admitted.
- These patients need daily clinical and/or laboratory assessment by trained doctors or nurses until the danger period has passed.

If dengue is suspected or confirmed, disease notification is mandatory.

Indication for Hospitalisation

- Presence of warning signs.
- Infants.
- Children with co-morbid factors (diabetes, renal failure, immune compromised state, hemoglobinopathies and obesity).
- Social factors - living far from health facilities, transport issues.

The THREE major priorities of managing hospitalized patient with dengue in the critical phase are:

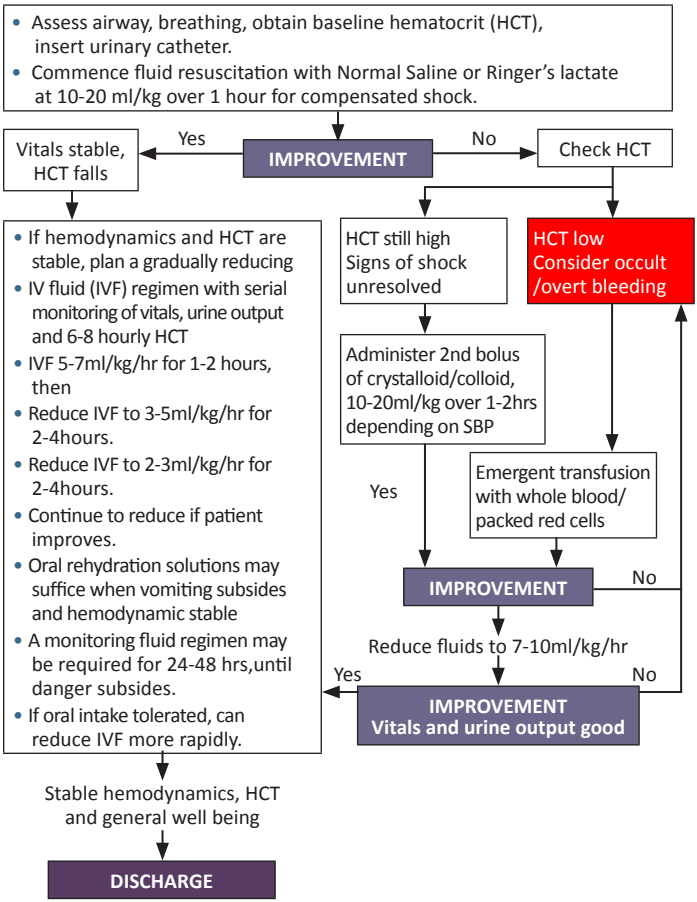
A - Replacement of plasma losses.

B - Early recognition and treatment of hemorrhage.

C - Prevention of fluid overload.

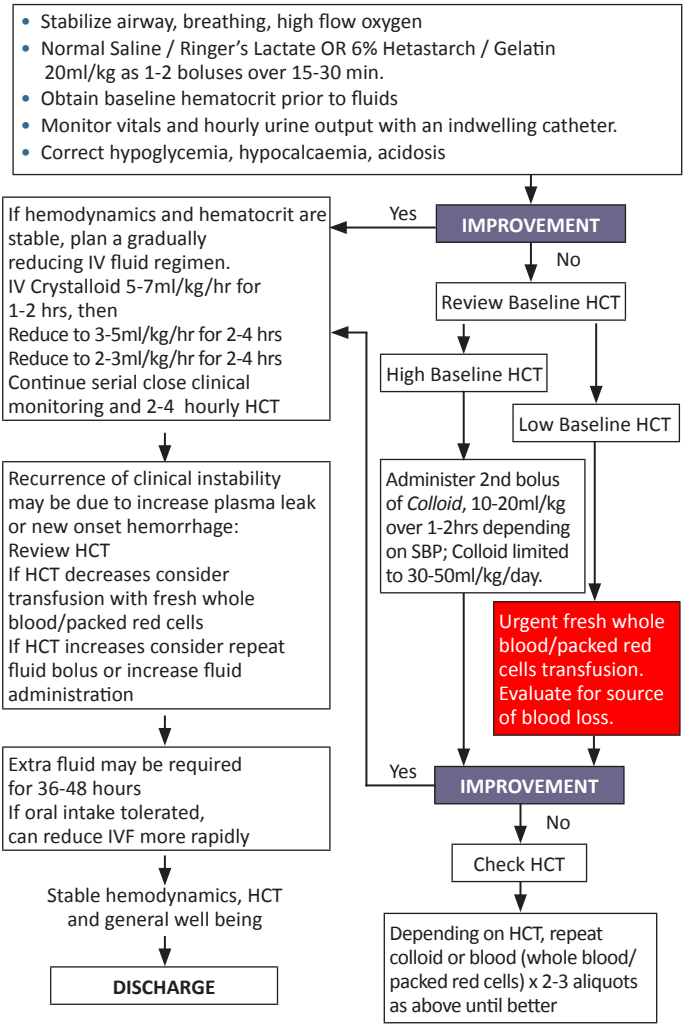
- Fluid therapy in a patient with dengue shock has two parts: initial, rapid fluid boluses to reverse shock followed by titrated fluid volumes to match ongoing losses.
- However, for a patient who has warning signs of plasma leakage but is not yet in shock, the initial fluid boluses may not be necessary.
- Fluids in dengue MUST be managed in way that it is given ONLY when its needed and off when patient enter convalescent/recovery phase.
- Haemodynamic state should be used as MAIN driver of IVF therapy. HCT as guide. Not the other way around.
- Limit fluid in febrile phase. If IVF is needed to correct hydration USE only isotonic solutions (example NS).

VOLUME REPLACEMENT FLOWCHART FOR PATIENTS WITH SEVERE DENGUE AND COMPENSATED SHOCK



Note:

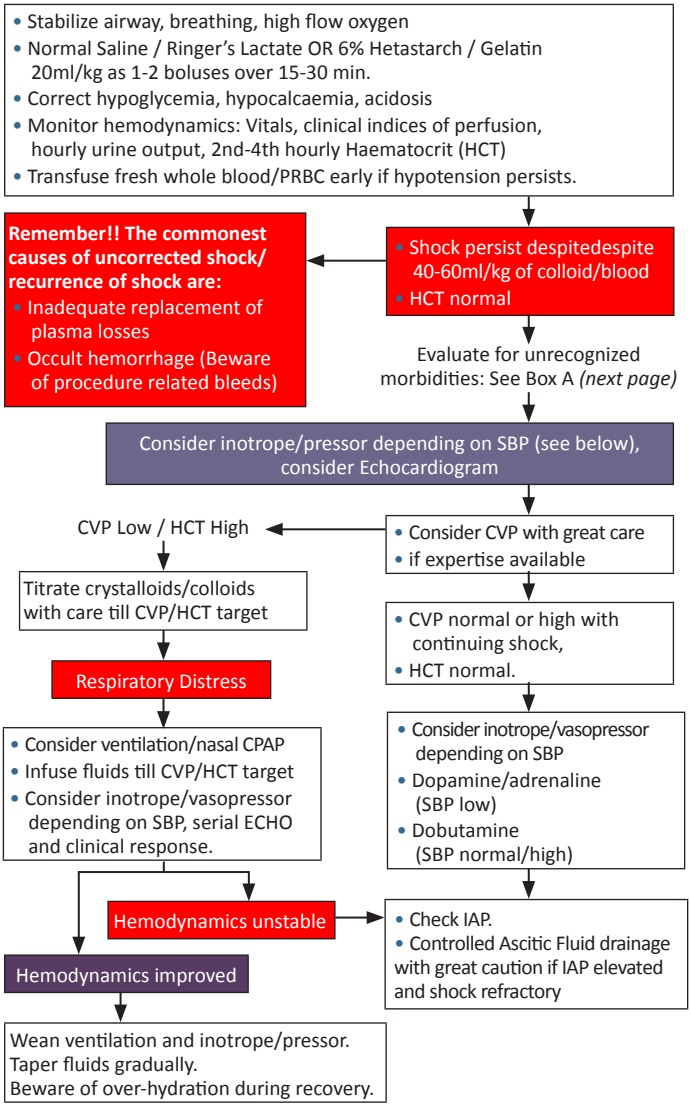
- Recurrence of clinical instability may be due to increased plasma leak or new onset hemorrhage.
- Review HCT before and after fluid therapy.



Remember!

- The commonest causes of uncorrected shock/recurrence of shock are:
- Inadequate replacement of plasma losses
- Occult hemorrhage (Beware of procedure related bleeds)
- Be aware of side effects of colloids like allergic reaction/coagulopathy.

APPROACH TO A CHILD WITH SEVERE DENGUE AND REFRACTORY SHOCK (LATE PRESENTERS).



SBP: Systolic blood pressure, PRBC: Packed red blood cell, CVP: Central venous pressure, ECHO: Echocardiogram, IAP: Intra-abdominal pressure

BOX A: Unrecognized morbidities that may contribute to refractory dengue shock.

Occult bleeds
Rx: Whole blood/PRBC transfusion

Co-Existing bacterial septic shock/Malaria/leptospira, etc
Rx: antibiotics/antimalarials, cardiovascular support, blood transfusion. Do not start antibiotic for pleural effusion since it's part and parcel of plasma leakage in dengue or to correct persistent acidosis/high lactate (usually due to prolonged/refractory shock).
Use of large amount of NS also can give rise to hyperchloraemic acidosis.

Myocardial Dysfunction (systolic or diastolic)
Rx: Cardiovascular support, evaluate with ECHO if available

Positive pressure ventilation contributing to poor cardiac output
Rx: Titrated fluid and cardiovascular support

Elevated intra-abdominal pressure (IAP)
Rx: Cautious drainage

Wide-Spread Hypoxic-ischemic injury with terminal vasoplegic shock
No treatment effective

ECHO: Echocardiogram; IAP: Intra-abdominal pressure; Rx: Treatment

Volume replacement flowchart for patient with dengue with "warning signs"

- Assess airway and breathing and obtain baseline HCT level.
- Commence fluid resuscitation with normal saline/Ringers lactate at 5-7ml/kg over 1-2 hours.
- If hemodynamic and HCT are stable, plan a gradually reducing IVF regime.
- Titrate fluid on the basis of vital signs, clinical examination, urine output (aim for 0.5ml-1ml/kg/hr),and serial HCT level.
- IVF:5-7ml/kg/hr for 1-2 hours, then:
- Reduce IVFs to 3-5ml/kg/hr for 2-4hours;
- Reduce IVFs to 2-3ml/kg/hr for 2-4 hours;
- Continue serial close monitoring and every 6-8hourly HCT level.
- Oral rehydration solutions may suffice when vomiting subsides and hemodynamic stabilize.
- A monitored fluid regimen may be required for 24-48hours until danger period subsides

HCT-hematocrit; IVF, intravenous fluid

Guidelines for reversing dengue shock while minimizing fluid overload

Severe dengue with compensated shock:

- Stabilize airway and breathing, obtain baseline Hct level, initiate fluid resuscitation with NS/RL at 10-20 mL/kg over 1 hr, and insert urine catheter early.

Severe dengue with hypotension:

- Stabilize airway and breathing, obtain baseline Hct level, initiate fluid resuscitation with 1-2 boluses of 20 mL/kg NS/RL or synthetic colloid over 15-30 mins until pulse is palpable, slow down fluid rates when hemodynamics improve, and repeat second bolus of 10 mL/kg colloid if shock persists and Hct level is still high.
- Synthetic colloids may limit the severity of fluid overload in severe shock.

End points/goals for rapid fluid boluses:

- Improvement in systolic BP, widening of pulse pressure, extremity perfusion and the appearance of urine, and normalization of elevated Hct level.
- If baseline Hct level is low or "normal" in presence of shock, hemorrhage likely to have worsened shock, transfuse fresh WB or fresh PRBCs early.
- After rapid fluid boluses, continue isotonic fluid titration to match ongoing plasma leakage for 24–48 hrs; if patient not vomiting and is alert after shock, correction with oral rehydration fluids may suffice to match ongoing losses.
- Check Hct level 2-4 hourly for first 6 hrs and decrease frequency as patient improves.

Goals for ongoing fluid titration:

- Stable vital signs, serial Hct measurement showing gradual normalization (if not bleeding), and low normal hourly urine output are the most objective goals indicating adequate circulating volume; adjust fluid rate downward when this is achieved.
- Plasma leakage is intermittent even during the first 24 hrs after the onset of shock; hence, fluid requirements are dynamic.
- Targeting a minimally acceptable hourly urine output (0.5-1 mL/kg/hr) is an effective and inexpensive monitoring modality that can signal shock correction and minimize fluid overload.
- A urine output of 1.5–2 mL/kg/hr should prompt reduction in fluid infusion rates, provided hyperglycemia has been ruled out.
- Separate maintenance fluids are not usually required; glucose and potassium may be administered separately only if low.
- Hypotonic fluids can cause fluid overload; also, avoid glucose-containing fluids, such as 1/2Glucose Normal Saline (GNS or I/2 GNS): the resultant hyperglycemia can cause osmotic diuresis and delay correction of hypovolemia. Tight glucose monitoring is recommended to avoid hyper/hypoglycemia.

Guidelines for reversing dengue shock while minimizing fluid overload *(cont)*

- Commence early enteral feeds when vital signs are stable, usually 4–8 hrs after admission.
- All invasive procedures (intubation, central lines, and arterial cannulation) must be avoided; if essential, they must be performed by the most experienced person. Orogastric tubes are preferred to nasogastric tubes. Avoid repeated veno-puncture.
- Significant hemorrhage mandates early fresh WB or fresh PRBC transfusion; minimize/avoid transfusions of other blood products, such as platelets and fresh-frozen plasma unless bleeding is uncontrolled despite 2–3 aliquots of fresh WB or PRBCs.

NS/RL, normal saline/Ringer's lactate; Hct, hematocrit; BP, blood pressure; WB, whole blood; PRBC - Packed Red Blood Cells; HCT-hematocrit; IVF, intravenous fluid GNS-glucose/normal saline

*** It is recommended that baseline hematocrit is obtained for all cases and repeat hematocrit done following each fluid resuscitation to look at child 's response and to plan subsequent fluid administration. In PICU/HDW settings, ABG machine can be used to look at HCT and in general wards, either, SPIN PCV or FBC (sent to lab).*

Discharge of Children with Dengue

- Patients who are resuscitated from shock rapidly recover. Patients with dengue hemorrhagic fever or dengue shock syndrome may be discharged from the hospital when they meet the following criteria:
- Afebrile for 24 hours without antipyretics.
- Good appetite, clinically improved condition.
- Adequate urine output.
- Stable hematocrit level.
- At least 48 hours since recovery from shock.
- No respiratory distress.
- Platelet count greater than 50,000 cells/μL.

HOME CARE CARD FOR DENGUE PATIENTS

(Please take this card to your health facility for each visit)

What should be done?

- Adequate bed rest.
- Adequate fluid intake:
  - >5 glasses for average-sized adults or accordingly in children.
  - Milk, fruit juice (caution with diabetes patient) and isotonic electrolyte solution (ORS) and barley/rice water.
  - Plain water alone may cause electrolyte imbalance.
- Take Paracetamol (not more than 4 grams per day for adults and 15mg/kg/dose 4-6 hourly in children).
- Tepid sponging.
- Look for mosquito breeding places in and around the home and eliminate them.

What should be avoided?

- Do not take acetylsalicylic acid (Aspirin), mefenamic acid (Ponstan), ibuprofen or other non-steroidal anti-inflammatory agents (NSAIDs), or steroids.

If you are already taking these medications please consult your doctor.
Antibiotics are not necessary.

If any of following is observed, take the patient immediately to the nearest hospital. These are warning signs for danger:

- Bleeding:
  - Red spots or patches on the skin; bleeding from nose or gum, vomiting blood; black-colored stools; heavy menstruation/vaginal bleeding.
- Frequent vomiting.
- Severe abdominal pain.
- Drowsiness, mental confusion or seizures.
- Pale, cold or clammy hands and feet.
- Difficulty in breathing.

Laboratory Monitoring					
Visit (date)					
White blood cells					
Hematocrit					
Platelets					

Chapter 89: Diphteria

Introduction

- Diphtheria is a clinical syndrome caused by *Corynebacterium diphtheria.*
- Diphtheria can be classified based on site of disease: nasal diphtheria, pharyngeal and tonsillar diphtheria, laryngeal or laryngotracheal diphtheria, and cutaneous diphteria.
- Diphtheria may cause systemic complication such as myocarditis (mortality 50%), neuritis presenting as paralysis of soft palate and rarely non-oliguric acute kidney injury.

Management of an Acute Case

- All suspected and confirmed patients must be placed under strict isolation until bacteriological clearance has been demonstrated after completing treatment. Strict droplet precautions and hand hygiene must be observed by healthcare workers.
- Obtain specimens for culture from nose, throat, or any mucosal membrane (tissue). Obtain specimen before the commencement of antibiotic and specimen must be transported to the laboratory promptly.
- Notify laboratory personnel as special tellurite enriched culture media (Loffler's or Tindale's) are needed.

Diphtheria Antitoxin (derived from horse serum)

- Definitive treatment :
  - Early, single dose of IV infusion (over 60minutes) diphtheria antitoxin should be administered on the basis of clinical diagnosis, even before culture results are available.
- Tests for hypersensitivity is recommended for IV administration.

Form of diphtheria	Dose (units)	Route
Pharyngeal/Laryngeal disease of 48 hours or less	20,000 to 40,000	IM OR IV
Nasopharyngeal lesions	40,000 to 60,000	IM OR IV
Extensive disease of 3 or more days durations or diffuse swelling of the neck (bull-neck diphtheria)	80,000 to 120,000	IM OR IV
Cutaneous lesions (not routinely given)	20,000 to 40,000	IM

Begin antibiotic therapy

Antibiotic is indicated to stop toxin production, treat localised infection, and to prevent transmission of the organism to contacts. It is not a substitute for antitoxin treatment.

REGIME

- Penicillin
  - IV aqueous crystalline Penicillin 100,000 to 150,000 U/kg/day in 4 divided doses, maximum 1.2 million U.

Or

- IM procaine Penicillin 25,000 to 50,000 U/kg/day (maximum 1.2million U, in 2 divided doses.
  - Change to oral Penicillin V 125-250mg QID once patient can take orally.
  - Total antibiotic duration for 14 days.

OR

- Erythromycin
  - IV OR Oral 40-50 mg/kg/day, maximum 2g/day.
  - Total antibiotic duration for 14 days.

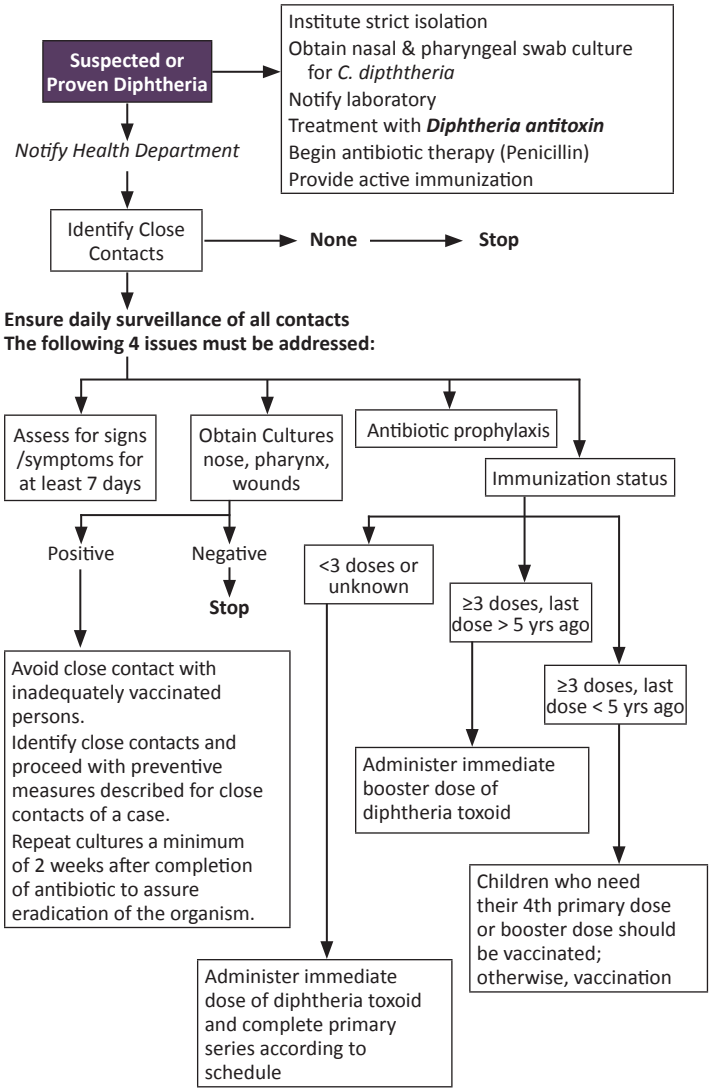
Immunization

- Before discharge, to catch up diphtheria toxoid immunization as
- diptheria infection does not necessary confer immunity

Management of close contacts and asymptomatic carriers

- Refer to diphtheria protocol.

FLOW CHART FOR THE CASE MANAGEMENT AND INVESTIGATION OF CLOSE CONTACTS IN DIPHTHERIA



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Chapter 90: Atopic Dermatitis

Introduction

- A chronic inflammatory itchy skin condition that usually develops in early childhood and follows a remitting and relapsing course. It often has a genetic component.
- Leads to the breakdown of the skin barrier making the skin susceptible to trigger factors, including irritants and allergens, which can make the eczema worse.
- Although not often thought of as a serious medical condition, it can have a significant impact on quality of life.

Diagnostic criteria
Major features (must have 3) *Hanifin and Rajka criteria*
Pruritus
Typical morphology and distribution • Facial and extensor involvement in infancy, early childhood • Flexural lichenification and linearity by adolescence
Chronic or chronically relapsing dermatitis
Personal or family history of atopy (asthma, allergic rhinoconjuctivitis, atopic dermatitis)
Minor / less specific features
Xerosis
Preauricular fissures
Icthyosis / palmar hyperlinearity / keratosis pilaris
Ig E reactivity
Hand/foot dermatitis
Cheilitis
Scalp dermatitis (cradle cap)
Susceptibility to cutaneous infection (e.g. *Staph. aureus* and Herpes simplex virus)
Perifollicular accentuation (especially in pigmented races)

Triggering factors

- Infection: Bacterial, viral or fungal
- Emotional stress
- Sweating and itching
- Irritants: Hand washing soap, detergents
- Extremes of weathers
- Allergens
- Food : egg, peanuts, milk, fish, soy, wheat.
- Aeroallergens : house dust mite, pollen, animal dander and molds.

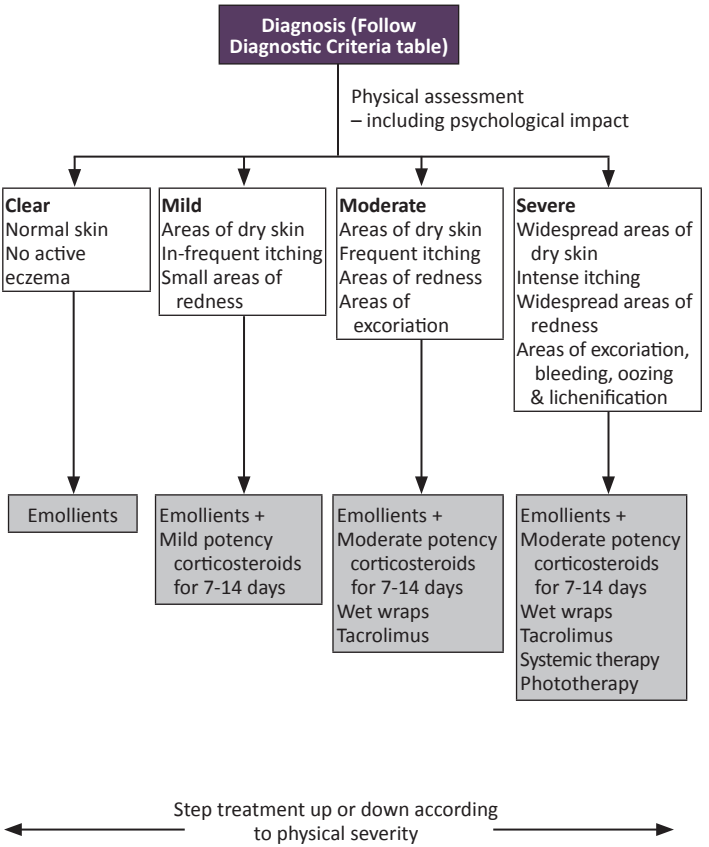
Management

- Tailor the treatment of atopic dermatitis individually depending on
  - The severity.
  - Patient's understanding and expectation of the disease and the treatment process.
  - Patient's social circumstances.
- Comprehensive patient education is paramount, and a good doctor-patient relationship is essential for long-term successful management.
- In an acute flare-up of atopic dermatitis, evaluate for the following factors:
  - Poor patient compliance
  - Secondary infection: bacterial (e.g. *Staphylococcus aureus*), viral
  - (e.g. herpes simplex virus)
  - Persistent contact irritant/allergen.
  - Physical trauma, scratching, friction, sweating and adverse environmental factors.

Bath & Emollients

- Baths soothe itching and removes crusting. They should be lukewarm and limited to 10 minutes duration. Avoid soaps. Use soap substitute e.g. aqueous cream or emulsifying ointment.
- Moisturizers work to reduce dryness in the skin by trapping moisture.
- Apply to normal and abnormal skin at least twice a day and more frequently in severe cases.
- Emollients are best applied after bath. Offer a choice of unperfumed emollients and suitable to the child's needs and preferences, e.g. Aqueous cream, Ung. Emulsificans, and vaseline.

N.B. Different classes of moisturizer are based on their mechanism of action, including occlusives, humectants, emollients and protein rejuvenators. In acute exudation form $KMNO_4$ 1:10,000 solutions or normal saline daps or soaks are useful – as mild disinfectant and desiccant.


Diagnosis (Follow Diagnostic Criteria table)
Physical assessment
– including psychological impact
Clear
Normal skin
No active eczema
Mild
Areas of dry skin
In-frequent itching
Small areas of redness
Moderate
Areas of dry skin
Frequent itching
Areas of redness
Areas of excoriation
Severe
Widespread areas of dry skin
Intense itching
Widespread areas of redness
Areas of excoriation, bleeding, oozing & lichenification
Emollients
Emollients +
Mild potency corticosteroids for 7-14 days
Emollients +
Moderate potency corticosteroids for 7-14 days
Wet wraps
Tacrolimus
Emollients +
Moderate potency corticosteroids for 7-14 days
Wet wraps
Tacrolimus
Systemic therapy
Phototherapy
Step treatment up or down according to physical severity

Topical Corticosteroids

- Topical corticosteroid is an anti-inflammatory agent and the mainstay of treatment for atopic eczema.
- Topical steroid are often prescribed intermittently for short term reactive treatment of acute flares and supplemented by emollients.
- Choice depends on a balance between efficacy and side-effects.
- The more potent the steroid, the more the side-effect.
- Apply steroid cream once or twice daily.
- Avoid sudden discontinuation to prevent rebound phenomenon.
- Use milder steroids for face, flexures and scalp.
- Amount of topical steroid to be used – the finger tip (FTU) is convenient way of indicating to patients how much of a topical steroid should be applied to skin at any one site. 1 FTU is the amount of steroid expressed from the tube to cover the length of the flexor aspect of the terminal phalanx of the patient's index finger.
- Number of FTU required for the different body areas.
  - 1 hand/foot/face 1 FTU
  - 1 arm 3 FTU
  - 1 leg 6 FTU
  - Front and back of trunk 14 FTU
- Adverse effect results from prolonged use of potent topical steroids.
- Local effects include skin atrophy, telangiectasia, purpura, striae, acne, hirsutism and secondary infections. Systemic effects are adrenal axis suppression, Cushing syndrome.

Steroid Potency	
Potency of topical steroid	Topical steroid
Mild	Hydrocortisone cream/ointment 1%
Moderate	Bethametasone 0.025% (1:4dilution) Eumovate (clobetasone butyrate)
Potent	Bethametasona 0.050% Elomet (mometasone furoate)
Super potent	Dermovate (clobetasone propionate)

Systemic Therapy

Consist of:

- Relief of pruritus
- Treatment of secondary infection, and
- Treatment of refractory cases

Relief of Pruritus

- Do not routinely use oral antihistamines.
- Offer a 1-month trial of a non-sedating antihistamine to:
  - Children with severe atopic eczema
  - Children with mild or moderate atopic eczema where there is severe itching or urticaria.
- If successful, treatment can be continued while symptoms persist.
- Review every 3 months.
- Offer a 7–14 day trial of a sedating antihistamine to children over 6 months during acute flares if sleep disturbance has a significant impact. This can be repeated for subsequent flares if successful.

Treatment of secondary infection

- Secondary bacterial skin infection is common and may cause acute exacerbation of eczema. Systemic antibiotics are necessary when there is evidence of extensive infection.
- Commonly *Staphyloccus aureus.*
- Useful in exudation form where superinfection occurs.
- Choice:
  - Oral cloxacillin 15mg/kg/day 6 hourly for 7-14 days, *or*
  - Oral Erythromycin / cephalosporin
- Secondary infection can arise from Herpes simplex virus causing *Eczema Herpeticum.* Treatment using antiviral e.g. Acyclovir may be necessary.

Refractory cases

- Refractory cases do not response to conventional topical therapy and have extensive eczema. Refer to a Dermatologist (who may use systemic steroids, interferon, Cyclosporine A, Azathioprine or/and phototherapy).

Other Measures

- Avoid woolen toys, clothes, bedding.
- Reduce use of detergent (esp. biological).
- BCG contraindicated till skin improves.
- Swimming is useful (MUST apply moisturizer immediately upon exiting pool).
- Avoid Aggravating Factors.

For Relapse

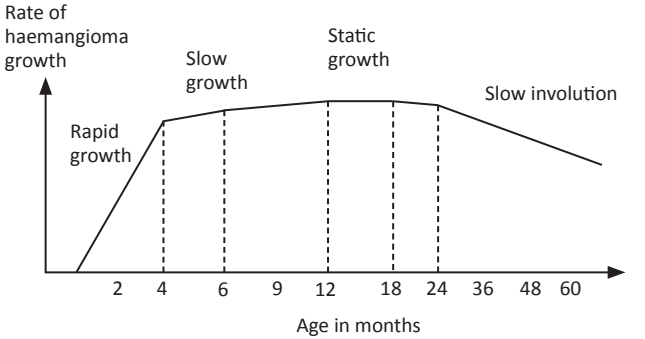
- Check compliance.
- Suspect secondary infection – send for skin swab; start antibiotics.
- Exclude scabies.
- For severe eczema, emollient and topical steroid can be applied under occlusion with 'wet wrap'. This involves the use of a layer of wet, followed by a layer of dry Tubifast to the affected areas i.e. limbs and trunk. The benefits are probably due to cooling by evaporation, relieving pruritus, enhanced absorption of the topical steroid and physical protection of the excoriation.

Prognosis

- Tendency towards improvement throughout childhood.
- Two third will clear by adolescence.

Infantile haemangiomas

- Are the most common benign vascular tumour of infancy.
- Clinical course is marked by rapid growth during early infancy followed by slower growth, then gradual involution.
- A minority cause functional impairment and even more cause psychosocial distress.
- Once resolved, a significant minority (20-40%) leave residual scarring, fibrofatty tissue, telangiectases, and other skin changes which can have a lasting psychological effect.



- By 5 years of age, 50% of hemangiomas involute, 70% by age 7, and 90% by age 9. 20-40% leave residual changes in the skin.
- Approximately 10% require treatment, and < 1% are life threatening.
- In 95% of cases, diagnosis can be established on the basis of history and physical examination alone:
  - Typical-appearing vascular tumors.
  - History of the lesion seen at birth or shortly thereafter, with characteristic proliferation in early infancy.

Clinical subtypes of haemangiomas:

- *Superficial haemangiomas* are most common (50%-60%).
- *Deep haemangiomas* (15%): bluish soft-tissue swellings without an overlying superficial component.
- *Mixed haemangiomas* (both a superficial and deep component) (25%-35%).
- *Multiple neonatal haemangiomatosis* (15%-30%), consists of multiple small lesions ranging from a few millimeters to 1 to 2 cm.

Management

- Most hemangiomas require no treatment.
- Active nonintervention is recommended in order to recognize those that may require treatment quickly.
- When treatment is undertaken, it is important that it be customized to the individual patient, and that the possible physical, and psychological complications be discussed in advance. Often, a multidisciplinary approach is recommended.
- Individualized depending on: size of the lesion(s), location, presence of complications, age of the patient, and rate of growth or involution at the time of evaluation. The potential risk(s) of treatment is carefully weighed against the potential benefits.

No risk or low-risk haemangiomas

(Small, causing no functional impairment and unlikely to leave permanent disfigurement)

- Wait and watch policy (active non-intervention)
- Patient education: Parent education may include the following:
  - The expected natural history without treatment
  - Demonstration whenever possible serial clinical photographs of natural involution.

High-risk haemangiomas

(Large, prognostically poor location, likely to leave permanent disfigurement, causing functional impairment, or involving extracutaneous structures)

- Large cutaneous or visceral haemangiomas (particularly liver) can result in high-output cardiac failure.
- Haemangiomas on the 'special sites' with associated complications are given on the table below.

Special site	Complications
Beard	Airway compromise
Eye	Amblyopia, strabismus, astigmatism
Lumbar	Tethered cord, imperforate anus, renal anomalies, sacral anomalies.
Facial	PHACES

- Segmental haemangiomas, which cover a particular section or area of skin, may be markers for underlying malformations or developmental anomalies of the heart, blood vessels, or nervous system (PHACE and PELVIS syndromes and lumbosacral haemangiomas) and, depending on the severity of the associated anomaly, can result in increased morbidity or mortality.
- PHACE syndrome is posterior fossa structural brain abnormalities (Dandy-Walker malformation and various forms of hypoplasia); haemangiomas of the face, head, and neck (segmental, >5 cm in diameter); arterial lesions (especially carotid, cerebral, and vertebral); cardiac anomalies (coarctation of the aorta in addition to many other structural anomalies); eye abnormalities; and, rarely, associated midline ventral defects such as sternal cleft or supraumbilical raphe).
- PELVIS syndrome is perineal haemangioma with any of the following: external genital malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and/or skin tags.

Treatment

The listed treatments may be used singly, in combination with each other, or with a surgical modality.

