CME CREDIT

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Fever in a returned traveler

TWO WEEKS after returning from a trip to Manaus, Brazil, a military officer sought care for a febrile illness characterized by nausea, vomiting, diarrhea, headache, and malaise. He reported using mefloquine for malaria prophylaxis. He was diagnosed with a viral syndrome. After a brief period of improvement, his illness recurred, and he went to a different facility, where he was diagnosed with atypical pneumonia.

He now comes to your clinic because his symptoms continue to recur. It has been 6 weeks since he returned from his trip. His vital signs and physical examination are normal. He is afebrile. Initial routine laboratory results, including a complete blood cell count and liver functions tests, are normal.

■ **WHAT TEST IS NEEDED?**

1 What test should be performed next?

❏ Acute viral hepatitis panel
❏ Sputum and blood culture
❏ Thick and thin blood parasite smears
❏ Stool cultures

Although some textbooks state that most fevers in returned travelers are due to illnesses other than malaria, such as diarrhea or viral upper respiratory illness,[1] malaria was the most common cause of fever in three large case series of ill returning travelers, particularly those requiring hospitalization.[2–4] Therefore, blood parasite smears should be performed next.

Other top causes of fever in these cohorts included gastroenteritis, dengue fever, and bacterial pneumonia. If aminotransferase lev-els are elevated, it would be worthwhile to evaluate for acute hepatitis. Stool cultures could be obtained in this situation while evaluation for malaria proceeded.

Even though knowledge has advanced and malaria has been eradicated in the United States, the death rate from malaria in US citizens has not declined, but rather has remained constant over the last half century.[5] In fact, both the risk of infection and the range of endemic malaria have worsened over the last 30 years.[6] Cases of malaria acquired by travelers from industrialized countries probably number 25,000 annually; of these, about 10,000 are reported, and 150 are fatal.[7] These numbers are growing because of increased international travel, increased risk of transmission in areas where malaria control has faded, and spread of drug-resistant strains.[7,8]

■ **IS MALARIA ALWAYS SYMPTOMATIC?**

2 True or false? Absence of typical signs and symptoms such as fever and rigors rules out malaria.

❏ True
❏ False

False. The diagnosis of malaria is often missed, and delays in diagnosis and treatment are common.[5,9] One study found that malaria was missed in more than half of cases, and microscopic diagnosis misidentified the species in 64%.[8] After presentation, the average delay before treatment was 7.6 days for *Plasmodium falciparum* malaria and 5.1 days for *P vivax*.[8]

Malaria can be difficult to recognize
Malaria can be difficult to recognize and manage, especially if it is recurrent or of late onset, for many reasons. Medical practitioners may

Any history of fever or chills and travel to endemic areas should prompt an evaluation for malaria

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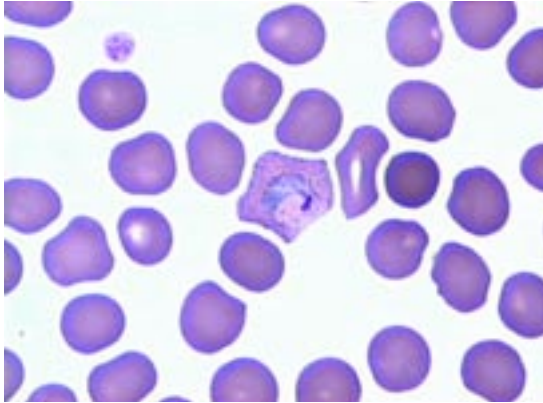
The patient's blood smear

FIGURE 1. Peripheral blood smear showing mature ring form in an enlarged coarse-appearing erythrocyte.
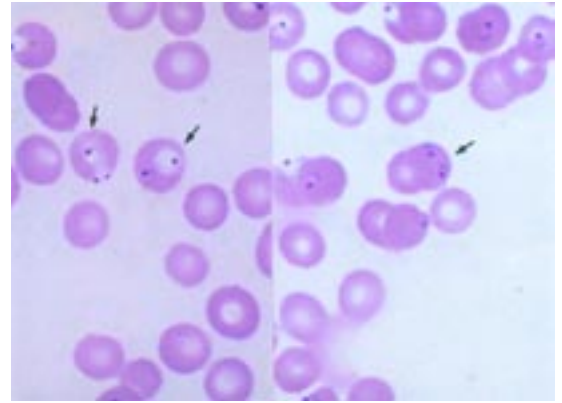
Plasmodium falciparum

FIGURE 2. Multiple ring forms within single red blood cells, suggestive of *P falciparum.*

Up to 40% of people with malaria may be afebrile when examined

be unfamiliar with the disease. Further, the delayed symptoms of malaria that occur in people who have taken prophylaxis or are partially immune (eg, those who lived until recently in endemic area) can be easily overlooked. Clinicians and patients may disregard travel to endemic areas months previous to presentation, assuming this exposure is not significant.

