

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

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

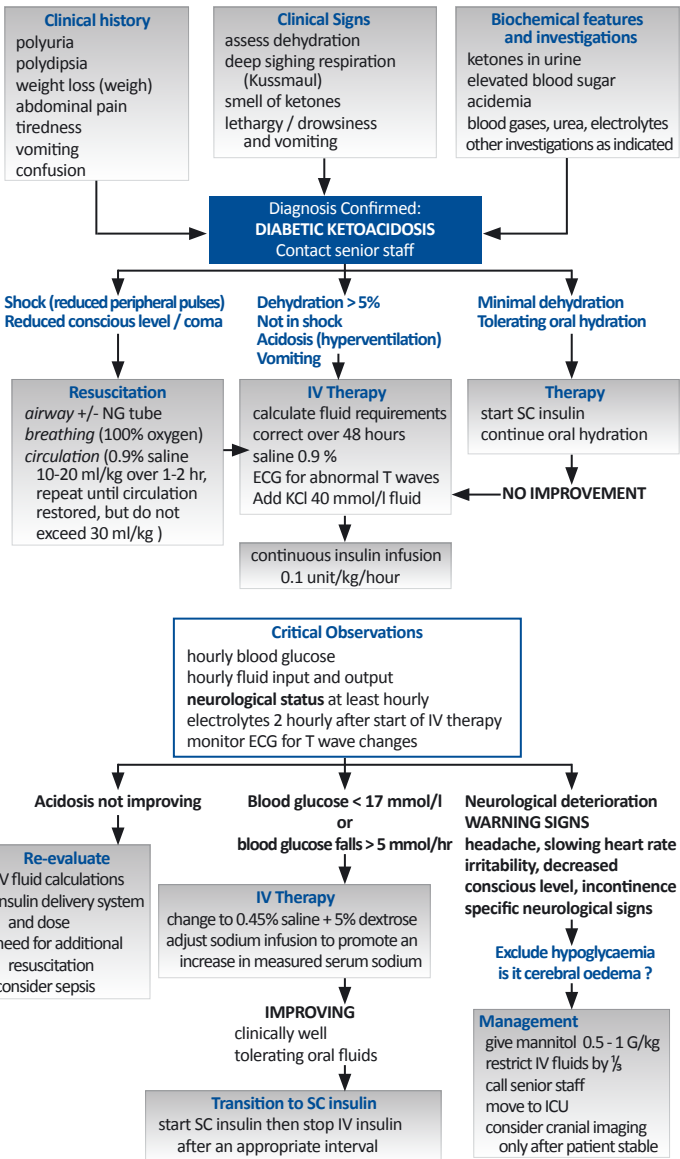
Emergency management

- 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 catheter (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)

Figure 1. Algorithm for the immediate assessment and management of diabetic ketoacidosis (DKA)



ENDOCRINOLOGY

Clinical and biochemical monitoring

- monitoring should include the following:
 - hourly (or more frequently as indicated) vital signs (heart rate, respiratory rate, blood pressure), head chart, accurate fluid I/O (including all oral fluid).
 - amount of administered insulin
 - hourly capillary blood glucose (must be cross checked against laboratory venous glucose)
 - 2-4 hourly (or more frequent in more severe cases): BUSE, glucose, calcium, magnesium, phosphorus, hematocrit and blood gases
 - 2 hourly urine ketones until cleared or blood b-hydroxybutyrate (BOHB) concentrations (if available)

Calculations

1. 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
2. Corrected sodium (mmol/L) = $measured\ Na + \frac{2 \times (plasma\ glucose - 5.6)}{5.6}$
3. Effective osmolality (mOsm/kg) = $2 \times (Na + K) + plasma\ glucose + urea$

Fluids and Salt

Principles of water and salt replacement

- begin with fluid replacement before insulin therapy.
- fluid bolus (resuscitation) required ONLY if needed to restore peripheral circulation
- subsequent fluid administration (including oral fluids) should rehydrate evenly over 48 hrs at a rate rarely in excess of 1.5–2 times the usual daily maintenance

Acute Resuscitation

- if child is in shock, fluid resuscitation is needed to restore peripheral circulation, fluid boluses 10–20 mL/kg over 1–2 hrs of 0.9% saline is used. Boluses may be repeated, if necessary. There is no evidence that the use of colloids is better.

