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Higher Rates of Misdiagnosis in Pediatric Patients versus Adults Hospitalized with Imported Malaria

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Abstract

Objectives—Despite the availability of effective anti-malarial prophylaxis, imported adult and pediatric malaria occurs in the United States and this can pose diagnostic issues. We examined the clinical characteristics and diagnostic challenges of imported malaria requiring adult or pediatric inpatient admission at Montefiore Medical Center (MMC) in the Bronx which provides care for a large population of immigrants from malaria endemic areas.

Study Design—We conducted a retrospective single center review of patients admitted with a diagnosis of malaria at MMC from 2005 through 2012. We extracted historical, clinical, and laboratory values from the electronic medical record and patient charts.

Results—We identified 95 patients who were diagnosed and hospitalized with malaria from 2005–2012, 33 (35%) of them children and 17 (18%) with severe malaria. Most patients contracted malaria while visiting friends and relatives (VFR) in West Africa. Only 38% of travelers took prophylaxis, and fewer than half reported taking it as prescribed. Misdiagnosis by emergency room or primary care doctors was observed in almost one quarter of all of the patients. Misdiagnosis occurred significantly more frequently in children (43%) compared to adults (13%) (p=0.002). Pediatric patients were more likely to present with abdominal pain (42% vs 15%, p=0.005).

Conclusions—Pediatric patients admitted for imported malaria at MMC had a higher rate of misdiagnosis and presented with more gastrointestinal symptoms than hospitalized adults. By describing the clinical characteristics of patients with imported malaria, we hope to improve diagnostic accuracy by healthcare workers and raise awareness that VFRs may require more intensive pre-travel counseling.

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Keywords

Abdominal Pain; Adult; Child; Diagnostic Errors; Fever; Malaria; Travel

Introduction

Although malaria is one of the major causes of morbidity and mortality globally, endemic transmission of malaria in the United States (US) was eliminated over fifty years ago. In 2011, 1,925 cases of malaria were treated in the US, including 281 children.[1] The majority (70%) of US patients who contracted malaria traveled to visit friends and relatives (VFR) in endemic areas. VFR travelers are 1st and 2nd generation immigrants from malaria endemic countries who return to their countries of origin to visit friends and relatives.[2] This group of travelers has been recognized as a high-risk group for travel associated infections, including malaria.[3] New York City, especially the Bronx, has a high number of residents born outside the US. According to the 2010 US census, 37% of people who live in New York City were born outside the US compared with only 13% in the general population.[4] Many of these New York City immigrants are originally from malaria endemic areas, including 40,000 African-born individuals who reside in the Bronx. Because of the large at-risk population, understanding the impact of imported malaria is essential for improving the health of the Bronx population. Here, we compare the epidemiology and clinical characteristics of children and adults hospitalized with imported malaria at Montefiore Medical Center (MMC), the largest tertiary care hospital in the Bronx, over an eight-year period. We identify differences in clinical presentation between adults and children and highlight the diagnostic challenges in each group to inform malaria diagnostic strategies for front line health care providers and improve patient outcomes.

Methods

Patients and Data Collection

We conducted a cross-sectional case series of hospitalized patients diagnosed with malaria at MMC in the Bronx, New York, from 2005 to 2012. MMC is a large, tertiary care medical center with 1491 beds, including 106 pediatric beds, and provides healthcare services for over 2 million people. We identified subjects by searching the electronic medical record through the Clinical Looking Glass (CLG) software (Emerging Health IT, Yonkers, New York).[5] Search parameters were set to identify hospital inpatients with malaria diagnosis-related ICD-9 codes (084.0–084.9) from 2005 through 2012. We only included patients with positive, speciated asexual malaria smears in the analysis. Malaria diagnosis and species identification was based on the MMC laboratory report of a microscopic examination of a thick blood film by an experienced technician. The Institutional Review Board of the Albert Einstein College of Medicine approved the study protocol.

Patient epidemiologic, laboratory, and clinical data were extracted through CLG, including gender, age, race, and length of hospital stay. Additional information was obtained through review of the medical record from the admission notes, infectious disease service consult notes, progress notes, and discharge summaries. Extracted variables included patient country

visited, chemoprophylaxis, history of present illness, previous providers visited, presenting symptoms, and inpatient management data. If conflicting data were identified, information in the infectious diseases consult note data was used for this analysis.