In addition, the clinical presentation of malaria among partially immune people is usually less severe than in nonimmune people. Up to 80% of immune people with evidence of parasitemia on smears may have no symptoms,[10–12] although they may have splenomegaly or anemia from chronic infections. Furthermore, although people with malaria usually have a *history* of fever, 10% to 40% may be afebrile when first examined.[13] Any history of fever or chills and travel to endemic areas, regardless of presenting vitals signs, should prompt an evaluation for malaria.

Finally, clinicians may be led to initiate unfruitful workups, since malaria has a variety of possible presenting symptoms. One is respiratory disease—including acute respiratory distress syndrome (ARDS). Even fatal cases of malaria can initially present as non-specific respiratory symptoms, as it did in almost 10% of 123 travelers who succumbed to their malaria.[5] Another relatively common presentation is gastrointestinal, as in our patient.

■ IS PROPHYLAXIS 100% EFFECTIVE?

3 True or false? The use of prophylaxis rules out malaria as a cause of fever in returning travelers.

❑ True
❑ False

False. Although many physicians and travelers believe that taking prophylactic drugs completely prevents malaria,[14] the disease should not be eliminated from the differential diagnosis of fever in a returned traveler simply because he or she took or reports taking prophylaxis. No prophylaxis is 100% effective, and patients may be reluctant to disclose nonadherence.

Additionally, some travelers may still contract malaria despite having taken appropriate prophylactic regimens. This failure may be a result of inadequate blood levels of the drug (due to poor absorption or rapid metabolism) or parasite resistance to the drug. Resistance is probably the less likely reason, and it may actually be overreported as a cause of failure of prophylaxis.[15] When resistance is suspected, the first step should be to confirm that the initial diagnosis of malaria was correct.

■ WHAT TYPE OF MALARIA?

4 Our patient's peripheral blood smear (**FIGURE 1**) indicates that his fevers are due to infection with which of the following organisms?

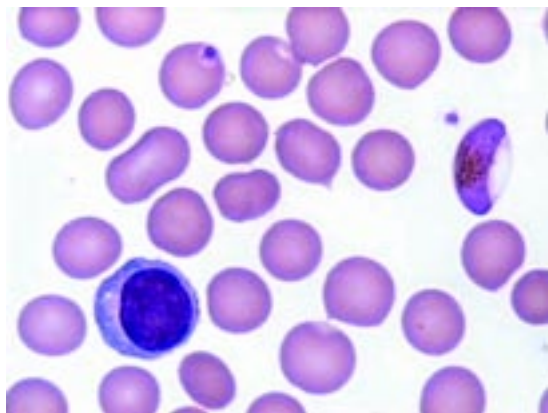❑ *P vivax*

Plasmodium falciparum

FIGURE 3. Banana-shaped gametocyte, characteristic of *P falciparum.*

❏ *Babesia*
❏ *P falciparum*
❏ *Ehrlichia*

P falciparum is the worst

When the blood smear contains malaria parasites, the most important initial step is to rule out *P falciparum*. *P ovale*, *P vivax*, and *P malariae* are usually not fatal, but *P falciparum* can cause multiorgan failure, including ARDS, cerebral malaria, renal failure, and severe anemia, and can be fatal if not promptly treated. Nearly all deaths from malaria are caused by *P falciparum* infections.[14]

Furthermore, *P falciparum* is the most common cause of malaria worldwide,[16] although returning US travelers are more often infected with *P vivax*, reflecting travel patterns of American travelers.

Clues indicating *P falciparum* include multiple ring forms within a single red blood cell (**FIGURE 2**), banana-shaped gametocytes (**FIGURE 3**), and accolade forms. Although *P falciparum* classically presents with a high degree of parasitemia, sometimes few parasites are visible on the smear because they are sequestered in deep vessels.

