Characteristics and Severity of Disease among 100 Cases of Imported Malaria Seen at a U.S. University Hospital, 2000–2017

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Abstract. Malaria acquired in endemic areas poses a substantial risk to travelers arriving in or returning to the United States. Timely diagnosis and recognition of severe illness are crucial; however, many U.S.-based clinicians lack familiarity with this disease. We conducted a retrospective review of 100 cases of malaria in adults seen at a single urban university hospital during 2000–2017. Descriptive and analytical statistics were calculated, including logistic regression modeling case severity. Most of the patients presented with *Plasmodium falciparum* (76%), most commonly after travel from sub-Saharan Africa (94%). Prior malaria experience was common (50%), but adherence to a prophylactic regimen was exceedingly rare (4%). Twenty-one patients had severe malaria, including 10 with cerebral malaria. Severity was predicted by high parasitemia, bandemia, hypoglycemia, and hypotension at the time of presentation. In 24 patients, the initial treatment regimen was changed, usually because of the appearance of clinical deterioration or drug toxicity. One patient required intravenous artesunate. All patients survived, although one suffered fetal loss. Among 30 patients initially evaluated at other institutions, 43% had been treated for an alternative diagnosis. The most common reasons for transfer of patients to our hospital were inadequate facilities and lack of expertise with malaria. There needs to be increased awareness among U.S.-based travelers and clinicians regarding malaria as a potentially lethal condition, emphasizing the use of appropriate prophylaxis. Our simple model of disease severity could serve frontline physicians when deciding which patients should be admitted to the intensive care unit or transferred for higher level care.

INTRODUCTION

In the United States, endemic malaria was eliminated in the 1940s, but with increasing international travel, the number of imported cases has been rising in recent years. In 2015, there were 1,517 confirmed cases of malaria reported in the United States.¹ Reducing the burden of malaria in non-endemic countries is a complex task that requires understanding of patient and parasite characteristics, chemoprophylaxis behavior, travel routes, and exposures in endemic areas.² Malaria is of particular concern in urban and regional medical centers caring for large numbers of international travelers. Aggregate data on the presentation and management of the disease in these non-endemic settings are limited because cases are usually dispersed in both geography and time. Although the major risk factors for malaria are travel to sub-Saharan Africa and trips to visit friends or relatives, business travelers are also increasingly recognized as being at risk for morbidity and mortality from malaria.^{1,3–6} A U.S. National Inpatient Sample (NIS) analysis found malaria-related hospitalizations occurring disproportionately among patients who are male, black, 25–44 years of age, seen at urban academic medical centers, and concentrated in the Middle and South Atlantic regions. The average length of duration of hospitalization for malaria was 4.36 days; however, 22% of malaria admissions involved severe disease and longer stays.⁷ Such aggregate analyses illustrate the scope of the problem, but do not capture information on the use of prophylactic regimens, pre-hospitalization management, or the details of clinical management. The aim of the present study was to describe

how adult patients with malaria present for care in the United States and how to improve their clinical management.

METHODS

Data collection. We conducted a retrospective review of electronic health records (EHR) and clinical laboratory data of adult patients seen from 2000 to 2017 at a 370-bed metropolitan tertiary care hospital. One hundred consecutive cases were identified and included in the analysis. Variables extracted from the EHR included patient characteristics (demographics, travel and medical history, and use of antimalarial prophylaxis), disease characteristics (*Plasmodium* species, parasite load, and disease severity), admission details (clinical parameters at presentation, level of care, treatment course, and complications), and outcomes (survival to discharge and outpatient follow-up). All research was approved by our Office of Human Research Institutional Review Board.