Adult patients were defined as age ≥18. Severe malaria was defined using the World Health Organization (WHO) criteria.[6] `Days from misdiagnosis' was defined as the number of days between the patient's initial contact with a medical provider (and not diagnosed with malaria) and admission to the hospital. Data was managed using the REDCap electronic data capture tool, hosted at Albert Einstein College of Medicine.[7]

Statistical Analysis

Bivariate analysis was conducted using the Mann-Whitney U test for continuous variables and χ^2 or Fisher's exact test for discrete variables when appropriate. Statistical analysis was done using Stata version 12.1 (StataCorp, College Station, Texas). A two-tailed $p<0.05$ was used for statistical significance. Figures were made using Microsoft Excel.

Results

Between 2005 and 2012, 95 patients were hospitalized with malaria at MMC, 62 adults and 33 children (Figure 1). All patients reported recent travel in malaria endemic areas. Seventy-nine patients (83%) visited friends and relatives (VFR), 12 patients (13%) had recently immigrated to the US, 2 patients were visiting the US, and 2 patients traveled for business. There were no US tourists or volunteers in our cohort. The vast majority of patients became infected while traveling to West Africa, including Ghana (n=28), Nigeria (n=19), Sierra Leone (n=12), The Gambia (n=6) and Ivory Coast (n=4) (Figure 2). Eighty-two patients were infected with *P. falciparum*, 8 with *P. ovale*, 3 with *P. vivax*, and 2 with *P. malariae*. No patients presented with mixed species infections. Patients that were infected with *P. falciparum* malaria had a significantly shorter median length of time back in the US and significantly fewer symptomatic days before admission to the hospital (Table 1).

Seventeen (18%) individuals were diagnosed with severe malaria and all were due to *P. falciparum*. Eleven of the severe cases (65%) were children, with a higher proportion of the pediatric malaria cases presenting with severe disease than adults (32% vs 10%, p=0.004). All severe cases were either managed in the Intensive Care Unit (n=15) or on telemetry floors (n=2). Among those with severe disease, 11 patients were hyperparasitemic (8 pediatric), 2 had acute renal failure (pediatric), and 2 had hyperbilirubinemia (1 pediatric). Two patients (1 pediatric and 1 adult) had CNS involvement: the pediatric case had seizures and the adult patient presented with altered mental status. All pediatric and adult patients recovered fully and no deaths were noted in our cohort.

Thirty-eight percent of patients who had traveled (31/81) reported taking chemoprophylaxis while abroad (45% of children vs. 26% of adults, p=0.052). Of these, 16 reported not taking the medication as directed (20%), with a similar proportion in children and adults (57% vs 67%, p=0.701). Reasons given for not taking adequate prophylaxis included an insufficient supply of medications, medication left at home, ran out of medication during travel, or misunderstanding of prescription instructions. In the cases where the prescribed antimalarial

prophylactic regimen was recorded, all drugs were appropriate for the region where they traveled.

Eleven patients with severe disease were treated with quinidine gluconate and clindamycin (ten pediatric and one adult), and 5 with quinidine gluconate and doxycycline (all adults). All patients treated with quinidine were appropriately given a quinidine load at initiation of therapy. All quinidine gluconate treated patients who were not admitted to the ICU were placed on telemetry. Only one patient experienced QT interval prolongation (QTc=0.53 seconds), which resolved with cessation of treatment. Side effects of treatment included nausea/vomiting (n=3), hypoglycemia (n=1), and neutropenia (n=1). Patients with severe disease (both pediatric and adult) were hospitalized longer compared to patients with uncomplicated malaria (median of 5 vs 3 days, $p<0.001$).

To determine if there were significant epidemiologic differences between adults and children hospitalized with imported malaria, we compared characteristics in each group (Table 2). Sixty-two adults, including four pregnant women, were compared to 33 children. Compared to adults, pediatric patients had similar gender distributions, race, length of travel, length of symptoms, time back in the US, rate of prophylaxis utilization, and length of ICU stay. There was also no difference in the countries visited or the species of malaria contracted between pediatric and adult patients (data not shown).

