

# Difficulties in the Prevention, Diagnosis, and Treatment of Imported Malaria

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**Background:** Imported malaria is quite common in the United States. Increasing antimalarial drug resistance and changes in travel patterns may have important implications for the prevention, clinical presentation, and management of this disease.

**Methods:** Medical records were reviewed for 121 patients with microscopically confirmed malaria diagnosed at 2 university-affiliated hospitals in San Francisco, Calif, between 1988 and 1997.

**Results:** Among 57 travelers from the United States, only 13 (23%) had been compliant with an appropriate chemoprophylactic regimen. No patients developed falciparum malaria after consistent chemoprophylactic therapy with mefloquine hydrochloride. However, 12 (19%) of US residents with imported malaria developed *Plasmodium vivax* or *Plasmodium ovale* infections despite an appropriate chemoprophylactic regimen, generally with a late onset suggestive of relapsing disease. Clinical presentations were similar between foreign residents and American travelers and between patients with falcipa-

rum and nonfalciparum infections; 98% of patients had a history of fever. Sixteen percent of patients had received previous evaluations during which the diagnosis of malaria was not considered. In 9% of patients, there were errors in treatment. Only 1 patient developed severe malaria.

**Conclusions:** Our results suggest that a standard chemoprophylactic regimen is highly effective in preventing falciparum malaria, but that many American travelers do not receive it. Also, relapsing *P vivax* or *P ovale* infection despite appropriate chemoprophylactic therapy was not uncommon among our cases. The presentation of imported malaria is nonspecific, highlighting the need to consider the diagnosis in any febrile patient who has been in a malaria-endemic area. Although errors in diagnosis and treatment were quite common in our study population, patient outcomes were good once the appropriate therapy was initiated.

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**M**ALARIA REMAINS one of the most important infectious diseases in the world.<sup>1</sup> An estimated 300 to 500 million cases occur each year, causing 1.5 to 2.7 million deaths.<sup>2</sup> In the United States, the incidence of imported malaria began to rise in the 1970s, and recent reports have documented well over 1000 cases per year.<sup>3</sup> These reports likely understate the true incidence of malaria, as it is estimated that 40% to 70% of cases are not reported.<sup>4-6</sup> Many cases of imported malaria appear to be preventable, as travelers often fail to follow appropriate guidelines for prevention,<sup>7-11</sup> and this failure has been associated with an increased risk for malaria.<sup>12</sup> Delays in diagnosis and therapy have also been common<sup>7,8,10</sup> and have been associated with increases in morbidity and mortality.<sup>8,13,14</sup>

The rise in the incidence of imported malaria is probably attributable to the increase in travel by Americans to countries where malaria is endemic<sup>15</sup> and to increases in immigration and travel to the United States by persons living in endemic countries. Also, the resistance of malaria parasites to available antimalarial agents is increasing.<sup>1,16</sup> Owing to the spread of antimalarial drug resistance and the availability of new drugs, standard recommendations for chemoprophylaxis and treatment have changed over the last decade.<sup>11,17-19</sup> To evaluate the impact of changes in travel patterns and chemoprophylaxis on the epidemiology of imported malaria and to highlight the difficulties encountered in prevention, diagnosis, and therapy, we reviewed 121 cases of imported malaria diagnosed at 2 urban university hospitals.

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## PATIENTS AND METHODS

All smear-positive malaria cases diagnosed between 1988 and 1997 by the microbiology laboratories at San Francisco General Hospital, a city hospital serving a largely indigent population, and Moffit-Long Hospital, San Francisco, Calif, a tertiary referral center, were reviewed. Diagnoses were based on thin and thick smears stained with 5% Giemsa stain (Moffit-Long Hospital and San Francisco General Hospital) or 0.4% Wright stain (San Francisco General Hospital) and examined by experienced laboratory personnel. Cases were defined as patients with thin or thick malaria-positive smears who were seen at either hospital during the acute phase of illness. Patients with relapsing or recrudescing infections were counted only once. Medical records were reviewed, and data were collected on a standardized form. Severe malaria was defined according to World Health Organization criteria.<sup>20</sup> For the purpose of our analysis, US residents were defined as patients living in non-endemic areas who acquired malaria through travel to endemic areas. Foreign residents were defined as patients who were living in malaria-endemic areas when they acquired the disease. Statistical analysis of categorical data was performed using  $\chi^2$  or Fisher exact test for dichotomous variables and the Mann-Whitney test of means. Significance was defined as  $P \leq .05$  (2-tailed).