MEDICAL

- *Propranolol* is the first-line therapy; Patients are admitted to ward for propranolol therapy for close monitoring of any adverse effects.
  - *Dose:* Start at 0.5 mg/kg/d in 2 to 3 divided doses orally and then increased if tolerated. An increase in dose by 0.5 mg/kg/d is given until the optimal therapeutic dose of 1.5 to 2 mg/kg/day.
  - *Duration:* Ranges from 2 - 15 months but it is proposed that propranolol should be continued for 1 year or until the lesion involutes completely, as rebound growth has been noted if treatment is withdrawn too early.
  - Propranolol is withdrawn by halving the dose for 2 weeks, then halving again for 2 weeks, before stopping.
  - Adverse effects: hypotension, bradycardia, hypoglycemia, bronchospasm, sleep disturbance, diarrhea, and hyperkalemia.
- *Systemic corticosteroids* (indicated mainly during the growth period of haemangiomas):
  - Prednisolone 2 to 4 mg/kg/ day in a single morning dose or divided doses. Watch out for growth retardation, blood pressure elevation, insulin resistance, and immunosuppression.
  - Intralesional corticosteroid therapy for small, bossed, facial hemangioma.
  - Triamcinolone, 20mg/ml, should be injected at low pressure, using a 3 ml syringe and 25-gauge needle. Do not exceed 3-5mg/kg per procedure.
  - Periocular regions must be done only by an experienced ophthalmologist as there is a risk of embolic occlusion of the retinal artery or oculomotor nerve palsy.

- Other systemic therapy:
  - *Interferon alfa*. Very effective but is used mainly as a second-line therapy for lesions not responsive to corticosteroids because of the possible severe neurotoxicity, including spastic diplegia.
  - *Vincristine*. Some consider this as second-line treatment for corticosteroid resistant hemangiomas.

SURGERY

- The benefits and risks of surgery must be weighed carefully, since the scar may be worse than the results of spontaneous regression.
- Surgery is especially good for small, pedunculated hemangiomas and occasionally, in cases where there may be functional impairment. It is usually used to repair residual cosmetic deformities.
- Generally, it is recommended that a re-evaluation be done when the child is 4 years old, in order to assess the potential benefit of excision.

Chapter 92: Scabies

Definition

Infestation caused by the mite *Sarcoptes scabei*. Any part of the body may be affected, and transmission is by skin to skin contact.

Clinical features

Symptoms

- Mites burrow into the skin where they lay eggs. The resulting offspring crawl out onto the skin and makes new burrows.
- Absorption of mite excrement into skin capillaries generates a hypersensitivity reaction.
- The main symptom, which takes 4-6 wks to develop, is generalised itch – especially at night.

Signs

- Characteristic silvery lines may be seen in the skin where mites have burrowed.
- Classic sites: interdigital folds, wrists, elbows, umbilical area, genital area and feet.
- *Nodular Scabies*- papules or nodules seen at the site of mite infestation often affect the scrotum, axillae, back, or feet of children.
- *Crusted or Norwegian Scabies*- seen in young infants or immunosuppressed patients. Widespread mite infestation causing a hyperkeratotic and/or crusted generalized rash.

Diagnosis

- The clinical appearance is usually typical, but there is often diagnostic confusion with other itching conditions such as eczema.
- Scrapings taken from burrows examined under light microscopy may reveal mites.

Management

General advice

- Educate the parents about the condition and give clear written information on applying the treatment.
- Treat everyone in the household and close contacts.
- Only allow the patient to go to school 24 hours after the start of treatment.
- Wash clothing and bedding in hot water or by dry cleaning. Clothing that cannot be washed may be stored in a sealed plastic bag for three days.
- The pruritis of scabies may be treated with diphenhydramine or other anti-pruritic medication if necessary. The pruritis can persist up to three weeks post treatment even if all mites are dead, and therefore it is not an indication to retreat unless live mites are identified.
- Any superimposed bacterial skin infection should be treated at the same time as the scabies treatment.

Doses and side effects of common agents used in scabies management.				
Treatment	Treatment regime	Contraindication/Caution	Side effects	Comments
Permethrin 5% Cream /lotion	Rinse off after 8 to 12 hrs & repeat 1 week later	Percutaneous absorption in animal tests shows 40-400 times lower than Lindane 1%	Itching & burning / stinging sensation on application.	First-line therapy by CDC. Effective, well tolerated and safe
Benzyl Benzoate 10 – 25% lotion	Rinse off after 24 hrs then reapply. To be kept on the skin surface continuously for 24 hrs for 2-3 days (with baths taken between each application)	Pregnant and breast feeding women and infants < 2 years	Skin irritation and burning sensation. May cause conjunctivitis if exposed to eyes. May worsen/cause post- scabetic eczematous reaction. Affects compliance.	Effective & inexpensive Compliance is an issue.
Precipitated Sulphur 6 to 10% Petroleum base	Rinse off after 24 hrs and then reapply every 24 hrs for next 3 days (with a bath taken between each application)	Low toxicity	Messy, malodourous, stain clothing, causes irritant contact dermatitis	Safe for infants, pregnant and breastfeeding women
Crotamiton 10% Ointment	*Classical scabies:* Rinse off after 24 hrs and reapply for 5-7 additional days *Nodular scabies:* Apply to nodules 3x/day for 7-14 days	Avoid massive and prolonged use in pregnant women and infants	Irritant contact dermatitis	Use for treatment of nodules in children. Lack of efficacy and toxicity data.

Doses and side effects of common agents used in scabies management (continued)				
Treatment	Treatment regime	Contraindication/Caution	Side effects	Comments
Ivermectin	Oral drug 200uµg/kg single dose and repeat after 2 weeks	Not for children < 5 years old or < 15kg. Avoid in pregnant and lactating women.	Use with other drugs which reinforces GABA activity can lead to augmented activity (valproate, barbiturates, benzodiazepines)	Suitable for patients unlikely to adhere to topical therapy. Useful for mass treatment or outbreaks. Effective if combined with Benzyl Benzoate in patients with AIDS

Treatment of scabies in special considerations				
Clinical condition	Recommended therapy	Alternative therapy	Additional measures	Comments
Classical scabies				
i. Infants < 2 months	Sulphur 6% in petroleum in ointment base for 3 days	-	Treat whole body including face (avoid eyes and mouth)	Treat all family members/ close contacts simultaneously
ii. Children < 2 years	Two applications of Permethrin 5% for 8-12 hrs at one week apart	Sulphur 6% in petroleum in ointment base for 3 days	Treat whole body including face (avoid eyes and mouth)	Crotamiton cream TDS for 5-7 days for nodular scabies
iii. Children < 12 years	Two applications of Permethrin 5% for 8-12 hrs at one week apart	Benzyl Benzoate 12.5% Whole body neck and below for 3 consecutive days	-	Crotamiton cream TDS for 7-14 days for nodular scabies
iv. Adults	Two applications of Permethrin 5% for 8-12 hrs at one week apart	Benzyl Benzoate 25% Whole body neck and below for 3 consecutive days		People in close physical contact, even without symptoms, should receive treatment at the same time
v. Pregnancy/ lactating women	Two applications of Permethrin 5% for 8-12 hrs at one week apart	-	-	-
Crusted scabies	Permethrin and Ivermectin for Scabies	Oral ivermectin alone or in combination with permethrin is very useful OR Several applications of Benzyl Benzoate	Apply keratolytic agents (salicylic acid ointment) to hyperkeratotic areas. Keep nails short and apply medication to subungual areas.	Patients may need admission. Strict control to prevent spread of infection

Chapter 93: Steven Johnson Syndrome

Definitions

STEVEN JOHNSON SYNDROME (SJS)

- Severe erosions of at least two mucosal surfaces with extensive necrosis of lips and mouth, and a purulent conjunctivitis.
- Epidermal detachment may occur in SJS, but less than 10% of the body surface area is involved.
- Morbidity with this disease is high, and can include photophobia, burning eyes, visual impairment and blindness.

TOXIC EPIDERMAL NECROLYSIS (TEN)

- Severe exfoliative disease associated with systemic reaction characterized by rapid onset of widespread erythema and epidermal necrolysis. Involves more than 30% loss of epidermis.

Aim of treatment: To remove the cause and prevent complications

Salient features

- Acute prodromal flu-like symptoms, fever, conjunctivitis and malaise.
- Skin tenderness, morbilliform to diffuse or macular erythema target lesions, vesicles progressing to bullae. Blisters on the face, and upper trunk, then exfoliation with wrinkled skin which peels off by light stroking (Nikolksy' sign).
- Buccal mucosa involvement may precede skin lesion by up to 3 days in 30% of cases.
- Less commonly the genital areas, perianal area, nasal and conjuctival mucosa.
  In the gastrointestinal tract, esophageal sloughing is very common, and can cause bleeding and diarrhoea.
- In the respiratory tract, tracheobronchial erosions can lead to hyperventilation, interstitial oedema, and acute respiratory disease syndrome.
- Skin biopsy of TEN - Extensive eosinophilic necrosis of epidermis with surabasal cleavage plane.
- Renal profile – raised blood urea, hyperkalaemia and creatinine.
- Glucose - hypoglycaemia.

Aetiology in Steven Johnson Syndrome / TEN
Drugs Antibiotics: Sulphonamides, amoxycillin, ampicillin, ethambutol, isoniazid Anticonvulsants: Phenobarbitone, carbamazepine, phenytoin Non-Steroidal Anti-Inflammatory Drugs: Phenylbutazone, salicylates
Infection Virus: herpes simplex, enteroviruses, adenoviruses, measles, mumps Bacteria: *Streptococcus, Salmonella typhi, Mycoplasma pneumoniae*

Management

Supportive Care

- Admit to isolation room where possible.
- May need IV fluid resuscitation for shock.
- Good nursing care (Barrier Nursing and hand washing).
- Use of air fluidized bed, avoid bed sores.
- Adequate nutrition – nasogastric tubes, IV lines, parenteral nutrition if severe mucosal involvement.

Specific treatment

- Eliminate suspected offending drugs
- IV Immunoglobulins at a dose of 0.4 Gm/kg/per day for 5 days. IVIG is a safe and effective in treatment for SJS/TEN in children. It arrests the progression of the disease and helps complete re-epithelialization of lesions.

Monitoring

- Maintenance of body temperature. Avoid excessive cooling or overheating.
- Careful monitoring of fluids and electrolytes – BP/PR.
- Intake / output charts, daily weighing and renal profile.

Prevent Complications

Skin care

- Cultures of skin, mucocutaneous erosions, tips of Foley's catheter.
- Treat infections with appropriate antibiotics.
- Topical antiseptic preparations: saline wash saline wash or $KMnO_4$ wash.
- Dressing of denuded areas with paraffin gauze / soffra-tulle.
- Surgery may be needed to remove necrotic epidermis.

Eye care

- Frequent eye assessment.
- Antibiotic or antiseptic eye drops 2 hourly.
- Synechiea should be disrupted.

Oral care

- Good oral hygiene aimed at early restoration of normal feeds.

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Chapter 94: Inborn errors of metabolism (IEM): Approach to Diagnosis and Early Management in a Sick Child

Introduction

- Over 500 human diseases due to IEM are now recognized and a significant number of them are amenable to treatment.
- IEMs may present as
  - An acute metabolic emergency in a sick child.
  - Chronic problems involving either single or multiple organs, either recurrent or progressive, or permanent.
- It will become ever more important to initiate a simple method of clinical screening by first-line paediatric doctors with the goal 'Do not miss a treatable disorder'.

Classification
From a therapeutic perspective, IEMs can be divided into 5 useful groups:

Group	Diseases	Diagnosis and Treatment
Disorders that give rise to acute or chronic intoxication	Aminoacidopathies (MSUD (Maple syrup urine disease), tyrosinaemia, PKU (Phenylketonuria), homocystinuria), most organic acidurias (methylmalonic, propionic, isovaleric, etc.), urea cycle defects, sugar intolerances (galactosaemia, hereditary fructose intolerance), defects in long-chain fatty acid oxidation	Readily diagnosed through basic IEM investigations: blood gases, glucose, lactate, ammonia, plasma amino acids, urinary organic acids and acylcarnitine profile Specific emergency and long term treatment available for most diseases.
Disorders with reduced fasting tolerance	Glycogen storage diseases, disorders of gluconeogenesis, fatty acid oxidation disorders, disorders of ketogenesis/ketolysis	Persistent/recurrent hypoglycemia is the first clue to diagnosis. Specific emergency and long term treatment available for most diseases.
Neurotransmitter defects and related disorders	Nonketotic hyperglycinemia, serine deficiency, disorders of biogenic amine metabolism, disorders of GABA metabolism, antiquitin deficiency (pyridoxine dependent epilepsy), pyridoxal phosphate deficiency, GLUT1 deficiency	Diagnosis requires specialized CSF analysis. Some are treatable.

Classification *(continued)*		
Group	Diseases	Diagnosis and Treatment
Disorders of the biosynthesis and breakdown of complex molecules	Lysosomal storage disorders, peroxisomal disorders, congenital disorders of glycosylation, sterol biosynthesis disorders, purine and pyrimidine disorders	Specialized diagnostic tests required. Very few are treatable.
Mitochondrial disorders	Respiratory chain enzymes deficiencies, PHDc deficiency (Pyruvate Dehydrogenase Deficiency complex) , pyruvate carboxylase deficiency	Persistent lactate acidemia is often the first clue to diagnosis. Mostly supportive care.

Screening for treatable IEM in a sick child

- In an acutely ill child, IEM should be considered a differential diagnosis along with other diagnoses:
  - In all neonates with unexplained, overwhelming, or progressive disease particularly after a normal pregnancy or birth, but deteriorates after feeding.
  - In all children with acute encephalopathy, particularly preceded by vomiting, fever or fasting.
  - In all children with unexplained symptoms and signs of metabolic acidosis, hypoglycaemia, acute liver failure or Reye-like syndrome.
- The aim is targeted to pick up treatable diseases in Group 1 and 2 as early as possible.
- Many clues may be gained from a detailed history and physical examination
  - Unexplained death among sibling(s) due to sepsis or "SIDS".
  - Unexplained disorders in other family members (HELLP syndrome (Haemolysis, Elevated Liver enzyme levels, and Low Platelet levels), progressive neurological disease).
  - Consanguinity.
  - Deterioration after a symptom-free interval in a newborn.
  - Unusual smell - burn sugar (MSUD), sweaty feet (isovaleric acidemia).
- Actively investigate for IEM in any acutely ill child of unknown aetiology, as early as possible during the course of illness. According to the clinical situation, basic and special metabolic investigations must be initiated in parallel.

Basic metabolic investigations [1]	Special metabolic investigations [1]
Blood count, electrolytes, ALT, AST, CK, creatinine, urea, uric acid, coagulation Must be included in work-up of an acutely ill child of unknown aetiology [4]: • Ammonia[2] • Glucose • Lactate[2] • Blood gases • Ketostix (urine)	• Acylcarnitines • Amino acids (plasma or serum)[3] • Organic acids (urine) • Orotate (urine): if suspected urea cycle defects *[Send to the metabolic lab immediately (e.g. by courier) especially when the basic metabolic investigations are abnormal, particularly if there is hyperammonemia or persistent ketoacidosis]*

1. Will pick up most diseases from Group 1 and 2, and some diseases in other groups (which often require more specialized tests)
2. Send immediately (within 15 minutes) to lab with ice
3. Urinary amino acids are the least useful as they reflect urinary thresh old. Their true value is only in the diagnosis of specific renal tubular transport disorders (eg cystinuria).
4. Routine analysis of pyruvate is not indicated.

Useful normal/abnormal values		
Basic tests	**Values**	**Note**
Ammonia	*Neonates* Healthy: <110µmol/L Sick: up to 180µmol/L Suspect IEM: >200µmol/L *After the Neonatal period* Normal: 50-80 µmol/L Suspect IEM: >100µmol/L	1. False elevations are common if blood sample is not analyzed immediately. 2. Secondary elevated may occur in severe liver failure.
Anion Gap	*Calculation* [Na+] + [K+] – [Cl-] – [HCO3-] Normal :- 15-20mmol/L	1. Normal: renal / intestinal loss of bicarbonate. 2. Increased: organic acids, lactate, ketones.
Lactate	Blood: < 2.4mmol/L CSF: < 2.0mmol/L	False elevations are common due to poor collection or handling techniques

Disorders"Typical" basic laboratory constellations						
Disorders	Ammonia	Glucose	Lactate	pH	Ketonuria	Others
Urea cycle defects	↑↑↑	N	N	↑	N	
Organic acidemias	↑↑	↓, N, ↑	↑↑	↓↓↓	↑↑↑	↑anion gap, neutropenia, thrombocytopenia
MSUD	N	N	N	N	N,↑	
GSD	N	↓↓↓	↑↑	↓	N	↑triglyceride, ↑uric acid, ↑ALT
FAOD	↑	↓↓↓	↑	↓	↓↓↓	↑CK
Mitochondrial disorders	N	N	↑↑↑	↓↓	N	↑alanine
Tyrosinemia I	N	N-↓	N	N-↓	N	Liver failure, ↑α-fetoprotein, Renal fanconi

Early contact to the metabolic laboratory will help target investigations, avoid unnecessary tests, and speed up processing of samples and reporting of results.

Emergency management of a sick child suspected IEM

In the critically ill and highly suspicious patient, treatment must be started immediately, in parallel with laboratory investigations. This is especially important for Group 1 diseases.

STEP 1

If the basic metabolic test results and the clinical findings indicate a disorder causing acute endogenous intoxication due to disorder of protein metabolism (Group 1 diseases - UCD, organic acidurias or MSUD), therapy must be intensified even without knowledge of the definitive diagnosis.

Anabolism must be promoted and detoxification measures must be initiated.

- Immediately stop protein intake. **However, the maximum duration without protein is 48 hours.**
- Correct hypoglycaemia and metabolic acidosis.
- Reduce catabolism by providing adequate calories. Aim for 120kcal/kg/day, achieved by
  - IV Glucose infusion (D10%, 15% or 20% with appropriate electrolytes).
  - Intralipid 20% at 2-3g/kg/day **(Except when a Fatty Acid Oxidation Disorder is suspected).**
  - Protein-free formula for oral feeding [eg Pro-phree® (Ross), Calo-Lipid (ComidaMed®), basic-p (milupa)].
- Anticipate complications:
  - Hyperglycemia/glucosuria - Add IV Insulin 0.05U/kg/hr if blood glucose > 15mmol/L to prevent calories loss.
  - Fluid overload: IV Frusemide 0.5-1mg stat doses.
  - Electrolytes imbalances: titrate serum Na+ and K+.
  - Protein malnutrition – add IV Vamin or oral natural protein (eg milk) after 48 hours, starts at 0.5g/kg/day.
- Carry out detoxifying measures depending on the clinical and laboratory findings.
- Continue all conventional supportive/intensive care
  - Respiratory insufficiency: artificial ventilation.
  - Septicaemia: antibiotics.
  - Seizures: anticonvulsants.
  - Cerebral edema: avoid hypotonic fluid overload, hyperventilation, Mannitol, Frusemide.
  - Early central line.
- Consult metabolic specialist.

Specific detoxification measures for hyperammonemia
Hyperammonemia due to Urea cycle defects
Anti-hyperammonemic drugs cocktail Indication: 1. Ammonia level > 200µmol/L 2. Symptomatic (encephalopathic) *Loading dose* IV Sodium benzoate 250mg/kg IV Sodium phenylbutyrate 250mg/kg IV L-Arginine 250mg/kg (mix together in D10% to a total volume of 50mls, infuse over 90 min) *Maintanence dose* Same dilution as above but infuse over 24 hours
Dialysis
Indication: 1. Ammonia level > 400µmol/L 2. Symptomatic (encephalopathic) 3. Inadequate reduction/raising NH3 despite drugs cocktail Hemodialysis or hemofiltration if available. If not, peritoneal dialysis is the alternative. Exchange transfusion is not effective. *(Method of choice depends on local availability, experience of medical staff)*
Hyperammonemia due to Organic aciduria
Give oral Carglumic acid, 100 - 250mg/kg/day in divided doses

Other specific Detoxification measures		
Disorder	Pharmacological	Non-pharmacological
MSUD	nil	Dialysis. *Indication:* 1. Leucine >1,500µmol/L 2. Symptomatic (encephalopathic)
Organic acidurias	Carnitine 100mg/kg/day	Dialysis. *Indication:* 1. intractable metabolic acidosis 2. Symptomatic (encephalopathic)
Tyrosinemia type 1	NTBC 1-2mg/kg/day	Nil
Cobalamin disorders	IM Hydroxocobalamin 1mg daily	Nil

STEP 2

- Adaptation and specification of therapy according to the results of the special metabolic investigations/definitive diagnosis.
- For protein metabolism disorders, the long term diet is consists of
  - Specific precursor free formula
  - Natural protein (breast milk or infant formula). This is gradually added when child is improving to meet the daily requirement of protein and calories for optimal growth.
- Other long term treatment includes
  - Oral anti-hyperammonemic drugs cocktail (for urea cycle defects)
  - Carnitine (for organic acidemias)
  - Vitamin therapy in vitamin-dependent disorders (eg Vit B12-responsive methylmalonic acidemia and cobalamine disorders).
- Transfer the child to a metabolic centre for optimisation of therapy is often necessary at this stage in order to plan for the long term nutritional management according to child's protein tolerance.

STEP 3

- Be prepared for future decompensation
  - Clear instruction to parents.
  - Phone support for parents.
  - Provide a letter that includes the emergency management protocol to be kept by parents.

Role of first-line paediatric doctors

1. Help in early diagnosis
2. Help in initial management and stabilization of patient
3. Help in long term care (shared-care with metabolic specialist)
  - Rapid action when child is in catabolic stress (febrile illness, surgery, etc)
  - Adequate hydration and temporary adjustment in nutrition management and pharmacotherapy according to emergency protocol will prevent catastrophic metabolic decompensation.

Key points in managing acute metabolic decompensation in children with known disorders of protein metabolism (UCD, MSUD, Organic acidurias)

- Consult metabolic specialist if you are uncertain.
- Perform clinical and biochemical assessment to determine the severity.
- Stop the natural protein but continue the special formula as tolerated (PO or per NG tube/perfusor).
- IV Glucose and Intralipid to achieve total calories 120kcal/kg/day.
- IV antiemetic (e.g. Granisetron) for nausea or vomiting.
- Management of hypoglycemia, hyperammonemia and metabolic acidosis as above.
- Gradually re-introduce natural protein after 24-48 hours.

Acute intoxication due to classical galactossemia (Group 1)

- Clinical presentation: progressive liver dysfunction after start of milk feeds, cataract.
- Diagnosis: dry blood spots (Guthrie card) for galatose and galactose-1-P uridyltransferase (GALT) measurement
- Treatment: galactose-free infant formula
- **Neonatal intrahepatic cholestasis caused by Citrin Deficiency (NICCD) may mimic classical Galactosemia.**

Disorders with reduced fasting tolerance (Group 2)

- Clinical presentation: recurrent hypoglycemia ± hepatomegaly.
- Treatment: - 10% glucose infusion, 120- 150ml/kg/day.
- This therapy is usually sufficient in acute phase.
- Long term: avoid fasting, frequent meals, nocturnal continuous feeding, uncooked cornstarch (older children).
  (refer **Chapter on Hypoglycaemia**)

Neurotransmitter defects and related disorders (Group 3)

This group should be considered in children with neurological problems when basic metabolic investigations are normal.

- Diagnosis usually requires investigations of the CSF. Consider this in
  - Severe epileptic encephalopathy starting before birth or soon thereafter, especially if there is myoclonic component.
  - Symptoms of dopamine deficiency: oculogyric crises, hypokinesia, dystonia, truncal hypotonia/limb hypertonia.
  - Presence of vanillactate and 4(OH) Butyrate in urine.
  - Unexplained hyperprolactinemia.

Disorders of the biosynthesis and breakdown of complex molecules (Group 4)

- Disorders in this group
  - Typically show slowly progressive clinical symptoms and are less likely to cause acute metabolic crises.
  - Are not usually recognised by basic metabolic analyses but require specific investigations for their diagnosis.
- Lysosomal disorders:
  (1) screening tests: urine glycoaminoglycans (mucopolysacchardioses), urine oligosaccharides (oligosaccharidoses).
  (2) definitive diagnosis: enzyme assay, DNA tests.
- Peroxisomal disorders: plasma very long chain fatty acids (VLCFA).
- Congenital disorders of glycosylation: serum transferrin isoform analysis.

Mitochondrial disorders (Group 5)

- Clinical: suspect in unexplained multi-systemic disorders especially if involve neuromuscular system.
- Inheritance:
  (1) mtDNA defects –sporadic, maternal.
  (2) nuclear gene defects –mostly autosomal recessive.
- Laboratory markers: persistently elevated blood/CSF lactate and plasma alanine.
- Diagnosis: respiratory enzyme assay in muscle biopsy/skin fibroblast, targeted mtDNA mutation study in patients with a clear clinical picture (e.g. LHON, MELAS, MNGIE) (discuss with metabolic specialist).
- Treatment: ensure adequate nutrition, treat fever/seizure/epilepsy efficiently, avoid drugs that may inhibit the respiratory chain (e.g. valproate, tetracycline, chloramphenicol and barbiturates).
- Use of vitamins and cofactors is controversial/insufficient evidence.
- Useful websites: http://www.mitosoc.org/, www.umdf.org/

Leigh Syndrome

- Leigh syndrome is the most frequent clinical phenotype in childhood.
- Onset is typically in infancy or early childhood with neurodevelopmental regression following an intercurrent viral illness (which may be mild) or other metabolic stress.
- There is frequently a preceding history of feeding difficulties and vomiting.
- Neurological findings include bouts of hyper- or hypo-ventilation, hypotonia, dystonia, ataxia, tremor, ophthalmoparesis and optic atrophy.
- Multisystem involvement may include cardiomyopathy, renal tubulopathy and gastrointestinal dysfunction (vomiting, diarrhoea, constipation, faltering growth).
- Periods of stability are interspersed by episodes of further neurodevelopmental regression, often without obvious triggers.
- Progressive brainstem involvement eventually leads to death from central respiratory failure.

- Diagnosis is based on a characteristic clinical history associated with typical brain magnetic resonance imaging (MRI) features (T2-weighted bilateral symmetrical hyperintense lesions affecting the basal ganglia and/or brainstem) and compatible biochemical findings (lactate elevation in blood and/or cerebrospinal fluid).
- Leigh synsdrome is genetically heterogeneous disorder (currently linked to >75 genes, both nuclear and mitochondrial genome).
- Targeted genetic study is indicated in only a few exceptions (e.g. maternally inherited Leigh syndrome due to MT-ATP6 mutations).
- Please discuss with metabolic specialist about the biochemistry and molecular diagnostics testing.

Management of a asymptomatic newborn but at risk of having potentially treatable IEM

- Ideally the diagnosis of treatable IEM should be made before a child becomes symptomatic and this may be possible through newborn screening for high risk newborns:
  - A previous child in the family has had an IEM.
  - Multiple unexplained early neonatal death.
  - Mother has HELLP/fatty liver disease during pregnancy (HELLP – Haemolytic Anaemia, Elevated Liver Enzymes, Low Platelets).
- Affected babies may need to be transferred in utero or soon after delivery to a centre with facilities to diagnose and manage IEM.
- Admit to nursery for observation.
- If potential diagnosis is known: screens for the specific condition, e.g. urea cycle disorders – monitor ammonia and plasma amino acid, MSUD – monitor plasma leucine (amino acids).
- If potential diagnosis is unknown: Collect dried blood spots for acylcarnitine profile, plasma amino acid and urine organic acid on 2nd or 3rd day after feeding, send it immediately and get result as soon as possible. Other essential laboratory monitoring: ammonia, VBG, blood glucose. Please discuss with metabolic specialist.
- Other essential laboratory monitoring: NH_3, VBG, blood glucose. Please discuss with metabolic specialist.
- To prevent decompensation before baby's status is known: provide enough calories (oral/IV), may need to restrict protein especially if index case presented very early (before 1 week). Protein-free formula should be given initially and small amount of protein (eg breast milk) is gradually introduced after 48 hours depending on baby's clinical status.
- If the index patient presented after the first week, the new baby should be given the minimum safe level of protein intake from birth (approximately 1.5 g/kg/day). Breast feeding should be allowed under these circumstances with top-up feeds of a low protein formula to minimise catabolism.
- Get the metabolic tests result as soon as possible to decide whether the baby is affected or not.

Chapter 95: Investigating Inborn errors metabolism (IEM) in a Child with Chronic Symptoms

Introduction

IEMs may cause variable and chronic disease or organ dysfunction in a child resulting in global developmental delay, epileptic encephalopathy, movement disorders, (cardio)-myopathy or liver disease. Thus it should be considered as an important differential diagnosis in these disorders.

The first priority is to diagnose treatable conditions. However, making diagnosis of non-treatable conditions is also important for prognostication, to help the child find support and services, genetic counselling and prevention, and to provide an end to the diagnostic quest.

PROBLEM 1: GLOBAL DEVELOPMENTAL DELAY (GDD)

- Defined as significant delay in two or more developmental domains.
- Investigation are done only after a thorough history and physical examination.
- If diagnosis is not apparent after the above, then investigations may be considered as listed below.
- Even in the absence of abnormalities on history or physical examination, basic screening investigations may identify aetiology in 10-20%.

Basic screening Investigations
Karyotyping
Serum creatine kinase
Thyroid function test
Serum uric acid
Blood Lactate
Blood ammonia
Metabolic screening using dried blood spots acylcarnitine profile [1]
Plasma Amino acids[2]
Urine organic acid[2]
Neuroimaging[3]
Fragile X screening (boy)

1. This minimal metabolic screen should be done in all patients even in the absence of risk factors.
2. This is particularly important if one or more of following risk factors: Consanguinity, family history of developmental delay, unexplained sib death, unexplained episodic illness
3. MRI is more sensitive than CT, with increased yield. It is not a mandatory study and has a higher diagnostic yield when indications exist (eg. macro/microcephaly; seizure; focal motor findings on neurologic examination such as hemiplegia, nystagmus, optic atrophy; and unusual facial features eg. hypo/hypertelorism)

- If history and physical examination reveals specific clinical signs and symptoms, special investigations may be required.
- Referral to a clinical geneticist or metabolic specialist is useful at this stage to help with test selection based on "pattern recognition".

Interpretation of basic screening investigations	
Test abnormality	**Possible causes of abnormal results**
Elevated Creatine kinase	Muscle injury Muscular dystrophy Fatty acid oxidation disorders
Elevated Lactate	Excessive screaming, tourniquet pressure Glycogen storage disorders Gluconeogenesis disorders Disorders of pyruvate metabolism Mitochondrial disorders *Is plasma alanine increased? If yes, suggest true elevation of lactate*
Elevated Ammonia	Sample contamination Sample delayed in transport/processing Specimen hemolysed Urea cycle disorders Liver dysfunction
Uric acids	An abnormality high or low result is significant: *High* Glycogen storage disorders Purine disorders *Low* Molybdenum cofactor deficiency

Metabolic/Genetic tests for specific clinical features	
Developmental delay and ...	Disorders and Tests
Severe hypotonia	*Peroxisomal disorders* Very long chain fatty acids (B) *Purine/pyrimidine disorders* Purine/pyrimidine analysis (U) *Neurotransmitters deficiencies* Neurotransmitters analysis (C) *Neuropathic organic acidemia* Organic acid analysis (U) *Pompe disease* Lysosomal enzyme *Prader Willi syndrome* Methylation PCR (B)
Neurological regression + organomegaly + skeletal abnormalities	*Mucopolysaccharidoses* Urine MPS (U) *Oligosaccharidoses* Oligosaccharides (U)
Neurological regression ± abnormal neuroimaging e.g. leukodystrophy	*Other lysosomal disorders* Lysosomal enzyme (B) *Mitochondrial disorders* Respiratory chain enzymes (M/S) *Biotinidase deficiency* Biotinidase assay *Peroxisomal disorders* Very long chain fatty acids (B) *Rett syndrome (girl)* MECP2 mutation study (B)
Abnormal hair	*Menkes disease* Copper (B), coeruloplasmin (B) *Argininosuccinic aciduria* Amino acid (U/B) *Trichothiodystrophy* Hair microscopy
B=blood, C=cerebrospinal fluid, U=urine	

Metabolic/Genetic tests for specific clinical features *(continued)*	
Developmental delay and ...	Disorders and Tests
Macrocephaly	*Glutaric aciduria type I* Organic acids (U) *Canavan disease* Organic acid (U) *Vanishing white matter disease* DNA test (B) *Megalencephalic leukodystrophy with subcortical cysts (MLC)* DNA test (B)
Dysmorphism	*Microdeletion syndromes* FISH, aCGH (B) *Peroxisomal disorders* Very long chain fatty acids (B) *Smith Lemli Opitz syndrome* Sterol analysis (B) *Congenital disorders of glycosylation* Transferrin isoform (B)
Dystonia	*Wilson disease* Copper (B), coeruloplasmin (B) *Neurotransmitters deficiencies* Phenylalanine loading test, Neurotransmitters analysis (C) *Neuroacanthocytosis* Peripheral blood film, DNA test (B)
B=blood, C=cerebrospinal fluid, U=urine, aCGH=array comparative genomic hybridization	

Metabolic/Genetic tests for specific clinical features *(continued)*	
Developmental delay and ...	Disorders and Tests
Epileptic encephalopathy	*Nonketotic hyperglycinemia* Glycine measurement (B and C) *Molybdenum cofactor deficiency/ sulphite oxidase deficiency* Sulphite (fresh urine) *Glucose transporter defect* Glucose (blood and CSF) *Pyridoxine dependency* Pyridoxine challenge, alpha aminoadipic semiadehyde (U) *PNPO deficiency* Amino acid (C), Organic acid (U) *Congenital serine deficiency* Amino acid (B and C) *Cerebral folate deficiency* CSF folate *Ring chromosome syndromes* Karyotype *Neuronal ceroid lipofuscinosis* Peripheral blood film, lysosomal enzyme (B) *Creatine biosynthesis disorders* MR spectroscopy *Adenylosuccinate lyase deficiency* Purine analysis (U) *Cerebral dysgenesis e.g. lissencephaly* MRI brain *Angelman syndrome* Methylation PCR
Spastic paraparesis	*Arginase deficiency* Amino acid (B) *Neuropathic organic academia* Organic acid (U) Sjogren Larsson syndrome Detailed eye examination
B=blood, C=cerebrospinal fluid, U=urine, aCGH=array comparative genomic hybridization	

PROBLEM 2: LIVER DISEASE

- A considerable number of IEM cause liver injury in infants and children, either as isolated liver disease or part of a multisystemic disease.
- Hepatic clinical response to IEM or acquired causes such as infection is indistinguishable.
- While IEM should be considered in any child with liver disease, it is essential to understand many pitfalls in interpreting the results.
- Liver failure can produce a variety of non-specific results: hypoglycaemia, ↑ammonia, ↑lactate, ↑plasma amino acids (tyrosine, phenylalanine, methionine), positive urine reducing substances (including galactose), an abnormal urine organic acid/blood acylcarnitine profiles.