Diagnosis and treatment. Thick and thin blood smears were prepared and *Plasmodium* species identified using standard methods.⁸ All smears were reviewed by the pathologist (J. K.) and infectious disease staff. When infection with more than one *Plasmodium* species was suspected, samples were sent to a reference laboratory for polymerase chain reaction analysis. Clinical treatment was guided by the infectious disease consultants, and when necessary, the Centers for Disease Control and Prevention (CDC) Malaria Hotline was consulted for intravenous artesunate.^{9,10}

Definitions and data analysis. The following criteria for inclusion in the analysis were used: patients aged ≥ 18 years and seen in the hospital with malaria diagnosed either by hematologic smear (thick and thin smears, performed in our microbiology laboratory) or rapid diagnostic test (if performed at an outside facility). The criteria for severe malaria were consistent with standard definitions and included impaired consciousness, seizures, renal failure, respiratory failure, circulatory shock,

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acidosis, severe anemia, coagulopathy, and/or parasitemia of $\geq 5\%$. Statistical analysis was carried out using R software (The R Project, version 3.3.3, <https://www.r-project.org/>), using Chi-square and Fisher's exact tests for categorical variables, *t*-test for continuous variables, and logistic regression analysis for modeling disease severity.

RESULTS

Demographics and travel history. Of 100 cases of malaria in adults seen at our institution, 60% were male, with mean age at presentation of 41.9 years (Table 1). Although the place of birth was not always noted, of the 70 patients for whom it was known, 41 were born in Africa. Ninety-four patients had traveled to Africa—predominantly to East and West Africa, with the five most common destinations being Nigeria, Ghana, Sierra Leone, Ivory Coast, and Uganda. Seven patients had traveled to Asia, three to South or Central America (including the Caribbean), and four had visited more than one continent.

TABLE 1
Patient characteristics

Patient characteristics	Value
Age (years)	
Mean $\pm$ SD	41.9 $\pm$ 13.4
Gender	
Female	40 (40.0%)
Male	60 (60.0%)
Birthplace	
Africa	41 (41.0%)
Asia	4 (4.0%)
Europe	5 (5.0%)
South/Central America/Caribbean	1 (1.0%)
North America	19 (19.0%)
Unknown	30 (30.0%)
Region visited*	
Africa†	94
Asia	7
South/Central America/Caribbean	3
> 1 continent	4
Type of travel	
U.S.-based traveler returning	76 (76.0%)
Work- or study-related travel	37
Visited family/friends	23
Outdoors/tourism	3
Foreign-based visitor to the United States	19 (19.0%)
Immigrating to the United States	3 (3.0%)
Unknown	2 (2.0%)
Duration of time overseas	
Median (IQR)	29 (14,98)
< 14 days	11 (15.2%)
2–4 weeks	29 (40.2%)
1–6 months	21 (29.1%)
6–12 months	3 (4.1%)
1–5 years	3 (4.1%)
> 5 years	5 (6.9%)
Days from travel to presentation	
Median (IQR)	8 (5,20)
1–2 days	10 (10.9%)
3–5 days	17 (18.5%)
6–10 days	27 (29.3%)
11–20 days	15 (16.3%)
> 20 days	23 (25.0%)

* Number of visits exceeds the number of cases, because of multiple stops per trip. Of the 100 patients, 90 visited Africa only, four visited Asia only, two visited South/Central America/Caribbean regions only, and four visited > 1 continent. Only one patient had traveled exclusively within the Western Hemisphere (Haiti).

† Travel to Africa included Central Africa (visited by 5), East (35), North (9), South (4), West (53), and more than one region (visited by 13). The five most common destinations were Nigeria, Ghana, Sierra Leone, Ivory Coast, and Uganda.

Patients whose primary residence was in the United States (*N* = 76) traveled mainly for professional reasons (48.7%; most frequently associated with governmental or nongovernmental organizations based in Washington, DC) or to visit family (30.3%). Only three cases of malaria occurred in recent immigrants. The duration of travel ranged from < 14 days to > 5 years (median: 29 days).