Replacement of water and salt deficits

- patients with DKA have a deficit in extracellular fluid (ECF) volume. Clinical estimates of the volume deficit are subjective and inaccurate; therefore in
 - moderate DKA use 5–7% deficit
 - severe DKA use 7–10% dehydration
- the rate of fluid (IV, oral) should be calculated to rehydrate evenly over 48 hours
 - as a guide fluid infused each day usually < 1.5 - 2 times usual daily maintenance
 - IV or oral fluids given in another facility before assessment should be factored into calculation of deficit and repair.
- replacement should begin with 0.9% saline or Ringer's lactate for at least 4–6 h. Thereafter, use a solution that has a tonicity equal to or greater than 0.45% saline with added potassium chloride (see below under potassium replacement)
- urinary losses should not routinely be added to the calculation of replacement fluid, but may be necessary in rare circumstances
- calculate the corrected sodium (formula as above) and monitor changes:
 - as plasma glucose decreases after IV fluids and insulin, the serum sodium should increase: this does not indicate a worsening of the hypertonic state

- a failure of sodium levels to *rise* or a further decline in sodium levels with therapy may signal impending cerebral oedema: may need to increase sodium in IV fluids
- the use of large amounts of 0.9% saline has been associated with the development of hyperchloraemic metabolic acidosis

Insulin therapy

- *DKA is caused by either relative or absolute insulin deficiency.*
- *start insulin infusion 1–2 h AFTER starting fluid replacement therapy*
- correction of insulin deficiency
 - dose: 0.1 unit/kg/h IV infusion. (one method is to dilute 50 units regular insulin in 50 ml normal saline, 1 unit = 1 ml)
 - an *initial IV bolus of insulin is not necessary*, and may increase the risk of cerebral oedema and should not be given
- *the dose of insulin should usually remain at 0.1 unit/kg/h at least until resolution of DKA* (evidenced by pH > 7.30, HCO₃ > 15 mmol/L and/or closure of the anion gap), which takes longer than normalization of blood glucose concentrations.
- if the patient as a marked sensitivity to insulin (e.g. young children with DKA, patients with Hyperglycemic Hyperosmolar State (HHS), and older children with established diabetes), the dose may be decreased to 0.05 unit/kg/h, or less, provided that metabolic acidosis continues to resolve.
- during initial volume expansion the plasma glucose concentration falls steeply. After commencing insulin therapy, the plasma glucose concentration typically decreases at a rate of 2–5 mmol/L/h.
- to prevent an unduly rapid decrease in plasma glucose concentration and hypoglycemia, *add 5% glucose to the IV fluid (e.g., 5% glucose in 0.45% saline) when plasma glucose falls to 14–17 mmol/L, or sooner if the rate of fall is rapid*
 - it may be necessary to use 10% or even 12.5% dextrose to prevent hypoglycemia while continuing to infuse insulin to correct the metabolic acidosis.
- if blood glucose falls very rapidly (>5 mmol/L/h) after initial fluid expansion add glucose even before plasma glucose has decreased to 17 mmol/L.
- if biochemical parameters of DKA (pH, anion gap) do not improve, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin; e.g. infection, errors in insulin preparation.
- if continuous IV insulin is not possible, hourly / 2-hourly subcutaneous (SC) or IM administration of a short or rapid-acting insulin analog (insulin lispro or insulin aspart) is safe / effective. (do not use in patients with impaired peripheral circulation)
 - initial dose SC: 0.3 unit/kg, followed 1 h later at SC 0.1 unit/kg every hour, or 0.15–0.20 units/kg every 2 h
 - if blood glucose falls to <14 mmol/L before DKA has resolved (pH still <7.30), add 5% glucose and continue with insulin as above
 - when DKA has resolved and blood glucose is < 14 mmol/L, reduce SC insulin to 0.05 unit/kg/h to keep blood glucose around 11 mmol/L