Citrin deficiency

Recognized clinical phenotypes:

- Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD)
  - Characterized by transient neonatal cholestasis and variable hepatic dysfunction.
  - Diagnosis: elevated plasma citrulline, galactossemia (secondary).
  - Treatment: lactose-free and/or MCT-enriched formula.
- Failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD)
  - Characterized by post-NICCD growth retardation and abnormalities of serum lipid concentrations.
  - A strong preference for protein-rich and lipid-rich foods and an aversion to carbohydrate-rich foods.
  - Diagnosis: mutation testing (plasma citrulline is normal at this stage)
  - Treatment: diet rich in protein and lipids and low in carbohydrates, sodium pyruvate.
- Citrullinemia type II (CTLN2)
  - Characterized by childhood- to adult-onset, recurring episodes of hyperammonemia and associated neuropsychiatric symptoms.
  - Treatment: liver transplant.

IEM presenting mainly with Liver disease			
Leading manifestation patterns	Metabolic/genetic causes to be considered	Clues	Diagnostic tests
Acute/subacute hepatocellular necrosis (↑AST, ↑ALT jaundice, hypoglycaemia, ↑NH3, bleeding tendency, ↓albumin, ascitis)	*Neonatal/ early infantile*		
	*Neonatal haemochromatosis	↑↑↑ferritin	Buccal mucosa biopsy
	*Galactosemia	Positive urine reducing sugar, cataract	GALT assay
	*Long-chain fatty acid oxidation disorders	Associated (cardio)myopathy	Blood acylcarnitine
	*mtDNA depletion syndrome	Muscular hypotonia, multi-systemic disease, encephalopathy, nystagmus, ↑↑lactate (blood and CSF)	Liver biopsy for mtDNA depletion study
	*tyrosinemia type I	Severe coagulopathy, mild ↑AST/ALT, renal tubulopathy, ↓PO_4,↑↑↑AFP	Urine succinylacetone
	*Congenital disorders of glycosylation	Multi-system disease, protein-losing enteropathy	Transferrin isoform analysis
	Must rule out infections	Aetiology: TORCHES, parvovirus B19, echovirus, enteroviruses, HIV,EBV, HepB, Hep C	Serology, urine/stool viral culture

IEM presenting mainly with Liver disease *(continued)*			
Leading manifestation patterns	Metabolic/genetic causes to be considered	Clues	Diagnostic tests
Acute/subacute hepatocellular necrosis (↑AST, ↑ALT jaundice, hypoglycaemia, ↑NH3, bleeding tendency, ↓albumin, ascitis)	*Late infancy to childhood*		
	* above causes		
	*α-1-antitrypsin deficiency	Commonly presents as cholestatic jaundice, gradually subsides before 6 months. Some develop cirrhosis later. Less commonly may present as liver failure in early infancy	α-1-antitrypsin
	*Fructosemia	Symptoms after fructose intake, renal tubulopathy	
	*Wilson disease	KF ring, neurological symptoms, haemolysis	Serum/urine copper, coeruloplasmin
	Must rule out chronic viral hepatitis and autoimmune diseases		

IEM presenting mainly with Liver disease *(continued)*			
Leading manifestation patterns	Metabolic/genetic causes to be considered	Clues	Diagnostic tests
Cholestastic liver disease (conjugated bilirubin >15%, acholic stool, yellow brown urine, pruritus, ↑↑ALP) GGT may be low, normal or high - useful to differentiate various causes	*Neonatal*		
	*Alagille syndrome	Eye/cardiac/vertebral anomalies	DNA study
	*Inborn error bile acid synthesis	↓ or normal GGT	Liver biopsy,DNA study
	*Progressive familial intra-hepatic cholestasis (PFIC)	↓or normal GGT except PFIC type III	Liver biopsy,DNA study
	* Citrin deficiency	↑plasma citrulline, ↑galactose, +ve urine reducing sugar	Plasma Amino acids, DNA study
	* Niemann Pick C	Hypotonia, opthalmoplegia, hepatospleno-megaly	Bone marrow examination
	* Peroxisomal disorders	Severe hypotonia, cataract, dysmorphic, knee calcification	Plasma VLCFA
	*α-1-antitrypsin deficiency	see above	α-1-antitrypsin
	Must exclude extrahepatic biliary disease		

IEM presenting mainly with Liver disease *(continued)*			
Leading manifestation patterns	Metabolic/genetic causes to be considered	Clues	Diagnostic tests
Cholestastic liver disease (conjugated bilirubin >15%, acholic stool, yellow brown urine, pruritus, ↑↑ALP) GGT may be low, normal or high - useful to differentiate various causes	*Late infancy to childhood*		
	* above causes		
	* Rotor syndrome	Normal liver function	Diagnosis by exclusion
	* Dublin-Johnson	Normal liver function	Diagnosis by exclusion
Cirrhosis (end stage of chronic hepato-cellular disease) chronic jaundice, clubbing, spider angiomatoma, ascites, portal HPT	*Wilson disease	KF ring, neurological symptoms, haemolysis	Serum/urine copper, coeruloplasmin
	*Haemochromatosis	↑↑ferritin, Cardiomyopathy, hyperpigmentation	Liver biopsy, DNA study
	*GSD IV	Cirrhosis around 1 year, splenomegaly, muscular hypotonia/atrophy, cardiomyopathy, fatal < 4year	Liver biopsy
	* α-1-antitrypsin	See above	α-1-antitrypsin
	Must rule out: chronic viral hepatitis, autoimmune diseases, vascular diseases, biliary malformation etc		

PROBLEM 3: CARDIOMYOPATHY

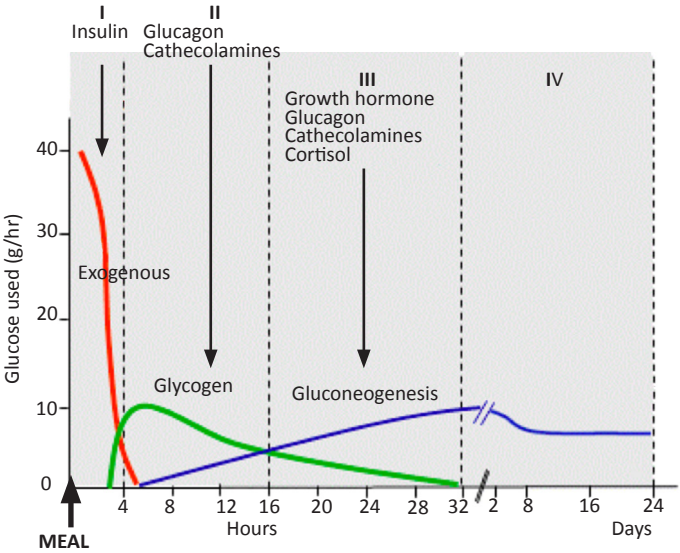
- Cardiomyopathy can be part of multi-systemic manifestation of many IEMs.
- In a child with an apparently isolated cardiomyopathy, must actively screen for subtle/additional extra-cardiac involvement included studying renal and liver function as well as ophthalmological and neurological examinations.
- Cardiomyopathy may be part of clinical features of some genetic syndromes especially Noonan syndrome, Costello syndrome, Cardiofaciocutaneous syndrome.
- Sarcomeric protein mutations are responsible for a significant cases of familial cardiomyopathy.

IEM that may present predominatly as Cardiomyopathy (CMP)		
Disorder	Cardiac finding	Clues
Primary carnitine deficiency	Dilated CMP	Low serum free carnitine
Long chain fatty acid oxidation disorders	Hypertrophic/ Dilated CMP	Myopathy, retinopathy, hypoketotic hypoglycaemia, abnormal acylcarnitne profile
Mitochondrial disorders	Hypertrophic/ Dilated CMP	Associated with multi-system abnormalities, ↑↑lactate *Kearns– Sayre syndrome:* Chronic progressive external ophthalmoplegia ,complete heart block
Barth syndrome	Dilated CMP	Neutropenia, myopathy, abnormal urine organic acid (↑3 methylglutaconic aciduria)
Infantile pompe disease	Hypertrophic CMP	Short PR, very large QRS, ↑CK, ↑AST, ↑ALT, deficient alpha acid glucosidase enzyme activity (could be done using dried blood spots)
Glycogen Storage Disease type III	Hypertrophic CMP	Hepatomegaly, ↑CK, ↑AST, ↑ALT, ↑postprandial lactate, ↑uric acid, ↑TG

IEMs presenting as mainly a Haematological disorder	
Clinical problem	Metabolic/Genetic causes and Clues/tests
Megaloblastic anemia	*Defective transportation or metabolism of B12* Methylmalonic aciduria, ↑homocysteine, low/normal serum B12. *Orotic aciduria* ↑↑ urinary orotate. *Disorders of folate metabolism* ↓serum folate.
Global marrow failure	*Pearson syndrome* Exocrine Pancreatic dysfunction, lactate, renal tubulopathy. *Fanconi anemia* Cafe au lait spots, hypoplastic thumbs, neurological abnormalities, increased chromosomal breakage. *Dyskeratosis congenita* Abnormal skin pigmentation, leucoplakia and nail dystrophy; premature hair loss and/or greying.

Introduction

- Definition of hypoglycemia: Blood glucose **<2.6 mmol/L (45 mg/dl) at all ages.**
- In reality, hypoglycemia is difficult to define at a specific blood glucose concentration.
- Neurogenic and neuroglycopenic symptoms usually occur when the plasma glucose concentration decreases to 2.8-3.9 mmol/L
- Therefore, treatment targets are aimed at avoiding activation of neuroendocrine responses by maintaining plasma glucose within the normal range of 3.9-5.6 mmol/L.



Phase	I: Post Prandial	II: Short to Middle Fast	III: Long Fast	IV: Very Long Fast
Glucose source	Exogenous	Glycogen Gluconeo-genesis	Gluconeo-genesis (hepatic) Glycogen	Gluconeo-genesis (hepatic and renal)
Counsuming tissues	All	All but liver, muscle	-	Brain, blood cell, medullary kidney
Greatest brain nutrient	Glucose	Glucose	Glucose	Ketone bodies Glucose

Clinical classification of hypoglycemia

- According to its timing:
  - Only postprandial.
  - Only at fast.
  - Permanent/hectic.
- According to liver findings:
  - With prominent hepatomegaly.
  - Without prominent hepatomegaly.
- According to lactic acid:
  - With lactic acidosis (lactate > 6mmol/l).
  - With hyperlactatemia (lactate 2.5–6mmol/l).
  - With normal lactate (lactate < 2.5 mmol/l).
- According to ketosis:
  - Hyper/normoketotic.
  - Hypoketotic/nonketotic.

Laboratory tests during symptomatic hypoglycemia

- Adequate laboratory tests must be done to identify the cause, or else the diagnosis may be missed.
- Ensure samples are taken before correcting the hypoglycemia.

Laboratory tests during symptomatic hypoglycemia	
Essential Tests	Other tests
Ketone (serum or urine) Acylcarnitine (dry blood spots on Guthrie card) Blood lactate VBG Blood ammonia Urine organic acids Free fatty acids (if available) Serum insulin Serum cortisol Serum growth hormone	Serum cholesterol/triglyceride Serum uric acid Liver function Creatine kinase Urine reducing sugar Urine tetraglucoside Plasma amino acid Consider toxicology tests (C-peptide) Fasting tolerance test (only by metabolic specialist/ endocrinologist) Other special tests e.g. fatty oxidation study in cultured fibroblasts

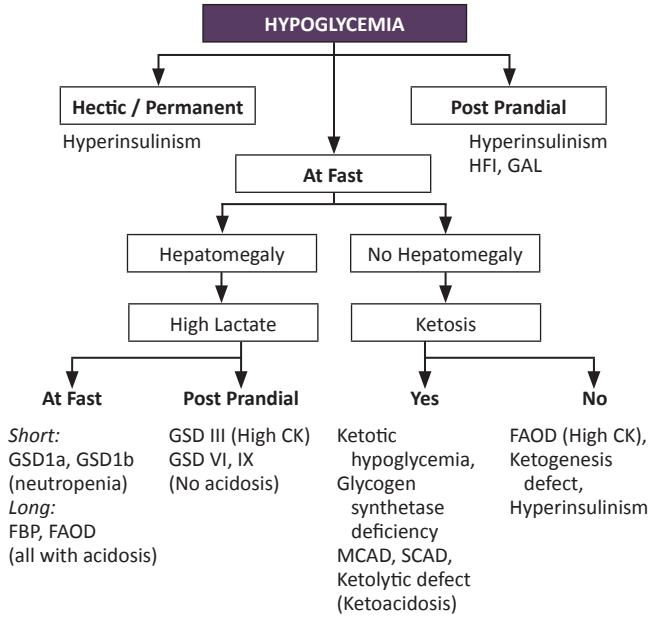
DETERMINE THE CAUSE

This can be approached using the following algorithm which is based first on 2 major clinical findings :

(1) Timing of hypoglycemia and

(2) Permanent hepatomegaly.

Then looking carefully at the metabolic profile over the course of the day, checking plasma glucose, lactate, and ketones before and after meals and ketones in urines will allow one to reach a diagnosis in almost all cases..



Abbreviations:

HFI, Hereditary fructose intolerance; GAL, Galactosemia; GSD, Glycogen storage disease; FBP, Fructose-1,6-bisphosphatase deficiency; FAOD, Fatty acid oxidation disorders; MCAD, Medium chain acyl dehydrogenase deficiency; SCAD, Short chain acyl dehydrogenase deficiency.

GLYCOGEN STORAGE DISEASE

- *Hepatic type:* Type Ia, Ib, III, IV, VI, IX.
- *Clinical presentation:* Recurrent hypoglycemia, hepatomegaly, failure to thrive, "doll face", bleeding tendency (GSD I), hypertrophic cardiomyopathy (GSD III).
- *Laboratory findings:* ↑lactate, ↑uric acid, ↑triglycerides, (↑) transaminases, ↑CK (GSD III), ↑ urine tetraglucosides.
- *Glucose challenge test:* Type Ia, Ib: ↓in lactate; Type III, VI, IX: ↑in lactate.
- *Diagnosis:* enzyme studies (liver), mutation analysis.
- *Treatment:*
  - Avoid hypoglycemia by means of continuous carbohydrate intake.
  - Frequent meals (every 2-3 hours): Slowly resorbed carbohydrates (glucose polymer/maltodextrin, starch), avoid lactose.
  - Nights: Continous intake of glycose polymer/maltodextrin via nasogastric tube, uncooked cornstarch in children > 1 year age.
- *Complications:* liver tumours, osteoporosis, cardiomyopathy (GSD III).

HYPERINSULINAEMIC HYPOGLYCAEMIA

Diagnostic criteria

- Glucose infusion rate at 8-10 mg/kg/min to maintain normoglycaemia.
- Detectable serum insulin (+/- C-peptide) when blood glucose < 3mmol/l.
- Low or undetectable serum fatty acids.
- Low or undetectable serum ketone bodies.
- Sr ammonia may be high (Hyperinsulinism/hyperammonaemia syndrome).
- Glycaemic response to glucagon at time of hypoglycaemia.
- Absence of ketonuria.

Causes

- Congenital hyperinsulinism (CHI) (also called Familial Hyperinsulinism (FHI)) occurs due to mutations in key genes which play a role in insulin secretion from pancreatic B-cells.
  - Commonly presents during the neonatal period, sometimes in infancy or childhood.
  - Mutations have been identified in nine different genes.
  - The most severe forms are due to mutations in the *ABCC8* and *KCNJ11* genes (both AR and AD)
- Secondary to (usually transient, may last few days to weeks)
  - Maternal diabetes mellitus (gestational and insulin dependent).
  - IUGR.
  - Perinatal asphyxia.
  - Rhesus isoimmunisation.
- Metabolic conditions
- Congenital disorders of glycosylation (CDG), Tyrosinaemia type I.
- Associated with Syndromes
  - Beckwith-Wiedemann, Soto, Kabuki, Usher, Timothy, Costello, Trisomy 13, Mosaic Turner, Central Hypoventilation Syndrome.
- Other causes: Dumping syndrome, Insulinoma (sporadic or associated with MEN Type 1), Insulin gene receptor mutations, Factitious HH (Munchausen-by-proxy).

Treatment for Hyperinsulinism
Medication
Diazoxide *Dose:* Oral, 5–20mg/kg/day divided into 3 doses *Side Effects* • Common: fluid retention, hypertrichosis. • Others: hyperuricaemia, eosinophilia, leukopenia. *Practical Management* • Use in conjunction with thiazide diuretic especially in neonates who are at risk of fluid overload and heart failureRestrict fluid intake, especially on the higher doses. • Carefully monitor fluid balance.
Hydrochlorothiazide *Dose:* Oral, 2-4mg/kg/day divided into 2 doses (in conjunction with diazoxide) *Side Effects* • Hyponatraemia, hypokalaemia *Practical Management* • Monitor serum electrolytes
Nifedipine *Dose:* Oral, 0.25-2.5mg/kg/day divided into three doses *Side Effects* • Hypotension *Practical Management* • Monitor blood pressure. • Inhibits insulin secretion by inactivating the voltage-gated calcium channels. Some success reported but majority of patients fail to show any response.
Glucagon (± Octreotide) *Dose:* • Glucagon infusion 5-10 ug/kg/hr, high doses > 20 ug/kg/hr may cause paradoxical insulin secretion and rebound hypoglycemia. • IM glucagon 0.5-1mg (or 0.03mg/kg) may be used for emergency situations eg symptomatic hypoglycaemia with no IV access. *Side Effects* • Nausea, vomiting, skin rashes. • Paradoxical hypoglycaemia in high doses. *Practical Management* • Avoid high doses. • Watch for rebound hypoglycaemia when used as an emergency treatment for hypoglycaemia.

Treatment for Hyperinsulinism

Medication

Octreotide (± Glucagon)

Dose: SC/IV 5–35µg/kg/day continuous infusion
or 6–8-hourly SC injections

Side Effects

- Acute: tachyphylaxis, nausea, abdominal distension, necrotising enterocolitis, drug-induced hepatitis, steatorrhoea, long QT syndrome.
- Long term : decreased intestinal motility, bile sludge, cholelithiasis, suppresion of growth hormone, TSH, ACTH

Practical Management

- Use with caution in infants at risk of necrotising
- enterocolitis, (reduces blood flow to the splanchnic circulation).
- Follow-up with serial ultrasound scans of the biliary tree, if on long-term treatment with Octreotide.
- Monitor long-term growth.

Incidence of Down syndrome	
Maternal Age-Specific Risk for Trisomy 21 at Livebirth	
Overall Incidence: 1 in 800-1000 newborns	
Age (years)	**Incidence**
20	1 in1500
30	1 in 900
35	1 in 350
40	1 in 100
41	1 in 70
42	1 in 55
43	1 in 40
44	1 in 30
45	1 in 25
Source Hecht and Hook '94	

Medical problems

Newborn

- Cardiac defects (50%): AVSD [most common], VSD, ASD, TOF or PDA.
- Gastrointestinal (12%): duodenal atresia [commonest], pyloric stenosis, anorectal malformation, tracheo-oesophageal fistula, and Hirshsprung disease.
- Vision: congenital cataracts (3%), glaucoma.
- Hypotonia and joint laxity.
- Feeding problems. Usually resolves after a few weeks.
- Congenital hypothyroidism (1%).
- Congenital dislocation of the hips.

Infancy and Childhood

- Delayed developmental milestones.
- Mild to severe intellectual impairment (IQ 30-70).
- Autistic spectrum disorder and attention deficit hyperactivity disorder
- Maladaptive behaviour such as using social distraction to avoid a given task and stubbornness.
- Seizure disorder (6%).
- Recurrent respiratory infections.
- Hearing loss (>60%) due to secretory otitis media, sensorineural deafness, or both.
- Visual Impairment – squint (50%), cataract (3%), nystagmus (35%), glaucoma, refractive errors (70%) .
- Sleep related upper airway obstruction. Often multifactorial.
- Leukaemia (relative risk:15 to 20 times). Incidence 1%.

- Atlantoaxial instability. Symptoms of spinal cord compression include neck pain, change in gait, unusual posturing of the head and neck (torticollis), loss of upper body strength, abnormal neurological reflexes, and change in bowel/bladder functioning. *(see below)*
- Hypothyroidism (10%). Prevalence increases with age.
- Short stature – congenital heart disease, sleep related upper airway obstruction, coeliac disease, nutritional inadequacy due to feeding problems and thyroid. Hormone deficiency may contribute to this.
- Over/underweight.

Adolescence and Adulthood

- Puberty:
  - In Girls menarche is only slightly delayed. Fertility presumed.
  - Boys are usually infertile due to low testosterone levels.
- Obstructive sleep apnoea is common.
- May have internalizing symptoms such as social withdrawal and depression.
- Increased risk of dementia /Alzheimer disease in adult life.
- Shorter life expectancy.

Management

- Communicating the diagnosis is preferably handled in private by a senior medical officer or specialist who is familiar with the natural history, genetic aspect and management of Down syndrome.
- Careful examination to look for associated complications.
- Investigations:
  - Echocardiogram by 2 weeks (if clinical examination or ECG were abnormal) or 6 weeks.
  - Chromosomal analysis.
  - T4 /TSH at birth or by 1-2 weeks of life.
- Early intervention programme should begin at diagnosis if health conditions permit.
- Assess strength & needs of family. Contact with local parent support group should be provided *(Refer list of websites below).*
- Health surveillance & monitoring: *see table below*

Atlantoaxial instability

- Seen in X rays in 14% of patients; symptomatic in 1-2%.
- Small risk for major neurological damage but cervical spine X rays in children have no predictive validity for subsequent acute dislocation/ subluxation at the atlantoaxial joint.
- Children with Down syndrome should not be barred from taking part in sporting activities.
- Appropriate care of the neck while under general anaesthesia or after road traffic accident is advisable.

Karyotyping in Down syndrome	
Non-disjunction trisomy 21	95%
Robertsonian Translocation	3%
Mosaicism	2%
Recurrence Risk by Karyotype	
Nondisjunction Trisomy	
47(XX or XY) + 21	1% or age related risk, whichever is higher
Translocation	
Both parents normal	low; <1%
Carrier Mother	10%
Carrier Father	2.5%
Either parent t(21q;21q)	100%
Mosaics	< 1%

Useful web resources

- The Down Syndrome Medical Interest Group (UK)
  www.dsmig.org.uk
- Down Syndrome: Health Issues
  www.ds-health.com
- Growth charts for children with Down Syndrome
  www.growthcharts.com
- Educational issues
  www.downsed.org
- Kiwanis Down Syndrome Foundation
  http://www.kdsf.org.my/
- Educational & support centre.
  http://www.malaysiancare.org/pwd_list
- Persatuan Sindrom Down Malaysia
  http://downsyndromemalaysia.com/
- Jabatan Pendidikan Khas
  http://www.moe.gov.my/index.php/my/pendidikan-khas
- Jabatan Kebajikan Malaysia.
  http://www.jkm.gov.my/

Recommendations for Medical Surveillance for children with Down Syndrome						
	Birth - 6 weeks	6 - 10 months	12 months	18 mths - 2½ yrs	3 - 3½ years	4 - 4½ years
Thyroid tests[1]	T4, TSH		T4, TSH, antibodies		T4, TSH, antibodies	
Growth monitoring [2]	Length, weight and head circumference checked regularly and plotted on Down's syndrome growth charts.			Length and weight should be checked at least annually and plotted on Down's syndrome growth charts.		
Eye examination	Visual behaviour. Check for congenital cataract	Visual behaviour. Check for congenital cataract	Visual behaviour. Check for congenital cataract	Orthoptic, refraction, ophthalmic examination[3]		Visual acuity, refraction, ophthalmic examination[3]
Hearing check	Neonatal screening	Full audiological review (hearing, impedance, otoscopy) by 6-10 months and then annually.				
Cardiology, Other advice	Echocardiogram 0-6 weeks			Dental assessment		

Age 5 to 19 years	
Paediatric review	Annually
Hearing	2 yearly audiological review (as above)
Vision / Orthoptic check	2 yearly
Thyroid blood tests	At age 5 years, then 2 yearly
School performance	Check performance and placement
Sexuality and employment	To discuss when appropriate, in adolescence.

Note: The above table are suggested ages. Check at any other time if parental or other concerns. Perform developmental assessment during each visit.

Footnote:
1, Asymptomatic patients with mildly raised TSH (<10mu/l) but normal T4 does not need treatment but test more frequently for uncompensated hypothyroidism.
2, Down syndrome centile charts at www.growthcharts.com. Consider weight for length charts of typically developing children for weight assessment. If BMI > 98th centile or underweigh, refer for nutritional assessment and guidance. Re-check thyroid function if accelerated weight gain.
3, Performed by optometrist/ophthalmologist.

Adapted from Down Syndrome Medical Interest Group (DSMIG) guidelines

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Chapter 98: Appendicitis

Appendicitis is the most common surgical condition of the abdomen in children over the age of 4 years and yet can be a challenge to diagnose and manage. Although diagnosis and treatment have improved over the years, it continues to cause considerable morbidity and even mortality in Malaysia. The deaths appear to be due to delay and difficulty in diagnosis, inadequate perioperative fluid replacement and sepsis.

Clinical Features

- *Abdominal pain* – Lower abdominal pain is an early and almost invariable feature. Usually the pain starts in the epigastrium or periumbilical region before localising to the lower abdomen or the right iliac fossa. However the younger child may not be able to localise the pain. If there is free pus, the pain is generalised.
- *Nausea and vomiting* occurs in about 90% of children and is an early symptom. Most children have a loss of appetite. A hungry child rarely has appendicitis.
- *Diarrhoea* is more common in the younger age group causing confusion with gastroenteritis. It can also be due to pelvic appendicitis or collection of pus within the pelvis.
- *Dysuria and frequency* are also commonly present in the child with pelvic appendicitis or perforated appendicitis.

Physical Findings

- *General* – the child is usually *quiet* and may be dehydrated.
- *Dehydration* must be actively sought for especially in the obese child and the child with perforated appendicitis. A history of vomiting and diarrhoea, tachycardia, poor urine output and poor perfusion of the peripheries are indicators of dehydration.
- *Tenderness* on palpation or percussion is essential for the diagnosis. It may be localised to the right iliac fossa or be generalised. The tenderness may also be mild initially and difficult to elicit in the obese child or if the appendix is retrocaecal. Eliciting rebound tenderness is usually not required to make the diagnosis and can cause unnecessary discomfort.
- *Guarding* signifies peritonitis but may be subtle especially if the child is toxic, obese and very dehydrated.
- Rectal examination is only required if other diagnosis are suspected e.g. ovarian or adnexal pathology.

Investigations

- *Full blood count* – The total white blood cell count may be elevated but a normal count does not exclude appendicitis.
- *Blood Urea and Serum Electrolytes* – The sodium level may be apparently normal if the child is dehydrated.
- *Serum Amylase* – If pancreatitis cannot be ruled out as the cause of the abdominal pain.
- *Ultrasound* increases accuracy of diagnosis and can rule out other causes of pain but is dependent on the operator, patient habitus and cooperation.
- *CT scan with IV contrast* - high degree of diagnostic accuracy but is associated with high radiation risks and costs.

- Therefore in our setting, the recommendation is that the child is assessed by a surgeon or a paediatrician preoperatively before further imaging.
- If the diagnosis cannot be made with certainty or the child is very ill and there are no facilities or personnel for intensive care, the child must be referred to the nearest paediatric surgical unit.

Complications

- *Perforation* can occur within 36 hours of the onset of symptoms. Perforation rate increases with the duration of symptoms and delayed presentation is an important factor in determining perforation rate.

  Perforation rate: Adolescent age group - 30-40%
  Younger child - up to about 70%.

  If unsure of the diagnosis, active observation with adequate fluid resuscitation can be done. Antibiotics are to be started once the diagnosis is made. This has not been shown to increase the morbidity or mortality. Delaying surgery till daytime, while resuscitating and giving antibiotics also does not significantly affect the perforation rate, complications or operating time.
- *Appendicular abscess*, mass and perforation may be treated with IV antibiotics to settle the inflammatory and infectious process. If the child settles, this can then be followed by an interval appendicectomy, done within 6 weeks of the original disease, as the rate of recurrent appendicitis is between 10-46%.

Management

- Children with appendicitis (suspected or confirmed) should be reviewed by a specialist.
- Dehydration should be actively looked for. The heart rate, blood pressure, perfusion and the urine output should be closely monitored. The blood pressure is usually maintained in the children until they have decompensated.
- Rehydration must be aggressive, using 20 mls/kg aliquots of normal saline or Hartmann's solution (Ringer's lactate) given fast over ½ - 2 hours. The child should be reviewed after each bolus and the rehydration continued until the child's heart rate, perfusion and urine output and electrolytes are within normal limits. Maintenance fluid – ½ saline + 5% D/W + KCl.
- Antibiotics should be started soon after the diagnosis is made. While the preliminary literature for non-operative management of UNCOMPLICATED appendicitis is increasing, patient selection criteria are still unclear especially if the diagnosis cannot be made with certainty on ultrasound.
- However, operation is recommended in the child with perforated appendicitis.
- Inotropes may need to be started early if the child is in severe sepsis.
- Operation - There is no rush to take the child to the operating theatre. It is recommended that appendicectomies not be performed after 11 pm, especially in the sick child. However, the time should be utilised to continue the resuscitation and antibiotics with close monitoring of the child.
- At surgery, if there is free pus in the peritoneal cavity, a thorough peritoneal washout with copious amount of normal saline is done after the appendicectomy. No drains are required and the skin can be closed with a subcuticular suture.

- Vomiting in the child is NOT normal.
- Bilious vomiting is ALWAYS significant until otherwise proven.

When is the vomiting significant?

- Vomiting from Day 1 of life.
- Vomit contains blood (red/black).
- Bilious vomiting: green, not yellow. Bowel obstruction must be ruled out.
- Faeculent vomiting.
- Projectile vomiting.
- Baby is unwell - dehydrated/septic.
- Associated failure to thrive.
- Associated diarrhoea/constipation.
- Associated abdominal distension.

Causes of Persistent Vomiting
Neonates
General • Sepsis • Meningitis • Hydrocephalus/ neurological disorder • Urinary tract infection • Motility disorder • Inborn errors of metabolism • Congential adrenal hyperplasia • Poor feeding techniques *Oesophagus* • Atresia • Webs • Swallowing disorders *Stomach* • Gastro-oesophageal reflux • Duodenal atresia/ stenosis *Small intestine* • Malrotation • Stenosis/ atresia • Adhesions/ Bands • Meconium peritonitis/ ileus • Enterocolitis • Incarcerated hernia *Colon/ rectum* • Stenosis/ atresia • Hirschprung's disease • Anorectal malformation

Causes of Persistent Vomiting *(continued)*	
Infants	**Older Child**
General • Sepsis • Meningitis • Hydrocephalus/ neurological disorder • Urinary tract infection • Tumours eg neuroblastoma • Metabolic disorders *Oesophagus* • Oesophageal stricture *Stomach* • Gastro-oesophageal reflux • Pyloric stenosis *Small intestine* • Malrotation/ volvulus • Adhesions • Meckel's diverticulum • Incarcerated hernias • Appendix- rare *Colon/rectum* • Intussusception • Hirschprung's disease • Enterocolitis/gastroenteritis	*General* • Sepsis • Neurological disorder • Tumours • Metabolic disease *Oesophagus* • Oesophageal stricture *Stomach* • Gastro-oesophageal stricture/ reflux • Peptic ulcer disease • Gastric volvulus *Small intestine* • Malrotation/ volvulus • Adhesions • Meckel's diverticulum • Appendicitis/ peritonitis *Large intestine/colon* • Intussusception • Foreign body • Worm infestation • Constipation: habitual with faecal impaction

GASTRO-OESOPHAGEAL REFLUX

- More common in infancy than generally recognized.
- Majority (>90%) resolve spontaneously within the first year of life.
- Small percentage develop complications.
- Please refer **Chapter on Gastroesophageal Reflux Disease (GERD)**

PYLORIC STENOSIS

- Cause- unknown; Strong familial pattern.
- Usually first born baby boy; usual presentation at 2nd to 8th week of life.

Clinical Features

- Vomiting -Frequent, forceful, non-bilious with/without haematemesis.
- The child is keen to feed but unable to keep the feed down.
- Failure to thrive.
- Dehydration.
- Constipation.
- Seizures.

Physical Examination

- Dehydrated

  A test feed can be given with the child in the mother's left arm and visible gastric peristalsis (left to right) observed for. The doctor's left hand then palpates beneath the liver feeling for an "olive sized pyloric tumour" palpable against the vertebra.

Investigations

Investigation to confirm diagnosis are usually unnecessary.

- Ultrasound - 100% accuracy. Pyloric muscle thickness > 3 mm, and length > 15mm.
- Barium meal - string sign and shouldering of pyloric muscle

However, pre-operative assessment is very important:

- Metabolic alkalosis is the first abnormality
- Hypochloraemia < 100 mmol/l
- Hyponatraemia < 130 mmol/l
- Hypokalaemia < 3.5 mmol/l
- Hypocalcaemia < 2.0 mmol/l
- Jaundice.
- Hypoglycemia.
- Paradoxical aciduria - a late sign.

Therapy

Rehydration

- Slow (rapid rehydration will cause cerebral oedema) unless the child is in shock
- Fluid
  - 0.45% saline + 10%D/W (+ 5-10 mmol KCl/kg/day once the child has passed urine).
  - Rate (mls/hr) = [Maintenance (150 ml/kg body weight) + 5-10 % dehydration {% dehydration x body weight (kg) x 10}] /24 hours.
  - Replace gastric losses with normal saline.
  - *Do NOT give Hartmann's solution (the lactate will be converted to* bicarbonate which worsens the alkalosis)
- Insert a nasogastric tube – 4 hourly aspiration with free flow.
- Comfort glucose feeds maybe given during the rehydration period but the nasogastric tube needs to be left on free drainage.
- Pyloromyotomy after the electrolytes have been corrected.

MALROTATION OF THE MIDGUT

A term that embraces a number of different types of abnormal rotation that takes place when the bowel returns into the intra-abdominal cavity in utero. This is important because of the propensity for volvulus of the midgut around the superior mesenteric artery causing vascular compromise of most of the small bowel and colon.

Types of Clinical Presentation

Acute Volvulus

- Sudden onset of bilious/ non-bilious vomiting.
- Abdominal distention with/without a mass (late sign).
- Bleeding per rectum (late sign).
- Ill baby with distended tender abdomen.