Pediatric patients who traveled and were not recent immigrants were significantly more likely to have used chemoprophylaxis (57% vs 29%, p=0.013) and have received antimalarial treatment abroad (12% vs 2%, p=0.048). Overall, pediatric patients were more likely to have presented with abdominal pain than adults (42% vs 15%, p=0.002) and less likely to have chills (36% vs 59%, p=0.034) (Table 3). Children had significantly lower median hematocrits (30 vs 39, $p< 0.001$).

Thirteen percent of adults and 43% of pediatric patients admitted for malaria treatment had been seen previously in the emergency department (ED) or by their primary care physician (PCP) and not diagnosed with malaria (p=0.002) (Table 2). Misdiagnoses included allergies, Group A streptococcal pharyngitis, upper respiratory infection, and viral syndrome. Patients who were misdiagnosed were also more likely to have presented with gastrointestinal symptoms (46% vs 18% with abdominal pain (p=0.008) and 41% vs 18% with diarrhea (p=0.024)).

Discussion

The number of imported malaria cases has recently been increasing in the United States, from 1,298 in 2008 to 1,925 in 2011.[1] The higher rate of infections may be due to the increased travel to sub-Saharan Africa and low use of malaria prophylaxis, specifically among VFRs.[8, 9] To evaluate the epidemiology of hospitalized malaria in returning travelers to the Bronx, we carried out a retrospective review of all malaria inpatient admissions to MMC from 2005–2012. We identified 95 patients who required hospitalization for malaria, including 33 children. The majority of admitted patients were VFRs traveling to Africa. There was a low rate of antimalarial prophylaxis and, in patients who were prescribed

antimalarials, a poor rate of adherence to the prescribed regimens. Pediatric patients hospitalized with malaria were more likely to have been previously misdiagnosed and manifested different clinical presentations compared to hospitalized adults.

The Bronx has a large number of African immigrants, who are at risk of contracting malaria when they return to their homeland to visit friends and relatives if no preventative measures are taken.[10] A series of 51 hospitalized malaria cases in the Bronx from 1986 to 1991 found 64% of patients had acquired malaria from sub-Saharan Africa, which has since increased to 96% in our series ($p<0.001$).[11] They noted that only 17% of patients born outside of the US received chemoprophylaxis, which is consistent with the low (38%) use of prophylaxis in our study. These low proportions are similar to the 25% chemoprophylaxis use by US travelers diagnosed with malaria reported by the CDC.[1]

Insufficient use of anti-malarial prophylaxis in some VFRs may be related to a lack of awareness of the risks, fewer pre-travel health care encounters, financial barriers to medical care, complex travel plans, or a belief that they carry life-long immunity.[2] Focus groups of African volunteers in London showed a great variability in beliefs and practices regarding chemoprophylaxis among travelers that reflects the variability in communities, socioeconomic status, and circumstances.[12] Patient failure to access malaria prophylaxis was influenced by perceiving malaria as innocuous and easily treatable illness along with a belief that they were immune or not at personal risk. Health care system barriers included drug cost, waiting time for appointments, and uncertainty regarding appropriate chemoprophylactic regimens. Adherence was hindered by difficulty remembering complex drug regimens, lack of understanding the need to continue medication after returning, and leaving anti-malarials for relatives in Africa. Strategies proposed for increasing VFR utilization of the medical system and changing behaviors when abroad include promoting health education in the population, more effective healthcare personnel training, developing specific prevention programs, and increased epidemiology research.[13] Improving compliance with anti-malarial prophylaxis will likely require a multi-dimensional approach that involve both health care services and the target population.

We found that 23% of patients were misdiagnosed prior to admission, with 43% of children being initially misdiagnosed. Because malaria is no longer an endemic disease in the US, misdiagnosis of imported malaria patients is common in primary care and emergency settings, especially among children.[14–18] By including patients from the Children's Hospital at Montefiore in our study, we were able to directly compare the clinical characteristics and diagnostic accuracy of adult and pediatric patients with malaria. We found that pediatric patients have a higher rate of misdiagnosis than adults. This may be related to the higher rate of presentation with abdominal pain than adults. Prior studies have found that the presence of gastrointestinal symptoms, such as vomiting, anorexia, abdominal pain, diarrhea and jaundice, may suggest a non malarial diagnosis.[19] This may be particularly true in children, where the clinical presentation of malaria can mimic common pediatric illness such as viral gastroenteritis, allergies, and influenza-like illnesses, which can lead to a delay in diagnosis.[20–23]