Malaria presentations peaked in the months of July through October, likely reflecting increased travel during that period and seasonal prevalence of malaria in the source countries. More than half of the patients (62%) presented for medical care within 1–10 days of arrival in the United States; however, 25% presented after 3 weeks or more. *Plasmodium falciparum* cases presented earlier after returning (median: 7 days, interquartile range [IQR]: 5–14 days), whereas non-falciparum cases presented later (median: 75 days, IQR: 18–120 days). Overall, our patients had low prevalence of medical comorbidities (hypertension in 8%, diabetes mellitus in 4%, history of malignancy in 5%, hepatitis C in 1%, and sickle-cell disease in 1%). Two patients were pregnant. No patients had known human immunodeficiency virus (HIV) infection at the time of presentation (three patients had positive HIV enzyme-linked immunosorbent assay tests during medical workup; of these, two proved to be false-positives, while the third patient refused further testing or follow-up).

Prophylaxis, presentation, and case severity. The most frequent symptoms at the time of presentation included fever (92%), chills (78%), and headache (64%); fatigue, nonspecific myalgias, and gastrointestinal symptoms were also common (Table 2). Nine patients had altered mentation at presentation, and one developed symptoms of cerebral malaria several hours after admission. Fifty-one patients reported a prior history of malaria, including 10 who were treated for malaria within the previous year; of these, seven were treated within the previous month and three had received artemisinin-based therapy. Two of the 51 patients with previous malaria experience reported taking prophylaxis before the index presentation, and a third patient took an incomplete course. The majority of patients (74%) reported taking no antimalarial prophylaxis; another 18% reported an incomplete course. Only 4% became infected despite reportedly adhering to a prophylactic regimen. Doxycycline, atovaquone/proguanil, and mefloquine were all prescribed for prophylaxis with approximately equal frequency, although a number of patients could not recall the name of the medication that they failed to take.

Plasmodium falciparum was the most frequently identified species (76%), with parasitemia ranging from < 1% to 20% (Table 3). There were 21 cases of severe malaria, of whom 14 had parasitemia $\geq 5\%$ in addition to clinically severe disease; the remaining seven met other criteria for severe disease (including cerebral malaria, shock, renal failure, or respiratory distress requiring intensive care unit [ICU] care). Three patients with parasitemia of 6–13% had mild symptoms and a prior history of malaria; these were treated as uncomplicated, and improved rapidly. Interestingly, eight of the patients with severe malaria reported a prior history of malaria (including one patient who reported three prior episodes of malaria). Of the patients with severe malaria, 18 were U.S.-based returning travelers and three were foreign-based visitors. Twenty of the severe cases had *P. falciparum* and one had *Plasmodium malariae*. Mean parasitemia was 8.7% among severe cases,

TABLE 2
Infection characteristics

Infection characteristics	Value
Duration of symptoms (days)	
Mean $\pm$ SD	5.6 $\pm$ 6.0
Presenting symptoms	
Fever	92 (92.0%)
Chills	78 (78.0%)
Headache	64 (64.0%)
Myalgias/arthralgias	53 (53.0%)
Nausea/vomiting	35 (35.0%)
Diarrhea	26 (26.0%)
Fatigue/malaise/weakness	25 (25.0%)
Abdominal pain	18 (18.0%)
Altered mentation*	9 (9.0%)
Prior malaria	
Yes	50 (50.0%)
No	38 (38.0%)
Unknown	12 (12.0%)
Prophylaxis behavior	
No prophylaxis	74 (74.0%)
Incomplete course	18 (18.0%)
Full course of prophylaxis	4 (4.0%)
Not documented	4 (4.0%)
Prophylaxis medication	
Doxycycline	5 (21.7%)
Atovaquone/proguanil	6 (26.1%)
Mefloquine	4 (17.4%)
Unknown/other	8 (34.8%)
<i>Plasmodium</i> species	
<i>Plasmodium falciparum</i>	76 (76.0%)
Non-falciparum	18 (18.0%)
<i>Plasmodium ovale</i>	6 (6.0%)
<i>Plasmodium vivax</i>	7 (7.0%)
<i>P. ovale</i> vs. <i>P. vivax</i>	3 (3.0%)
<i>Plasmodium malariae</i>	2 (2.0%)
Mixed†	2 (2.0%)
Unknown	4 (4.0%)
Peak parasitemia	
< 1%	55 (55.0%)
1–4.5%	20 (20.0%)
5–9.5%	7 (7.0%)
10–14.5%	4 (4.0%)
$\geq$ 15%	7 (7.0%)
Unknown	7 (7.0%)

* A total of 10 patients had cerebral malaria; of these, nine had altered mental status at the point of presentation and another patient deteriorated several hours after admission.