Chronic Volvulus

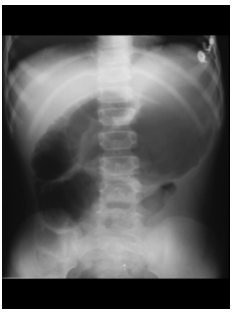
- Caused by intermittent or partial volvulus resulting in lymphatic and venous obstruction.
- Recurrent colicky abdominal pain.
- Vomiting (usually bilious).
- Malabsorption.
- Failure to thrive.

Internal Herniation

- Due to lack of fixation of the colon.
- Results in entrapment of bowel by the mesentery of colon.
- Recurrent/intermittent intestinal obstruction.

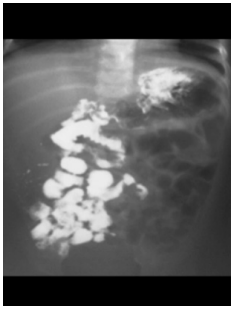
Investigations

- Plain Abdominal X-ray
  - All the small bowel is to the right side.
  - Dilated stomach +/- duodenum with rest of abdomen being gasless.



- Ultrasound - looks at the relationship of the Superior mesenteric artery and vein and a whirlpool sign to indicate volvulus

- Upper Gastrointestinal contrast study with follow through
  - Duodeno-jejunal flexure to the right of the vertebra.
  - Duodenal obstruction, often with spiral or corkscrew appearance of barium flow.
  - Presence of small bowel mainly on the right side.



Treatment

Pre-operative Management

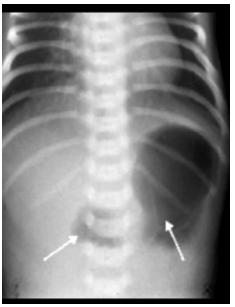
- Rapid rehydration and correction of electrolytes
- Fluids
  - Maintenance – 0.45% saline + 5% (or 10% if neonate) Dextrose Water with added KCl.
  - Rehydration – Normal saline or Hartmann's Solution (Ringer's Lactate)
- Orogastric or nasogastric tube with 4 hourly aspiration and free drainage.
- Antibiotics (+ inotropes) if septic.

Operative

- Emergency surgery is required if there is volvulus
- De-rotation of volvulus.
- ± Resection with an aim to preserve maximum bowel length (consider a second look operation if most of the bowel appears of doubtful viability).
- Division of Ladd's bands to widen the base of the mesentery to prevent further volvulus.
- Appendicectomy.

Duodenal Stenosis/ Atresia

- Antenatal diagnosis associated with polyhydramnios
- Usually at the second part of the duodenum.
- Presents with bilious/non-bilious vomiting.
- Can be associated with Down's Syndrome and gastro-oesophageal reflux.
- Abdominal X-Ray: double - bubble with or without gas distally.



Management

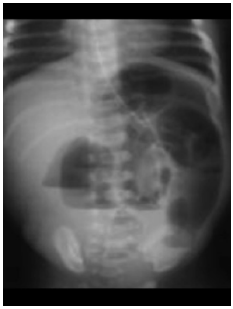
- Slow rehydration with correction of electrolytes and nutritional deficiencies.
- Decompression of the stomach with an orogastric tube
- Rule out associated anomalies
- Duodeno-duodenostomy as soon as stabilized.
- Postoperatively, the bowel motility may be slow to recover.

Ileal /Jejunal Atresia

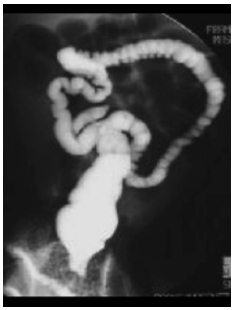
- Atresia anywhere along the small bowel. Can be multiple.
- Presents usually with abdominal distension and vomiting within the first 48 hours of life (non-bilious initially and then bilious).
- Usually pass white or pale green stools, not normal meconium.
- Abdominal Xray - multiple dilated loops of bowel
- Differential diagnoses – Long segment Hirschsprung's disease, Meconium ileus.
- Contrast enema - demonstrates a microcolon differentiating it from a Hirschsprung's disease and Meconium ileus

Management

- Evaluation for associated anormalities.
- Insertion of an orogastric tube – 4 hourly aspiration and free drainage.
- Slow rehydration with correction of electrolyte abnomalities and nutrition.
- Laparotomy and resection of the dilated bowels with primary anastomosis, preserving as much bowel length as possible.
- Parenteral nutrition as the motility of the bowel can be abnormal and takes a long time to recover.
- AXR – dilated loops of small bowel.



- Contrast enema – microcolon



- Intussusception is the invagination of one portion of intestine into another with 80% involving the ileocaecal junction. The mortality and morbidity from intussusception in Malaysia is still high due to delay in diagnosis, inadequate IV fluid therapy and surgical complications.
- It is the most common form of intestinal obstruction in infancy and early childhood with the peak age group being 2 months to 4 years. Majority of the children in this age group have no pathological lead point. Lymphoid hyperplasia has been implicated. Children may also have a preceding viral illness.

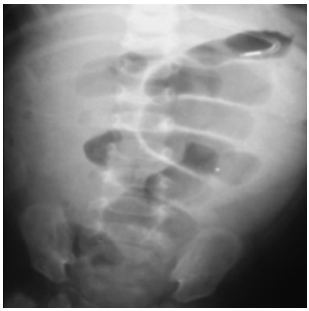
Common lead points (usually in the age group outside the above):
- Structural – Meckel's diverticulum, duplication cysts.
- Neoplastic – Lymphoma, polyps, vascular malformations.
- Vascular – Henoch-Schonlein purpura, leukaemia.
- Miscellaneous – Foreign body.

Clinical Features
- Previously healthy or preceding viral illness.
- Pain - Sudden onset, severe intermittent cramping pain lasting seconds to minutes.
- During the time in-between attacks lasting between 5 to 30 minutes, the child may be well or quiet.
- Vomiting – Early reflex vomiting consists of undigested food but if the child presents late, the vomiting is bilious due to obstruction.
- Stools- Initially normal, then become dark red and mucoid ("redcurrant jelly").
- Note that small bowel intussusception may have an atypical presentation.

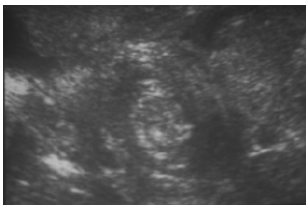
Physical Findings
- Well- looking/drowsy/dehydrated/fitting (due to hyponatremia) depending on the stage of presentation.
- Abdominal mass (sausage shaped but may be difficult to palpate in a distended abdomen).
- Abdominal distension is a late sign.

Investigations

- Plain abdominal X-ray – Absence of caecal gas, paucity of bowel gas on the right side with loss of visualization of the lower border of the liver, dilated small bowel loops (see figure below).



- Ultrasound – Useful diagnostic tool. Target sign (see figure below) on transverse section and pseudo-kidney sign on longitudinal section. May also help to identify lead points if present.



- Barium enema – for diagnosis and reduction if required.

Management

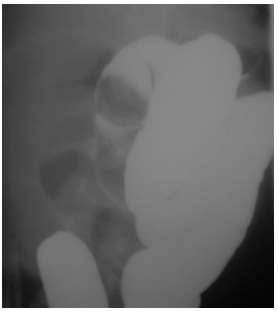
Resuscitation

- Aggressive rapid rehydration with boluses of 20 mls/kg of Normal saline/Hartmann's solution (Ringer's lactate) till parameters are normal.
- Do NOT proceed to hydrostatic reduction or surgery till fully resuscitated.
- Close monitoring of vital signs and urine output.
- Antibiotics and inotropes may be required if the child is septic.

Non-operative reduction

- Should be attempted in most patients, if there are trained radiologists and surgeons available, successful reduction rate is about 80-90%.
- Types
  - Hydrostatic reduction with saline under ultrasound guidance is now our preferred choice.
  - Air/Oxygen reduction.
  - Barium enema reduction.

  (see figure: "claw sign" of intussusceptum is evident).



- The younger child who has been sick for a longer duration of more than 36 hours and has complete bowel obstruction is at risk of colonic perforation during attempted enema reduction.
- Delayed repeat enemas done after 30 minutes or more after the initial unsuccessful reduction enema may improve the outcome of a select group of patients. This select group of patients should be clinically stable and the initial attempt had reduced the intussusceptum till the ileocaecal valve.

Contraindications to enema reduction

- Peritonitis.
- Bowel Perforation.
- Severe Shock.
- Neonates or children more than 4 years old (relative contraindication).
- History more than 48 hours.

Indications for surgery

- Failed non-operative reduction.
- Bowel Perforation.
- Suspected lead point.
- Small bowel intussusception.

Recurrence of intussusception

- Rate: 5-10% with lower rates after operative reduction.
- Success rate for non-operative reduction in recurrent intussusception is about 30-60%.

Successful management of intussusception depends on high index of suspicion, early diagnosis, adequate resuscitation and prompt reduction.

Both are due to a patent processus vaginalis peritonei. The patent communication in the hydrocoele is smaller, so the sac contains only fluid. The hernial sac can contain bowel, omentum or ovaries.

INGUINAL HERNIA

- Incidence: 0.8%-4.4% in children, but 16-25% in premature babies.
- Boy:girl ratio = 6 : 1.
- Site: 60% right side but 10% may be bilateral.

Presentation

- Reducible bulge in groin – extends into scrotum when crying/straining.
- With complications.
- Lump in groin (girls) – sliding hernia containing ovary (rule out testicular feminization syndrome if bilateral).

Complications

- Incarceration/Irreducibility – Highest incidence (2/3) before age of 1 year
- Testicular atrophy.
- Torsion of ovary.

Management

Reducible hernia

- To operate (herniotomy) as soon as possible.
  - Premature: before discharge (if possible at corrected age-44 - 60 weeks)
  - Infant: as soon as possible.
  - Older child: on waiting list.

Incarcerated hernia

- Attempt manual reduction as soon as possible to relieve compression on the testicular vessels. The child is rehydrated and then given intravenous analgesic with sedation. Constant gentle manual pressure is applied in the direction of the inguinal canal to reduce the hernia. The sedated child can also be placed in a Trendelenburg position for an hour to see if the hernia will reduce spontaneously.
- If the manual reduction is successful, herniotomy is performed 24-48 hours later when the oedema subsides. If the reduction is not successful, the operation is performed immediately.

HYDROCOELE

- Usually present since birth. May be communicating or encysted.
- Is typically a soft bluish swelling which is not reducible but may fluctuate in size.

Management

- The patent processus vaginalis may close spontaneously within the first year of life
- If the hydrocoele does not resolve after the age of 2 years, herniotomy with drainage of hydrocoele is done.

Chapter 102: Undescended Testis

An empty scrotum may be due to the testis being undescended, ectopic, retractile or absent. Familial predisposition present in 15%. 10 - 25% are bilateral.

Incidence

- At birth: Full term 3.4%
  Premature 30.3%
- At 1 year: Full term 0.8%
  Premature 0.8%
- Adult 0.7-1%
- Spontaneous descent may occur within the 1st year of life after which descent is rare.

Complications

- Trauma (especially if in inguinal canal).
- Torsion - extravaginal type.
- Decreased spermatogenesis. Damage occurs in the first 6-12 months of life. 90% of patients with orchidopexy before 2 years have satisfactory spermatogenesis. If done after >15 years old, fertility is 15%. Fertility is also affected by ductal anomalies.
- Testicular tumour: Risk is 22 times higher than the normal population (Intra-abdominal 6 times more than inguinal). Surgery makes the testis more accessible to palpation and thus an earlier diagnosis.
- Associated hernias (up to 65%), urinary tract anomaly (3%, e.g. duplex, horseshoe), anomalies of epididymis or vas deferens and intersex problems.
- Psychological problems.

Management

- Ask mother whether she has ever felt the testis in the scrotum, more easily felt during a warm bath and when squatting.
  Examine patient (older children can be asked to squat). A normal sized scrotum may suggest a retractile testis. A retractile testis, once brought down to the scrotum, can stay in the scrotum transiently. Surgery is usually not required for the retractile testis.
- The scrotum tends to be hypoplastic in true cryptorchidism.
- If bilateral need to rule out dysmorphic syndromes, hypopituitarism, and chromosomal abnormalities (e.g. Klinefelter). Exclude intersex disorders.
- Observe the child for the 1st year of life. If the testis remains undescended after 1 year of life surgery is indicated. Surgery should be done between 6-18 months of age. Results of hormonal therapy (HCG, LH-RH) have not been good. However, the use of gonadotropin releasing hormone as an adjuvant to orchidopexy appears to possibly improve germ cell maturation in child with bilateral non palpable testes.
- A non-palpable testis may represent an inguinal testis that is difficult to palpate, an intra-abdominal testis, a vanishing testis or true tesiticular agenesis.
- For bilateral impalpable testis: Management of choice is Laparoscopy ± open surgery. Ultrasound, CT scan or MRI to locate the testes have not been shown to be useful. Check chromosomes and 17 OH progesterone levels if genitalia are ambiguous.

Causes of Acute Scrotum
Acute testicular torsion.
Torsion of epididymal and testicular appendages.
Epididymo-orchitis.
Incarcerated inguinal hernia.
Idiopathic scrotal oedema.
Acute hydrocele.
Henoch-Schonlein purpura.
Tumours.
Trauma.
Scrotal (Fournier's) gangrene.
Symptomatic varicocele.

TORSION OF THE TESTIS

Torsion of the testis is an emergency as failure to detort testis within 6 hours will lead to testicular necrosis.

Symptoms

- Sudden severe pain (scrotum and referred to lower abdomen)
- Nausea and vomiting
- No fever or urinary tract infection symptoms until later

Physical Findings

Early

- Involved testis - high, tender, swollen.
- Spermatic cord – swollen, shortened and tender.
- Contralateral testis - abnormal lie, usually transverse.

Late

- Same findings as above
  However, reactive hydrocele and scrotal oedema make it difficult to examine.

There are 2 types of torsion:

Extravaginal

- The torsion usually occurs in the perinatal period or during infancy and is thought to be probably due to an undescended testis.

Intravaginal

- This is due to a high investment of tunica vaginalis causing a "bell-clapper" deformity.
- It usually occurs in boys between 10-14 years old.
- The deformity is usually bilateral.

Investigation
- Urinalysis - normal
- Colour Doppler Ultrasonography - 85% sensitivity and 100% specificity looking for intratesticular arterial blood flow and spiral twisting of the spermatic cord. Highly operator dependent.

Management
- If unable to rule out testicular torsion, to explore immediately.
- Exploration: salvage rate: 83% if explored within 5 hours; 20% if explored after 10 hours.
- If the testis is viable, bilateral orchidopexy after detorsion is done.
- If the testis is not viable, then an ipsilateral orchiectomy and a contralateral orchidopexy needs to be done.

TORSION OF APPENDAGES OF TESTIS AND EPIDIDYMIS
Appendages are Mullerian and mesonephric duct remnants.
Importance: in a late presentation, may be confused with torsion of testis.

Symptoms
- Age – 8-10 years old.
- Sudden onset of pain, mild initially but gradually increases in intensity.

Physical Examination
Early
- Minimal redness of scrotum with a normal non-tender testis.
- Tender nodule "blue spot" (upper pole of testis) is pathognomonic.

Late
- Reactive hydrocele with scrotal oedema makes palpation of testis difficult.

Treatment
- If sure of diagnosis of torsion appendages of testis, the child can be given the option of non-operative management with analgesia and bed rest.
- If unsure of diagnosis, explore and remove the twisted appendage (this ensures a faster recovery of pain too!).

EPIDIDYMO-ORCHITIS

Can occur at any age.

Route of infection

- Reflux of infected urine
- Blood borne secondary to other sites
- Mumps
- Sexually transmitted infection

Symptoms

- Gradual onset of pain with fever.
- May have a history of mumps.
- ± Dysuria/ frequency.

Physical examination

- Testis may be normal with a reactive hydrocoele.
- Epididymal structures are tender and swollen.

Investigation

- Urinalysis and urine culture
- Investigate for underlying structural anomalies of the urinary tract and voiding dysfunction
- Rule out sexual abuse

Treatment

- If unsure of diagnosis, explore.
- Investigate underlying abnormality (renal ultra sound, MCU and IVU if a urinary tract infection is also present)
- Treat infection with antibiotics.

IDIOPATHIC SCROTAL OEDEMA

The cause is unknown but has been postulated to be due to an allergy.

Symptoms

- Sudden acute oedema and redness of scrotum.
- Painless.
- Starts as erythema of perineum and extending to lower abdomen.
- Well child, no fever.
- Testes: normal.

Treatment

- This condition is self –limiting but the child may benefit from antibiotics and antihistamines.

Phimosis

Definition - Preputial stenosis or fibrosis with symptoms.
(In a normal child the foreskin is non-retractile till age of 5 years)

Causes

- Congenital - rare
- Infection- balanoposthitis
- Recurrent forceful retraction of foreskin
- *Balanoxerotica obliterans (BXO)

Symptoms

- Ballooning of foreskin on micturition.
- Recurrent balanoposthitis.
- Urinary retention.
- Urinary tract infection.

Management

- Treat infection if present.
- Elective circumcision.

**BXO:*

- Chronic inflammation with fibrosis of foreskin and glans causing a whitish appearance with narrowing of prepuce and meatus.

Treatment: careful circumcision ± meatotomy.
(Will require long term follow-up to observe for meatal stenosis)

Balanoposthitis

(Balanitis - inflamed glans, Posthitis - inflamed foreskin)

Cause effect: phimosis with or without a urinary tract infection

Treatment

- Check urine cultures.
- Sitz bath.
- Analgesia.
- Antibiotics.
- Circumcision later if there is associated phimosis or recurrent infection.

Paraphimosis

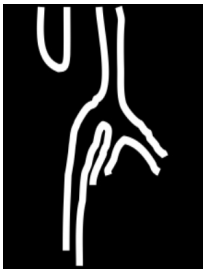
Cause: Forceful retraction of the phimotic foreskin resulting in a constriction band causing oedema, pain and possible ischaemia of the glans and urine retention.

Treatment

- Immediate reduction of the foreskin under sedation/analgesia (Use an anaesthetic gel or a penile block, apply a warm compress to reduce oedema and then gentle constant traction on foreskin distally).
- If reduction is still unsuccessful under a general anaesthetic then a dorsal slit is performed.
- The child will usually need a circumcision later.

OESOPHAGEAL ATRESIA WITH OR WITHOUT A TRACHEO-OESOPHAGEAL FISTULA

Presentation



- Antenatal: polyhydramnios, absent gastric bubble, distension of upper oesophageal pouch during swallowing
- "Mucousy" baby with copious amount of oral secretions.
- Unable to insert orogastric tube.
- Respiratory distress syndrome.
- Aspiration pneumonia and sepsis.

The Figure showing commonest type of configuration: oesophageal atresia with distal fistula.

Problems

- Oesophageal Atresia: Inability to swallow saliva with a risk of aspiration pneumonia.
- Tracheo-oesophageal fistula: Reflux of gastric contents, difficult to ventilate.
- Distal obstruction: If present and the baby is ventilated, prone to perforation of bowel.
- Prematurity: If present, associated problems.

Management

- Evaluate the type of oesophageal atresia with/without fistula and associated anomalies eg penumonia, cardiac, chromosomal, duodenal and intestinal atresias, anorectal anomalies.
- Suction of the upper oesophageal pouch: A sump suction tube ("Replogle©") should be inserted and continuous low pressure suction done. Otherwise frequent intermittent (every 10-15 mins) suction of the oesophageal pouch and oropharnyx is done. This is continued even during transport of the baby, to prevent aspiration pneumonia.
- Maintain good oxygenation. Mechanical ventilation only if absolutely necessary.
- Fluids - Maintenance and resuscitation fluids as required.
- Position - Lie the baby horizontal and lateral or prone to minimise aspiration of saliva and gastric contents
- Monitoring – Pulse oximetry and cardiorespiratory monitoring.
- Keep baby warm.
- Refer to nearest centre with neonatal and paediatric surgical facilities.

CONGENITAL DIAPHRAGMATIC HERNIA

Types

- Bochdalek: Posterolateral, commonest, more common on left side.
- Eventration of the diaphragm.
- Morgagni – anterior, retrosternal.

Problems

- Associated pulmonary hypoplasia.
- Herniation of the abdominal viscera into thoracic cavity causing mechanical compression and mediastinal shift.
- Reduced and abnormal pulmonary arterial vasculature resulting in persistent pulmonary hypertension of the newborn (PPHN) and reversal to foetal circulation.
- High mortality rate (40-60%) associated with early presentation.

Presentation

Antenatal findings

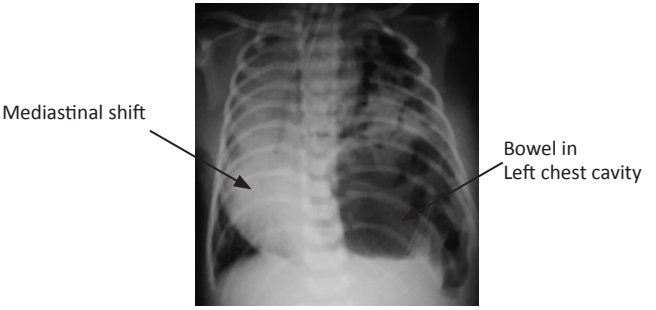
- *Ultrasound: Absence of intra-abdominal stomach, presence of abdominal contents in the thorax
- Prognostic Antenatal Investigations:
  - *Foetal MRI - location of liver, lung -head ratio and observed to expected ratio of lung volumes.
  - *ECHO
  - *Karyotyping

Presentation at birth

- Respiratory distress, absent breath sounds in chest.
- Chest X-Ray: bowel loops within the chest and minimal bowel in abdomen.

Late presentation

- Bowel obstruction
- Recurrent lower respiratory chest infections.
- Asymptomatic incidental chest x-ray finding.



Differential Diagnoses

- Congenital cystic adenomatoid malformation.
- Pulmonary sequestration.
- Mediastinal cystic lesions e.g. teratoma, bronchogenic/duplication cysts.

Management

- Antenatal counselling: For delivery at hospital with neonatal intensive care facilities.
- Babies with sufficient respiratory effort may be monitored closely with minimal supplemental oxygen.
- Evaluation for associated anomalies and persistent pulmonary hypertension of the newborn (PPHN).
- Ventilation: Direct endotracheal intubation and ventilation without face mask- bag ventilation is required for those with significant respiratory distress at delivery and pre transport. Low ventilatory pressures are to be used to prevent pneumothorax. A contralateral pneumothorax or PPHN need to be considered if the child deteriorates. If the baby is unstable or high ventilatory settings are required, the baby should not be transported.
- Frequent consultation with a paediatrician or paediatric surgeon to decide when to transport the baby.
- Chest tube: If inserted, it should not be clamped during the journey.
- Orogastric Tube: Gastric decompression is essential here. A Size 8 Fr tube is inserted, aspirated 4 hourly and placed on free drainage.
- Fluids: Intravenous fluid management is critical and based on blood glucose and hydration state. Fluid overload must be avoided.
- May need inotropic support and other modalities to optimize outcome.
- Monitoring: Pre-ductal and post-ductal pulse oximetry to detect PPHN.
- Position: Lie baby lateral with the affected side down to optimise ventilation.
- Warmth.
- Consent: High risk.
- Air transport considerations.
- Referral to the paediatric surgeon for surgery when stabilised.

ABDOMINAL WALL DEFECTS

- Exomphalos and Gastroschisis are the more common abdominal wall defects.
- *Gastroschisis*: Defect in the anterior abdominal wall of 2-3 cm diameter usually to the right of the umbilicus with loops of small and large bowel prolapsing freely without a covering membrane.
- *Exomphalos*: Defect of anterior abdominal wall of variable size (diameter of base). It has a membranous covering (Amnion, Wharton's jelly, peritoneum) and the umbilical cord is usually attached to the apex of the defect. The content of the large defect is usually liver and bowel but in the small defect the content may just be bowel loops.

Problems

- Fluid loss: Significant in gastroschisis due to the exposed loops of bowel.
- Hypothermia: Due to the larger exposed surface area.
- High incidence of associated syndromes and anomalies especially in exomphalos.
- Hypoglycemia can occur in 50% of babies with Beckwith-Wiedermann's Syndrome (exomphalos, macroglossia, gigantism).

Management

- Evaluation: for hydration and associated syndromes and anomalies.
- Fluids: IV fluids are essential as losses are tremendous especially from the exposed bowel. Boluses (10-20 mls/kg) of normal saline, Sterofundin or colloids must be given frequently to keep up with the ongoing losses. A maintenance drip of ½ Saline + 10% D/W at 60 – 90 mls/kg (Day 1 of life) should also be given.
- Orogastric tube: Gastric decompression is essential here and a Size 8 Fr tube is inserted, aspirated 4 hourly and placed on free drainage.
- Warmth: Pay particular attention to the temperature control. The increased exposed surface area and the fluid exudation will cause the baby to be wet and cold. Wrapping the baby's limbs with cotton and plastic will help.
- Care of the exposed membranes: The bowel/membranes should be wrapped with a clean plastic film without compressing, twisting and kinking the bowel. Please do NOT use "warm, saline soaked gauze" directly on the bowel as the gauze will get cold and stick to the bowel/membranes.
- Disposable diapers or cloth nappies changed frequently will help to keep the child dry.
- Monitoring: Heart rate, Capillary refill time, Urine output (the baby may need to be catheterised to monitor urine output or have the nappies weighed).
- Position: The baby should be placed in a lateral position to prevent tension and kinking of the bowel.
- Referral to the surgeon as soon as possible.

INTESTINAL OBSTRUCTION

Cause -May be functional e.g. Hirschsprung's disease or mechanical e.g. atresias, midgut malrotation with volvulus, anorectal malformations.

Problems

- Fluid loss due to the vomiting, bowel dilatation and third space losses.
- Dehydration.
- Sepsis.
- Diaphragmatic splinting.
- Aspiration secondary to the vomiting.
- Nutritional deficiencies.

Presentation

- Antenatal diagnosis – dilated fluid-filled bowels.
- Delay in passage of meconium (Hirschsprung's disease, atresias).
- Vomiting – bilious/non-bilious (Bilious vomiting is due to mechanical obstruction until proven otherwise).
- Abdominal distension (In malrotation with volvulus, abdominal distension is a late sign).
- Abdominal X-ray – dilated loops of bowel.

Management

- Evaluation – for onset of obstruction and associated anomalies (including anorectal anomalies).
- Fluids – Intravenous fluids are essential.
- Boluses - 10-20 mls/kg Normal saline, Sterofundin or colloids to correct dehydration and replace the measured orogastric losses.
- Maintenance - 0.45% Saline + 10% D/W + KCl as required.
- Orogastric tube – Gastric decompression is essential, a Size 8 Fr tube is inserted, aspirated 4 hourly and placed on free drainage.
- If Hirschsprung's disease is suspected, a gentle rectal washout with 30 ml aliquots of warm normal saline can be performed after consultation with a paediatrician or a paediatric surgeon.
- Warmth.
- Monitoring – vital signs and urine output.
- Air transport considerations during transfer to the referral centre.

ANORECTAL MALFORMATIONS

- Incidence – 1:4,000-5,000 live births
- Cause- unknown
- Antenatal diagnosis - rare
- Newborn Check – Important to clean off any meconium, part the cheeks of the buttocks and look for the anus. *DO NOT insert a rectal thermometer* as the incidence of perforation and false positives is high.

Krickenbeck Classification for Anorectal Malformations (2005)	

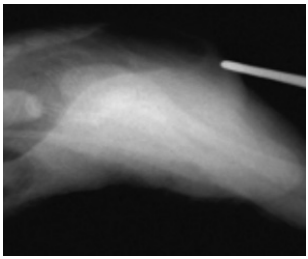
Major Clinical Groups
• Perineal(cutaneous) fistula
• Rectourethal fistula
  • Prostatic
  • Bulbar
• Rectovesical fistula
• Vestibular fistula
• Cloaca
• No fistula
• Anal stenosis
	Rare/Regional Variants
	• Pouch colon
	• Rectal atresia/stenosis
	• Rectovaginal fistula
	• H fistula
	• Others

Associated Anomalies

- Sacrum and Spine
  - Anomalies and spinal dysraphism is common.
  - Good correlation between degree of sacral development and final prognosis. Absence of more than 3 sacrum: poor prognosis.
- Urogenital
  - Common anomalies – vesicoureteric reflux, renal agenesis.
  - Incidence – low in low types and high in cloaca (90%).
  - Vaginal anomalies – about 30%.
- Others
  - Cardiac anomalies.
  - Gastrointestinal anomalies e.g. duodenal atresia.
  - Syndromes e.g. Trisomy 21.

Investigations

- Chest and Abdominal X-ray.
- Lateral Pronogram. (see Figure)
- Echocardiogram.
- Renal and Sacral Ultrasound.
- Micturating cystourethrogram.
- Distal loopogram.



Management

- Boys and Girls
  - Observe for 12-24 hours.
  - Keep nil by mouth.
  - If abdomen is distended, to insert an orogastric tube for 4 hourly aspiration and free drainage.
  - IV fluids – ½ saline with 10% Dextrose Water with KCl. May need rehydration fluid boluses if child has been referred late and dehydrated.
  - Start IV antibiotics.
  - Assess for urogenital, sacral and cardiac anomalies.

Boys

- Inspect the perineum and the urine – if there is clinical evidence of a low type, the child needs to be referred for an anoplasty. If there is evidence of meconium in the urine, the child requires a colostomy followed by the anorectoplasty a few months later.
- If there is no clinical evidence, a lateral pronogram should be done to check the distance of the rectal gas from the skin to decide if a primary anoplasty or a colostomy should be done.

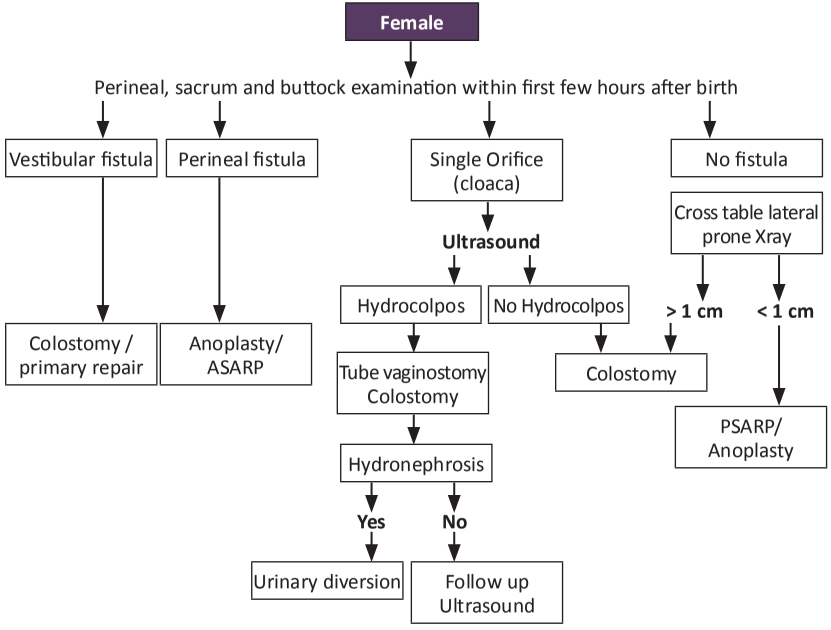
Girls

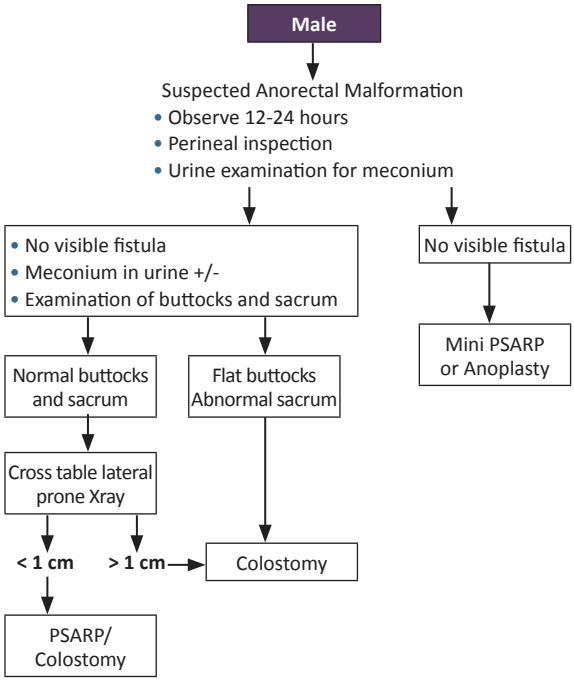
- Inspect the perineum.
- If there is a rectovestibular fistula or a cutaneous fistula, then a primary anoplasty or a colostomy is done.
- If it is a cloacal anomaly, the child needs to be investigated for associated genitourinary anomalies. The baby then requires a colostomy with drainage of the bladder and hydrocolpos if they are not draining well. The anorectovaginourethroplasty will be done many months later.
- If there is no clinical evidence, a lateral pronogram should be done to check the distance of the rectal gas from the skin to decide if a primary anoplasty or a colostomy should be done.

Definitive surgical procedures

- Perineal operation (Anoplasty)
- Anterior sagittal approach (ASARP)
- Sacroperineal approach
- Posterior sagittal anorectoplasty (PSARP)
- Posterior sagittal anorectovaginourethroplasty (PSARVUP)
- Abdominoperineal pullthrough
- Laparoscopic assisted pullthrough

MANAGEMENT OF GIRLS WITH SUSPECTED ANORECTAL MALFORMATIONS




Male
Suspected Anorectal Malformation
• Observe 12-24 hours
• Perineal inspection
• Urine examination for meconium
• No visible fistula
• Meconium in urine +/-
• Examination of buttocks and sacrum
No visible fistula
Mini PSARP or Anoplasty
Normal buttocks and sacrum
Flat buttocks Abnormal sacrum
Cross table lateral prone Xray
< 1 cm
> 1 cm
Colostomy
PSARP/ Colostomy

HIRSCHSPRUNG'S DISEASE

- Common cause of intestinal obstruction of the newborn.

Aetiology

- Aganglionosis of variable length of the bowel causing absent peristalsis and functional obstruction of the distal bowel.
- The primary aetiology has been thought to be due to cellular and molecular abnormalities during the development of the enteric nervous system and and a failure of migration of ganglion cells from the neural crest into the developing intestine.
- Genetic factors play a role with an increased incidence in siblings, Down Syndrome, congenital central hypoventilation syndrome and other syndromes.

Types

- Rectosigmoid aganglionosis: commonest, more common in boys.
- Long segment aganglionosis.
- Total colonic aganglionosis: extending into the ileum or jejunum, almost equal male: female ratio.

Clinical Presentation

May present as a neonate or later in life.