Our study adds to the previously reported cases of malaria patients returning from abroad that show high rates of misdiagnosis among patients who present with signs and symptoms commonly associated with gastroenteritis and viral syndromes.[15–17, 24] Clinicians may be less aware that malaria can involve the GI tract in the setting of acute uncomplicated and complicated malaria.[25, 26] Therefore, malaria should be on the clinicians' differential when encountering a patient returning from an endemic area with fever, even if the presence of certain symptoms, like abdominal pain, leads them to favor an alternative diagnosis. Delays in diagnosis and treatment have been shown to increase the likelihood of progression to severe disease and death.[27] Epidemiologic surveillance, led by physicians reporting cases, is therefore essential in understanding the local trends in imported malaria and preventing future infections.

Although we conducted a comprehensive analysis of pediatric and adult patients hospitalized with malaria at our institution, there are limitations to our study. Although MMC has a large catchment area, there are additional medical institutions in the Bronx. It is also unknown whether any diagnostic testing for malaria was done on the initial visit as many patients did not originally present to a MMC provider. Additionally, we only studied hospitalized patients. The clinical presentation and diagnostic accuracy of outpatient managed malaria may differ from the inpatient analysis. It would be important to know the uptake of chemoprophylaxis use among all travelers to malaria endemic areas in our catchment area to inform further health care interventions for travelers, however this was outside the scope of this analysis.

In conclusion, malaria infection requiring hospitalization continues to occur in the Bronx, typically in immigrants VFR. Low rates of chemoprophylaxis and high misdiagnosis rates remain a challenge. Enhanced outreach is needed in the Bronx VFR community to improve the utilization of appropriate prophylaxis and among physicians to increase awareness and diagnosis of malaria among travelers. Additional work is needed to design effective community and health care interventions to further reduce the risk of acquiring this preventable infection during travel.

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Abbreviations

CDC	Centers for Disease Control and Prevention
CLG	Clinical Looking Glass
ICU	Intensive care unit
MMC	Montefiore Medical Center

VFR	Visiting friends and relatives
WBC	White Blood Cells

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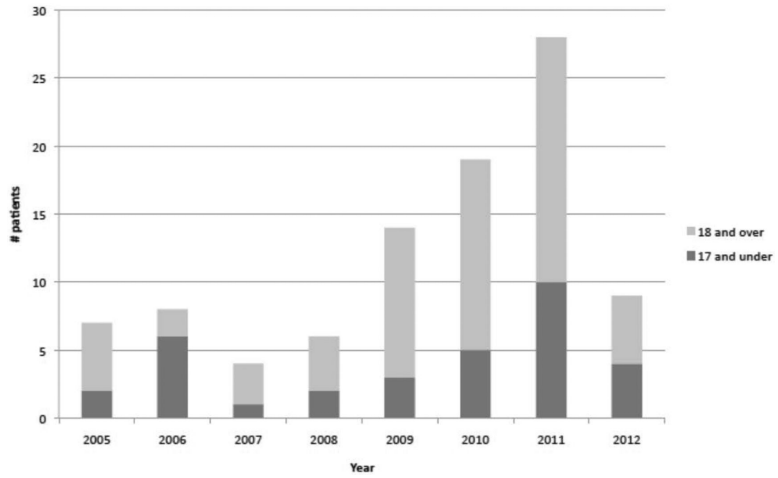
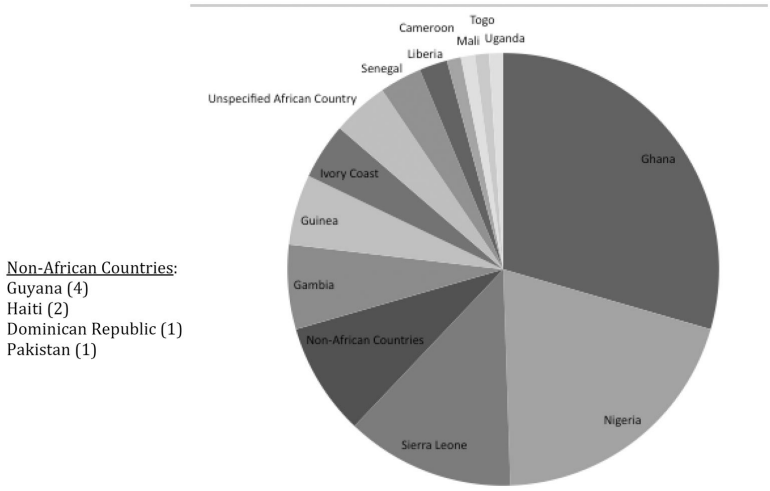


Figure 1.