† Of the mixed cases, one was *P. falciparum* with *P. ovale* and the other *P. falciparum* with either *P. ovale* or *P. vivax*.

versus < 1% among those with non-severe disease ($P < 0.05$). The mean duration of symptoms before presentation did not differ significantly between severe and non-severe cases (4.9 $\pm$ 3.3 versus 5.7 $\pm$ 6.5 days, respectively, $P = 0.43$).

Severely ill patients were admitted to the ICU for support, which included intubation (six patients), vasopressors (four patients), exchange transfusion (two patients), and dialysis (one patient). Of the rest, 64 were admitted to the general medical wards, whereas 15 patients—those with uncomplicated, non-falciparum malaria, and those who refused admission—were seen by the infectious disease consult team in the emergency department, and treated as outpatients. The median length of stay for all patients who were hospitalized was 3 days, but 8 days for those with severe malaria; one patient with cerebral malaria and renal failure was hospitalized for 1 month. All patients, including all those with severe malaria, survived to discharge. However, a pregnant patient with severe malaria suffered fetal loss.

Management and clinical course. Complications, adverse effects, and changes in therapy were common among

TABLE 3
Disease severity and management

Disease severity and management	Value
Case definition	
Severe malaria	21 (21.0%)
Uncomplicated malaria	79 (79.0%)
Management setting	
Inpatient ICU	21 (21.0%)
Inpatient ward	64 (64.0%)
ED/Outpatient only	15 (15.0%)
LOS days—median (IQR)	
All inpatient cases	3 (2,5)
Severe malaria only	8 (6,10)
Complications	
ARDS	10 (10.0%)
AKI	7 (7.0%)
Transfusion*	7 (7.0%)
Intubation	6 (6.0%)
QT prolongation	6 (6.0%)
DIC†	6 (6.0%)
Nosocomial infection	5 (5.0%)
Initial treatment	
Quinidine gluconate IV	14 (14.0%)
QG IV + doxycycline PO	10
QG IV + clindamycin PO	2
QG IV alone until stabilized	2
Quinine sulfate PO	24 (24.0%)
QS PO + doxycycline PO	23
QS PO + clindamycin PO	1
Atovaquone/proguanil	29 (29.0%)
Artemether/lumefantrine	19 (19.0%)
Chloroquine	8 (8.0%)
Mefloquine	3 (3.0%)
Other/unknown	3 (3.0%)
Treatment changed	24 (24.0%)
Reason for treatment change	
Treatment failure/persistent parasitemia	11 (45.8%)
QT prolongation	4 (16.7%)
Gastrointestinal intolerance	3 (12.5%)
Non-falciparum diagnosed	3 (12.5%)
Convenience/cost/other	3 (12.5%)

AKI = acute kidney injury; ARDS = acute respiratory distress syndrome; DIC = disseminated intravascular coagulation; ED = emergency department; ICU = intensive care unit; LOS = length of stay; QG = quinidine gluconate; QS = quinine sulfate.

* A total of seven patients received packed red blood cell transfusions; of these, two were exchange transfusions and five were supportive transfusions for severe/symptomatic anemia. Exchange transfusions are no longer favored in clinical practice.

† One patient with severe DIC received fresh frozen plasma and platelet transfusions.

our patients (Table 3). Of the 21 patients with severe malaria requiring intravenous therapy and ICU care, five did not initially meet the criteria for severe malaria, but worsened within 24 hours of admission. The most common complication was acute respiratory distress syndrome, requiring intubation in six cases. Transfusions were given in seven cases (two exchange transfusions and five supportive transfusions of packed red blood cells). Seven patients developed acute kidney injury, including one requiring hemodialysis. Nosocomial infections developed in five cases, including three hospital-acquired pneumonias, one staphylococcal bacteremia, and one catheter-associated urinary tract infection.