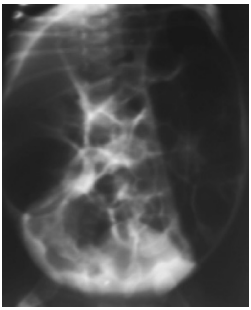
- Neonate.
  - Delay in passage of meconium (94-98% of normal term babies pass meconium in the first 24 hours).
  - Abdominal distension.
  - Vomiting – bilious/non-bilious.
  - Hirschsprung-associated enterocolitis (HAEC) – fever, foul smelling, explosive diarrhoea, abdominal distension, septic shock. Has a high risk of mortality and can occur even after the definitive procedure.
- Older child.
  - History of constipation since infancy.
  - Abdominal distension.
  - Failure to thrive.
  - Recurrent enterocolitis.

Other causes of delay in passage of meconium

- Prematurity.
- Sepsis, including urinary tract infection.
- Intestinal atresias.
- Meconium ileus.
- Hypothyroidism.

Investigation

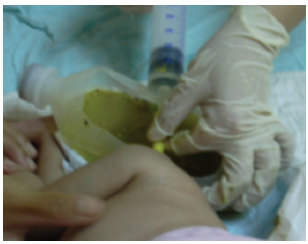
- Plain Abdominal X-ray – dilated loops of bowel with absence of gas in the rectum, sometimes a megacolon is demonstrated. *(Figure below)*



- Contrast enema – presence of a transition zone with an abnormal rectosigmoid index.
- Rectal Biopsy: Absence of ganglion cells and calretinin and presence of acetylcholinesterase positive hypertrophic nerve bundles (>40 microm diameter) confirms the diagnosis.

Management

- Aggressive intravenous fluid resuscitation
- Intravenous broad spectrum antibiotics
- Gastric decompression
- Rectal washouts:
  Using a large bore soft catheter inserted into the colon past the transition zone, the colon is washed out with copious volumes of warm normal saline in aliquots of 10-30mls till toxins are cleared.
  Rectal washout is discontinued if there is pain, bleeding or more that 20mls/kg of fluid is retained.
  (See Figure)



- If the decompression is difficult with rectal washouts, an urgent ileostomy or colostomy is required. Stomas are also required for severe, recurrent enterocolitis, perforation of the bowel, malnutrition or a grossly dilated colon.
- Definitive surgery, with frozen section to confirm the level of aganglionosis, is planned once the diagnosis is confirmed.
- Postoperatively, the child needs close follow-up for bowel management and the development of enterocolitis.

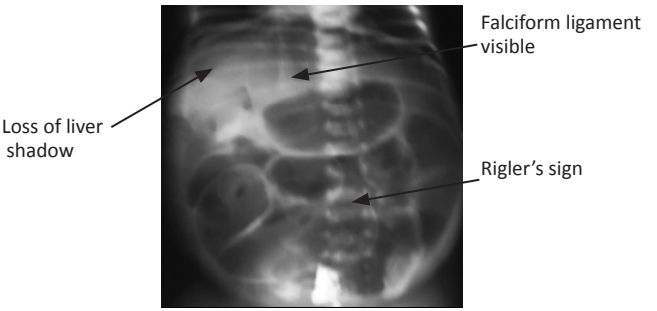
PERFORATED VISCUS

Causes

- Perforated stomach.
- Necrotising enterocolitis.
- Spontaneous intestinal perforations.
- Intestinal Atresias.
- Anorectal malformation.
- Hirschsprung's disease.

Management

- Evaluation: These babies are usually septic with severe metabolic acidosis, coagulopathy and thrombocytopenia.
- Diagnosis: A meticulous history of the antenatal, birth and postnatal details may elicit the cause of the perforation. Sudden onset of increased abdominal distension and deteriorating general condition suggests perforation.
- Supine abdominal x-ray showing free intraperitoneal gas. (Figure below)



- Ventilation: Most of the babies may require intubation and ventilation if they are acidotic and the diaphragm is splinted.
- Fluids: Aggressive correction of the dehydration, acidosis and coagulopathy should be done.
- Orogastric tube: It should be aspirated 4 hourly and left on free drainage.
- Urinary Catheter: Monitor hourly urine output
- Drugs: Will require antibiotics and possibly inotropic support
- Consultation with the paediatrician or paediatric surgeon of the regional referral centre before transfer of the baby.
- Peritoneal Drain: If there is a perforation of the bowel, insertion of a peritoneal drain (using a size 12-14 Fr chest tube or a peritoneal dialysis drain into the right iliac fossa) with/without lavage with normal saline or an isotonic peritoneal dialysate solution should be considered as a temporising measure while stabilising the baby prior to surgery. This can help to improve the ventilation as well as the acidosis.

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Chapter 106: Juvenile Idiopathic Arthritis (JIA)

Definition

JIA is a heterogenous group of chronic arthritides in childhood.
To diagnose JIA, one requires presence of definite arthritis of:

- Unknown aetiology
- Onset before the age of 16 years
- Persists for at least 6 weeks

Symptoms and Signs in JIA	
Articular Joint swelling Joint pain (may be absent) Joint stiffness / gelling after periods of inactivity Joint warmth Restricted joint movements Limping gait	**Extra-articular** *General* • Fever, pallor, anorexia, loss of weight *Growth disturbance* • General: growth failure, delayed puberty • Local: limb length / size discrepancy, micronagthia *Skin* • Subcutaneous (rheumatoid) nodules • Rash – systemic, psoriasis, vasculitis • Nail pitting *Others* • Hepatomegaly, splenomegaly, lymphadenopathy, • Serositis, muscle atrophy / weakness • Uveitis: chronic (silent), acute in Enthesitis related arthritis (ERA) *Enthesitis**
** inflammation of the entheses (the sites of insertion of tendon, ligament or joint capsule into bone)*	

Helpful pointers in assessing articular symptoms			
	Inflammatory	Mechanical	Psychosomatic
Pain	+/-	+	+++
Stiffness	++	-	+
Swelling	+++	+/-	+/-
Instability	+/-	++	+/-
Sleep disturbance	+/-	-	++
Physical signs	++	+	+/-

Diagnosis and Differential diagnosis

- JIA is a diagnosis of **exclusion.**

Differential diagnosis of JIA	
Monoarthritis *Acute* • Acute rheumatic fever • Reactive arthritis: Post viral/ post enteric /post streptococcal infection • Septic arthritis / osteomyelitis • Early JIA • Malignancy: leukaemia, neuroblastoma • Haemophilia • Trauma *Chronic* • JIA: oligoarthritis, ERA, psoriatic • Chronic infections: TB, fungal, brucellosis • Pigmented villonodular synovitis • Sarcoidosis • Synovial haemangioma • Bone malignancy	**Polyarthritis** • JIA – polyarthritis (RF positive or negative), ERA, psoriatic arthritis • Reactive arthritis • Lyme disease • Systemic Lupus Erythematosus • Other connective tissue diseases • Inflammatory bowel disease • Sarcoidosis • Familial hypertrophic synovitis syndromes • Immunodeficiency syndromes • Mucopolysaccharidoses

Helpful pointers in diagnosis

- Avoid diagnosing arthritis in peripheral joints if no observed joint swelling.
- Consider other causes, particularly if only one joint involved.
- Active arthritis can be present with the only signs being decreased range of movement and loss of function.
- In axial skeleton (including hips), swelling may not be seen. Diagnosis is dependent on inflammatory symptoms (morning stiffness, pain relieved by activity, pain on active and passive movement, limitation of movement). Investigations to exclude other diagnosis are important.
- In an ill child with fever, loss of weight or anorexia, consider infection, malignancy and other connective tissue diseases.
- In any child with severe pain (especially night pain), consider malignancy.

Investigations

- The diagnosis is essentially clinical; laboratory investigations are only supportive.
- No laboratory test or combination of tests can confirm the diagnosis of JIA.
- FBC and Peripheral blood film – exclude leukaemia. BMA may be required if there are any atypical symptoms/signs even if PBF is normal
- ESR or CRP – markers of inflammation.
- X-ray/s of affected joint/s: esp. if single joint involved to look for malignancy.
- Antinuclear antibody – identifies a risk factors for uveitis
- Rheumatoid factor – assess prognosis in polyarthritis and need for more aggressive therapy.

**Antinuclear antibody and Rheumatoid factor are NOT required to make a diagnosis.*

** Other Ix done as neccesary : complement levels, ASOT, Ferritin, immunoglobulins (IgG, IgA and IgM), HLA B27, synovial fluid aspiration for microscopy and culture, echocardiography, MRI/CT scan of joint, bone scan .*

Management

Medical treatment

- Refer management algorithms based on number of joints affected (see following pages)

Dosages of drugs commonly used in JIA

Name	Dose	Frequency
Ibuprofen	5 - 10 mg/kg/dose (max 2.4 Gm/day)	3-4/day
Naproxen	5 - 10 mg/kg/dose (max 1 Gm/day)	2/day
Indomethacin	0.5 - 1 mg/kg/dose (max 150mg/day)	2-3/day
Diclofenac	0.5 - 1 mg/kg/dose	3/day
Methotrexate	10 - 15 mg/m^2/dose (max 25 mg/dose)	1/week
Folic acid	2.5 - 5.0 mg per dose	1/week
Sulphasalazine	15 - 25 mg/kg/dose (start 2.5 mg/kg/dose and double weekly; max 2 Gm/day	2/day
Hydroxychloroquine	5 mg/kg/dose	1/day
Methylprednisolone	30 mg/kg/dose (max 1 Gm / dose)	1/day x 3 days
Prednisolone	0.1 - 2 mg/kg/dose	1-3/day

Note: Patients on DMARDS (e.g Methotrexate, Sulphasalazine) require blood (FBC, LFT, creatinine) monitoring for toxicity : 1 mth after drug initiation, 1-2 mths after increase in dosages, and every 2-3 mths once on stable doses. Patients on long term NSAIDs require 3 mthly creatinine , ALT and UFEME.

Physiotherapy

- Avoid prolonged immobilization
- To improve and maintain range of joint motion, to strengthen muscles, to stretch deformities, to condition patient and improve endurance

Occupational Therapy

- Splinting when necessary to reduce pain and preserve joint alignment
- To adopt joint protection techniques
- To improve quality of life by adaptive aids and modification of environment

Ophthalmology referral

- All patients must have uveitis screening at initial diagnosis (uveitis can be asymptomatic but cause loss of vision) and have follow-up at regular intervals (frequency depending on risk) even if initial screening is normal.

Psychosocial support

- To improve self esteem
- Counselling and family support may be necessary

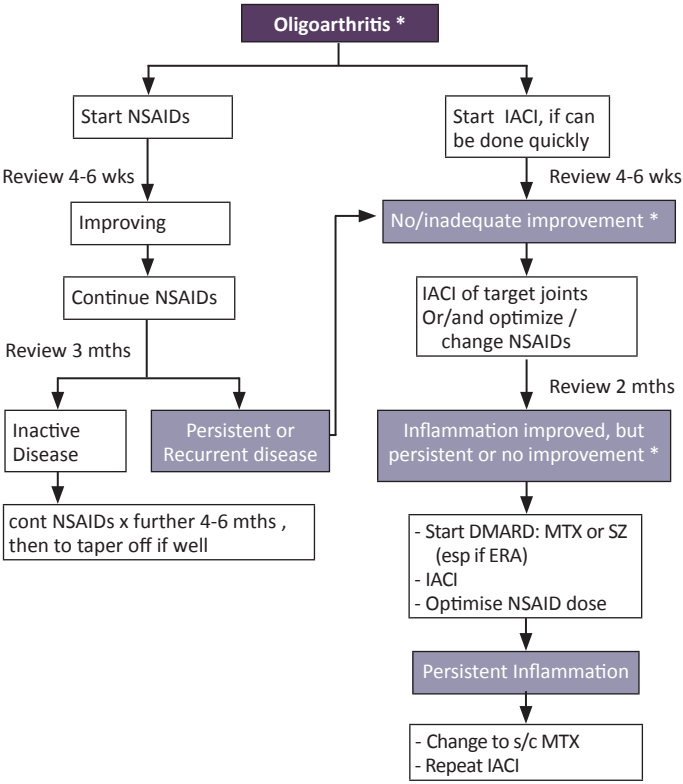
Nutritional support

- Ensure a healthy well balanced healthy diet, with special emphasis on calcium intake (to promote bone health)

Others

- Disease education is important to promote acceptance and compliance
- Encourage regular exercise and participation in sports
- Encourage school attendance with adjustments to school life (classroom location, stairs etc) and physical education classes
- Dental care important
- Orthopedic referral when necessary (e.g. synovectomy, arthrotomy, arthrodesis, joint replacements)

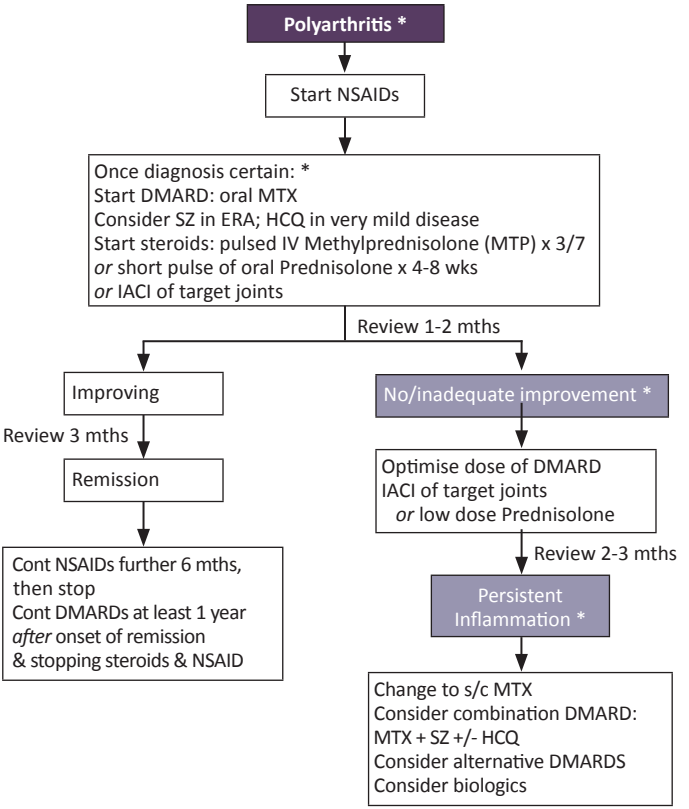
Oligoarthritis (1-4 joints)



Note:
- Remember to screen for Uveitis
- All patients with persistent inflammation should be on DMARDs within 6 months of diagnosis even if only having oligoarthritis.

*, Consider referral to Paeds Rheumatologist / reconsider diagnosis;
Abbreviations:
IACI, Intra-articular corticosteroid injection; MTX , Methotrexate;
SZ, Sulphasalazine; DMARD, Disease modifying anti-rheumatic drugs.
s/c , subcutaneous

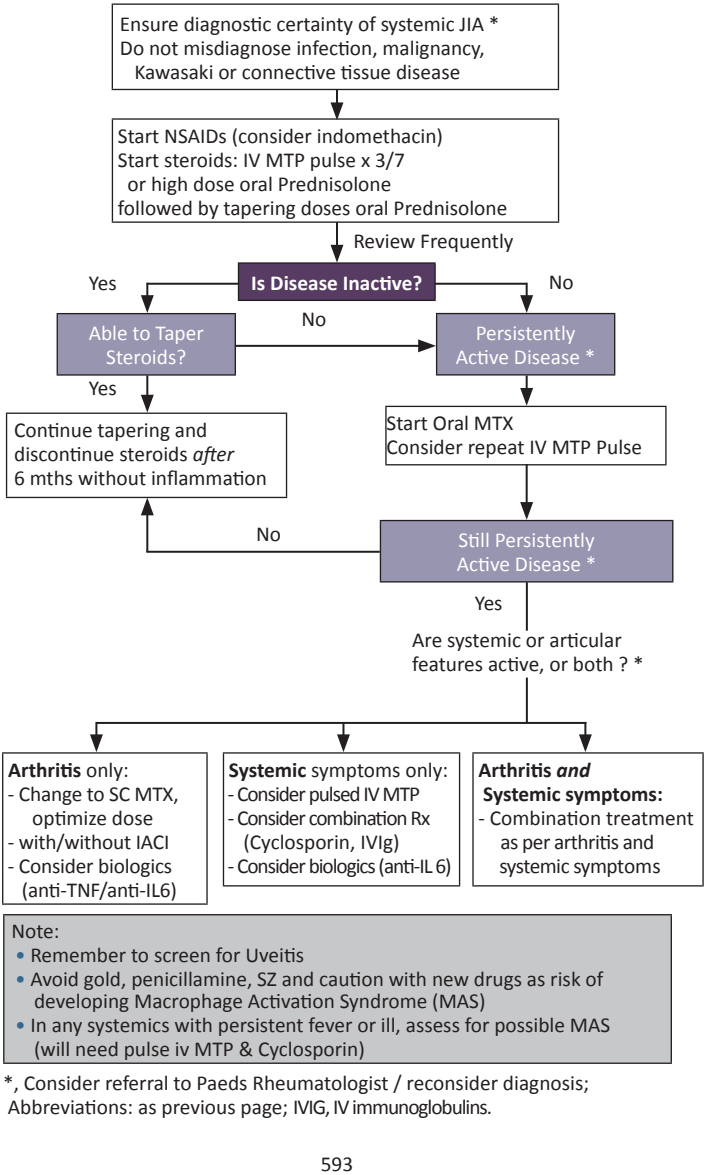
Polyarthritis (> 5 joints)



Note:
- Remember to screen for Uveitis
- Consider s/c route of MTX at diagnosis if polyarthritis severe
- Best opportunity to achieve remission in first two years of disease
- Avoid accepting low grade inflammation until all avenues explored

*, Consider referral to Paeds Rheumatologist / reconsider diagnosis;
Abbreviations:
IACI, Intra-articular corticosteroid injection; MTX , Methotrexate;
SZ, Sulphasalazine; HCQ, Hydroxychloroquine; ERA, enthesitis related arthritis;
DMARD, Disease modifying anti-rheumatic drugs.

Systemic onset JIA



Note:
- Remember to screen for Uveitis
- Avoid gold, penicillamine, SZ and caution with new drugs as risk of developing Macrophage Activation Syndrome (MAS)
- In any systemics with persistent fever or ill, assess for possible MAS (will need pulse iv MTP & Cyclosporin)

*, Consider referral to Paeds Rheumatologist / reconsider diagnosis;
Abbreviations: as previous page; IVIG, IV immunoglobulins.

Definition

- A chronic multisystem autoimmune condition with widespread inflammation of blood vessels and connective tissue, characterized by autoantibodies against self-antigens especially presence of Antinuclear antibody (ANA positive in 95% untreated SLE).
- Severity ranges from mild to life threatening and onset can be insidious or acute.
- Disease runs an unpredictable course, evolves over time and can result in significant long-term morbidity and mortality.

Epidemiology

- Only 15-20% of all SLE patients occur before the age of 18 years.
- Onset commonly around puberty (median age 10-12 years).
- Majority (85%) present > 8 years, rare under age 5 years.
- Female: male ratio = 4.5:1.

Clinical presentation

- Clinical manifestations of juvenile SLE (jSLE) are protean, variable and often involve multiple organ systems.
- If jSLE is suspected, a meticulous assessment of all organ systems needs to be performed.
- In general, jSLE is a more severe disease when compared to adult SLE, often presenting with severe renal, cerebral and haematological manifestations, and with higher overall disease activity, accruing more organ damage with time resulting in more long term morbidity and mortality.

Common presentations of JSLE (not exhaustive)

Constitutional
Fever, loss of appetite, loss of weight, lethargy, lymphadenopathy

Mucocutaneous
Malar rash (60% jSLE), oral/nasal erythema and ulcers, maculopapular, vasculitic rash (petechiae, purpura, nodules, ulcers), photosensitivity, discoid rash (10%), diffuse alopecia, Raynaud's phenomenon, bullous, livedo reticularis.

Cardiac
Chest pain, pericarditis, pericardial effusion, myocarditis with heart failure, Libmann-Sacks endocarditis.

Respiratory
Shortness of breath, decrease effort tolerance, interstitial lung disease, pleuritis and pleural effusion, pulmonary haemorrhage.

Gastrointenstinal tract
Hepatosplenomegaly, hepatitis (25%), diffuse abdominal pain, serositis, diarrhoea, pancreatitis, gastrointenstinal tract vasculitis + bowel perforation.

Renal
Nephrotic syndrome, proteinuria, haematuria, hypertension, renal impairment, acute renal failure.

Common presentations of JSLE *(continued)*

Musculoskeletal
Arthralgia, arthritis (usually non-erosive and non-deforming), myalgia, myositis, tenosynovitis

Neuropsychiatric
Headache, migraine, mood disorder, cognitive impairment, seizures (differential diagnosis - Posterior reversible encephalopathy syndrome (PRES)), stroke, psychosis (visual > auditory hallucinations), acute confusional state, cranial and peripheral neuropathies.

Haematological
Autoimmune hemolytic anemia, leucopenia, lymphopenia, thrombocytopenia, Coombs positivity, Thrombotic thrombocytopenic purpura, antiphospholipid antibodies (40% jSLE, only half have thrombosis)

Ocular
Uveitis, optic neuritis, vaso-occlusive retinal vasculitis, retinopathy (cotton-wool spots), episcleritis

Diagnosis

- Diagnosis is based on the presence of clinical features supported by positive laboratory findings.
- Early diagnosis is crucial as a delay in treatment is associated with increased mortality and less likelihood of achieving remission.
- However, diagnosis can sometimes be challenging and thus early referral to a paediatric rheumatologist or paediatrician experienced in the care of jSLE is recommended.
- Differential diagnosis of SLE is broad and must include infection, malignancy and other inflammatory conditions.
- Various criteria have been developed for the classification of SLE (e.g. revised ACR criteria and SLICC criteria – see tables at the end of chapter) but these are primarily meant for research purposes.
- However, these criteria are often used to aid diagnosis. ACR criteria of fulfilling > 4 out of 11 criteria have high sensitivity (96%) and specificity (96%) for diagnosis of SLE.
- Caution: in some children with early SLE, these criteria may not be met yet and children can also present with isolated organ involvement (e.g. renal disease) which may not fulfill these criteria. Thus, criteria alone should not be a pre-requisite for diagnosis or instituting treatment.

Investigations For Initial assessment:

Investigation	Common results and interpretation
Full blood count & reticulocyte count (+ Peripheral Blood Film)	Low Hb: hemolytic, usually warm type /secondary to chronic disease/ iron deficiency; Low WCC, if high: consider infection, stress response, or due to steroids; Low lymphocytes: disease/ immunosuppression; Low neutrophils: rare; Low platelet: disease. (not to forget rarer causes of cytopenias - MAS or TTP)
Erythrocyte sedimentation rate	High, if paradoxically low ESR in an ill patient with pancytopenia; consider MAS
C-reactive protein	Normal, if high: consider infection, serositis, arthritis
Renal profile	Hyperkalemia, high creatinine in renal involvement, electrolyte imbalance
Liver function test	Raised ALT (AIH, active disease, fatty liver, adverse effect of drugs), low albumin, high bilirubin, high GGT
Cardiac enzymes	High (myositis, but note that myositis can be subclinical)
Urine FEME	Proteinuria, haematuria, urinary casts (especially red blood cell cast). If proteinuria present, quantify with urine protein: creatinine index or 24-hour urine protein.
ANA	Positive in 95% active untreated SLE. (Note: ANA is not diagnostic)
Anti-dsDNA Ab	Positive in 60% SLE (more specific than ANA), correlated with renal disease
ENA	Most common: anti-Ro, anti-La (both associated with neonatal lupus); anti Sm – correlated with renal disease
Complement 3 & 4	Low, complement levels correlate with disease activity. NB. Some patients have normal levels even if active disease, some may have congenital C4 deficiency
Thyroid function	Low or high (if abnormal to do thyroid autoantibodies)
Direct antibody test (direct Coombs')	Positive, but may not reflect on-going active hemolysis
Coagulation profile	Prolonged aPTT suggests presence of lupus anticoagulant
Thrombophilia screen	Lupus anticoagulant and antiphospholipid antibodies (anticardiolipin and β2 glycoprotein 1 antibodies)

*MAS: Macrophage activation syndrome, TTP: Thrombotic thrombocytopenic purpura, AIH: Autoimmune hepatitis; ENA: Extractable Nuclear Antigen

Other investigations (as indicated)

- IgG, IgA, IgM: usually high IgG (acute inflammation), to also rule out underlying primary immunodeficiency
- Rheumatoid factor: positive in10-30% jSLE, consider overlap if significant arthritis
- CXR
- Echocardiography, ECG
- Bone marrow aspiration
- Ophthalmology assessment
- Other organ assessment as indicated: Renal biopsy, Skin biopsy, MRI/MRV/MRA brain, EEG, Lumbar puncture, Abdominal ultrasound, OGDS and Colonoscopy, HRCT, Lung function test
- Fasting serum lipid, fasting blood sugar

MANAGEMENT

- Management of the child with SLE can be challenging and treatment must be individualized.
- Treatment options vary depending on organ involvement, disease activity and damage, access to medications as well as patient and institution preferences.
- The information below is a broad general guide based on common principles.

Aims

- Rapid reduction and control of disease activity to prevent long term organ damage.
- Maintain health and function, and aid patient and family to cope with disease and treatment.
- Minimise side effects of treatment

General

- Sun protection: sunblock SPF 50-60, avoid sun (hats, umbrellas and protective clothing) and avoid activities carried out under the sun (e.g. sports, school assembly)
- Adequate nutrition (especially dietary intake of calcium and vitamin D) and appropriate rest (but discourage inactivity)
- Treat any infections promptly and aggressively (60-80% infections due to bacteria, prone to encapsulated bacteria like pneumococcus, meningococcus, salmonella and haemophilus; virus like cytomegalovirus, herpes zoster and opportunistic organisms like pneumocystis jiroveci or cryptococcus)
- Immunisations: all routine immunisations recommended (especially pneumococcal and influenza). Live vaccinations contraindicated if on immunosuppressive agents.

SPECIFIC PHARMACOTHERAPY

Corticosteroids

- Usually required by all children even in the absence of major organ involvement.
- Is the mainstay of pharmacologic therapy but is associated with significant side effects. Need to balance the requirement versus side effects carefully aiming for lowest possible dose to maintain disease control with the least side effects.
- Can be given orally (Prednisolone) or intravenously (Methyl Prednisolone).
- Initial does varies depending on severity of disease and extent of organs involved, Prednisolone: 0.5-2 mg/kg/day in at least 2 divided doses or IV Methylprednisolone 10-30mg/kg/day for 3-5 days, may be repeated up to weekly (max 1 gram, but generally not more than 500 mg/day as patients prone to infection/ sepsis)
- Tapering of steroid dose should occur once disease is controlled aiming for lowest possible dose. The rapidity of steroid taper depends on clinical response (resolution of symptoms and physical abnormalities), control of disease activity and towards normalization of laboratory findings (e.g. no cytopenias, improving or near normal complement levels, reducing proteinuria, improving urinalysis, lowering of antidsDNA levels)
- Generally, the higher the dose, the faster the taper. During active phase, will require divided doses. Once daily dose usually not recommended till 10 mg/day or less. Alternate day dosing may be inadequate to control active SLE despite lower risk of side effects.

Immunosuppressive agents

- Immunosuppressive agents are now started early soon after diagnosis for rapid control of disease with improved long-term outcome and as a steroid-sparing agent.
- The choice of immunosuppressive agents is largely dictated by the organ system/s involved and the severity of involvement.
- Azathioprine (1-2.5 mg/kg/day) is the most commonly used immunosuppressive agent, especially for haematological, dermatological, serositis, vasculitis and sometimes as maintenance therapy for lupus nephritis. Generally well tolerated, side effects include nausea, GI symptoms, hair loss, bone marrow suppression.
- Major organ involvement like renal, cerebral, cardiac and pulmonary or other life-threatening manifestations usually will warrant pulses of IV Cyclophosphamide together with generally a single pulse of IV Methylprednisolone at monthly intervals for minimum 6 months.
- Cyclophosphamide (500-1000mg/m^2/dose, max dose 1.2 g) is effective but associated with significant risks of infection (immunosuppression), haemorrhagic cystitis (prevented by Mesna), infertility and long term risk of cancer.
- Mycophenolate mofetil (600-1200mg/m^2/day): used for induction phase of lupus nephritis, but the cost precludes its use as first line. It is also used for various other significant manifestations including haematological, dermatological and myositis. Main side effect is GI upset which can be minimized by slow introduction.

- Methotrexate (10-15 mg/m2/week): arthritis, myositis and skin disease.
- Cyclosporin (3-5 mg/kg/day): nephritis especially membranous

Hydroxychloroquine

- An antimalarial recommended for all lupus patients as it can help reduce flares, reduce autoantibody production and cardio protective (lipid regulating, anti-platelet and anti-thrombotic, anti-hypertensive).
- Hydroxychloroquine (4-6mg/kg/day) is also useful for mild arthritis and skin disease.
- Needs yearly eye screening (for hydroxychloroquine induced retinopathy – present with subtle changes in colour vision and paracentral scotoma) and hearing assessment (ototoxicity)
- Caution in impaired renal function – consider stopping as increased risk of toxicity.

Others

- NSAIDs: myalgia, arthralgia, arthritis; and serositis
- Folic acid
- Bone health: Calcium, vitamin D
- Antihypertensive agents: as required in lupus nephritis. ACE inhibitors/ ARBs helpful to reduce proteinuria.
- Aspirin: low dose for those with significant titers of antiphospholipid antibodies, heparin (LMWH) followed by warfarin in the presence of thrombosis. (aim for INR 2.5-3.5)
- Intravenous immunoglobulin: sometimes used in ill children, in whom the possibility of severe infection cannot be excluded which precludes a pulse of iv Methylprednisolone.
- Plasmapheresis: occasionally used for severe refractory disease e.g. pulmonary haemorrhage, TTP.

Biological therapies – for resistant cases

- Newer therapies are showing promise with many more being researched.
- The currently used biological agents include Rituximab (anti-CD20 antibody) and Belimumab (anti-B lymphocyte stimulator antibody), first FDA approved drug for lupus.

Follow-up management

At every clinic visit, perform meticulous assessment looking for:

- Evidence of active disease
  - Detailed systematic assessment of all organ systems looking for symptoms of active disease & response to treatment.
  - Complete physical examination (CVS, Respiratory, Abdomen, Neurology including muscle power, Musculoskeletal, Skin including scalp and hair & mucosa, Fundus) including growth parameters, blood pressure, pubertal staging.
- Complications of disease (e.g. organ damage, atherosclerosis) or treatment (e.g. infections, immunosuppression, steroid toxicity - myopathy, AVN, cataract, glaucoma).
- Psychological issues – self-image & self-esteem, school issues, bullying, family support.
- Compliance to treatment regimen

Perform the following investigations to support assessment with the aim to adjust treatment:

- Full blood count
- ESR
- C-reactive protein
- Renal profile
- Liver function test
- Complement 3 & 4
- UFEME
- UPCI (Urine protein-to-creatinine index): if has proteinuria
- antidsDNA levels: if positive and able to measure titers, useful to monitor disease activity.
- Ca, PO4, VBG: for those with significant renal disease
- Muscle enzymes: if has myositis
- PT/INR: if on warfarin

Investigations to be done on a yearly basis to look for complications

- Fasting serum lipid
- Fasting blood sugar or HbA1c
- Thyroid function test

ACR Classification criteria for Systemic Lupus Erythematosus

(> 4 out of 11 criteria present simultaneously or serially over time)

Criteria	Definition
1. Malar rash	Flat or rash erythema over the malar eminences and spares the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
3. Photosensitivity	Skin rash following sunlight exposure, by history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
5. Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion
6. Serositis	Pleuritis – convincing history of pleuritic pain or rub on auscultation or evidence of pleural effusion or Pericarditis – documented by electrocardiogram, echocardiogram or rub
7. Renal disorder	Persistent proteinuria greater than 0.5g/day or Cellular casts – may be red cell, hemoglobin, granular, tubular or mixed
8. Neurological disorder	Seizures in the absence of offending drugs or metabolic derangements, Or Psychosis in the absence of offending drugs or metabolic derangements
9. Haematological disorder	Hemolytic anemia with reticulocytosis or Leucopenia < 4000/ mm^3 on ≥ 2 occasions or Lymphopenia < 1500/ mm^3 on ≥ 2 occasions or Thrombocytopenia < 100,000/mm^3 on ≥ 2 occasions
10. Immunological disorder	Antibody to native DNA, or Antibody to Sm protein, or Antiphospholipid antibodies - either anticardiolipin antibodies, presence of lupus anticoagulant, or false positive serological test for syphilis
11. Antinuclear antibody	Presence of antinuclear antibody by immunofluorescence or an equivalent assay

Adapted from Tan EM, Cohen AS, Fries JF et al. The 1982 revised criteria for the classification of systemic lupus erythematosus, Arthritis Rheum 25:1271-1277, 1982; and Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, Arthritis Rheum 40: 1725, 1997.

