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Malaria Prophylaxis in Children

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Objectives After completing this article, readers should be able to:

1. Differentiate among the four species of *Plasmodium*.
2. Recognize the life cycle stages of the malaria parasite.
3. Identify the geographic areas endemic for chloroquine-sensitive and chloroquine-resistant malaria.
4. Identify the appropriate chemoprophylactic regimen(s) for malaria in areas with and without chloroquine resistance.
5. Recognize the site of action of the chemoprophylactic agents in the life cycle of the parasite.
6. List nonchemoprophylactic prevention strategies for malaria.

Case Report

An 8-year-old girl weighing 25 kg presented at the clinic with a 2-day history of fever, chills, malaise, fatigue, cough, and one episode of vomiting. The child had been born in Nigeria, immigrated to the United States at the age of 2 years, and just returned 5 days ago from a 3-week visit to Nigeria with her parents. Two weeks prior to travel, the entire family had been prescribed weekly chloroquine for malaria chemoprophylaxis. The girl had taken the initial 250-mg dose of chloroquine and subsequently had followed the weekly regimen; she took the last dose the day she presented to the clinic. The clinician initially diagnosed the girl with an upper respiratory tract infection along with nausea and vomiting and prescribed an oral cephalosporin antibiotic and an antiemetic agent. However, the girl's symptoms continued, and 4 days later she collapsed, was transported to a local hospital, and

died in the emergency department. Examination of a peripheral blood film on stored blood from the clinic visit and a film from blood taken in the emergency department demonstrated *Plasmodium falciparum* parasites. A blood sample taken postmortem revealed a chloroquine level of 1,800 ng/mL whole blood, a level consistent with recent ingestion of chloroquine and sufficient to inhibit *P falciparum* parasites sensitive to the drug.

Introduction

Malaria is the world's most important and devastating parasitic disease, affecting more than 300 million people worldwide annually. The incidence of malaria has increased over the past 20 years, which has resulted in more than 3,000 pediatric deaths per day. Malaria now represents the leading cause of mortality among children older than 5 years of age in Africa. More than 10,000 cases were reported in United States civilian travelers from 1985 to 2001. More than 1,300 cases were reported in 2002, and all but 5 of these cases were found in immigrants. It is estimated that 20% of these cases oc-

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curred in patients younger than 18 years of age.

Although good preventive measures are available, the appearance and spread of resistance combined with an increased number of travelers worldwide may be responsible for the increase in malaria cases. In areas where malaria is not endemic, such as the United States, health-care practitioners frequently are unfamiliar with the appropriate preventive measures as well as the disease symptoms, resulting in suboptimal chemoprophylaxis and delays in diagnosis and treatment. Almost all fatal cases of imported malaria are preventable, but because of inadequate chemoprophylaxis, missed diagnosis, or noncompliance by the traveler, death has been the result. This article is an overview of the current approach to preventing malaria, specifically in children, with recommendations based on the increase in drug resistance in endemic malarial regions and the drugs' site of action in the life cycle of the parasite.

The Parasite

Four species of the genus *Plasmodium* are known to infect humans through transmission by anopheline mosquitoes: *P falciparum*, *P vivax*, *P ovale*, and *P malariae*. *P falciparum*, which is associated with the greatest morbidity and mortality, and *P vivax* are responsible for more than 90% of all reported malarial cases. Increased drug resistance of *P falciparum* and a growing resistance of *P vivax* make choosing the appropriate chemoprophylactic regimen challenging.

In addition to the issue of resistance, another challenge is providing a chemoprophylactic regimen that covers both stages of the life cycle of the parasite in humans. The first stage occurs in the liver, where the parasites multiply in hepatocytes un-

til they rupture. The second stage occurs when the parasites are released into the bloodstream, invade the erythrocytes, and cause clinical symptoms. If the parasite stays in a persistent liver stage, clinical symptoms can recur months to years later. Both *P vivax* and *P ovale* are associated with persistent liver stages and, thus, with late-onset illness (eg, months after return from an endemic area), especially if the chemoprophylactic regimen included drugs that affected the parasite life cycle only at the blood stage. When considering the appropriate chemoprophylactic and treatment regimen, it is important to keep in mind that the species of *Plasmodium* most likely involved is based on travel location, the issue of resistance, and the life cycle of the parasite.