## RESULTS

### PATIENT CHARACTERISTICS

Of 123 malaria cases diagnosed between 1988 and 1997, 121 cases (81 at San Francisco General Hospital and 40 at Moffit-Long Hospital) were available for review and included in the study. Cases presented to the emergency department (69%), pediatric clinics (13%), general medical clinics (10%), infectious diseases clinics (7%), and obstetric clinics (1%).

Patient demographics are summarized in **Table 1**. All patients acquired malaria while traveling or living in endemic areas. Approximately 50% of the patients (classified as US residents) had been living in nonendemic areas and had acquired the disease through travel; the other 50% (classified as foreign residents) had been living in endemic areas before coming to the United States. The median duration of travel for US residents was 60 days (range, 10 days to 2 years). The purpose of travel for US residents included tourism (84%), foreign employment (14%), and missionary work (2%). The median length of stay for foreign residents in the United States prior to their presentation was 90 days (range, 1 day to 4 years). Areas of travel or prior residence are detailed in **Table 2**. US residents were most likely to have traveled to Africa or Southeast Asia, while more than 80% of foreign residents had come from Central America or the Indian subcontinent.

**Table 1. Patient Demographics**

Characteristic	No. (%)
Sex	
Male	87 (72)
Female	34 (28)
Age, y	
Mean ( $\pm$ SD)	29.2 ( $\pm$ 12.6)
Range	2-60
<19	23 (19)
US residents	
<b>Total</b>	<b>57 (47)</b>
US-born travelers	42 (35)
US residents returning to country of birth	12 (10)
Travelers from other nonendemic countries	3 (2)
Foreign residents	
<b>Total</b>	<b>64 (53)</b>
Immigrants	55 (46)
Foreign visitors	9 (7)

**Table 2. Areas of Exposure to Malaria**

Area of Exposure	No. (%)		
	Total	US Residents*	Foreign Residents
Central America	46 (35)	9 (13)	37 (58)
East Africa	12 (9)	8 (12)	4 (6)
West Africa	29 (22)	24 (35)	5 (8)
Indian subcontinent	26 (20)	11 (16)	15 (23)
Southeast Asia	12 (9)	12 (18)	0
South America	4 (3)	1 (1)	3 (5)
Oceania	3 (2)	3 (4)	0

\*Some travelers visited more than 1 area.

### CHEMOPROPHYLAXIS

Of 57 US residents, 33 (58%) reported using some form of chemoprophylaxis. Only 2 (3%) of 64 foreign residents used chemoprophylaxis; 1 of these 2 was pregnant. Among the 33 US residents who reported taking chemoprophylaxis, 28 (85%) took medications recommended by the Centers for Disease Control and Prevention, Atlanta, Ga, at the time of travel,<sup>11,17-19</sup> and 13 (48%) of these individuals reported compliance with chemoprophylaxis. Thus, overall, only 13 (23%) of the 57 US residents were compliant with a currently recommended chemoprophylactic regimen.

### PREVIOUS EVALUATIONS

Previous evaluations during which the diagnosis of malaria was not considered were performed in 19 patients (16%), 16 of whom had been seen at 1 of our 2 institutions. Eight of these patients had 2 prior visits before the correct diagnosis was made. Missed diagnosis led to a mean delay in therapy of 5.6 days (range, 1-23 days). Incorrect diagnoses included viral syndrome, fever of unknown origin, upper respiratory tract infection, bronchitis, hepatitis, drug fever, urinary tract infection, and iron deficiency anemia. There were 2 dramatic misdiag-

**Table 3. Number of Cases by *Plasmodium* Species and Area of Exposure**

Area of Exposure	<i>Plasmodium vivax</i>	<i>Plasmodium falciparum</i>	<i>Plasmodium ovale</i>	<i>Plasmodium malariae</i>	Mixed
Central America	45	1	0	0	0
East Africa	6	5	1	0	0
West Africa	7	19	1	1	1
Indian	21	4	1	0	0
Southeast Asia	8	2	1	0	1
South America	4	0	0	0	0
Oceania	2	1	0	0	0
<b>Total No. of Patients*</b>	<b>87</b>	<b>29</b>	<b>2</b>	<b>1</b>	<b>2</b>

\*Each patient was counted once, although some had multiple areas of exposure.