SLICC classification criteria for Systemic Lupus Erythematosus

(At least 4 items of which one must be clinical and one immunologic, or biopsy proven nephritis with positive ANA and antidsDNA)

Clinical Criteria	
1.	Acute cutaneous lupus, including: • Lupus malar rash (do not count if malar rash discoid) • Bullous lupus • Toxic epidermal necrolysis variant of SLE • Maculopapular lupus rash • Photosensitive lupus rash • In the absence of dermatomyositis OR Subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with post inflammatory dyspigmentation or telangiectasia
2.	Chronic cutaneous lupus, including: • Classic discoid rash • Localised (above the neck) • Generalised (above and below the neck) • Hypertrophic (verrucous) lupus • Lupus panniculitis (profundus) • Mucosal lupus • Lupus erythematosus tumidus • Chilblains lupus • Discoid lupus/lichen planus overlap
3.	Oral ulcers *(In the absence of other causes, such as vasculitis, Behcet's disease, infections (herpesvirus), inflammatory bowel disease reactive arthritis and acidic foods)* • Palate, Buccal, Tongue OR Nasal ulcers
4.	Non scarring alopecia (diffuse thinning or hair fragility with visible broken hairs) *in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia*
5.	Synovitis involving 2 or more joints, characterized by swelling or effusion OR Tenderness in 2 or more joints and at least 30 minutes of morning stiffness
6.	Serositis *(In the absence of other causes, such as infection, uremia, and Dressler's pericarditis)* • Typical pleurisy for more than 1 day OR pleural effusion OR pleural rub • Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day OR pericardial effusion OR pericardial rub OR pericarditis by electrocardiography

SLICC classification criteria for Systemic Lupus Erythematosus

(At least 4 items of which one must be clinical and one immunologic, or biopsy proven nephritis with positive ANA and antidsDNA)

Clinical Criteria *(continued)*	
7.	Renal • Urine protein-to-creatinine ratio (or 24 hour urine protein) representing 500 mg protein/24 hours OR red blood cell casts
8.	Neurologic • Seizures • Psychosis • Mononeuritis multiplex (In the absence of other know causes such as primary vasculitis) • Myelitis • Peripheral or cranial neuropathy (In the absence of other known causes such as primary vasculitis, infection and diabetes mellitus) • Acute confusional state (In the absence of other causes, including toxic/ metabolic, uremia and drugs)
9.	Hemolytic anemia
10.	• Leucopenia (< 4000/mm^3 at least once) (In the absence of other known causes such as Felty's syndrome, drugs and portal hypertension) OR • Lymphopenia (<1000/mm^3 at least once) (In the absence of other known causes such as corticosteroids, drugs and infection.)
11.	Thrombocytopenia (<100,000/mm^3) at least once In the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura)
Immunologic criteria	
1.	ANA level above laboratory reference range
2.	Anti-ds DNA antibody level above laboratory reference range (or > 2-fold reference range if tested by ELISA)
3.	Anti-Sm: presence of antibody to Sm nuclear antigen
4.	Antiphospholipid antibody positivity as determined by any of the following: • Positive test result for lupus anticoagulant • False-positive test result for rapid plasma regain • Medium – or high titer anticardiolipin antibody level (IgA, IgG, or IgM) • Positive test result for anti-β2 glycoprotein 1 (IgA, IgG or IgM)

SLICC classification criteria for Systemic Lupus Erythematosus

(At least 4 items of which one must be clinical and one immunologic, or biopsy proven nephritis with positive ANA and antidsDNA)

Immunologic Criteria *(continued)*	
5.	Low complement • Low C3 • Low C4 • Low CH50
6.	Direct Coombs' test *in the absence of hemolytic anemia*

Petri M, Orbai A, Alarcon G et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus. *Arthritis & Rheumatism, vol 64, No 8, Aug 2012, pp 2677-2686.*

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Chapter 107 Systemic Lupus Erythematosus

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Introduction

- Different geographical region and countries will have different snake species of medical importance.
- Snakes of medical importance in Malaysia are either equipped with specialised front fangs or without front fangs. The front-fanged snakes are either in the family Elapidae (cobras, kraits, coral snakes and sea snakes) or Crotalinae (Pit vipers). Pythons and some non-front fanged colubroids may also pose danger to humans.
- All front-fanged and a few rear-fanged snakes are equipped with venom.
- Snake venoms are made of complex and diverse group of proteins, many with enzymatic activity. Envenoming syndromes are treated with timely administration of the appropriate antivenom in adequate amount
- It is important to note that a medically important snake found in one state in Malaysia may not be indigenous in another. Therefore, the requirement for antivenom may differ from hospitals to hospitals in the country.
- Early access to experts in the field (Clinical Toxinologist) will assist healthcare providers in snake species identification and optimal management, saving lives and limbs.

Note: Assistance/query/consultation for identification and clinical management of snakebite can be obtained from the National Poison Centre Malaysia and the Remote Envenomation Consultation Services (RECS) Malaysia (http://mstoxinology.blogspot.com/p/recs.html).

Clinical features of common snakebite envenoming

- Local envenoming syndrome by cobra (*Naja*) species include immediate pain, progressively worsening swelling, blistering and necrosis. Systemic envenoming manifest as acute neurological and cardiac dysfunction including ptosis [an early sign], ophthalmoplegia, dysphagia [drooling of saliva], aphasia, dyspnea, muscle paralysis and arrhythmias.
- Krait (*Bungarus*) species bites may cause minimal local effects and may go unnoticed. Systemic envenoming may be delayed and manifest as sudden onset of rapidly progressive myalgia and muscle paralysis.
- Sea snake bites cause minimal local effects. Systemic envenoming may present as generalised myalgia, stiffness, paresis, paralysis and myoglobinuria (dark coloured urine). Rhabdomyolysis may lead to acute renal failure.
- Pit viper bite envenoming may cause progressively worsening pain and swelling, haemorrhagic blisters, necrosis, hypovolaemic shock from third space fluid loss and bleeding due to coagulopathy.

Note: These clinical features are the manifestations of various toxins in the venom. Toxic venom components can vary even within the same snake species. The age, geographical distribution and prey specificity factors may influence the compositions of venom toxins.

MANAGEMENT

Prehospital care / First Responder

The objectives are to provide basic life support, to reduce the rate of venom absorption and to prevent further complications.

Prehospital care interventions include:

- Calm the patient down and move to safety.
- Remove jewellery on the affected limb and loosen tight-fitting clothing.
- Immobilise the affected limb with a splint or sling and reduce movements. Pressure Bandaging and Immobilization (PBI) is to be applied only by a trained first-aider. Indications for PBI include 1) the snake is identified as krait, coral snake or sea snake; 2) if the snake is unidentified, the transport time to the hospital is prolonged (more than an hour).
- If venom enters the eye (venom ophthalmia), immediately irrigate with copious amounts of clean water.
- Transfer all patients to the nearest healthcare facility with emergency care.

Note: Document all symptoms and signs that may manifest prior to arrival to the hospital. Do not interfere with the bitten area by applying tourniquet, doing incisions, sucking, rubbing, vigorous cleaning, applying herbs/chemicals, massage or electrical shocks. Avoid wasting time to search or kill the snake. Take several good quality pictures of the snake at a safe distance e.g. using mobile phone camera. If the snake was killed, bring the it along in a secure container.

Emergency and Hospital

- Triage to resuscitation zone and Perform rapid clinical assessment (Primary survey).
- Monitor vital signs and cardiac rhythm, and resuscitate as indicated.
- Obtain detailed history of presenting complaint:
  1) time of incident
  2) location of incident
  3) how exactly did the patient get bitten
  4) what happened to the snake
  5) part of body bitten
  6) what was done after bitten
  7) pain score progression (PSP) since incident
  8) current complaints
  9) allergy history (to horse or papaya) and other co-morbidities
- Perform close serial examination at fixed time intervals (every hour) for any changes over the bitten area (bite marks and surrounding skin), the rate of proximal progression of the oedema (RPP), PSP, palpable tender lymph nodes draining the area, and distal neurovascular status of the affected limb. Taking serial pictures of the affected area helps.

- Examine for neurological dysfunction (tailored according to child's age group), bleeding tendencies, and muscle tenderness and rigidity.
- Send initial laboratory investigations (full blood count, coagulation profile and Creatine Kinase) and repeat serially every 6 hours for the first 24 hours of incident. Consider other tests as necessary (renal function tests, liver function test, fibrinogen level, D-dimer and urine examination). Review the trends.
- If laboratory blood test is not available or delayed and the diagnosis is unidentified snakebite or a pit viper bite, consider performing serial bedside 20-min Whole Blood Clotting Test (20WBCT).
  Put 2mls of venous blood in a clean and dry *glass* test tube, leave it standing for 20 min, and then tipped once.
  Note: Unclotted blood suggests a pit viper bite with systemic envenomation.
- Review immunisation status: administer IM anti-tetanus injection if indicated. (Note: Arterial puncture and Intramuscular injections are contraindicated if the coagulation profile is abnormal)
- Administer analgesia (avoid NSAIDs in pit viper envenoming) and antivenom as indicated.
- Admit to medical ward for close serial observation of the progress and response to therapy (vitals, RPP, PSP, LN and blood tests). If there is no signs and symptoms of envenomation for at least 24hrs or if an expert verifies the snake to be a non-venomous species and asymptomatic, the patient may not require hospitalisation.

Antivenom

- Antivenom (AV) is the only proven antidote for envenomation.
- Not all snakebites, even by snakes equipped with venom, results in envenoming syndrome.
- Antivenoms carries a (low) risk of adverse reactions. Therefore, the appropriate antivenom should be used only when it is indicated and administered as early as possible.
- Antivenoms appropriate for use in Malaysia are currently imported from Thailand and Australia.
  The dosage for children is the same as for adults (Table 1)
- Adrenaline, steroid and antihistamine should not be given prophylactically unless indicated.
- Skin sensitivity test is not necessary as it poorly predicts anaphylactic reactions, may induce hypersensitivity and will cause unnecessary delay in antivenom therapy.

Indications for antivenom

Systemic envenomation

- Coagulopathy.
- Neurological abnormalities.
- Cardiovascular abnormalities.
- Generalised rhabdomyolysis / haemolysis.
- Acute kidney injury.
- Supporting laboratory results.

Local envenomation (with other considerations)

- Progressive significant oedema of the bitten area, especially if involving the fingers.
- Rapid speed of progression of oedema (trends of RPP) within a few hours.
- Palpable tender lymph node draining the affected limb.
- Rapidly expanding local necrosis.

Note: Helpful laboratory results suggesting envenomation include prolonged PT/APTT, raised INR (>1.2), reducing fibrinogen level, thrombocytopenia, leucocytosis, anaemia, hyperkalaemia, hyponatraemia, myoglobinuria and raised serum enzymes (e.g. Creatine kinase, aminotransferases).

Choice of antivenom

- If snake species is identified and AV is indicated, consider monovalent/ mono-specific antivenom.
- If snake species is unidentified and AV is indicated, consider Neuro Polyvalent or Hemato Polyvalent antivenom.

Preparation and administration

- Prepare adrenaline, hydrocortisone, antihistamines and resuscitative equipment prior to antivenom infusion.
- Reconstitute freeze-dried antivenom with the solution supplied or 10ml WFI (water for injection). Gently swirl (never shake) to dissolve the freeze-dried powder. Further dilute in 5-10ml/kg of hypotonic crystalloid solution for children (250-500ml isotonic crystalloid for adults).
- Infuse at a slow rate (1 to 2 ml/min) for 5-10min and if there is no reaction, increase the rate to 5-10mls/min to complete the infusion in less than one hour.
- Closely observe patient during and for at least 1 hour after completion of intravenous infusion. Document pain score prior to, during and after the antivenom infusion. Document vital signs and clinical progression (RPP, PSP, LN) every 10-15 min then hourly.
- Repeat antivenom administration until satisfactory response or improvement of envenoming signs is observed.

Antivenom reactions

Early hypersensitivity reactions are mostly rate dependent anaphylactoid reaction. Symptoms range from itching, urticaria, nausea, vomiting, palpitation, bronchospasm, laryngeal oedema to hypertensive shock.

In the event of antivenom reaction:

- Stop antivenom infusion.
- Give adrenaline IM 0.01 mg/kg of 1:1,000 (1 mg/mL) solution, into upper lateral thigh and repeat 5 to 10 minutes if not improved (max of 0.5 mg total dose). If IM injection is contraindicated, give slow IV boluses of 0.01 mg/kg of 1:10,000 (0.1mg/mL) solution every 2 min (max of 0.3 mg total dose). If not improving start IV infusion at 0.05-1 mcg/kg/min titrated to response.
- Give boluses of IV 0.9% saline at 20 mL/kg as required.
- Give slow IV antihistamine and steroid (e.g. chlorpheniramine maleate 0.2mg/kg), hydrocortisone 4mg/kg/dose).
- Give nebulised adrenaline in the presence of stridor or partial obstruction.
- Give nebulised salbutamol in the presence of bronchospasm or wheeze
- Once the patient is hemodynamically stabilised and the signs and symptoms subsided, the antivenom infusion should be restarted at a slower rate with very close vigilance for further reactions.

Pyrogenic reactions usually develop 1-2 hours after treatment and is believed due to pyrogenic contamination during the manufacturing process. Symptoms include fever, rigors, vomiting, tachycardia and hypotension. In the event of such reaction, provide treatment as above and treat fever with paracetamol and tepid sponging.

Late reactions (serum sickness) may occur between 1 to 12 days (mean 1 week) with symptoms of fever, arthralgia, lymphadenopathy, etc.

Treatment of serum sickness:

- Give chlorpheniramine maleate 0.25mg/kg/day in divided doses for 5 days.
- If fails to respond in 24hrs, give oral prednisolone (0.7mg/kg/day) for 5 days.

Anticholinesterases

- Should be considered in severe neurotoxic envenoming when antivenom is inadequate or unavailable.
- Give test dose of either IV Edrophonium chloride (Tensilon) 0.25mg/kg (max 10mg) or IV Neostigmine 0.05-0.07mg/kg (max 0.5-2.5mg), with IV Atropine sulphate 50µg/kg (max 0.6mg).
- If patient convincingly responds, maintain with IV Neostigmine methylsulphate (50-100µg/kg) and Atropine, 4 hourly by continuous infusion.

Supportive treatment

- Provide respiratory support/assisted ventilation in those with clinical signs of respiratory compromise/paresis.
- Give analgesia to relief pain (avoid aspirin/NSAIDs). In severe pain, IV tramadol may be given. Pain relief will normally be seen following optimal antivenom therapy.
- Give broad-spectrum antibiotics if the wound appears contaminated with devitalised tissues or necrosis has developed.
- Correction of coagulation abnormalities with fresh frozen plasma and platelets is strictly per case-by-case basis.
- Renal failure requires measurement of daily urine output, serum creatinine, urea and electrolytes. If urine output fails to increase after rehydration and diuretics (e.g. frusemide), start renal dose of dopamine (2.5µg/kg/minute IV infusion) and place on strict fluid balance. Dialysis may be required in severe cases of envenoming with renal complications.
- Clean and dress wound. Debridement of necrotic tissues should be carefully carried out as needed and should not be mistaken with the debridement for necrotising fasciitis.
- Observe for the unlikely event of compartment syndrome (pain, swelling, cold distal limbs and muscle paresis). Orthopaedic opinion regarding surgical intervention must be supported with significantly raised (>40mmHg) intracompartmental measurements using Stryker or Wick catheters.
- Give optimal amount of appropriate antivenom prior to any urgent surgical intervention.

Guide to dosages of appropriate antivenom for Malaysia		
Species the AV is raised from	Manufacturer: Antivenom	First Dose ml/vial
Monocle cobra, *Naja kaouthia*	QSMI Thai Red Cross: Cobra Antivenin	100mls/10 vials Subsequent dose 1-2 hr
King Cobra, *Ophiophagus hannah*	QSMI Thai Red Cross: King Cobra Antivenin	
Malayan krait, *Bungarus candidus*	QSMI Thai Red Cross: Malayan Krait Antivenin	50mls/5 vials Subsequent dose 1-2 hr
Banded krait, *Bungarus fasciatus*	QSMI Thai Red Cross: Banded Krait Antivenin	
Malayan pit viper, *Calloselasma Rhodostoma*	QSMI Thai Red Cross: Malayan Pit Viper	30mls/3 vials Subsequent dose 6 hr
Green pit viper, *Cryptelytrops Albolabris*	QSMI Thai Red Cross: Green Pit Viper Antivenin	
Malayan pit viper, *Calloselasma rhodostoma*, Green pit viper, *Cryptelytrops Albolabris*, Thai Russell's Viper, *Daboia siamensis*	QSMI Thai Red Cross: Hemato Polyvalent Snake Antivenom	30mls/3 vials Subsequent dose 6 hr
Monocled Cobra, *Naja kaouthia*, King Cobra *Ophiophagus hannah*, Banded Krait *Bungarus fasciatus*, Malayan Krait, *Bungarus candidus*.	QSMI Thai Red Cross: Neuro Polyvalent Snake Antivenom	50-100mls/ 5-10 vials Subsequent dose 1-2 hr
Beaked sea snake, *Hydrophis (Enhydrina) schistosus*.	Seqirus, Australia: Sea snake Polyvalent Antivenom	10-30mls/1-3 vials Subsequent dose 1-2 hr

Note:

- Subsequent doses are indicated according to the clinical signs and symptoms.
- The doses are based on animal studies and manufacturer's recommendations.
- Monocle cobra, *Naja kaouthia* antivenom has good cross neutrality with the Equatorial spitting cobra, *Naja sumatrana* venom.
- Green pit viper antivenom has good cross neutralization with venom from other green pit vipers belonging to the *Trimeresurus* complex group.
- Beaked sea snake, *Hydrophis schistosus* antivenom has good cross neutralization with many other sea snake venom.

Measuring Rate of Proximal Progression (RPP) of the oedema

1. A more informative parameter for reviewing progressive painful swelling
2. First: Determine the border of the micropore to be used to mark the proximal margin of the oedema, e.g. distal border to distal border of the micropore markers (Figure 1).
3. Second: Palpate for the most proximal margin of the swelling and apply a small strip of micropore tape to the most proximal margin of the oedema.
4. Label the current time and date on the micropoer tape.
5. Determine a fixed interval to review the progression, e.g. every 1-2 hours.
6. Measure the distance between two micropore tape borders over the fixed time interval (Figure 2).
7. The RRP for that interval will be documented in **cm/hr.**

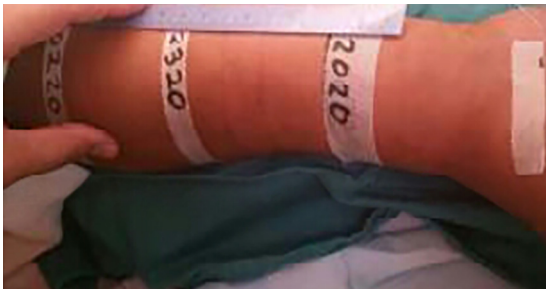


Figure 1 (above).

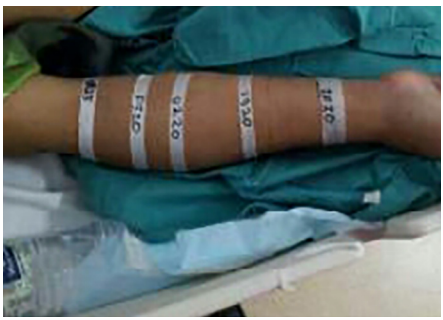


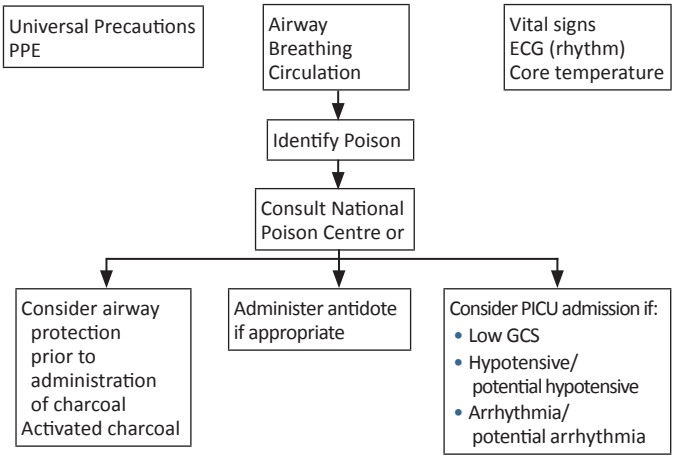
Figure 2 (above).

Serial Clinical Progress Observation Chart at fixed regular time intervals									
Date d/m	**Time** am/pm	**GCS** 3-15	**PR** bpm	**BP** mmHg	**RR** bpm	**SpO_2** %	**PSP** 0-10	**RPP** cm/hr	**LN** Yes/No
PSP= pain score progression, RPP = rate of proximal progression, LN = enlarged tender lymph node									

Serial Blood Results (evey 4-6 hours for first 24 hours or after Antivenom administratrion)									
Date	**Time**	**20WBCT**	**WBC**	**Hb**	**Platelets**	**PT**	**APTT**	**INR**	**CK**

- Poisonings in pediatric patients are usually unintentional and the amount of toxin ingested is often minimal obviating the need for gastric lavage.
- However, in some situations related to dose per body weight even small amounts ingested can be fatal.
- The ingestion of anti-hypertensives, oral hypoglycemic agents, psychiatric drugs, toxic alcohols, salicylate oils and narcotics require special care and consideration.

PRINCIPLES IN APPROACH TO POISONING



Key points

- All poisoning cases should be investigated for any suspicion of neglect or abuse.
- Prehospital care personnel should be wary of contact or inhalation exposure causing poisoning.
- Gastric lavage in children has more risks than benefits and is rarely performed. It should only be initiated in patients who have ingested large amounts of a potentially life threatening toxin. The airway must be secured and the toxin must not be a corrosive or hydrocarbon.
- Whole bowel irrigation can be performed as another method of gastrointestinal decontamination in situations where the toxin can cause prolonged gut transit.
- Skin decontamination with water is usually sufficient for corrosives. Continue irrigation till skin pH tested with litmus paper is neutral to ensure proper decontamination. Soap and water will be required for hydrocarbons and organophosphates.
- Multiple doses of activated charcoal (MDAC) are indicated for theophylline, phenobarbital, carbamazapine, dapsone, quinine poisonings, extended-release preparation and bezoar-forming medication.

- Administer antidotes if indicated. If the antidote you require is not available at your center, contact the hospital pharmacist on call to help source the antidote. Hospital Kuala Lumpur and Hospital Tengku Ampuan Rahimah, Klang pharmacists can assist in sourcing antidotes.
- Ensure the patient is well hydrated with good urine output as this will facilitate renal excretion of most toxins.
- Correct acidosis with hydration first followed by sodium bicarbonate infusions. If the acidosis continues to worsen the patient should be referred for hemodialysis urgently.
- Toxinz®,Poisondex® and Uptodate® are a few resources currently available in most Malaysian hospitals. If the information you require is not available, you may consult a clinical toxicologist or call the national poison center.

National Poison Center		
Day	Time	Contact
Weekdays	8:10am-5:10pm	+604-6570099
	5:10pm-10:10pm	+012-4309499
Weekends & Public Holidays	8:10am-5:10pm	+012-4309499

Laboratory investigations

A careful history may obviate the need for blood tests.

Investigation	Indication
Blood glucose	All cases with altered sensorium
Blood gas analysis	Patients with respiratory insufficiency, hyperventilation or suspected metabolic acid base disturbance (A wide anion gap is seen in methanol, paraldehyde, iron, ethanol, salicylate poisoning.
Electrolytes	Hypokalaemia may occur in acute poisoning, i.e salicylate/ theophylline
Paracetamol level	Should be performed in deliberate poisoning in an older child
ECG	Detection of dysrhythmia i.e widened QRS or prolonged QT interval. Tricyclic antidepressant poisoning may manifest as myocardial depression, ventricular fibrillation or ventricular tachycardia
Radiology	Suspected ingestion of metallic objects, iron salts.

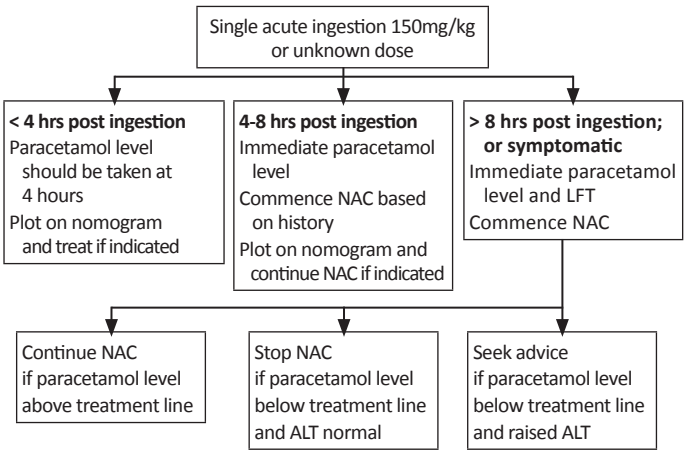
- Other investigations may be required depending on the type of poison ingested.

TOXIDROMES				
Cholinergic	Organophosphates Carbamates	Salivation, lacrimation, diaphoresis, vomiting, urination, defecation, muscle fasciculations, weakness, bronchorrhea	Bradycardia, miosis, seizures, respiratory failure, paralysis.	Airway protection and ventilation, atropine, pralidoxime
Anticholinergic	Scopalamine Atropine	Altered mental status, mydriasis, dry/flushed skin, urinary retention, decreased bowel sounds, hyperthermia, dry mucus membranes	Seizures, dysrhythmias, rhabdomyolysis.	Physostigmine(if appropriate), sedation with benzodiazepines, cooling, supportive management
Salicylates	Aspirin Salicylate oils	Altered mental status, metabolic acidosis, tinnitus, hyperapnea, tachycardia, diaphoresis, vomiting	Low grade fever, ketonuria, acute lung injury.	MDAC, alkalinsation of the urine with potassium repletion, hemodialysis, hydration
Hypoglycemia	Sulfonylureas Insulin	Altered mental status, diaphoresis, tachycardia, hypertension	Slurring of speech, seizures.	Intravenous glucose, oral feeding if able, frequent capillary blood for glucose measurement, octreotide
Serotonin syndrome	Pethidine SSRI TCA Amphetamines	Altered mental status, hyperreflexia, hyperthermia, mydriasis, increased muscle tone	Intermittent whole body tremor.	Cooling, sedation with benzodiazepines, hydration, supportive management

PARACETAMOL

A single ingestion of > 150mg/kg paracetamol can cause significant toxicity. Patients may be asymptomatic or exhibit nausea, vomiting and abdominal pain. If left untreated, may progress to liver failure. Therapy involves the administration of N-acetylcysteine (NAC), a precursor to facilitate the synthesis of glutathione.

MANAGEMENT ALGORITHM



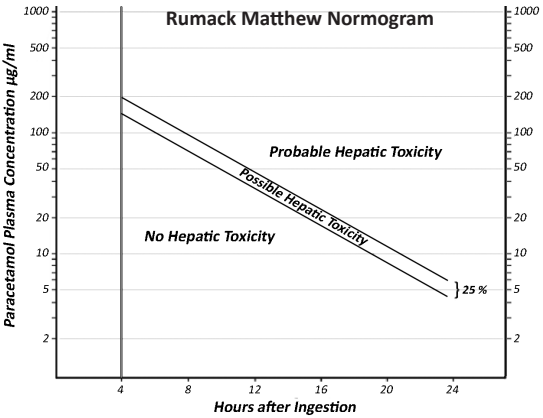
Key points

- As history may be inaccurate especially in intentional poisonings it is important to correlate with clinical features and laboratory investigations
- Patients who present > 8 hours of ingestion or with symptoms of toxicity (right upper quadrant pain, nausea, vomiting) should be given NAC immediately.
- The paracetamol level does not need to be repeated unless the patient is suspected to have taken another dose of paracetamol in hospital.
- Other investigations: RBS/ALT/ALP/INR/RFT/Lactate daily till improvement.
- IV NAC is administered if the plasma paracetamol level exceeds toxic level by Rumack Matthew nomogram.
- Ensure NAC is appropriately diluted and patient does not develop fluid overload.
- Adverse reactions to NAC are flushing, aching, rashes, angioedema, bronchospasm and hypertension. NAC should be stopped and if necessary, IV antihistamine given. Once adverse reactions resolve, NAC can be re-started at 50mg/kg over 4 hours.
- Loading dose: 150mg/kg in 3mls/kg 5% dextrose over 15 minutes, followed by 50mg/kg in 7 mls/kg 5% dextrose over 16 hours.
- If patient is on enzyme-inducing drugs, they should be given NAC if the paracetamol levels are 50% or more of the standard reference line.
- Continue NAC beyond 24 hours at 50mg/kg in 7 mls/kg 5% dextrose over 16 hours if the repeated LFT, lactate and INR levels worsen.
- Stop NAC with clinical and laboratory improvement (ALT/ALP/INR/Lactate).

HIGH RISK TREATMENT LINE
At RIsk Patients
At R Regular use of enzyme inducing drugs e.g. carbamazapines, phenytoin, phenobarbitone, rifampicinisk Pati
Conditions causing glutathione depletion Malnutrition, HIV, eating disorders, cytic fibrosis

Supratherapeutic paracetamol ingestion

- Management of a single overdose is straightforward and guided by the above. However when cases are associated with staggered overdoses or repeated supratherapeutic doses, patient with high risk factors or late presentations, management decisions become more complex.
- Consider supratherapeutic paracetamol poisoning in children who have ingested more than 90mg/kg/day.
- Decision to start NAC should be guided by clinical presentation and laboratory investigations. Patients who present with abdominal pain, vomiting and a deranged liver function test should be started on NAC.
- As the patient has taken multiple doses rather than a single dose the Rumack Matthew nomogram cannot be used to decide on NAC. A plasma paracetamol level of more than 10mg/L can be significant.



Indicators of severe paracetamol poisoning (when to refer to a specialist centre)

- Progressive coagulopathy, INR>2 at 24 hours, >4 at 48 hours or >6 at 72 hours
- Renal impairment with creatinine > 200 umol/L
- Hypoglycaemia
- Metabolic acidosis despite rehydration
- Hypotension despite fluid rescusitation
- Encephalopathy

SALICYLATE

- Ingestion of salicylate oil or "Minyak Cap Kapak" is a common cause of pediatric salicylate poisoning in Malaysia. Ingestion of 1 ml of salicylate oil is equivalent to 150mg of salicylate.
- Ingestion of more than 0.15mg/kg will cause symptoms.
- The fatal dose is estimated to be 0.2-0.5g/kg.
- Its main effects are as a metabolic poison causing metabolic acidosis and hyperglycemia.

Clinical Manifestations of Salicylate poisoning	
General	Hyperpyrexia, profuse sweating and dehydration
CNS	Delirium, seizures, cerebral oedema, coma, Reye's syndrome
Respiratory	Hyperventilation
GIT	Epigastric pain, nausea, vomiting, UGIH, acute hepatitis
Renal	Acute renal failure
Metabolic	Hyper/hypoglycaemia, anion gap metabolic acidosis, hypokalaemia
Cardiovascular	Non-cardiogenic pulmonary oedema
Investigations : FBC, PCV, BUSE/Serum creatinine, LFT/PT/PTT, RBS; ABG Serum salicylate level at least 6 hours after ingestion	

Management

- Activated charcoal at 1gm/kg can be administered orally or via ryle's tube depending on patient's clinical condition.
- Correct dehydration, hypoglycemia, hypokalemia, hypothermia and metabolic acidosis.
- Patients presenting with coma, convulsions, acute renal failure and pulmonary edema should be referred for hemodialysis urgently. For infants exchange transfusion is preferable.
- The Dome Nomogram is not recommended as a guide for treatment. Treatment is guided by clinical presentation, severity of acidosis and plasma salicylate levels.
- Plasma salicylate level can be taken at 4 hours and repeated every 3 hours till the level peaks i.e. the current level is less than the previous level.

Salicylate poisoning guide for children < 12 years		
Severity	Level	Treatment
Mild	1.5-3.3 mmol/l or 200-450mg/l	Hydration and monitor level
Moderate	3.3-5.1 mmol/l or 450-700mg/l	Intravenous fluids and urinary alkalinasation, monitor level
Severe	>5.1 mmol/l or >700mg/l	Hemodialysis

- In mild poisonings hydration is usually sufficient. If the acidosis persists or worsens despite hydration sodium bicarbonate infusion should be commenced.
- Dilute 1ml/kg 8.4% sodium bicarbonate in 10ml/kg sterile water for injection, Normal saline or Dextrose 5% and add 1mmol/kg potasium. This should be given at a rate of 2ml/kg/hr intravenous infusion.
- Check urinary pH hourly aiming for a ph of 7.5-8.5. The rate of sodium bicarbonate administration given above will need to be increased if the urine pH remains <7.5.
- Check serum potasium every 3 hours and maintain at 4-4.5 mmol/l.
- Treat hypoglycemia with 2-5ml/kg of 10% dextrose.
- Hemodialysis is indicated for cases with serum salicylate level more than 700mg/L(>5.1mmol/l), refractory acidosis, renal failure, non-cardiogenic pulmonary edema, coma and seizures. For infants exchange transfusion is preferable.

IRON

- Dangerous dose of iron can be as small as 30mg/kg. The toxic effect of iron is due to unbound iron in the serum.

Iron Preparation	Elemental Iron (%)
Ferrous gluconate	12
Ferrous lactate, sulfate	20
Ferrous chloride, fumerate	30

To calculate the amount of elemental iron taken by the patient:

$$\text{Amount} = \frac{\text{mg per tablet x number of tablets x percentage of elemental iron}}{\text{Body weight (Kg) x 100}}$$

Clinical Manifestations in Iron poisoning	
Stage 1 (6 - 12hrs)	Gastrointestinal bleeding, vomiting, abdominal pain, diarrhoea, hypotension, dehydration, acidosis and coma.
Stage 2 (8 - 16hrs)	Symptom free period but has nonspecific malaise.
Stage 3 (16-24hrs)	Profound hemodynamic instability and shock.
Stage 4 (2 - 5wks)	Liver failure and gastrointestinal scarring with pyloric obstruction.

- Ingestion <40mg/kg elemental iron, patients are unlikely to require treatment.
- Ingestion of >40mg/kg will require observation and monitoring of serum iron levels.
- Ingestion of >60mg/kg with serum iron levels exceeding 60 micromol/L should be referred to a tertiary center able to administer desferrioxamine.

Management

- Emphasis is on supportive care with an individualised approach to gastrointestinal decontamination and selective use of antidotes.
- Resuscitate and stabilise as necessary.
- Perform an abdominal X-ray. If pellets are seen, whole bowel irrigation (WBI) with polyethylene glycol can be performed (500ml/hr in children <6 yrs, 1000ml/hr in children 6-12 yrs and 1500-2000ml/hr in children >12 yrs).
- Contraindications: paralytic ileus, intestinal obstruction or GI bleeding, significant haematemesis, hypotension. After WBI the abdominal X-ray should be repeated to exclude gastric adherence. If gastric adherence noted surgical removal should be considered.
- Blood should be taken at 2-4 hrs post ingestion:
  - If level <60micromol/l, unlikely to develop toxicity.
  - If level 60-90micromol/l observe for 24-48 hours. Chelate if symptomatic i.e. haematemesis or meleana
  - If level >90micromol/l or significant symptoms present, chelation with IV Desferrioxamine 15mg/kg/h till max of 80mg/kg in 24 hours.
  - If serum iron is not available, severe poisoning is indicated by nausea, vomiting, leucocytosis >15 X 109 , metabolic acidosis and hyperglycemia >8.3 micromol/l.
- Sustained release or enteric coated tablets will require a repeat level at 4-6 hours post ingestion.
- Caution: Desferrioxamine may cause hypotension and pulmonary fibrosis and Acute Respiratory Distress Syndrome (ARDS)
- Maintenance of fluid balance and good renal output is important to ensure removal of chelated iron.
- Hemodialysis will be required to remove chelated iron if patient develops anuria or oliguria.
- Continue chelation therapy till serum iron is normal, metabolic acidosis resolves and urine colour returns to normal.
- If symptoms are refractory to treatment following 24 hours of chelation, reduce rate of infusion of chelation therapy and consult clinical toxicologist because of its association with acute respiratory distress syndrome.
- Critical care management includes management of cardiopulmonary failure, hypotension, severe metabolic acidosis, hypoglycemia or hyperglycemia, anemia, GIT bleeding, liver and renal failure.
- Hepatotoxicity is an indicator of severe poisoning and poor outcome.