Initially, 38% of patients were started on quinine-based therapy, using either oral quinine sulfate (24%) or—in severe disease or if not tolerating oral medications—intravenous quinidine gluconate with cardiac monitoring (14%). Most patients on quinine- or quinidine-based regimens received concomitant doxycycline or clindamycin (the latter when doxycycline had been given for prophylaxis). More recently, there has been a shift away from the use of oral quinine

sulfate for initial treatment of uncomplicated malaria, and toward novel regimens, including atovaquone/proguanil (29%), artemether/lumefantrine (19%), and mefloquine (3%). Chloroquine was given as initial therapy when sufficient species information was available (8%), but more frequently empiric therapy for *P. falciparum* was started while awaiting definitive species identification. Eighteen patients received subsequent primaquine therapy for *Plasmodium vivax* or *Plasmodium ovale* infections.

Alteration in medication from the initial treatment regimen was documented in 24 patients, including six whose treatment was switched from oral therapy to intravenous (IV) quinidine. These were clinical decisions made after consideration of the patient's clinical status, telemetry monitoring, parasite levels, and input from other medical teams. The most common reasons for treatment change documented by the treating clinician were inadequate clinical improvement, change in *Plasmodium* species identification, or adverse effects of medication (e.g., QT-segment prolongation while receiving IV quinidine or gastrointestinal distress while receiving oral medications). Two patients had severe post-artemether hemolytic anemia and received supportive transfusions. One severely ill patient with 20% parasitemia, encephalopathy, coagulopathy, and acrocyanosis developed hypoglycemia and QT prolongation on IV quinidine; intravenous artesunate was procured from the Centers for Disease Control and used successfully to complete treatment.

Treatment before presentation. Thirty of the 100 patients included in this analysis were initially seen at another institution and transferred or referred to our hospital. The primary reasons cited for transfer of care from unaffiliated community-based providers were inadequate experience in treating malaria, lack of appropriate resources (including on-site laboratory and availability of antimalarial medications), or the requirement for ICU care. Of these patients, 13 (43.3%) had received initial treatment for conditions other than malaria. This included supportive-only care in five patients who were believed to have a viral syndrome. Other infectious diagnoses included urinary tract infections, respiratory infections, and Lyme disease. Noninfectious diagnoses included hypertension, relapsed acute myelogenous leukemia, and pancytopenia of unknown etiology. In two patients referred from outside institutions, the initial smears had been reported as negative; however, subsequent smears in our laboratory were positive.

Correlates of case severity. To construct a disease severity prediction model, we examined clinical variables recorded at the time of presentation to the emergency department. These included vital signs and basic laboratory values (complete blood count and metabolic panel results; lactate dehydrogenase and coagulation studies where available). Bivariate analysis identified the following potential predictors of disease severity ($P < 0.10$): hypotension (but not fever or other systemic inflammatory response syndrome criteria), elevation in total and non-segmented neutrophils (bands), thrombocytopenia, international normalized ratio elevation, creatinine elevation, hypoglycemia, hyponatremia, acidosis, hyperbilirubinemia, and elevated liver transaminases (Table 4). Additional baseline variables that showed individual association with malaria severity and were tested were altered mentation, shortness of breath, and diarrhea. A logistic regression model identified the following four variables as significant predictors of severe disease: high parasitemia ($\beta =$

0.3789, $P = 0.0004$), low systolic blood pressure ($\beta = -0.1081$, $P = 0.0078$), elevated bandemia ($\beta = 0.1178$, $P = 0.0555$), and low serum glucose ($\beta = -0.0385$, $P = 0.0722$). This model predicted 95.6% of severe malaria cases, with sensitivity 76.2% and specificity 98.6%. In recognition that not all laboratories reported a parasite load estimate in a timely manner, we also constructed a limited model that did not include parasitemia as a predictor. This limited model identified the following variables as significant: elevated bandemia ($\beta = 0.1107$, $P = 0.0079$), low systolic blood pressure ($\beta = -0.0799$, $P = 0.00312$), low serum glucose ($\beta = -0.0386$, $P = 0.0263$), and low platelet count ($\beta = -0.0166$, $P = 0.0279$). This model predicted 91.3% of severe malaria cases, but had sensitivity of only 55.0% with specificity 95.3%.