noses. The first misdiagnosis involved a 26-year-old man who had traveled to Mexico 9 months earlier and who had presented to an outside hospital with fever, headache, abdominal pain, diarrhea, and myalgias. Pancytopenia was identified and acute leukemia was diagnosed based on a peripheral blood smear. The patient was transferred to our hospital for a bone marrow biopsy, but review of the peripheral blood smear identified *Plasmodium vivax* infection. The second misdiagnosis involved a 53-year-old Nicaraguan man who had been living in the United States for many years and who had undergone liver transplantation 9 years earlier. He returned from a trip to Nicaragua with a 1-day history of fever, headache, and mildly elevated liver function test results. He was treated with pulse-dose methylprednisolone for presumptive rejection, and underwent a liver biopsy. On the following day, a routine manual blood smear revealed *P vivax*.

Before presenting to our institutions, 11 patients (9%) had been diagnosed with malaria at an outside hospital in the United States. Three were persons with *Plasmodium falciparum* infection who presented within 4 days after they did not respond to their initial therapy (1 discontinued quinine sulfate therapy owing to tinitis; 1 was treated with chloroquine phosphate; and 1 was treated with mefloquine after traveling in Southeast Asia). The remaining 8 patients presented with apparent relapses due to *P vivax* (at least 1 month after an apparently successful response to therapy).

### PARASITOLOGY

The causes of each case of malaria and the endemic areas of exposure are listed in **Table 3**. Patients with *P falciparum* infections were much more likely to have had an exposure in Africa than were patients with nonfalciparum infections (81% vs 17%,  $P < .001$ ). In 119 (98%) of 121 cases, the initial smear was positive. The remaining 2 cases were diagnosed on a second smear (1 of the 2 patients was receiving a chemoprophylactic regimen of chloroquine and proguanil at the time of evaluation). In 8 (7%) of 121 cases, there was a discrepancy between the initial smear reading and the final smear reading (5 cases initially read as possible *P falciparum* were determined to be *P vivax* or *P ovale*; 2 cases initially read as negative were determined to be *P vivax*; and 1 case initially read as *P vivax* or *P ovale* was determined to be *P ovale*).

**Table 4. Reported Frequency of Common Symptoms and Physical Signs**

Symptom	Prevalence, %	Physical Sign	Prevalence, %
Fever	98	Temperature, °C	
Chills	79	Mean ± SD	38.5 ± 1.3
Headache	73	≥38.0	60
Nausea	41	≥39.0	37
Myalgias/arthralgias	40	≥40.0	16
Malaise	33	Splenomegaly	22
Vomiting	32	Abdominal pain	20
Periodic fever	23	Hepatomegaly	11
Abdominal pain	23	Jaundice/icterus	11
Anorexia	22	None of the above	62
Diarrhea	14	physical findings	
Cough	12	excluding fever	
Dark urine	10		
Dysuria	5		
Dyspnea	5		
Confusion	3		

### CLINICAL MANIFESTATIONS

The most common signs and symptoms reported at the time of the initial positive smear are listed in **Table 4**. The only symptoms present in a majority of cases were fever, chills, and headache. While nearly all patients had a history of fever, in only 60% of the cases was the patient febrile ( $\geq 38.0^\circ\text{C}$ ) at the time of presentation. More than 60% of the patients presented with no significant physical findings other than fever. There were no significant differences in the prevalence of symptoms and physical findings between falciparum and nonfalciparum infections except that anorexia was more common with falciparum infection (50% vs 19%,  $P < .001$ ).

The average duration between the departure from an endemic area and the onset of symptoms was considerably longer in nonfalciparum infections than in falciparum infections (143 days vs 8.3 days,  $P < .001$ ). The average duration of symptoms before presentation was  $7.9 \pm 11$  (mean ± SD) days (range, 1-60 days). The patient with the longest duration of symptoms (60 days) had the only *Plasmodium malariae* monoinfection in the study. There was no difference in the duration of symptoms between patients with falciparum infections and pa-

**Table 5. Laboratory Findings\***

	No.†	Mean	Range	Decreased, %‡	Elevated, %‡
Hemoglobin, g/L	121	125	72-164	61 (52)	0
WBC count, × 10 <sup>9</sup> /L	121	5.7	1.2-19.2	24 (20)	1 (1)
Platelet count, × 10 <sup>9</sup> /L	93	125	23-374	66 (71)	0
Aspartate aminotransferase, U/L	84	37	11-222	...	16 (19)
Alkaline phosphatase, U/L	69	97	40-345	...	7 (10)
Bilirubin, μmol/L (mg/dL)	1282 (75)	29 (1.7)	7-132 (0.4-7.7)	...	41 (55)
Creatinine, μmol/L (mg/dL)	8575 (97)	88 (1.0)	27-186 (0.3-2.1)	...	8 (8)
Glucose, mmol/L (mg/dL)	4.9 (89)	6.4 (115)	3.2-10.8 (58-194)	1 (1)	8 (9)
Glucose-6-phosphate dehydrogenase level, (MU/mol of hemoglobin)	5.10	...	...	2 (3)	...