This patient's smear shows a mature ring form, large and coarse in appearance, characteristic of *P vivax*. Red cells infected with *P vivax* are usually enlarged, sometimes up to 1.5 to 1.75 times the usual size. Under ideal conditions, Schüffner dots can sometimes be seen (**FIGURE 4**). In contrast, *P falciparum* ring forms
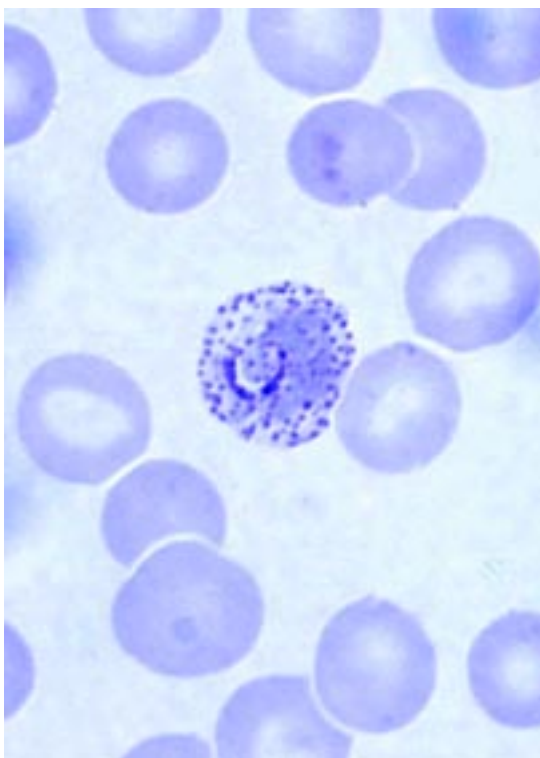
Plasmodium vivax

FIGURE 4. Enlarged erythrocyte containing Schüffner dots seen under ideal conditions and characteristic of *P vivax.*

tend to display a fine, delicate appearance, without enlargement of the infected red cell.

For *Babesia* infection, there is usually a history of travel to or residence in the coastal northeastern United States, not South America as in this case. The smear contains ring forms in classic appliqué form or in singles, doubles, or tetrads within red blood cells.

Diagnosis of *Ehrlichia* infection is primarily through serologic tests; uncommonly, morula can be seen within leukocytes on blood smears.

Occasionally co-infection with more than one species can occur in the same patient.

■ WHAT IS APPROPRIATE TREATMENT?

5 Which of the following would *not* be an appropriate regimens for this patient?

❏ Chloroquine initially, followed by primaquine, 30 mg of the base per day for 14 days

P falciparum can cause multiorgan failure, including ARDS, cerebral malaria, renal failure, and severe anemia

❑ Mefloquine
❑ Quinine and doxycycline initially, followed by primaquine, 15 mg base per day for 14 days
❑ Atovaquone-proguanil initially, followed by primaquine, 30 mg base per day for 14 days

The second choice—mefloquine by itself—is incorrect because it does not contain primaquine for terminal prophylaxis. Treatment of *P vivax* or *P ovale* malaria requires primaquine to eradicate the dormant hypnozoite stage.

The third choice is also incorrect because the dose of primaquine is too low. The traditional dose of 15 mg of primaquine base for terminal prophylaxis, which is still recommended in current editions of three infectious disease texts,[17–19] has recently been deemed inadequate by some experts.[20] An increasing number of reports[21–23] of relapsing malaria despite taking the standard 15-mg dose have resulted in a change in recommendations to a dose of 30 mg.[20,24]

Adding to the challenge of treating malaria is that most antimalarial drugs should be dosed with specific reference to the base, or the salt in the case of quinine. Primaquine is supplied as 26.4-mg tablets, but these contain only 15 mg of the base. To avoid confusion, providers should be careful to specify a dose of "primaquine, 30 mg base (two tablets)."

Other considerations include the severity of infection. Patients whose condition is stable can be treated with oral medications, whereas those with severe infection need immediate parenteral treatment. Severe infection is defined as one or more of the following: impaired consciousness, severe normocytic anemia, renal failure, pulmonary edema, ARDS, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, hemoglobulinuria, jaundice, repeated generalized convulsions, or parasitemia greater than 5% (ie, more than 5% of the red blood cells contain the parasites).[25]

The infecting *Plasmodium* species and where the infection was acquired determine whether chloroquine will be used. Chloroquine remains the treatment of choice for all *P vivax* and *P ovale* infections except for

CDC malaria hotline: (770) 488-7788; (770) 488-7100 (evenings and weekends)

P vivax infections acquired in Papua New Guinea or Indonesia, where chloroquine-resistant *P vivax* is common. Rare cases of chloroquine-resistant *P vivax* have also been documented in Myanmar (Burma), India, and South America. Patients who acquire *P vivax* infections from regions other than Papua New Guinea or Indonesia should initially be treated with chloroquine. Therefore, the first choice above—chloroquine initially, following by primaquine, 30 mg of the base per day for 14 days—would be the best regimen for our patient.