DISCUSSION

Although dwarfed by the global burden of an estimated 214 million infections and 438,000 deaths from malaria occurring annually primarily in endemic regions, malaria also presents a significant health risk for international travelers, with an estimated 30,000 cases occurring annually in association with travel throughout the world, and an incidence of 1,700–2,000 cases in the United States in recent years.^{1,3} Travelers are at risk because of a number of factors, including inaccurate risk perception, suboptimal pretravel preparation and prophylaxis, lack of familiarity with symptoms, and absence (or loss) of prior immunity.^{1,3,5} Such patients are at risk for severe disease, which may present within days to weeks of return.

In our study, 21% of patients presented with severe malaria, including 10% who had cerebral malaria and were thus at increased risk for long-term disability. It is somewhat surprising that nearly half of the patients with severe disease had a previous episode of malaria. The concept that prior disease provided some degree of partial immunity such that subsequent episodes are less severe did not seem to be evident in these patients. The mortality rate in our patient cohort was zero during the time period captured—in concordance with the mortality rate of $< 1\%$ reported in the NIS study of U.S.-based hospitalizations for malaria.⁷ These low mortality rates reflect the benefit of access to intensive care for severe cases. However, it must be noted that as malaria is not infrequently misdiagnosed, it may be similarly under-recognized as the cause of death outside of specialty hospitals. A higher mortality rate (2.9%) was reported in a retrospective study from Serbia for the corresponding time period.¹¹ It is imperative to identify patients with severe disease early to choose treatment and escalate care appropriately. Based on variables available at the time of initial evaluation, we were able to construct a simple model for predicting malaria severity which includes high parasitemia, hypotension, bandemia, and hypoglycemia. This model should be validated and refined using a larger data set.

The current recommended therapy for severe malaria in the United States is intravenous quinidine gluconate and doxycycline, administered for a minimum of 12 hours until parasitemia reduction to $< 1\%$, followed by oral therapy with artemether/lumefantrine, atovaquone/proguanil, or quinine sulfate plus doxycycline.^{9,10} These recommendations were followed in the management of severe malaria seen at our center. For non-severe malaria cases, as well as for subsequent management of severe cases after parasitemia