ANTIHYPERTENSIVES

- Calcium channel blocker and beta-blocker ingestion may cause significant hypotension depending on dose per body weight the weight of the child and number of tablets ingested.

Management

- All patients must be monitored for at least 24 hours.
- Patients who develop hypotension will require close monitoring of electrolytes especially calcium and potassium. Glucose monitoring will also be required.
- Hypotension should be treated with a fluid bolus first, 10-20 ml/kg over 5-10 minutes, may be repeated if hypotension is not resolved).
- Symptomatic bradycardia should be treated with IV Atropine 0.02mg/kg (min 0.1mg) repeated every 5 minutes as necessary.
- If the patient is still hypotensive administer IV Calcium Gluconate 0.5ml/kg over 5-10 minutes up to 30ml for calcium channel blocker poisoning. Repeated doses after 10 to 20 minutes can be administered but will require calcium level monitoring.
- For beta blocker poisoning administer bolus IV Glucagon 50-150 mcg/kg in dextrose 5% followed by an infusion of 50-150 mcg/kg/hr. Do not administer Glucagon for more than 48 hours.
- Further hypotension can be managed with a low dose of noradrenaline infusion at 0.05-0.1mcg/kg/min.
- If the patient remains hypotensive despite the above treatment the patient may benefit from a high dose insulin euglycemia treatment. Consult a clinical toxicologist or intensivist. Increasing the dose of noradrenaline infusion or adding further inotropes will worsen the patients condition and should be avoided.

METHADONE

The effect of Methadone is more prolonged as compared to Morphine. *Ingestion or exposure to any substance abuse or narcotics warrants a referral to SCAN team for further investigation.*

Management

- Identify opiod toxidrome of pin point pupils, bradypnea or apnea and depressed consiousness.
- Assist ventilation with a bag-valve-mask device immediately. Prepare equipment for intubation.
- Prepare IV Naloxone and administer starting with 0.1mg/kg. If no increase in respiratory rate in 2-3 minutes increase to 0.5mg. Double the dose of IV Naloxone if no increase in respiratory rate is seen every 2-3 minutes up to a maximum of 10mg. Once respiratory rate increases with further clinical improvement continue monitoring. Repeat dosing may be required or a maintenance infusion started of two thirds the effective reversal dose per hour. Continue to monitor respiration closely preferably in an intensive care unit.

- Proceed to intubation and further resuscitation if the Naloxone administered does not reverse apnea/bradypnea and consciousness. Investigate for other causes of reduced consciousness.
- Continue monitoring for signs of respiratory depression up to 48 hours from the time of ingestion.

ETHANOL AND ALCOHOLS

Toxic alcohols ingested in small doses can cause significant toxicity in children. Patients may present with vomiting, blurring or loss of vision, hypoglycemia, respiratory distress, unexplained metabolic acidosis, coma or cardiovascular collapse.

Alcohol	Content	Fomepizole	Dialysis
Ethanol	Alcoholic beverages	-	+/-
Methanol	Automobile coolant and anti-freeze, windshield washer fluid, paint and varnish remover	+	+
Ethylene glycol	Automobile coolant and anti-freeze, solvents	+	+
Isopropanol	Rubbing alcohol, solvents	-	+/-

Management

- Resuscitate and stabilise as necessary. Check blood glucose level and correct hypoglycemia with intravenous dextrose.
- Gastric lavage is only indicated if the airway is protected and the patient has ingested a large amount of the toxin. Activated charcoal is not recommended.
- Ensure good hydration. Sodium bicarbonate may be administered to correct metabolic acidosis pending hemodialysis.
- IV Fomepizole should be administered to block conversion of methanol and ethylene glycol to formic acid and glycolic acid. Please discuss with a clinical toxicologist regarding administration before and during hemodialysis. Ethanol infusion is not recommended for pediatric patients.
- Arrange for hemodialysis to remove toxin and metabolites as well as correct acidosis.

Antidepressants	
Tricyclic antidepressants (TCA)	Amitriptyline
Selective serotonin reuptake inhibitors (SSRI)	Citalopram, Escitalopram, Fluoxetine, Setraline, Fluvoxamine
Nonselective monoamine reuptake inhibitors	Venlafaxine, Duloxetine
Others	Mirtazapine, Buproprion

The newer generation of psychiatric drugs such as selective serotonin reuptake inhibitors(SSRI) and nonselective monoamine reuptake inhibitors (NSRI) are safer compared to tricyclic antidepressants.
As a result they are prescribed more often then TCAs but may still cause significant toxicity in children.

Management

- There is no specific antidote. Monitor for signs of serotonin syndrome (agitation, confusion, tachycardia, hypertension, dilated pupils, loss of muscle coordination, muscle rigidity, sweating, diarrhea and headache). In severe serotonin syndrome, patient may develop high fever, seizures, irregular heart beat, rhabdomyolysis and unconsciousness.
- Activated charcoal 1gm/kg can be administered orally if the patient is conscious and airway uncompromised, or airway is secured.
- Benzodiazepines e.g. IV Diazepam can be administered for seizures and to control agitation. Avoid physical restraints, as this will worsen rhabdomyolysis. Avoid phenytoin and fentanyl.
- Good hydration is required to enhance drug elimination and treat rhabdomyolysis.
- Treat hypotension with fluids resuscitation first followed by low dose noradrenaline infusion if necessary.
- Place patient on continuous ECG monitoring to look for QRS widening, QT prolongation, cardiac conduction abnormality.
  Monitor for arrhythmias, hypotension, altered sensorium or seizures, which usually occurs within the first 6 hours after ingestion.
- Treatment should be instituted for widened QRS complex and wide complex arrhythmias. QRS widening can be corrected with sodium bicarbonate bolus at 1-2mmol/kg, repeated boluses or starting infusion may be necessary.
- QTc monitoring is also required. QTc prolongation of more than 450mm with the presence of any arrhythmias, administer MgSO4 bolus or infusion.
- Use ACLS/APLS guidelines to treat life threatening arrhythmias.
  Identify the antidepressant taken to anticipate other possible complications.

INSECTICIDES

Common Insecticides in Malaysia	
Chemical Group	Active Ingredient
Organosphosphates	Malathion, Chlorpyrifos
Carbamates	Carbofuran
Pyrethins/Pyrethroids	Cypermethrin, Pyrethin, Permethrin

Household insecticides sold at supermarkets and department stores are usually minimally toxic consisting of pyrethins and pyrethenoids. In spite of this, organophosphates and carbamates can still be purchased and contents of the insecticide ingested should be confirmed to assess risk.

Management

- Resuscitate and stabilise the patient as necessary.
- Remove contaminated clothing and wash exposed areas with soap and water.
- Examine the patient for signs and symptoms of a cholinergic toxidrome (muscle fasciculation/weakness, fatigue, salivation, lacrimation, urination, diarrhoea, GI upsets, emesis, sweating, miosis, bradycardia, bronchospasm, hypotension, seizure and coma).
- If present, give IV Atropine 0.01-0.05mg/kg (minimum 0.1mg) every 5 minutes, doubling the dose each time, till secretions have reduced.
  Atropine administration is guided by the drying of secretions rather than the heart rate or pupil size.
  A continuous infusion of atropine can be started at 0.05mg/kg/hr. Once secretions have dried atropine infusion should be titrated down to avoid atropine toxicity. Signs of atropine toxicity i.e. agitation, dry skin, hyperthermia, tachycardia and mydriasis.
- Pralidoxime is only indicated for organophosphate poisoning, and it needs to be given early. Pralidoxime may prevent intermediate syndrome in organophosphate poisoning. Give IV Pralidoxime 25-50mg/kg as an infusion over 30 min, repeated in 6 to 8 hours (max 12g/day). Carbamate poisoning usually resolves in 24 - 48 hours and only requires minimal doses of atropine.
- Patients who have ingested an organophosphate and are not intubated should be monitored closely for signs of proximal muscle weakness that is an early sign of intermediate syndrome. Monitoring should continue until atropine administration has ceased for at least 24 hours.
- Patients who develop intermediate syndrome will have prolonged respiratory paralysis that may last from a few days to weeks. Support ventilation until muscle power improves.
- If intubation requires muscle relaxant, do not use succinylcholine as it has a prolonged action.
- Treat hypotension with Norepinephrine and epinephrine.
- Dopamine is not effective.

- Haemodiaysis/PD is not effective as tricyclics are protein bound. Important to avoid the use of flumazenil for reversal of co-ingestion of benzodiazepines as this can precipitate tricyclic induced seizure activity.

HERBICIDES

Common herbicides seen in Malaysia are glyphosate and paraquat. Glyphosate which is now the primary content of Roundup® may cause significant GI injury and is managed symptomatically.

Paraquat is sold as a green liquid.

- All patients who present with a history of herbicide ingestion must have a urine paraquat level on arrival. Test should be repeated if negative at 4 to 6 hours post ingestion if the first test was performed at less than 4 hours post ingestion.
- Patients who have ingested paraquat may present with the following :
  - Difficulty breathing (early)
  - Diarrhea and vomiting
  - Ulcers in the mouth and esophagus
  - Jaundice and liver failure
  - Renal failure

Management

- Remove contaminated clothes and wash skin with soap and water.
- Avoid unnecessary administration of oxygen, unless significant hypoxia.
- Gastric lavage is not recommended as paraquat and glyphosate may cause gastrointestinal injury. Some herbicides are also mixed with hydrocarbons. In large intentional ingestions, secure the airway and a Ryle's tube can be inserted gently, with stomach contents aspirated to remove any toxins in the stomach.
- Administer activated charcoal at a dose of 1g/kg on arrival and 6 hourly for at least 48 hours for paraquat poisoning. Activated charcoal has the same efficacy as Fuller's earth.
- Ensure good hydration to enhance elimination of the toxin through renal excretion.
- Patients with confirmed paraquat poisoning who develop respiratory distress and shock have a poor prognosis. Palliative care with oxygen and analgesics should be administered for patient comfort.

KEROSENE INGESTION AND HYDROCARBONS

All cases should be observed for at least 12 hours. Children who present with multiple bouts of vomiting are at a higher risk of aspiration pneumonitis.

- Decontamination and charcoal is contraindicated.
- Monitor for cough, fever and rapid breathing. Children who develop these symptoms should have a chest x-ray.
- Cerebral effects may occur from hypoxia secondary to massive inhalation.
- Antibiotics and steroids may be useful in lipoid pneumonia (esp. liquid paraffin).
- Support ventilation as indicated till recovery.

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Chapter 110: Anaphylaxis

Introduction

Anaphylaxis is likely when all of the following 3 criteria are met:

- Sudden onset and rapid progression of symptoms (minutes to hours)
- Life-threatening Airway and/or Breathing and/or Circulation problems
- Skin and/or mucosal changes (flushing, urticaria, angioedema)

Life threatening features are as follows:

- Airway problems:
  - Airway swelling e.g. throat and tongue swelling.
  - Hoarse voice.
  - Stridor.
- Breathing problems:
  - Shortness of breath (bronchospasm, pulmonary oedema).
  - Wheeze.
  - Confusion cause by hypoxia.
  - Cyanosis is usually a late sign.
  - Respiratory arrest.
- Circulation problems
  - Shock.
  - Cardiovascular collapse with faintness, palpitations, loss of consciousness.
  - Cardiac arrest

The following supports the diagnosis:

- Exposure to a known allergen for the patient

Other considerations:

- Skin or mucosal changes alone are not a sign of an anaphylactic reaction
- Skin and mucosal changes can be subtle or absent in up to 20% of reactions (some patients can have only a decrease in blood pressure, i.e., a Circulation problem)
- There can also be gastrointestinal symptoms (e.g. vomiting, abdominal pain, incontinence)

Key points to severe reaction

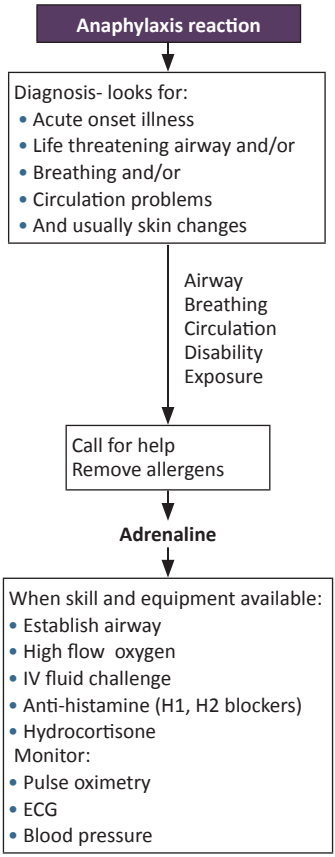
- Previous severe reaction.
- History of increasingly severe reaction.
- History of asthma.
- Treatment with β blocker.

Time course for fatal anaphylactic reactions.

When anaphylaxis is fatal, death usually occurs very soon after contact with the trigger. Fatal food reactions cause respiratory arrest typically after 30–35 minutes; insect stings cause collapse from shock after 10–15 minutes; and deaths caused by intravenous medication occur most commonly within 5 minutes

Approach to treatment (see following pages)

The clinical signs of critical illness are generally similar because they reflect failing respiratory, cardiovascular and neurological system.
Use ABCDE approach to recognise and treat anaphylaxis.


Anaphylaxis reaction
Diagnosis- looks for:
• Acute onset illness
• Life threatening airway and/or
• Breathing and/or
• Circulation problems
• And usually skin changes
Airway
Breathing
Circulation
Disability
Exposure
Call for help
Remove allergens
Adrenaline
When skill and equipment available:
• Establish airway
• High flow oxygen
• IV fluid challenge
• Anti-histamine (H1, H2 blockers)
• Hydrocortisone
Monitor:
• Pulse oximetry
• ECG
• Blood pressure

Emergency treatment in anaphylaxis				
Drugs in anaphylaxis	Dosage by age			
	< 6 months	6 mths to 6 years	6 years-12 years	> 12 years
Adrenaline IM- pre hospital practitioners	150 micrograms (0.15ml of 1000)		300micrograms (0.3ml of 1:1000)	500microgram (0.5ml of 1:1000)
Adrenaline IM- in hospital practitioners (rpt after 5 mins if no improvement)	10 micrograms/kg 0.1ml/kg of 1:10000 (infants/young children) OR 0.01ml/kg of 1:1000 (older children)			
Adrenaline IV	Start with 0.1microgram/kg/min and titrate up to 5microgram/kg/min*			
Crystalloid	20 mls/kg			
Hydrocortisone ** IM or Slow IV)	25mg	50mg	100mg	200mg

*If hypotensive persist despite adequate fluid (CVP>10), obtain echocardiogram and consider infusing noradrenaline as well as adrenaline.

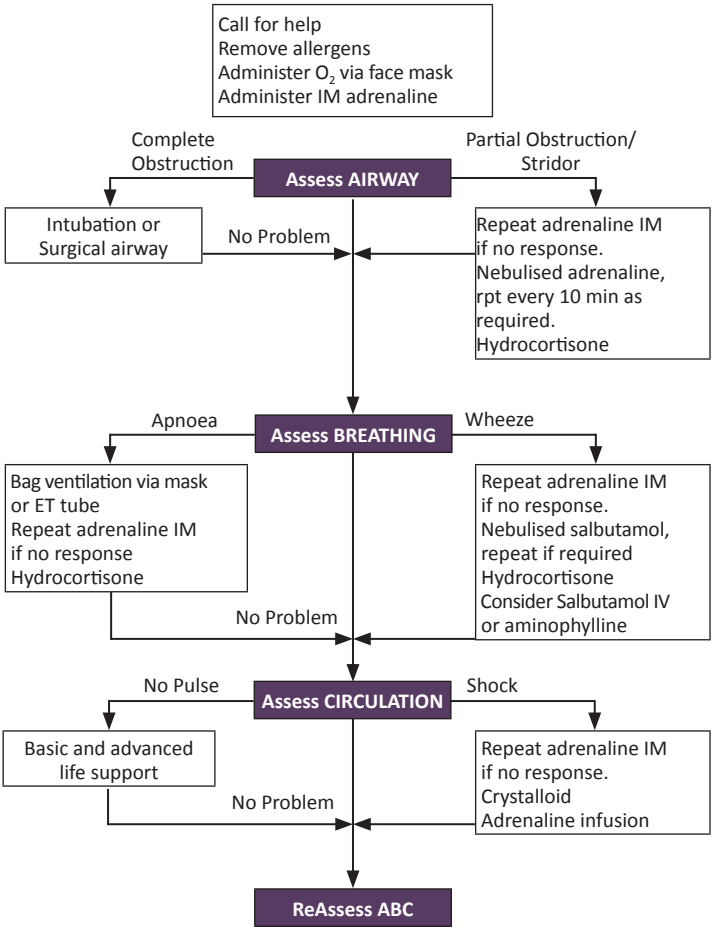
** Dose of intravenous corticosteroid should be equivalent to 1-2mg/kg/dose of methylprednisolone every 6 hours (prevent biphasic reaction).

Oral prednisolone 1m/kg can be used in milder case.

Antihistamine are effective in relieving cutaneous symptoms but may cause drowsiness and hypotension.

If the patient is on β-blocker, the effect of adrenaline may be blocked; Glucagon administration at 20-30µg/kg, max 1mg over 5 minutes followed by infusion at 5-15µg/min is useful.

Continue observation for 6-24 hours depending on severity of reaction because of the risk of biphasic reaction and the wearing off of adrenaline dose.


Call for help
Remove allergens
Administer O_2 via face mask
Administer IM adrenaline
Complete Obstruction
Partial Obstruction/ Stridor
Assess AIRWAY
Intubation or Surgical airway
No Problem
Repeat adrenaline IM if no response.
Nebulised adrenaline, rpt every 10 min as required.
Hydrocortisone
Apnoea
Assess BREATHING
Wheeze
Bag ventilation via mask or ET tube
Repeat adrenaline IM if no response
Hydrocortisone
Repeat adrenaline IM if no response.
Nebulised salbutamol, repeat if required
Hydrocortisone
Consider Salbutamol IV or aminophylline
No Problem
No Pulse
Assess CIRCULATION
Shock
Basic and advanced life support
Repeat adrenaline IM if no response.
Crystalloid
Adrenaline infusion
No Problem
ReAssess ABC

Discharge Planning

- Prevention of further episodes
- Education of patients and caregivers in the early recognition and treatment of allergic reaction
- Management of co-morbidities that increase the risk associated with anaphylaxis
- An adrenaline pen should be prescribed for those with history of severe reaction to food, latex, insect sting, exercise and idiopathic anaphylaxis and with risk factor like asthma.

REFERENCES

SECTION 15 POISONS AND TOXINS

Chapter 108 Snake Bite

For the Image Gallery of Land Snakes of Medical Importance in Malaysia go to http://mstoxinology.blogspot.my/p/info.html

Chapter 109 Common Poisons and Toxins

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3. Rogers textbook of Pediatric Intensive Care 4th edition Chapter 31
4. Wallace CI. Paracetamol overdose: an evidence based flowchart to guide management. Emerg Med J 2002; 19:202-205
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Chapter 110 Anaphylaxis

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4. Estelle F, Simons R. Anaphylaxis and treatment. Allergy 2011; 66 (Suppl 99) 31-34
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6. Graham RN, Neil HY. Anaphylaxis Medicine 2008; 37: 57-60
7. Tang MLK, Kang LW. Prevention and treatment of anaphylaxis. Paediatrics and Child Health 2008; 18: 309-316
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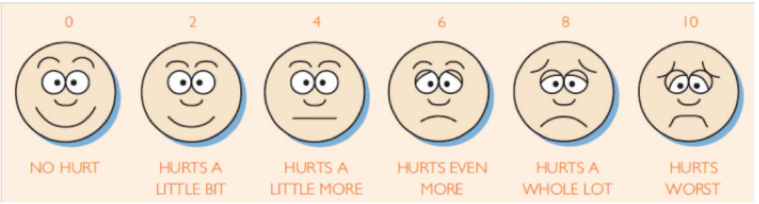
9. Emergency treatment of anaphylaxis reactions, APLS

The health care provider should decide on an appropriate level of pain relief for a child in pain and also before a diagnostic or therapeutic procedure.
We can assess a child in pain using an observational-based pain score or a self-assessment pain score. Repeated assessment needs to be done to guide further analgesia.

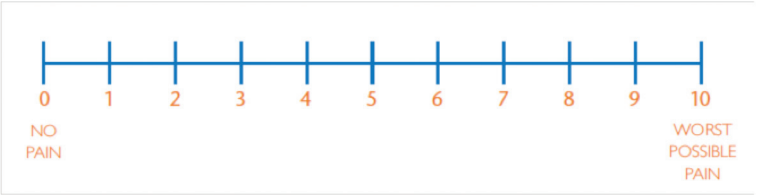
Observational-based Pain Score: The Alder Hey Triage Pain Score				
No.	Response	Score 0	Score 1	Score 2
1	Cry or voice	No complaint or cry Normal conversation	Consolable Not talking negative	Inconsolable Complaining of pain
2	Facial expression – grimace*	Normal	Short grimace <50% time	Long grimace >50% time
3	Posture	Normal	Touching / rubbing / sparing / limping	Defensive / tense
4	Movement	Normal	Reduced or restless	Immobile or thrashing
5	Colour	Normal	pale	Very pale / 'green'
*grimace – open mouth, lips pulled back at corners, furrowed forehead and /or between eye-brows, eyes closed, wrinkled at corners. From Appendix F, APLS 5th Edition; Score range from 0 to 10				

Self Assessment Pain Score:
The two examples are FACES Pain Scale (Wong & Baker) and Verbal Pain Assessment Scale (Likert Scale).

FACES Pain Scale - The child is more than 3 years old and he or she is asked to choose a face on the scale which best describes his / her level of pain. Score is 2, 4, 6, 8, or 10.



Verbal Pain Assessment Scale
A child who is more than 8 years old is asked to rate his or her pain by circling on any number on the scale of 0 to 10.



Chapter 112: Sedation and Analgesia for Diagnostic and Therapeutic Procedures

Definitions

- *Sedation* – reduces state of awareness but does not relieve pain.
- *Analgesia* – reduces the perception of pain.

Levels of sedation

Procedural sedation means minimal or moderate sedation / analgesia.

- *Minimal* sedation (anxiolysis): drug-induced state during which the patient responds normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.
- *Moderate* sedation / analgesia: drug-induced depression during which the patient responds to verbal commands either alone or accompanied by light tactile stimulation. The airway is patent and spontaneous ventilation is adequate. Cardiovascular function is adequate.

Note:

- Avoid deep sedation and general anesthesia in which the protective airway reflexes are lost and the patient needs ventilatory support.
- However, some children require general anesthesia even for brief procedures whether painful or painless because of their level of distress.

Indications

- Patients undergoing diagnostic or therapeutic procedures.

Contraindications

- Blocked airway including large tonsils or adenoids
- Increase intracranial pressure
- Reduce level of consciousness prior to sedation
- Respiratory or cardiovascular failure
- Neuromuscular disease
- Child too distressed (may need higher level of sedation or even anaesthesia)

Patient selection

The patients should be in Class I and II of the ASA classification of sedation risk.

- Class I – a healthy patient
- Class II – a patient with mild systemic disease, no functional limitation

Preparation

- Consent
- Light restraint to prevent self injury

Personnel

- At least a senior medical officer, preferably PLS or APLS trained.
- A nurse familiar with monitoring and resuscitation.

Facilities

- Oxygen source
- Suction
- Resuscitation equipment
- Pulse oximeter
- ECG monitor
- Non-invasive BP monitoring
- Defibrillator

Fasting

- Recommended for all major procedures:
  Nil orally: no solid food for 6 hours
  no milk feeds for 4 hours
- May allow clear fluids up to 2 hours before, for infants
  (Note that it is difficult to sedate a hungry child)

Venous access

- Vein cannulated after applying local anaesthesia for 60 minutes, preferably done the day before.

Sedation for Painless Procedures

- *Non-pharmacologic measures* to reduce anxiety, e.g. let the mother feed, hold and talk to the child"
  - Behavioural management, child friendly environment
- Medication
  - Oral Chloral hydrate (drug 1 in table) should be used.

Note:

- Opioids should not be used.
- Sedatives such as benzodiazepine and dissociative anaesthesia ketamine should be used with caution and only by experienced senior medical officers.
- A few children may need general anaesthesia and ventilation even for painless procedure such as MRI brain if the above fails.

Sedation for Painful Procedures

- *Non-pharmacologic measures* to reduce anxiety
  - Behavioural management, child friendly environment.
- *Local anaesthesia*
  - Topical : Lignocaine EMLA ® 5% applied with occlusive plaster for 60 minutes to needle puncture sites, e.g. venous access, lumbar puncture, bone marrow aspiration.
  - Subcutaneous Lignocaine infiltrated to the anaesthesised area prior to prolonged needling procedure, e.g. insertion of chest drainage.

- Medications (see table next page)
  Many sedative and analgesic drugs are available; however, it is advisable to use the following frequently used medications:

1. *Narcotics (analgesia)* also have sedative effects
- Fentanyl
- Naloxone (narcotic reversal)
  - For respiratory depression* caused by narcotics.
- Morphine - general dissociative anaesthesia

2. Benzodiazepines (sedatives) have no analgesia effects
- Diazepam
- Flumazenil (benzodiazepine reversal)
  - Can reverse respiratory depression* and paradoxical excitatory reactions
- Midazolam.

3. Ketamine (to be used by senior doctors preferably in the presence of an anaesthesia doctor).
  Adverse effects include
- Increased systemic, intracranial and intraocular pressures.
- Hallucinogenic emergence reactions (usually in older children).
- Laryngospasm.
- Excessive airway secretions.

**provide bag-mask positive pressure ventilation whilst waiting for reversal agent to take effect.*

Post sedation monitoring and discharge

Patient can be discharged when:
- Vital signs and SaO_2 normal.
  And
- Arousable.
- Baseline level of verbal ability and able to follow age-appropriate commands.
- Sit unassisted (if appropriate for age).

Drug dosages used for sedation and analgesia in children			
Drug	Dose	Onset of action	Duration of action
Chloral Hydrate	Oral 25 - 50 mg/kg; Max 2g. For higher doses, i.e. 50 -100 mg/kg, please consult paediatrician or anaesthesiologist.	15 – 30 mins	2 -3 hours
Narcotics			
Morphine	IV >1 year: 200-500 mcg/kg <1 year: 80 mcg/kg	5 – 10 mins	2 – 4 hours
Fentanyl	IV 1 – 2 mcg/kg	2 – 3 mins	20 -60 mins
Benzodiazepines			
Midazolam	IV 0.05 – 0.1 mg/kg, max single dose 5 mg; may repeat up to max total dose 0.4 mg/kg (10 mg)	1 -2 mins	30 – 60 mins
Diazepam	IV 0.1 - 0.2 mg/kg	2 - 3 mins	30 – 90 mins
Ketamine	IV 0.5 - 2.0 mg/kg	1 – 2 mins	15 – 60 mins
Reversal agents			
Naloxone	Repeated small doses IV 1 - 10 mcg/kg every 1-2 mins		
Flumazenil	IV 0.01 – 0.02 mg / kg every 1 -2 minutes up to a maximum dose of 1 mg		

Chapter 113: Practical Procedures

Headings

1. Airway Access – Endotracheal Intubation
2. Breathing
3. Chest Compressions
4. Blood Sampling & Vascular Access
  4.1 Venepuncture & Peripheral Venous Cannulation
  4.2 Arterial Blood Sampling & Peripheral Arterial Cannulation
  4.3 Intra-Osseous Access
  4.4 Neonates – vascular access and sampling
    4.4.1 Capillary Blood Sampling
    4.4.2 Umbilical Arterial Catheterisation UAC
    4.4.3 Umbilical Venous Catheterisation UVC
  4.5 Central venous access - Femoral vein cannulation in children
5. Body Fluid Sampling
  5.1 CSF - Lumbar puncture
  5.2 Chest tube insertion (open method)
  5.3 Heart - Pericardiocentesis
  5.4 Abdomen
    5.4.1 Gastric lavage
    5.4.2 Abdominal paracentesis
    5.4.3 Peritoneal dialysis
    5.4.4 Bladder catheterisation
    5.4.5 Suprapubic bladder tap
  5.5 Bone marrow aspiration & trephine biopsy

Selective sedation and pain relief is important before the procedures.
(see refer **Chapter on Sedation and Analgesia for Diagnostic and Therapeutic Procedures**)

Introduction

APLS courses have been conducted in Malaysia since October 2010. Kindly refer to latest APLS textbook 6th Ed 2016:-

- Chapter 20: Practical procedures: airway and breathing
- Chapter 21: Practical procedures: circulation

1. AIRWAY ACCESS - ENDOTRACHEAL INTUBATION

Please request for assistance from the senior doctor in Paediatrics or Anaesthesiology Department whenever necessary. The other methods of opening airways are not described here, e.g. Guedel airway, nasopharyngeal airway, laryngeal mask airway and surgical airway.

- The control of airway and breathing is very important in a patient with respiratory or cardiopulmonary failure or cardiac arrest.

Indications

- When bag and mask ventilation or continuous positive airway pressure (CPAP) is insufficient.
- For prolonged positive pressure ventilation.
- Direct suctioning of the trachea.
- To maintain and protect airway.
- Diaphragmatic hernia (newborn).

Contra-indications

- If the operator is inexperienced in intubation, perform bag and mask ventilation (contra-indicated in diaphragmatic hernia) till help arrives.

Equipment

- Bag and mask with high oxygen flow.
- Laryngoscope.
- Blades:
  - Straight blade for infants, curved blades for an older child.
  - Size 0 for neonates, 1 for infants, 2 for children.
- Endotracheal tube – appropriate size as shown.
- Stylet (optional, usually not necessary).
- Suction catheter and device.
- Scissors and adhesive tape.
- Pulse oximeter and ECG monitoring
- Sedation (Midazolam or Morphine).
- Consider muscle relaxant (Rocuronium or Succinylcholine).

Size of ETT (mm):
2.5 for < 1kg 3.0 for 1-2kg 3.5 for 2-3kg 3.5 - 4.0 for > 3kg
Oral ETT length in cm for neonates: 6 + (weight in kg) cm
For Children > 1 year: ETT size (mm) = 4 + (age in years /4) Oral ETT length (cm) = 12 + (age in years /2)

Procedure

1. Position infant with head in midline and slightly extended (sniffling position in a child).
2. Continue bag and mask ventilation up to 3 minutes if necessary (omit this pre-oxygenation step in cardiac arrest child) with 100% oxygen till well saturated. In newborns adjust FiO_2 accordingly until oxygen saturation is satisfactory between 94 to 98%.
3. Medication used in rapid sequence induction RSI of emergency anaesthesia

- Consider induction agent ketamine 1 to 2 mg / kg (caution in patient with raised intracranial pressure)
- Give muscle relaxant if child still struggling, eg IV Succinylcholine (1-2 mg/kg) or Rocuronium 0.6-1.2 mg/kg.

Caution: must be able to bag the patient well (look for gentle chest rise) or have good intubation skills before giving muscle relaxant.

- Sedation IV Midazolam (0.1-0.2 mg/kg) or IV Morphine (0.1-0.2 mg/kg).

4. Monitor the child's vital signs continuously throughout the procedure.
5. Introduce the blade between the tongue and the palate with left hand and advance to the back of the tongue while assistant secures the head.
6. When epiglottis is seen, lift blade upward and outward to visualize the vocal cords.
7. Suck secretions if necessary.
8. Using the right hand, insert the ETT from the right side of the infant's mouth; a stylet may be required.
9. Keep the glottis in view and insert the ETT when the vocal cords are opened till the desired ETT length while assistant applies cricoid pressure.
10. If intubation is not done within 20 seconds, the attempt should be aborted and re-ventilate with bag and mask.
11. Once intubated, remove laryngoscope and hold the ETT firmly with left hand. Connect to the self-inflating bag and positive pressure ventilation.
12. Confirm the ETT position by looking at the chest expansion, listen to lungs air entry and also the stomach.
13. Secure the ETT with adhesive tape.
14. Connect the ETT to the ventilator or resuscitation bag.
15. Insert orogastric tube to decompress the stomach.
16. Check chest radiograph.

Complications and Pitfalls

- Oesophageal intubation (ETT could be in-situ initially and then dislodged).
- Right lung intubation.
- Trauma to the upper airway.
- Pneumothorax.
- Subglottic stenosis (late).
- ***Relative contra-indications for Succinylcholine*** are increased intra-cranial pressure, neuromuscular disorders, malignant hyperthermia, hyperkalaemia and renal failure.

2. BREATHING

After opening the airway, start ventilation using an appropriately sized mask or through the endotracheal tube of an intubated child. Look for gentle chest rise (tidal volume) and bagged at 10 to 12 breaths per minute in a cardiac arrest child with ongoing chest compressions (ratio of 2 ventilation to 15 chest compression). In a seriously ill child with inadequate respiratory effort, ventilate at a rate of 15 to 30 breaths per minute (faster rate in younger child).

3. CHEST COMPRESSION

Start IMMEDIATE chest compressions if

- There are no signs of life.
- There is no pulse.
- There is a slow pulse (less than 60 beats per minute with poor perfusion).

The cycles of 2 ventilations to 15 chest compression should be performed at a rate of 5 to 6 cycles per minute for a total of two minutes whilst waiting for help to arrive.

The chest should be compressed to one third the anterior-posterior diameter of the chest, about 4 cm for infant and 5 cm for a child.

The cardiac arrest child receiving uninterrupted BLS should be connected to the ECG monitor as soon as possible to ascertain whether it is an non-shockable (asystole or pulseless electrical activity) or shockable rhythm (ventricular fibrillation or pulseless ventricular tachycardia). Adrenaline should be given immediately to non-shockable rhythm and defibrillation performed on shockable rhythm.

4. BLOOD SAMPLING & VASCULAR ACCESS

4.1. VENEPUNCTURE & PERIPHERAL VENOUS LINE

Indications

- Blood sampling.
- Intravenous fluid, medications and blood components.

Equipment

- Glove
- Alcohol swab.
- Tourniquet.
- Topical anaesthetic (TA), e.g lignocaine EMLA® 5%, or ethyl chloride spray for rapid cannulation.
- Catheter 24 G, 22 G or needle; sizes 25, 23, 21 G.
- Heparinised saline, T-connector, rubber bung for setting an IV line.