Endemic Areas

Malaria is endemic in more than 100 countries, and more than 40% of the people in the world are at risk. Large areas of Central and South America, Haiti, the Dominican Republic, Africa, the Middle East, the Indian subcontinent, Southeast Asia, and Oceania are considered endemic areas. The current guidelines for chemoprophylaxis divide these endemic areas into two zones: 1) chloroquine-sensitive *P falciparum* and 2) chloroquine-resistant *P falciparum*. Due to the increase in resistance of *P falciparum*, it is advised that before selecting the appropriate chemoprophylactic drug regimen, the physician check either of the following Web sites for up-to-date information about country-specific malaria risk: 1) Centers for Disease Control and Prevention (www.cdc.gov/travel) and 2) World Health Organization (www.who.int/ith/). Currently, resistance to chloroquine has been confirmed in all areas that harbor *P falciparum* except for the Dominican Republic,

Haiti, Central America west of the former Panama Canal Zone, Egypt, and some countries in the Middle East.

Unfortunately, knowing the chloroquine sensitivity of *P falciparum* is only half the battle. It also is important to know if the country has a substantial amount of malaria caused by either *P vivax* or *P ovale* to know if the chemoprophylactic drug regimen should include an agent that covers the parasite liver stage. In endemic areas such as sub-Saharan Africa, where *P falciparum* is responsible for greater than 90% of infections, a nonchloroquine drug regimen covering the parasite blood stage is appropriate. However, if travel is in Ethiopia or Somalia, a nonchloroquine drug regimen covering the parasite liver stage is preferred due to the risk of infection by both *P falciparum* and *P vivax*. Prior to prescribing a chemoprophylactic regimen, the clinician should refer to either of the previously noted Web sites for the most complete information on the types of malaria in the country of travel.

Chemoprophylactic Drug Regimens

Once the geographic area has been defined in terms of chloroquine resistance and predominant *Plasmodium* species, other factors, including frequency of dosing and adverse effect profiles, need to be explored. The Table lists pediatric antimalarial chemoprophylactic options based on chloroquine sensitivity, including information on dose, duration, formulation, adverse effects, and site of action within the parasite life cycle. Overall, the adverse effects of antimalarials are rare at the lower prophylactic doses when compared with long-term treatment doses. However, if a patient experiences intolerable adverse effects, he or she should seek medical advice to discuss contin-

Table. Antimalarial Chemoprophylactic Options

	Chloroquine-sensitive Areas (Drug of Choice)	Chloroquine-resistant Areas (Drug of Choice)	Chloroquine-resistant Areas (Alternatives)
Drug	Chloroquine phosphate	Mefloquine	Primaquine
Prophylactic Type	Blood stage	Blood stage	Liver stage
Adult Dose	500 mg (300 mg base) once/wk	250 mg once/wk	15 mg/day (base) daily or 45 mg/week (base) weekly
Pediatric Dose	5 mg/kg base (max 300 mg base) once/wk	<15 kg: 1/8 tablet 15 to 19 kg: 1/4 tablet 20 to 30 kg: 1/2 tablet 31 to 45 kg: 3/4 tablet >45 kg: 1 tablet	0.3 mg/kg (base) daily (max 15 mg/d) OR 0.9 mg/kg (base) weekly (max 45 mg/wk)
Duration	Begin 1 to 2 weeks prior to travel, continue weekly through travel stay and for 4 weeks after return	Begin 1 to 2 weeks prior to travel, continue weekly through travel stay and for 4 weeks after return	Begin therapy during last 2 weeks of or following a course of suppression with chloroquine or comparable drug; use daily dose for 14 days or weekly dose for 8 weeks
Formulation	Tablets: (salt/base): 250/150 mg 500/300 mg	Tablets (salt/base): 250/228 mg	Tablets: 26.3 mg/15 mg base
Comments	May pulverize tablet for extemporaneous preparation	May pulverize tablet for use in children >7 years of age	May pulverize tablet; give with food to decrease gastrointestinal effects
Adverse Effects	Pruritis, nausea, headache, skin eruptions, psychosis, reversible corneal opacity, nerve deafness, seizures, myopathy, blood dyscrasia, nail and mucous membrane discoloration, photophobia	Dizziness, diarrhea, nausea, vivid dreams, irritability, mood alterations, headache, insomnia, anxiety, seizures, psychosis	Nausea, vomiting, hemolytic anemia, methemoglobinemia, pruritus, headache, visual accommodation disturbance

uation of medications or a possible change in regimen.