\*WBC indicates white blood cell; ellipses, not applicable.

†Number of patients for whom this value was recorded.

‡In reference to individual laboratory standards.

tients with nonfalciparum infections or between US residents and foreign residents.

### LABORATORY FINDINGS

The most common laboratory abnormalities were thrombocytopenia, elevated bilirubin levels, and anemia (**Table 5**). There were no significant differences in laboratory values between patients with falciparum infections and patients with nonfalciparum infections except that patients with falciparum infections were more likely to have elevated creatinine levels (20% vs 4%,  $P=.03$ ). There were no significant differences in laboratory values between US residents and foreign residents, except that US residents were more likely to have elevated aspartate aminotransferase levels (30% vs 8%,  $P=.009$ ).

### CASE MANAGEMENT AND OUTCOMES

Patients were admitted to the hospital in 37% of cases; 5% were admitted to the intensive care unit for intravenous quinidine therapy and cardiac monitoring for presumed falciparum malaria. Patients with falciparum malaria were more likely to be admitted than were those with nonfalciparum malaria (65% vs 38%,  $P<.001$ ). There was no difference in the admission rates between US residents and foreign residents either overall or stratified for plasmodial species. The median duration of hospitalization was 2 days (range, 1-17 days). Only 1 patient developed severe malaria (*P falciparum* infection complicated by acute respiratory distress syndrome, disseminated intravascular coagulation, hypoglycemia, hyperbilirubinemia, and renal insufficiency), and there were no deaths.

Errors in antimalarial treatment occurred in 11 patients (9%) in our series. Five patients with *P falciparum* infections acquired in areas with chloroquine resistance were treated with chloroquine or chloroquine plus primaquine phosphate. Two of these 5 patients developed recrudescence owing to treatment failure 8 and 25 days after their initial therapy. Other treatment failures included 5 patients who received unnecessary antimalarial medications (2 cases of *P vivax* infection acquired in India were treated with antimalarial agents other than chloroquine or primaquine; 2 cases of *P falciparum* in-

fection were treated with 3 active drugs; and 1 case of *P falciparum* infection was treated with primaquine), 1 patient with *P vivax* infection who did not receive primaquine, and 1 patient with *P vivax* infection who received no documented therapy because the smear was initially read as negative. Only 1 patient developed toxic effects that required a change in antimalarial therapy (neutropenia, possibly due to quinine use). In 7 patients (6%), there was a delay of 1 to 10 days in the initiation of therapy because the patient was sent home before the initial blood smear results were reported. Relapses following appropriate therapy occurred in 3 patients. Two of the 3 patients had received chloroquine and primaquine for vivax malaria and had recurrences of the same infection 2 and 3 months later. One of the infections was acquired in Indonesia, where chloroquine-resistant *P vivax* and failures of primaquine therapy have been described.<sup>11,21</sup> One patient who was treated with oral quinine and doxycycline for *P falciparum* infection relapsed with *P ovale* infection 1 month later.

### COMMENT

Imported malaria was neither rare nor exotic at our 2 institutions, as 123 cases were diagnosed over a 10-year period. The epidemiological distribution in our cases was consistent with recent national malaria surveillance statistics<sup>3</sup> except that we saw a higher percentage of *P vivax* infections, owing to excess cases in immigrants from Central America.