Non-African Countries:
Guyana (4)
Haiti (2)
Dominican Republic (1)
Pakistan (1)

Figure 2.

Table 1

Comparison of the characteristics of hospitalized patients by malaria species.

Characteristic	*P. falciparum* n=82	Non-*falciparum* malaria n=13	p-value*
Length of time abroad (days)	56 (31–75)	30 (21–180)	0.503
Length of symptoms (days)	4 (3–7)	7 (5–8)	*0.008*
Time back in US (days)	12 (7–18)	50 (19–102)	*<0.001*
Prophylaxis (among travelers)	39% (28/72)	33% (3/9)	>0.999
Treatment abroad	5% (4)	8% (1)	0.529
Misdiagnosed by previous provider	23% (19)	23% (3)	>0.999
Severe disease	21% (17)	0% (0)	0.116
Length of hospital stay (days)	4 (3–5)	3 (2–4)	0.100

*Continuous variables were compared using the Mann-Whitney U test and are presented as median and interquartile range. Categorical variables are compared using the χ^2 or Fisher's exact test where appropriate and presented as percent and number of subjects.

Table 2

Comparison of Demographics, Clinical and Laboratory Factors Between Pediatnc and Adult Patients with Malaria.

Characteristic	Adult n=62	Pediatric n=33	p-value*
Male Sex	73% (45)	67% (22)	0.638
African/African American	87% (54)	79% (26)	0.290
Length of time abroad (days)	42 (28–90)	60 (45–83)	0.053
Length of symptoms (days)	4 (3–7)	5 (3–7)	0.665
Time back in US (days)	12 (7–21)	14 (10–20)	0.357
Prophylaxis (among travelers)	29% (16/55)	57% (15/26)	*0.013*
Treatment abroad	2% (1)	12% (4)	*0.048*
Misdiagnosed by previous provider	13% (8)	43% (14)	*0.002*
Days from misdiagnosis to admission	3 (2–4)	4 (2–7)	0.557
Severe disease	10% (6)	32% (11)	*0.004*
ICU admission	10% (6)	27% (9)	*0.025*
ICU stay (days)	3 (2–3)	3 (2–4)	0.761
Length of hospital stay (days)	3 (2–5)	4 (3–5)	0.463
WBC ($\times 10^3$/ul)	6.2 (4.7–8.0)	6.8 (5.5–8.1)	0.140
Hematocrit (%)	39 (34–42)	30 (24–32)	*<0.001*
Platelets ($\times 10^3$/ul)	88 (59–136)	91 (54–163)	0.708

*Continuous variables were compared using the Mann-Whitney U test and are presented as median and interquartile range. Categorical variables are compared using the χ^2 or Fisher's exact test where appropriate and presented as percent and number of subjects. ICU-Intensive care unit; WBC-White Blood Cells.

Table 3

Clinical presentation of adults and pediatric patients with hospitalized malaria.

Symptom	Adult n=62	Children n=33	p-value*
Fever	94% (58)	100% (33)	0.294
Chills	59% (37)	36% (12)	*0.034*
Night sweats	16% (10)	6% (2)	0.206
Headache	36% (22)	39% (13)	0.643
Body aches/pain	18% (11)	9% (3)	0.366
Joint pain	8% (5)	0% (0)	0.160
Abdominal pain	15% (8)	42% (14)	*0.002*
Nausea	31% (19)	27% (9)	0.731
Vomiting	27% (17)	39% (13)	0.232
Diarrhea	24% (15)	21% (7)	0.743
Cough	2% (1)	6% (2)	0.276

*Categorical variables are compared using the χ^2 or Fisher's exact test where appropriate and presented as percent and number of subjects.