A limited number of liver-stage chemoprophylactic agents are available; even more limited is clinical experience with their use in children. Atovaquone/proguanil has been found to be effective for treating *P falciparum* in children and has been shown to be effective and well tolerated as a chemoprophylactic agent against *P falciparum*. However, data on that combination for prophylaxis or treatment of *P vivax* are more limited. Headache and abdominal pain are the most common adverse events (13% each) in pediatric patients taking prophylactic atovaquone/proguanil; these data have been found to be comparable to a placebo group. Primaquine has been used most frequently for terminal prophylaxis or for relapsing malaria. Several studies have demonstrated its protective effects against both *P falciparum* and *P vivax* in adults, with limited data available for children. One disadvantage of both agents is the need for daily administration.

The development of new preventive agents that act on the liver stage is underway. Tafenoquine, an 8-aminoquinolone (analog of primaquine), is undergoing clinical studies, with its primary advantage being an

extended elimination half-life of 14 days.

In general, all antimalarial drugs are very bitter. To administer these medicines to a child, it is recommended that the tablets be crushed and given with something sweet, such as chocolate syrup, jelly, or a creme-filled donut.

Other Prevention Strategies

Prevention of mosquito bites also can decrease the risk of malaria and other diseases spread by mosquitoes. Long-sleeved cotton shirts and pants should be worn during the mosquito-biting period (dusk to dawn). In addition to minimizing skin exposure, application of insect repellent containing no more than 20% to 30% DEET (N,N-diethyl-3-methylbenzamide; formerly N,N-diethyl-m-toluamide) to the exposed skin can be highly effective. Caution should be taken to avoid excessive use of a high concentration (greater than 30%) of DEET for children because of adverse reactions, including encephalopathy, seizures, and rashes. DEET-containing products, therefore, should be used according to the product label. Other preventive measures include using window screens and bed nets and applying per-

methrin, an insecticide, to clothing and bed nets.

Conclusion

Although effective chemoprophylaxis of malaria is available, it is not 100% effective, especially in the presence of noncompliance and even with adequate drug levels, as was seen in the case presented. Whenever a patient presents with fever and a history of traveling to a malaria-endemic area, the health-care practitioner's working diagnosis must include malaria until proven otherwise. Additionally, evaluation and treatment of malaria should be considered a medical emergency, even if the patient appears stable.

Suggested Reading

- Kain KC, Shanks GD, Keystone JS. Malaria chemoprophylaxis in the age of drug resistance. I. Currently recommended drug regimens. *Clin Infect Dis.* 2001; 33:226–234
- Schwartz E, Parise M, Kozarsky P, Cetron M. Delayed onset of malaria – implications for chemoprophylaxis in travelers. *N Engl J Med.* 2003;349:1510–1516
- Shanks GD, Kain KC, Keystone JS. Malaria chemoprophylaxis in the age of drug resistance. II. Drugs that may be available in the future. *Clin Infect Dis.* 2001; 33:381–385
- Stauffer W, Fischer PR. Diagnosis and treatment of malaria in children. *Clin Infect Dis.* 2003;37:1340–1348

PIR Quiz

Quiz also available online at www.pedsinreview.org.

13. Malaria always should be considered as a possible diagnosis for a child who has a fever after returning from living in an endemic malarial area. Two species of *Plasmodium* may cause malarial relapse months to years after children have returned from their stay and after having completed their antimalarial prophylaxis. The body site *most* likely to harbor these malarial parasites, which can result in late relapses, is the:
 - A. Blood.
 - B. Central nervous system.
 - C. Liver.
 - D. Lungs.
 - E. Lymph nodes.

14. The treatment and prophylaxis of malaria involves a number of different drugs, with selection of the optimal drug based on the types of malaria in the country being visited, the rate of chloroquine resistance, and the potential for drug reactions or adverse effects. The antimalarial drug that is *most* likely to result in psychosis is:
 - A. Atovaquone/proguanil.
 - B. Doxycycline.
 - C. Mefloquine.
 - D. Primaquine.
 - E. Tafenoquine.

15. A medical missionary and his family have volunteered to work in Haiti for the next year. The risk of malaria is of concern to this family. Which of the following prophylaxis regimens are you *most* likely to recommend?
 - A. Chloroquine 1 week prior to their departure, weekly during their stay, and weekly for 4 weeks after their return.
 - B. Doxycycline daily during their stay.
 - C. Primaquine for 2 weeks at the end of their trip.
 - D. Trimethoprim-sulfamethoxazole daily during their stay.
 - E. Weekly mefloquine during their stay and for 4 weeks after their return.

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