If a patient does not respond to treatment, the clinician should consider other illnesses along with malaria. Medications for treatment or prophylaxis that are effective in semi-immune or immune populations may not be as effective in nonimmune patients. In addition, treatment can be altered in these patients to another regimen that includes quinine plus doxycycline, atovaquone plus proguanil HCL, or mefloquine. All should be followed with a terminal phase of primaquine.

If the species is not known or cannot be determined, one should empirically treat for chloroquine-resistant *P falciparum*. In that case, the first answer would also be incorrect because the only place in tropical South America where chloroquine sensitivity can be assumed is Paraguay.[26]

Up-to-date information is crucial when treating malaria. Information and assistance can be obtained at the US Centers for Disease Control and Prevention at **www.cdc.gov**. The hotline numbers are (770) 488-7788 Monday through Friday, 8 am to 4:30 PM EST, or (770) 488-7100 after hours, weekends, and holidays (ask to page the malaria person on call).

■ **BEFORE PRESCRIBING PRIMAQUINE**

6 Before prescribing primaquine, you should screen the patient for what disorder?

❑ Hereditary spherocytosis
❑ Glucose-6 phosphate dehydrogenase (G-6PD) deficiency
❑ Wilson disease
❑ Beta-thalassemia

Before patients receive primaquine, they must be screened for G-6PD deficiency. G-6PD cat-

alyzes the first step in the hexose monophosphate shunt, which protects red blood cells by producing nicotinamide-adenine-dinucleotide phosphate (NADPH). Patients deficient in this enzyme are prone to hemolysis triggered by a variety of drugs (including primaquine and sulfa-containing medications), toxins, or infections. Patients present with jaundice, dark urine, and pallor 2 to 4 days after starting the medication.

There are several variants of G-6PD deficiency; some are associated with more severe hemolysis than others. Most Africans and African Americans with G-6PD deficiency still have approximately 20% normal G-6PD activity. In such people, primaquine destroys only senescent red blood cells, and further hemolysis does not occur. Even in the face of continuous dosing, the anemia remains mild and self-limited. Rarer variants (with less than 5% residual G-6PD activity) are associated with life-threatening acute intravascular hemolysis. These tend to occur in people of Mediterranean descent.

Since fetuses cannot be screened for G-6PD deficiency, primaquine cannot be given to pregnant women.

Case continued: After treatment, the patient's symptoms recur
Our patient is treated with chloroquine and instructed to take primaquine for 14 days. One month later, his symptoms have begun to recur. During these recurrences his malaria smears are negative.

■ RELAPSING MALARIA

7 Relapse can occur in malaria due to which of the following?

- ❑ *P falciparum*
- ❑ *P malariae*
- ❑ *P vivax*
- ❑ *P ovale*
- ❑ Both *P vivax* and *P ovale*

Only *P vivax* and *P ovale* cause true relapsing malaria (delayed parasitemia from release of dormant hepatic stages). Latent blood stages of the parasite account for the chronicity of malaria due to *P malariae*. Malaria due to *P falciparum* typically exhibits no chronic latency.

P vivax and *P ovale* have an additional liver stage
The human phase of the plasmodial life cycle begins when an infected Anopheles mosquito releases sporozoites into the human host. Within an hour,[6] sporozoites infect liver cells, where they mature into schizonts that rupture and release merozoites into the bloodstream. However, *P vivax* and *P ovale* have an additional hypnozoite stage that remains dormant in the liver. These dormant organisms can mature and cause parasitemia from 16 days to several years after the primary infection.

Next, the merozoites infect red blood cells. Early in this stage the organism is called a ring trophozoite. These trophozoites mature into schizonts, which are a collection of merozoites. The red blood cell's hemoglobin is digested in this stage, thus causing cell lysis and release of merozoites that can infect more red blood cells.

After several cycles of this asexual reproduction, the merozoites develop into gametocytes that await ingestion by a mosquito during a blood meal.

Case continued: The patient has missed doses
During another relapse, *P vivax* organisms are seen. After further discussion, the patient reveals he missed several doses of the mefloquine during his trip and of the primaquine after his discharge.

■ HOW TO INCREASE COMPLIANCE

8 Reasonable options for increasing compliance and reducing risk of relapse include which of the following?

- ❑ Supervised or directly observed therapy
- ❑ Primaquine as a single agent for prophylaxis
- ❑ Monthly tafenoquine
- ❑ All of the above

Most antimalarial medications for prophylaxis require a loading dose to achieve protective plasma levels and up to 4 weeks of therapy after returning or the last exposure to kill parasites that emerge from the liver. These dosing requirements are inconvenient for travelers who must depart on short notice or who go on brief trips.