Technique

1. Identify the vein for venepuncture. Secure the identified limb and apply tourniquet or equivalent. Note that the peripheral veins will be collapsed in a child with peripheral vasoconstriction, eg in circulatory shock or high fever.
2. TA may be applied with occlusive plaster an hour earlier or spray with ethyl chloride for a short procedure.

3. Clean the skin with alcohol swab.
4. Puncture the skin and advance the needle or catheter in the same direction as the vein at 15-30 degrees angle.
5. In venepuncture, blood is collected once blood flows out from the needle. The needle is then removed and pressure applied once sufficient blood is obtained.
6. In setting an intravenous line, the catheter is advanced a few millimetres further. Once blood appears at the hub, then withdraw the needle slightly while advancing the catheter over the needle.
7. Remove the tourniquet and flush the catheter with heparinised saline.
8. Secure the catheter and connect it to either rubber bung or IV drip.
9. Immobilise the joint above and below the site of catheter insertion with restraining board and tape.

Complications

- Haematoma or bleeding.
- Thrombophlebitis after a few days.
- Extravasation can lead to soft tissue injury resulting in limb or digital loss and loss of function.
  This complication is of concern in neonates, where digital ischaemia, partial limb loss, nerve damage, contractures of skin and across joints can occur.

Extravasation injury (prevention is the priority)

- Signs include:
  - Pain, tenderness at insertion site especially during infusion or giving slow bolus drugs.
  - Redness.
  - Swelling.
  - Reduced movement of affected site.

(Note – the inflammatory response can be reduced in neonates especially preterm babies)

- Inspection of injection sites
  The insertion site should be observed for signs of extravasation:
  - At least every 4 hours for ill patients.
  - Sick preterm in NICU: should be done more often, even every hour for continuous infusion.
  - Each time before, during and after slow bolus or infusion.
    (Consider re-siting the intravenous catheter every 48 to 72 hours)

If moderate or serious extravasation occurs, especially in the following situation:

- Preterm babies.
- Delay in detection of extravasation.
- Hyperosmolar solutions or irritant drugs (glucose concentration > 10g%, sodium bicarbonate, calcium solution, dopamine, cloxacillin, fusidic acid acyclovir).

Consider:

- Inform senior colleagues
- Refer to plastic surgeon / orthopaedics surgeon.
- Performing 'subcutaneous saline irrigation' as soon as possible especially in neonates

(ref Davies, ADC, Fetal and Neonatal edition 1994).

Give IV analgesia morphine, then perform numerous subcutaneous punctures around the extravasated tissue and flush slowly with generous amount of normal saline to remove the irritant. Ensure that the flushed fluid flows out through the multiple punctured sites.

Pitfalls in peripheral venous cannulation

- If the patient is in shock, the venous flow back and the arterial flow (in event of accidental cannulation of an artery) is sluggish.
- BEWARE! An artery can be accidentally cannulated, e.g. brachial artery at the cubital fossa and the temporal artery at the side of the head of a neonate and be mistaken as a venous access. Check for resistance to flow during slow bolus or infusion (e.g., frequent alarming of the perfusor pump) or watch for skin blanching or pulsation in the backflow or a rapid backflow. Rapid bolus or infusion of drugs can cause ischaemia of the limb. Where in doubt, gently remove the IV cannula.
- Ensure prescribed drug is given by the proper mode of administration. Some drugs can only be given by slow infusion (e.g. fusidic acid) instead of slow bolus in order to reduce tissue damage from extravasation.
- Avoid medication error (correct patient, correct drug, correct DOSE, correct route).
- Avoid nosocomial infection.

4.2. ARTERIAL BLOOD SAMPLING & PERIPHERAL ARTERIAL LINE CANNULATION

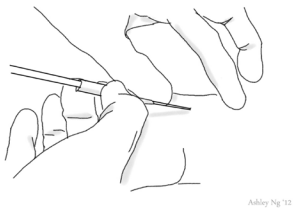
Note: this is a very painful procedure and should be done with proper analgesia and under supervision in a PICU setting.

Indications

- Arterial blood gases.
- Invasive blood pressure monitoring.
- Frequent blood taking.

Contraindications

- Presence or potential of limb ischaemia.
- Do not set arterial line if close monitoring cannot be done.



Equipment

- Topical anaesthetic (TA) like lignocaine EMLA® 5%.
- Alcohol swab.
- Needle size 27 G, 25 G; Catheter size 24, 22 G
- Heparinised saline in 5cc syringe (1 ml for neonate), T-connector.
- Heparinised saline (1u/ml) for infusion.

Procedure

1. Check the ulnar collateral circulation by modified Allen test.
2. The radial pulse is identified. Other sites that can be used are posterior tibial (posterior to medial malleolus while the ankle is in dorsiflexion) and dorsalis pedis artery (dorsal midfoot between the first and second toes while the ankle is in plantar flexion).
3. TA may be applied with occlusive plaster an hour before procedure.
4. Clean the skin with alcohol swab.
5. Dorsiflex the wrist slightly. Puncture the skin and advance the catheter in the same direction as the radial artery at a 30-40 degrees angle.
6. The catheter is advanced a 2-3 millimetres further when blood appears at the hub, then withdraw the needle while advancing the catheter.
7. Ensure good flow, then flush gently with a small amount of heparinised saline.
8. Peripheral artery successfully cannulated.

- Ensure that the arterial line is functioning. The arterial pulsation is usually obvious in the tubing.
- Connect to T-connector and 3-way stop-cock (red colour) to a syring pump.
- Label the arterial line and the time of the setting.

9. Run the heparinised saline at an appropriate rate:

- 0.5 to 1.0 mL per hour for neonates.
- 1.0 mL (preferred) or even up till 3.0 mL per hour for invasive BP line (stop if skin mottling or blanching)

10. Immobilize the joint above and below the site of catheter insertion with restraining board and tape, taking care not to make the tape too tight.

Complications and Pitfalls

- Arteriospasm which may lead to ischaemia and gangrene.
- Neonates especially – digital and distal limb ischaemia.

Precautions

Prevention of digital, distal limb ischaemia and gangrene

- *AVOID end arteries* e.g. brachial (in cubital fossa) and temporal artery (side of head) in babies (BEWARE - both these arteries can be accidentally cannulated and mistaken as 'veins' especially in ill patients with shock).
- *Test for collateral circulation*
- If a radial artery is chosen, please perform Allen's test (to confirm the ulnar artery collateral is intact) before cannulation.
- If either the posterior tibial or dorsalispedis artery on one foot is chosen, ensure that these 2 arteries are palpable before cannulation.
- *Circulation chart*

Perform observation and record circulation of distal limb every hour in the NICU/PICU, and whenever necessary to detect for signs of ischaemia, namely:

- Colour - pale, blue, mottled.
- Cold, clammy skin.
- Capillary refill > 2 seconds.

Treatment of digital or limb ischaemia (prevention is the priority)
This is difficult as the artery involved is of small calibre.

- Remove IV cannula.
- Confirm thrombosis with ultrasound doppler.
- May consider warming the contralateral unaffected lower limb to induce reflex vasodilatation of the affected leg (see **Chapter on Vascular spasm and Thrombosis**).
- Ensure good peripheral circulation and blood pressure
- Anticoagulant drugs and thrombolytic agents should be considered (refer to neonatal notes)
- Refer orthopaedic surgeon if gangrene is inevitable

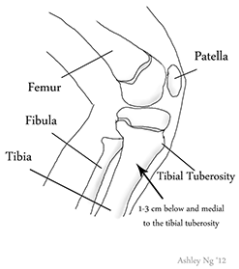
Reminders:

- PREVENTION of limb ischaemia is of utmost importance.
- Early detection of ischaemia is very important in order to avoid irreversible ischaemia.
- If the patient is in shock, the risk of limb ischaemia is greater.
- Small and preterm babies are at greater risk for ischaemia.
- No fluid or medication other than heparinized saline can be given through arterial line. This mistake can occur if the line is not properly labelled, or even wrongly labelled and presumed to be a venous line.

4.3. INTRAOSSEOUS ACCESS

Intraosseous infusion can be used for all paediatric age groups.
Sites:

- Most common site is the anterior tibia
- (all age groups)
- Infant – distal femur
- Child – anterior superior iliac spine, distal tibia.
- Adolescent/adult - distal tibia, medial malleolus, anterior superior iliac spine, distal radius, distal ulna.



All fluids and medications can be given intraosseously.
IO infusion is usually not recommended for use longer than a 24 hour period.

Indications

- Emergency access for IV fluids and medications when other methods of vascular access failed.
- In certain circumstances, e.g. severe shock with severe vasoconstriction or cardiac arrest, IO access may be the INITIAL means of vascular access.

Contraindications

- Fractures, crush injuries near the access site. IO itself can cause fractures especially in young infants.
- Conditions in which the bone is fragile e.g. osteogenesis imperfecta.
- Previous attempts to establish access inthe same bone.
- Infection over the overlying tissues.

Equipment

- Sterile dressing set.
- EZ-IO drill set if available.
- Intraosseous needle.
- Syringes for aspiration.
- Local anaesthesia.

Procedure

1. Immobilize the lower limb.
2. Support the limb with linen
3. Clean and draped the area
4. Administer LA at the site of insertion
5. Insert the IO needle 1-3 cm below and medial to the tibial tuberosity caudally.
6. Advance needle at a 60-90° angle away from the growth plate until a 'give' is felt.
7. Remove the needle trocar stylet while stabilizing the needle cannula
8. Withdraw bone marrow with a 5cc syringe to confirm access
9. Infuse a small amount of saline and observe for swelling at the insertion site or posteriorly to the insertion site. Fluid should flow in freely and NO swelling must be seen. (Swelling indicates that the needle has penetrated into and through the posterior cortical bone. If this happens remove the needle.)
10. Connect the cannula to tubing and IV fluids. Fluid should flow in freely
11. Monitor for any extravasation of fluids.

Complications

- Cellulitis.
- Osteomyelitis.
- Extravasation of fluids/compartment syndrome.
- Damage to growth plate.
- Fracture of bone especially in young infant.

4.4. NEONATES

4.4.1. CAPILLARY BLOOD SAMPLING


Ashley Ng '12

Indications

- Capillary blood gases
- Capillary blood glucose
- Serum bilirubin

Equipment

- Lancet or heel prick device
- Alcohol swab

Procedure

1. Either prick the medial or lateral aspect of the heel
2. For the poorly perfused heel, warm with gauze soaked in warm water.
3. Clean the skin with alcohol swab
4. Stab the sterile lancet to a depth of 2.5mm, then withdraw it. Intermittently squeeze the heel gently when the heel is re-perfused until sufficient blood is obtained.

Complications

- Cellulitis.
- Osteomyelitis.

2.4.2. UMBILICAL ARTERY CATHETERISATION (UAC)

An invasive procedure and should be done under supervision in a NICU setting.

Indications

- For repeated blood sampling in ill newborn especially those on ventilator.
- Occasionally it is used for continuous BP monitoring and infusion.

Contraindications

- Local vascular compromise in lower extremities
- Peritonitis
- Necrotising enterocolitis
- Omphalitis

Prior to procedure

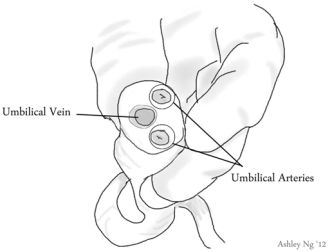
- Examine the infant's lower extremities and buttocks for any signs of vascular insufficiency.
- Palpate femoral pulses for their presence and equality.
- Evaluate the infant's legs, feet, and toes for any asymmetry in colour, visible bruising, or vascular insufficiency.
- Document the findings for later comparison. Do not set if there is any sign of vascular insufficiency.

Equipment

- UAC/UVC set.
- Umbilical artery catheter, appropriate size.
  - Size 2.5 F for <800g and most <1000g
  - Size 3.5F for preterm infants >1500g
  - Size 5F in term infants
- 5 cc syringes filled with heparinized saline.
- Three-way tap.
- Heparinized saline (1u/ml) for infusion.

Procedure

1. Clean the umbilicus and the surrounding area using standard aseptic technique. In order to observe for limb ischaemia during umbilical arterial insertion, consider exposing the feet in term babies if the field of sterility is adequate.



2. Catheterise the umbilical artery to the desired position.

The formula for UAC is:

- (Birth weight in kg x 3) + 9 + 'stump length' in cm (read length from the upper end of the stump) *(high position: tip above diaphragm between T6-9)*
- Birth weight in kg + 7 cm (*low position* is no longer recommended n)

3. Hold the stump gently (not taut) and cut the umbilicus horizontally leaving behind a 1 cm stump. If you pull the stump taut before cutting, you will end up with the arteries protruding 2 mm beyond the umbilicus jelly and this make successful cannulation more difficult.

There are 2 arteries and 1 vein. The artery is smaller in diameter, white and constricted. Hold the stump upright with your fingers or artery forceps.

Gentle and patiently dilate the lumen of the artery with a probe.

Insert the catheter to the desired distance.

4. Ensure the successful and correct cannulation of one umbilical artery.

- Tips for successful catheterisation of the umbilical artery:
  - In a fresh and untwisted umbilical stump, the two arteries can be clearly distinguished from the vein.
  - Stand to the left side of the baby if you are right-handed and direct the catheter posteriorly and inferiorly in the direction of the lower limbs.
  - The blood withdrawn is bright red.
  - Visible arterial pulsations can be seen in the column of blood withdrawn into the catheter. However, this pulsation may not be seen in very preterm babies and babies in shock, using the closed system.
- In *accidental cannulation* of the umbilical vein, the catheter tip can be in the left atrium (via the foramen ovale from the right atrium into left atrium) or in the left ventricle giving a backflow of oxygenated blood.
- Stick the label of the catheter onto patient's folder for future reference (brand and material of catheter) in the event of limb ischaemia or thrombosis of femoral artery occurring later.

5. Observe for signs of arterial ischaemia to the lower limbs and buttocks (colour, cold skin, capillary refill delayed, poor dorsalis pedis and posterior tibial pulses) during and after the procedure due to arterial vasospasm. An assistant lifts slightly the edge of the drape without compromising the sterility field to inspect the lower limbs circulation.
6. If there are no complications (limb ischaemia – see pitfalls), secure the UAC to avoid accidental dislodgement.
7. Perform a chest and abdominal X-ray to ascertain the placement of UAC tip
   - Between T 6-9 vertebra *(high position)* - preferred
   - At the L 3-4 vertebra *(low position)*

   Withdraw (do not push in, to maintain sterility) the catheter to the correct position, if necessary.
8. Monitor the lower limbs and buttock area for ischaemic changes 2-4 hourly
9. Infuse heparinised saline continuously through the UAC at 0.5 to 1 U/hr to reduce the risk of catheter occlusion and thrombotic events.
10. Note the catheter length markings every day and compare with the initial length (to check for catheter migration).
11. Remove the UAC as soon as no longer required to reduce the incidence of thrombus formation and long line sepsis.

Complications

- Bleeding from accidental disconnection and open connection.
- Embolisation of blood clot or air in the infusion system.
- Vasospasm or thrombosis of aorta, iliac, femoral or obturator artery leading to limb or buttock ischaemia. (see **Chapter on Vascular spasm and Thrombosis**)
- Thrombosis of renal artery (hypertension, haematuria, renal failure), mesenteric artery (gut ischaemia, necrotising enterocolitis).
- Vascular perforation of umbilical arteries, haematoma and retrograde arterial bleeding.
- Nosocomial infection.

4.4.3. UMBILICAL VEIN CATHETERISATION (UVC)

Indications

- UVC is used for venous access in neonatal resuscitation.
- As a venous access in preterm babies especially ELBW babies (<1000g) and also in sick babies in shock with peripheral vasoconstriction.
- For doing exchange transfusion for severe neonatal jaundice.

Contraindications

- Omphalitis, omphalocoele
- Necrotising enterocolitis
- Peritonitis

Equipment

- UVC set.
- Umbilical venous catheter, appropriate size
  - Size 3.5F for birth weight <1000 to 1500g
  - Size 3F for birth weight >1500g
- 5 cc syringes filled with heparinized saline.
- Three-way tap.
- Heparinized saline (1u/ml) for infusion.

Procedure

1. Clean umbilicus and its surroundings using standard procedures.
   In order to observe for limb ischaemia during insertion (in the event of accidental arterial catheterisation), consider exposing the feet in term babies whilst maintaining field of sterility.
2. Formula for insertion length of UVC:
   [0.5 x UAC cm (high position)] + 1 cm.
   Or
   (Birth weight in kg x 1.5) + 5.5 + stump length in cm
3. Perform the umbilical venous cannulation

- Tips for successful UV catheterisation:
  - In a fresh (first few hours of life) and untwisted umbilical stump, the umbilical vein has a thin wall, is patulous and is usually sited at the 12 o'clock position. The two umbilical arteries which have a thicker wall and in spasm, and sited at the 4 and 8 o'clock positions. However, in a partially dried umbilical cord, the distinction between the vein and arteries may not be obvious.
  - The venous flow back is sluggish and without pulsation (in contrast to the arterial pulsation of UAC).
  - The blood is dark red in colour.
  - Stand to the right of the baby (if you are right handed).
    Tilt the umbilical stump inferiorly at an angle of 45 degrees from the abdomen. Advance the catheter superiorly and posteriorly towards the direction of the right atrium.

- Central venous pressure
  - The UVC tip is sited in the upper IVC (inferior vena cava). The right atrial pressure in a term relaxed baby normally ranges from -2 to + 6 mmHg (i.e. - 3 cm to + 9 cm water).
- Negative intrathoracic pressure and air embolism
  - In a crying baby, the negative intrathoracic pressure can be significant during deep inspiration.
  - Ensure that no air embolism occurs during the procedure especially in the presence of negative pressure when the catheter tip is in the right atrium.
  - Air embolism can occur if the baby takes a deep inspiration when the closed UVC circuit is broken.
- Stick the label of the catheter onto the patient's folder for future reference (brand and material of catheter) in the event of thrombosis occurring in the cannulated vessel.

4. If there are no complications, secure the UVC to avoid accidental migration of the catheter.
5. If the UVC is for longer term usage such as for intravenous access / TPN, perform chest and abdominal radiograph to ascertain the tip of the catheter is in the inferior vena cava above the diaphragm.
6. Consider removing the UVC after 5 - 7 days to reduce incidence of line sepsis or thrombus forming around the catheter.

Complications

- Infections.
- Thrombo-embolic – lungs, liver, even systemic circulation
- Pericardial tamponade, arrhythmias, hydrothorax
- Portal vein thrombosis and portal hypertension (manifested later in life)

Pifalls

- The umbilical artery can be mistakenly cannulated during umbilical venous catheterisation.
- If you suspect that the umbilical artery was wrongly cannulated resulting in limb ischaemia, please refer **Chapter on Vascular spasm and Thrombosis.**

4.5 CENTRAL VENOUS ACCESS: FEMORAL VEIN CANNULATION IN CHILDREN

- The routes of central venous access includes peripherally inserted central catheter - PICC (eg through cubital fossa vein into SVC) and femoral, external / internal jugular and subclavian veins.
- These lines must be inserted by trained senior doctors in selected seriously ill paediatrics patients requiring resuscitation and emergency treatment.
- The benefits of a successfully inserted central venous access must be weighed against the numerous potential complications arising from the procedure.
- This includes pneumothorax and life-threatening injuries of the airway, lungs, great vessels and heart.
- The basic principle of Seldinger central line insertion applies to all sites and the femoral vein cannulation is described.
- Use ultrasound-guided needle approach for femoral vein cannulation (refer APLS 6th Ed, Chapter 5, page 230-231).

Indications

- Seriously ill ventilated paediatrics patients especially with difficult peripheral vein access.
- To obtain central venous pressure.
- Longer term intravenous infusion (compared to IO access).
- Haemodialysis.

Contraindications

- Absence of trained doctors for this procedure.
- Bleeding and clotting disorders.
- Risk of contamination of the cannulation site by urine and faeces for femoral vein cannulation.

Equipment

- Sterile set.
- Lidocaine (Lignocaine) 1% for local anaesthetic, 2 mL syringe, 23 G needle.
- 5 mL syringe and normal saline, t-connector and 3-way tap.
- Seldinger cannulation set – syringe, needle, guide wire, catheter.
- Sterile dressing.

Procedure

1. In a ventilated child, give a dose of analgesia (eg Morphine, Fentanyl) and sedation (e.g. Midazolam).
2. In the supine position, expose the chosen leg and groin in a slightly abducted position.
3. Identify the landmark by palpating the femoral artery pulse in the mid-inguinal region. The femoral vein is medial to the femoral artery, 5-6 mm in infants, 10-15mm in adolescents.
   Recommended to use ultrasound guidance for this procedure.
4. Clean the inguinal region thoroughly using iodine and 70% alcohol.
5. Infiltrate local lidocaine at the proposed site of skin insertion.
6. Insert the saline filled syringe and needle at 30° angle to the skin and parallel to the femoral artery pulsation. The needle enters skin 2-3 cm below inguinal ligament and vein 1-2 cm below inguinal ligament. Pull the plunger gently and advance superiorly in-line with the leg.
7. When there is a backflow of blood into the syringe, stop suction, and disconnect the syringe from the needle. The guide wire is then promptly and gently inserted into the needle.
8. Withdraw the needle gently and carefully without risking damage to the guide wire including kinking (will lead to difficulty or inability to remove guide wire after catheter insertion) and fracturing the guide wire.
9. Insert the cannula over the wire without risking displacement of the wire into the patient.
10. Once the cannula has been inserted, remove the guide wire and attach the infusion line securely onto the hub of the cannula. Check for easy backflow by gentle suction on the syringe.
11. Secure the line using sterile dressing and ensure the insertion site is clearly visible at all times.

Pitfalls

- Do not lose or kink the guide wire (inserted too deep into patient)
- Do not fracture the guide wire accidentally with the needle
- Do not accidentally cannulate the femoral artery (blood pressure could be low in a patient with shock and mistaken as femoral vein)
- Beware of local haematoma at injection site.
- Always check the distal perfusion of the leg and toes before and after procedure.

5. BODY FLUID SAMPLING

5.1. LUMBAR PUNCTURE

Indications

- Suspected meningitis / encephalitis.
- Intrathecal chemotherapy for oncology patients.
- In selected patients being investigated for neurometabolic disorders.

Contraindications

- Increased intracranial pressure (signs and symptoms, raised blood pressure, fundoscopic signs). Perform CT scan or MRI brain before LP.
- Bleeding tendency - platelet count <50,000/mm^3, prolonged PT or APTT.
- Skin infection over the site of lumbar puncture
- Patient with hypertensive encephalopathy

Equipment

- Sterile set.
- Sterile bottles for CSF, bottle for RBS (random blood sugar).
- Spinal needle 20-22G, length 1.5 inch with stylet; length 3.5 inches for children > 12 years old.

Procedure

1. Give sedation (midazolam), apply local anaesthetic.
2. Take a random blood sugar sample (RBS) after LP.
3. Place child in lateral recumbent position with neck, body, hips and knees flexed. Monitor oxygen saturation continuously.
4. Visualise a vertical line between the highest point of both iliac crests and its transection with the midline of the spine (at level between vertebrae L 3-4).
5. Clean area using standard aseptic techniques: povidone-iodine and 70% alcohol.
6. Gently puncture skin with spinal needle at the identified mark and point towards the umbilicus. The entry point is distal to the palpated spinous process L4.
7. Gently advance a few millimetres at a time until there is a backflow of CSF (there may be a 'give' on entering the dura mater before the CSF backflow). Collect the CSF in the designated bottles.
8. Gently withdraw needle, spray with op-site, cover with gauze and bandage.
9. Ensure that the child lies supine for the next 4 to 6 hours, continue monitoring child till he or she recovers from the sedation.

Complications

- Headache or back pain following the procedure (from arachnoiditis).
- Brain herniation associated with raised ICP. Look at brain imaging result before doing LP.
- Bleeding into CSF, or around the cord (extraspinal haematoma).

5.2. CHEST TUBE INSERTION

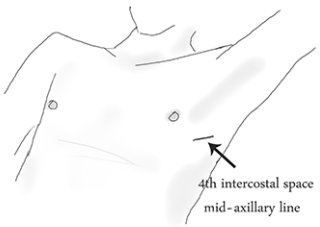
Indications

- Pneumothorax with respiratory distress. In tension pneumothorax, perform a needle thoracocentesis before chest tube insertion.
- Significant pleural effusion.
- Empyema.

NEEDLE THORACOCENTESIS

1. Indicated in *tension pneumothorax* as an emergency measure to decompress the chest until a chest tube is inserted.
2. Done under strict aseptic technique. Attach a 10ml syringe already filled with 2ml sterile normal saline to a 16 to 20 gauge angiocatheter. Gently insert catheter perpendicularly through the second intercostal space, over the top of the third rib, at the midclavicular line while applying a small negative pressure as the needle is advanced. Air will be aspirated on successful needle thoracocentesis. When this happens, remove the syring and needle while leaving the catheter in situ to allow the tension pneumothorax to decompress.
   Then, insert a chest tube as described below as soon as feasible.

SITE FOR CHEST TUBE INSERTION



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Equipment

- Suturing set.
- Local anaesthetic +/- sedation.
- Chest tube, appropriate size.
  - 8 Fr for < 2 kg body weight
  - Infants: 10 Fr for > 2kg body weight
  - Older children: 12-18 Fr depending on size
- Underwater seal with sterile water.
- Suction pump – optional.

Procedure

1. Sedate the child.
2. Position the child with ipsilateral arm fully abducted.
3. Clean and drape the skin.
4. Infiltrate LA into the skin at 4th or 5th intercostal space on the mid-axillary line. "Triangle of safety" – anterior to mid-axillary line, posterior to pectoral groove and above 5th ICS.
5. Check approximate length of the chest tube to be inserted as it follows the curve of the chest. Tip of the chest tube should be sited at the highest point of the chest (for pneumothorax) and lowest dependent chest (for pleural effusion).
6. ***For Open Method***

i. The open method (without the metal introducer) of chest tube cannulation is the preferred method. The closed method (with the introducer) is no longer recommended.

ii. Make a small incision in the skin just above the 5th rib. Use the blunt forceps to dissect through the subcutaneous tissue and puncture the parietal pleura with the tip of the clamp forcep. Put a gloved finger into the incision and clear the path into the pleura. This may be difficult in a small child. Advance the chest tube into the pleural space during expiration.

iii. For drainage of air, roll the child slightly to the opposite side for easier manoeuvring and advancement of the chest tube anteriorly. Place the tip of the chest tube at the incision. Point the catheter tip anteriorly and slowly advance the chest tube.

However, for drainage of empyema, maintain the child in the supine position and point the catheter tip posteriorly and proceed with the rest of the procedure.

iv. Connect the chest tube to underwater seal.

7. The water should bubble (if pneumothorax) and the fluid moves with respiration if chest tube is in the pleural space.
8. Secure the chest tube with purse string sutures in children or sterile tape strips in neonates.
9. Connect the underwater seal to suction pump (negative pressure not more than 100mmHg) if necessary for empyema.
10. Confirm the position with a chest X-ray.

5.3. PERICARDIOCENTESIS

This is a specialised procedure performed in the cardiac unit. Occasionally it can be performed as a life-saving procedure by the senior paediatric doctor.

Indications

- Symptomatic collection of air.
- Blood or other fluids / empyema in pericardial sac.

Equipment

- Suturing set.
- Angiocatheter – size 20 G for newborn, 18 G for older children.
- T-connector.
- 3-way stopcock.

Procedure

1. The patient should be given analgesia and sedation and be ventilated.
2. Place patient in supine position and on continuous ECG monitoring.
3. Clean and drape the subxiphoid area. Give local anaesthesia.
4. Insert the angiocatheter at about 1cm below the xiphoid process at angle of 45° to the skin and advance slowly, aiming at the tip of the left shoulder while applying light negative pressure with the syringe. Stop advancing the catheter if there is cardiac arrhythmia.
5. Once fluid or air is aspirated, withdraw the needle about 3 mm and advance the catheter into the patient.
6. Remove the needle, rapidly connect the hub of the catheter to a previously prepared T-connector, 3-way stopcock and a 10 cc syringe. .
7. Remove as much fluid and air as possible by manipulating the 3-way stopcock.
8. Secure the catheter in place.
9. Send any aspirated fluid for cell count, biochemistry and culture.
10. Perform CXR to confirm positioning and look for any complication.
11. The catheter should be removed within 72 hours. If further aspiration is required, placement of a pericardial tube (by the surgeon) is an option. Do not hesitate to consult cardiothoracic surgeon.

Complications

- Perforation of heart muscle leading to cardiac tamponade.
- Haemo / pneumo – pericardium
- Cardiac arrhythmias
- Pneumothorax

Indications

- Removal of ingested toxins
- Removal of meconium from stomach for newborn

Equipment

- Nasogastric tube size 8-12 Fr
- Syringes: 5cc for neonate, 20 cc for older children
- Sterile water

Procedure

1. Put the wrapped infant in a supine slight head-up position. A child should be in a comfortable sitting position held by the guardian or health care provider.
2. Estimate the length of *nasogastric* tube inserted by measuring the tube from the nostril and extending it over and around the ear and down to the epigastrium.
   For *orogastric* tube insertion, the length of tube inserted equal to the bridge of the nose to the ear lobe and to appoint halfway between the lower tip of sternum and the umbilicus.
3. Lubricate the tip of the tube with KY jelly. Insert the tube gently.
4. Confirm position by aspirating stomach contents. Re-check by plunging air into stomach whilst listening with a stethoscope, or check acidity of stomach contents.
5. Perform gastric lavage until the aspirate is clear.
6. If indicated, leave activated charcoal or specific antidote in the stomach.

Complications

- Discomfort.
- Trauma to upper gastrointestinal tract
- Aspiration of stomach contents into lungs.

5.4.2. ABDOMINAL PARACENTESIS

Indications

- Diagnostic procedure.
- Drain ascites.

Equipment

- Dressing set.
- Cannula size 16, 18, 20, 22G (depending on size of child and purpose of paracentesis)
- Syringes 10cc.

Procedure

1. Supine position. Catheterize to empty the bladder.
   Clean and drape abdomen. Give local anaesthesia and sedation.
2. Site of puncture is at a point in the outer 1/3 of a line drawn from the umbilicus to the anterior superior illiac spine.
3. Insert the catheter (connected to a syringe) at 45° aiming superiorly into the peritoneal cavity in a slight 'Z' track fashion (by pulling the skin inferiorly before needle insertion and release skin soon after that before pushing needle into peritoneum).
4. Aspirate while advancing the catheter until fluid is seen in the syringe. Remove the needle and reconnect the catheter to the syringe and aspirate the amount required. Use a three-way tap if large amounts need to be removed.
5. Once complete, remove the catheter (if paracentesis is for diagnostic purpose). Cover puncture site with sterile dry gauze.

Complications

- Infection
- Perforation of hollow viscus (usually does not lead to complications).
- Leakage of peritoneal fluid
- Hypotension if excessive amount is removed quickly

5.4.3. PERITONEAL DIALYSIS

(See **Chapter on Acute Peritoneal Dialysis**)

This procedure is similar to abdominal paracentesis. However, normal saline usually needs to be infused into the peritoneum through a small catheter to 'float' the intestines (create an ascites) before insertion of peritoneal dialysis catheter.

Note that haemodialysis is usually performed unless contraindicated.

5.4.4. BLADDER CATHETERISATION

Indications

- Obtain urine specimen to look for urinary tract infection
- Monitor urine output
- Relieve urinary retention
- MCUG - Patient for micturating cystourethrogram (MCU) may need to given either a stat dose of IV Gentamicin or trimethoprim 2mg/kg bd for 48 hours after the procedure
- Obtain urine specimen for microscopy and culture

Equipment

- Dressing Set.
- Urinary catheter of appropriate size
  - 4 Fr for < 3 kg body weight
  - 6 Fr for > 3 kg body weight
  - Older children: Foley's catheter 6-10 Fr depending on size
- LA / K-Y jelly.
- Syringe and water for injection.

Procedure

1. Position the child in a frog-leg position. Clean and drape the perineum.
2. In girls, separate the labia majora with fingers to expose the urethra opening.
3. In boys, hold the penis perpendicular to the body.
4. Pass catheter in gently till urine is seen then advance a few centimetres further.
5. Secure the catheter with adhesive tape to the lower body.
   Remove catheter after urine collection if the purpose is to obtain urine for microscopy and culture and sensitivity.
6. Connect the catheter to the urine bag.

Complications

- Infection
- Bleeding and trauma especially in a fearful struggling child which may lead to urethral stricture later on.

5.4.5. SUPRAPUBIC BLADDER TAP

This procedure is seldom used nowadays as most doctors use in-out catheterisation or urine bag to obtain urine specimen. It may be difficult to obtain a urine sample but if successful, the urine is not contaminated by perineal bacteria and will indicate a true positive urinary tract infection.

Indication

- Urine culture in a young infant.

Equipment

- Dressing set.
- Needle size 21, 23 G
- Syringe 5cc.
- Urine culture bottle.

Procedure

1. Make sure bladder is palpable. Give a drink to patient half to 1 hour before procedure.
2. Position the child in supine position. Clean and drape the lower abdomen. Use local anaesthesia.
3. Insert the needle attached to a 5cc syringe perpendicular or slightly caudally to the skin, 0.5 cm above the suprapubic bone.
4. Aspirate while advancing the needle till urine is obtained.
5. Withdraw the needle and syringe.
6. Pressure dressing over the puncture site.
7. Send urine for culture and microscopy.

Complications

- Microscopic haematuria from trauma to bladder mucosa.
- Infection
- Viscus perforation

5.5. BONE MARROW ASPIRATION AND TREPHINE BIOPSY

Indications

- Examination of bone marrow in a patient with haematologic or oncologic disorder.

Contraindications

- Bleeding tendency, platelet count < 50,000/mm^3.
- Consider transfusion of platelet concentrates prior to procedure.

Equipment

- Bone marrow set (Islam) 16 – 18 G

Procedure

1. Sedate child, monitor continuously with pulse oximeter.
2. Position child - either as for lumbar puncture or in a prone position.
3. Identify site for aspiration - posterior iliac crest preferred, upper anterior-medial tibia for child < 3 months old.
4. Clean skin using standard aseptic technique with povidone-iodine and 70% alcohol. Give local anaesthetic.
5. Make a small skin nick over the PSIS (posterior superior iliac spine). Hold the trocar firmly and gently enter the cortex by a twisting action. A 'give' is felt as the needle enters the bone marrow.
6. Trephine biopsy is usually done before marrow aspiration.
7. Withdraw needle, spray with op-site, cover with gauze and crepe bandage.
8. Lie child supine for the next 4 to 6 hours and observe for blood soaking the gauze in a child with bleeding diasthesis.

Complications

- Bleeding, haematoma
- Infection

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