Chemoprophylaxis is recommended for all American travelers to malaria-endemic areas. Only 23% of US residents in our series reported compliance with the chemoprophylactic regimens recommended by the Centers for Disease Control and Prevention. The most common errors were failure to initiate any chemoprophylactic regimen and noncompliance with a chosen regimen, as has consistently been reported over the last 20 years.<sup>7,8,10,22,23</sup> U.S. residents traveling back to their country of birth were significantly less likely than US-born travelers to have used any chemoprophylaxis (25% vs. 69%,  $P=.009$ ), identifying a high-risk group that often fails to seek pretravel advice.<sup>9</sup>

In contrast to some previous studies,<sup>10,22,24</sup> our study found that *P falciparum* infections were uncommon af-

ter appropriate chemoprophylaxis: there were only 2 cases, both of which occurred in the 1980s, before mefloquine was available. All the remaining 11 US residents who developed malaria despite appropriate chemoprophylactic therapy had *P vivax* or *P ovale* infections, and their symptoms began a mean of 125 days after they left the malaria-endemic area (range, 1 month to 1 year). These cases illustrate the fact that even with effective chemoprophylaxis, patients remain at risk for relapsing *P vivax* and *P ovale* infections. Although not truly a failure of chemoprophylaxis, this phenomenon has recently been recognized as an increasingly important limitation of all currently recommended prophylactic drugs, which target the erythrocytic phase of the parasite.<sup>25</sup> In our series, no patients reported terminal prophylaxis with primaquine, which is recommended by some authorities, especially for patients with heavy exposure or prolonged travel.<sup>11</sup> In no cases in our series did falciparum malaria develop after chemoprophylactic therapy with mefloquine. These results and other recent published observations support the effectiveness of mefloquine chemoprophylaxis in preventing the most lethal form of the disease.<sup>3,12</sup> However, these results should be interpreted with caution owing to recent reports of increasing mefloquine resistance in Southeast Asia and elsewhere.<sup>26-28</sup>

Overall, 19 (16%) of our patients had previously been seen by a physician who failed to consider a diagnosis of malaria. This error rate is consistent with rates reported by other hospitals with experience in the diagnosis of imported malaria, but considerably lower than those at less experienced centers.<sup>7,10,22</sup> Among patients in whom the diagnosis was missed, there was a significantly longer duration between exposure and onset of symptoms than among patients who received a correct diagnosis (mean 222 days vs 84 days,  $P=.003$ ), suggesting that physicians failed to obtain an adequate travel history or failed to appreciate the significance of fairly remote malaria exposure.

In our series, the clinical presentation of imported malaria was nonspecific and did not differ between falciparum and nonfalciparum malaria or between US residents and foreign residents. A history of fever was present in virtually all patients, although fever periodicity was uncommon and normal temperatures at presentation were common. Physical findings and laboratory test results were generally unhelpful as diagnostic aids, although anemia and thrombocytopenia were present in a majority of patients.

The sensitivity of microscopy in our series was excellent: 119 of 121 cases were diagnosed on the first blood smear. In 8 cases (7%), there was a discrepancy between the initial smear reading and the final reading. In most of these cases, smears were read as possible *P falciparum* until final species identification could be made. Results from our study and others<sup>7</sup> suggest that in the hands of experienced microscopists, the sensitivity of a single blood smear for the diagnosis of malaria is excellent. However, when the suspicion of malaria is high, especially if a patient has recently taken antimalarial agents, serial smears can increase sensitivity. In our series, errors were made in antimalarial therapy in

11 (9%) of 119 patients for whom this information was recorded. In a recent study of imported malaria in Canada, 8% of the patients who were treated at a tropical disease specialty unit received inappropriate initial therapy, compared with 48% of patients treated at outside hospitals.<sup>7</sup> Treatment errors in our series were more common in falciparum malaria than in nonfalciparum malaria (26% vs 3%,  $P<.001$ ). Although 7 US residents with falciparum malaria were treated successfully as outpatients, this number is too small to disprove the current dictum of admitting all nonimmune patients with falciparum malaria to the hospital.

In summary, imported malaria remains a significant problem in the United States. It has the potential to become increasingly common as the frequency of international travel continues to grow and antimalarial drug resistance increases. Effective chemoprophylactic regimens exist, but failure to use recommended regimens continues to be a frequent problem in travelers to endemic areas. Also, even when appropriate chemoprophylaxis is used, patients may develop malaria owing to drug resistance or relapsing infection. The clinical presentation of malaria was nonspecific and remarkably similar in US and foreign residents, as well as in cases of falciparum and nonfalciparum infections. Therefore, physicians should consider the diagnosis in any patient who has an exposure history, even if it is remote. The decision to order a simple blood smear remains the most important factor in the management of this disease. Imported malaria, especially falciparum malaria, has the potential to cause life-threatening illness, but with timely diagnosis and appropriate treatment, the outcome of this disease is generally quite good.

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