Primaquine prophylaxis is convenient, but is not approved in the United States

Primaquine prevents *P falciparum* and *P vivax* malaria by killing parasites as they develop in the liver; therefore, there is no need for loading or postexposure doses.[20] Travelers need only to begin primaquine on the first day of exposure and continue it for 3 days after returning. This enhances compliance and, compared with standard prophylaxis, is most convenient for people taking brief trips. Some consider primaquine or atovaquone-proguanil to be the best choice for travel of 1 month's duration or less.[20] Primaquine, however, is not yet licensed for use as prophylaxis in the United States.

Tafenoquine is a synthetic, long-acting prophylactic primaquine analogue that is taken once a month, which may enhance patient compliance. In a randomized controlled trial in 200 Thai soldiers, monthly doses of tafenoquine provided 100% protective efficacy against *P falciparum* malaria, and 96% against *P vivax*.[27] In another study, Kenyan adults who received only a 3-day tafenoquine loading dose (400 mg base/day) were protected against *P falciparum* malaria for up to 7 weeks with 82% protective efficacy.[28] However, this drug is not yet available in the United States.

Supervised therapy has been shown to markedly reduce the risk of relapse.[20] A summary and analysis of 12 studies of supervised vs unsupervised therapy revealed that 1% of 1,344 patients given supervised therapy had relapses, compared with 22% of 2,061 patients given unsupervised therapy (relative risk 0.05, $P < .001$).[20] Although appealing, this method of therapy has little application outside military medicine.

■ **FUTURE OPTIONS**

9 New or investigational antimalarial therapies and strategies showing promise as future alternatives include which of the following?

❏ Multidrug combinations
❏ Artemisinin derivatives
❏ Sulfadoxine-pyrimethamine
❏ Antiretroviral protease inhibitors

Multidrug combinations. Resistance has developed to all the antimalarial drug classes except one, the artemisinins.[29] This has rendered single-agent therapy less effective in most of the world.[30] Therefore, new regimens are very much needed. Malaria is now being approached in a manner similar to that for tuberculosis or human immunodeficiency virus infection, using multidrug combinations with differing mechanisms to reduce the probability of developing resistance.[29,30]

Fosmidomycin-clindamycin achieved rapid parasite clearance and up to 100% cure rates in patients up to 14 years of age.[31,32]

A low-cost combination of chlorproguanil and dapsone has been developed by a public-private partnership as an alternative to sulfadoxine-pyrimethamine. Phase III trials were completed in 2001, and it has been approved by the UK Medicines and Healthcare Products Regulatory Agent for the treatment of uncomplicated *P falciparum* infections in adults and children more than 3 months of age.[33] Unfortunately, resistant parasites have already appeared in some areas of Africa.[33]

Artemisinin-containing combinations are perhaps most promising.[20,34–36] The combination of artesunate and mefloquine remains one of the most effective regimens in Thailand.[20,34] This combination has also been shown to reduce transmission of drug-resistant parasites by reducing the gametocyte burden in patients.[34,35]

Sulfadoxine-pyrimethamine has become minimally useful, owing to rapid development of widespread resistance to it.[30] The risk-benefit ratio is even worse when considering the possibility of severe life-threatening reactions such as Stevens-Johnson syndrome, Lyell syndrome, hepatotoxicity, agranulocytosis, and toxic epidermal necrolysis.[30]

Antiretroviral drugs. Saquinavir, ritonavir, and indinavir inhibit *P falciparum* at achievable concentrations in vivo.[37] Investigators are attempting to exploit this property for the benefit of the many people in Africa co-infected with both human immunodeficiency virus and malaria.[37]

■ **TAKE-HOME POINTS**

• Malaria should always be foremost in the differential diagnosis of febrile travelers who have returned from areas where it is endemic.
• *P falciparum* malaria should be considered a medical emergency because of the possibility of multiorgan system failure and death.

New regimens for malaria are very much needed

- Single-agent primaquine is an effective alternative for prophylaxis, with more convenient dosing that may enhance compliance, although it has not been approved for widespread malaria prophylaxis.
- Traditional doses of 15 mg of primaquine base a day, when used as terminal prophylaxis to prevent relapse from *P vivax*, are probably inadequate. Doses of 0.5 mg/kg day or 30 mg of base per day are the new recommendations. Screening for G-6PD deficiency must be obtained before prescribing primaquine.

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