TABLE 4
Clinical parameters at presentation as correlates of disease severity

Parameter	All cases	Severe	Non-severe	P-value*	Logistic model
SIRS criteria					
≥ 2	49 (49.0%)	11 (51.9%)	38 (48.1%)	0.3095	
0–1	51 (51.0%)	10 (47.6%)	41 (51.9%)		
T _{max} 1 st 24 hour (°C)					
Mean ± SD	38.3 ± 1.0	38.4 ± 1.2	38.3 ± 1.0	0.7451	
Initial SBP (mmHg)					β = −0.1081
Mean ± SD	120.8 ± 19.5	108.4 ± 16.3	124.1 ± 19.1	0.0008†	P = 0.0078
Initial heart rate					
Mean ± SD	102 ± 18	102 ± 20	102 ± 18	0.9785	
Parasitemia (%)					β = 0.3789
Mean ± SD	2.7 ± 4.9	8.7 ± 6.6	0.9 ± 2.1	< 0.0001†	P = 0.0004
WBC (×10 ⁹ /L)					
Mean ± SD	5.5 ± 2.1	5.9 ± 2.0	5.4 ± 2.1	0.2892	
Neutrophilia					
Neuts ≥ 75%	35 (48.5%)	7 (33.3%)	28 (35.4%)	0.0687†	
Bandemia					β = 0.1178
Bands ≥ 10%	20 (20.4%)	11 (52.4%)	9 (11.7%)	0.0005†	P = 0.0555
Eosinophilia					
Eos ≥ 5%	5 (5.1%)	1 (5.0%)	4 (5.2%)	0.5940	
Hemoglobin (g/dL)					
(Mean ± SD)	12.7 ± 2.7	12.3 ± 2.7	12.8 ± 2.7	0.5060	
Hematocrit (%)					
(Mean ± SD)	37.6 ± 6.6	35.7 ± 7.6	38.1 ± 6.3	0.1390	
Platelets (×10 ⁹ /L)					
Mean ± SD	103.5 ± 61.5	60.6 ± 54.7	115.1 ± 58.4	0.0002†	
LDH (U/L; N = 27)					
Mean ± SD	1,265 ± 644	1,513 ± 477	1,162 ± 687	0.2010	
INR (N = 41)					
Mean ± SD	1.3 ± 0.3	1.5 ± 0.5	1.2 ± 0.1	0.0005†	
Serum glucose (mg/dL)					β = −0.0385
Mean ± SD	112.3 ± 44.3	102.0 ± 20.5	115.0 ± 48.5	0.0695†	P = 0.0722
Hyponatremia					
Na < 135 mEq/L	35 (35.0%)	12 (57.1%)	23 (29.1%)	0.0004†	
Acidosis					
CO ₂ < 22 mEq/L	8 (8.1%)	7 (33.3%)	1 (1.3%)	0.0087†	
Elevated creatinine					
Cr > 1.5 mg/dL	6 (6.0%)	5 (23.8%)	1 (1.3%)	0.0221†	
Transaminitis					
Elevated LFTs‡	32 (32.0%)	11 (52.4%)	21 (26.6%)	0.0349†	
Hyperbilirubinemia					
T.Bili > 1.3 mg/dL	45 (46.9%)	14 (70.0%)	30 (40.0%)	0.0168†	

INR = international normalized ratio; LDH = lactic acid dehydrogenase; LFTs = liver function tests (see below); SBP = systolic blood pressure; SIRS = systemic inflammatory response syndrome; T_{max} 1st 24 hour = maximum temperature in the first 24 hours of presentation; WBC = white blood cells count.

* Fisher's exact test used when individual cell frequencies were ≤ 5; Chi-square test used otherwise.

† Significance level of P < 0.10 required to test as a potential predictor and to include in the final logistic model.

‡ Transaminitis (LFT elevation) defined as one or more of the above: alanine aminotransferase > 70 u/L, aspartate aminotransferase > 45 u/L, alkaline phosphatase > 125 u/L.

reduction and symptom resolution, factors affecting the choice of treatment included any suspicion of infection with *Plasmodium* resistant to a particular antimalarial agent (e.g., travel to regions with reports of resistance), gastrointestinal intolerance, out-of-pocket cost for newer treatment agents, and in rare cases, the availability of medications at an out-patient pharmacy. The frequency with which atovaquone/proguanil and artemether/lumefantrine were used as the initial therapy increased over time, reflecting changes in drug availability. Nearly one in four patients in our study had a change from the initial therapy, mainly because of inadequate clinical response as assessed by the clinicians caring for the patient or to drug toxicity. These were multifactorial clinical decisions. It is important to note that no single parameter—even parasitemia, which in some cases can rise even after initiation of an effective anti-malarial drug¹²—defines treatment failure on its own. A more detailed exploration of the reason for medication change might include serum drug level monitoring, antimalarial drug resistance testing, and evaluation of provider preference factors.