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

- *there is always a deficit of total body of potassium (3-6 mmol/kg) even with normal or high levels of serum potassium at presentation. Replacement therapy is therefore required.*
 - if the patient is hypokalemic at presentation, start potassium replacement at the time of initial volume expansion and before starting insulin therapy, at a concentration of 20 mmol/L (0.75 g KCl per pint)
 - if patient is normokalemic, start replacing potassium after initial volume expansion and concurrent with starting insulin therapy. The starting potassium concentration in the infusate should be 40 mmol/L (1.5 g KCl/pint)
 - if the patient is hyperkalaemic ($K^+ > 5.5$ mmol/L), defer potassium replacement therapy until urine output is documented
 - if immediate serum potassium measurements are unavailable, an ECG may help to determine whether the child has hyper- or hypokalemia
- subsequent potassium replacement therapy should be based on serum potassium measurements
- potassium replacement should continue throughout IV fluid therapy
- the maximum recommended rate of IV potassium replacement is 0.5 mmol/kg/h
- if hypokalemia persists despite maximum rate of potassium replacement, then the rate of insulin infusion can be reduced

Phosphate

- depletion of intracellular phosphate occurs in DKA
- severe hypophosphatemia, with unexplained weakness, should be treated
- potassium phosphate salts may be safely used as an alternative to or combined with potassium chloride or acetate, provided that careful monitoring of serum calcium is performed as administration of phosphate may induce hypocalcaemia

Acidosis

- *severe acidosis is reversible by fluid and insulin replacement.*
- *there is no evidence that bicarbonate is either necessary or safe in DKA.* Bicarbonate therapy may cause paradoxical CNS acidosis; hypokalaemia and increasing osmolality.
- used only in selected patients:
 - severe acidaemia (arterial pH <6.9) in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion,
 - life-threatening hyperkalaemia.
 - cautiously give 1–2 mmol/kg over 60 min.

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.
- when ketoacidosis has resolved (pH > 7.3; $HCO_3^- > 15$ mmol/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 before bedtime. Total insulin dose is about 1u/kg/day.

- to prevent rebound hyperglycemia, the first SC injection is given 15 - 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.
- the dose of soluble insulin is titrated against capillary blood glucose.
- convert to long-term insulin regime when stabilized. Multiple dose injections 4 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% to 25% of survivors of cerebral edema have significant residual morbidity

Other rare causes of morbidity and mortality include: hypokalemia, hyperkalemia, severe hypophosphataemia; hypoglycaemia; sepsis; 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

Table 1. Diagnosis of cerebral oedema in children with diabetic ketoacidosis

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 HR deceleration (decrease > 20 bpm), not attributable to improved intravascular volume or sleep state age-inappropriate incontinence	vomiting headache lethargy or not easily arousable diastolic blood pressure >90 mmHg age <5 years

Note: 1 diagnostic criteria, or 2 major criteria, or 1 major and 2 minor criteria have a sensitivity of 92% and a false positive rate of only 4%.

Treatment of cerebral oedema

- initiate treatment as soon as the condition is suspected.
- give mannitol 0.5 - 1 g/kg IV over 20 min and repeat if there is no initial response in 30 minutes to 2 hours
- reduce the rate of fluid administration by one-third.
- hypertonic saline (3%), 5 - 10 ml/kg over 30 min, may be an alternative to mannitol, especially if there is no initial response to mannitol
- elevate the head of the bed.
- intubation may be necessary for the patient with impending respiratory failure. Maintain normocapnia. (PaCO₂ within normal range).
- after treatment for cerebral oedema has been started, a cranial CT scan should be done to rule out other possible intracerebral causes of neurologic deterioration