Clinicians managing severe malaria who suspect clinical failure or severe toxicity from intravenous quinidine should be ready to consult with the CDC regarding obtaining intravenous artesunate. The use of artesunate as first-line treatment for severe falciparum malaria outside the United States is well established in large-scale studies in Africa and Asia and recommended by the WHO.^{13–15} In Canada, where intravenous artesunate has been available for this indication since 2009, its use has been associated with faster clearance of parasitemia, shorter ICU stays, and a trend toward lower incidence of treatment complications.¹⁶ In the United States, artesunate is presently available under an Investigational New Drug protocol for compassionate use, and is stockpiled in multiple sites around the country for distribution under CDC guidance, available via a 24/7 telephone hotline.^{1,10} Among cases meeting the CDC criteria for artesunate treatment, the average time from drug request to administration of the first dose has been reported as 7 hours (range: 3.5–15.5 hours), with an average distance of 480 miles (range: 66–1,448 miles) between the hospital and the CDC quarantine station.¹⁷

Our findings are consistent with studies that highlight the importance of reducing the burden of malaria among patients returning from visiting friends and relatives abroad as well as those who travel for work. A high proportion of our patients failed to obtain or take prophylaxis despite frequent travel to high-risk areas and a more-than-rudimentary prior knowledge of the risk of malaria. From documented conversations with these patients, it became apparent that they did not perceive themselves to be personally at risk, or else believed that the illness would be mild, and that they would be able to obtain prompt treatment in the event they became ill. Several patients in this category suffered severe malaria, including one patient who required prolonged hospitalization and hemodialysis. Similar difficulties with travelers engaging in serial short-term business trips have been noted by others; in one CanTravNet study, business travelers had the highest rates of hospital admissions for malaria among all groups of travelers and immigrants.⁵ Notably, only 3% of the malaria cases in our study were among recent immigrants.

It is of concern that of the 30 patients in our study whose initial evaluation took place at an outside facility, 13 were initially misdiagnosed. This may be because of a failure to obtain a travel history or a lack of familiarity with the disease by the original medical provider. In the absence of a travel history, the nonspecific nature of the symptoms in many patients (fever, chills, and headaches) may make the diagnosis less apparent. Such delays to diagnosis have been documented in other studies, particularly with older patients, in whom the travel history was missed or the presence of comorbid conditions served as a diagnostic distraction.^{18,19} Limited access to diagnostic modalities may further contribute to the delays. Laboratory staff who lack experience in reviewing smears for *Plasmodium* may miss low-level parasitemia or require tests to be sent out to reference laboratories. Although a rapid diagnostic test for malaria was approved by the United States Food and Drug Administration for use in the United States by hospital-based and commercial laboratories, it is not approved for use by individual clinicians as a point-of-care test; in addition, its sensitivity is limited compared with microscopy, and may be especially so for *P. ovale*, *P. malariae*, and *Plasmodium knowlesi*.^{20–22} Posttreatment complications, such as delayed hemolysis, may also be unfamiliar to many physicians in the United States.²³ Among patients who are uninsured or otherwise fearful of the costs of seeking medical care, the delays to appropriate diagnosis and treatment may be even longer, resulting in more severe illness.²⁴

Limitations of our study include potential selection bias in favor of more severe cases, as these patients were more likely to be transferred to our hospital for care. Likewise, delayed and missed diagnoses may be overrepresented in our sample, as these were more likely to be referred (or self-referred) to an academic medical center after the failure of initial management by a community-based provider. Because of the highly mobile nature of our patient population, the total number of cases of malaria entering our geographic region during the study period is unknown, as is the number of cases that may have been missed entirely or diagnosed postmortem. Although clinical data (including symptoms and laboratory parameters at presentation, treatment regimens, length of stay, etc.) were available for all patients, other variables that may have affected treatment (including medication shortages or out-of-pocket costs) were less consistently documented.

Finally, follow-up data were limited to those patients who returned to the hospital or to their clinic appointments.

In conclusion, we find that appropriate diagnosis and early consultation are of paramount importance when managing malaria in travelers. With access to high-quality ICU care, survival is the rule rather than the exception, even in medically complicated and severely ill patients. However, the chain of appropriate care must commence at the initial presentation, starting with a brief but essential travel history, engaging appropriate laboratory support, and monitoring for early warning signs of severe disease.

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