ABIM CME MOC ACCREDITED

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Fever in a traveler returning from Ethiopia

A 44-YEAR-OLD MAN presented to an outpatient clinic after 11 days of fever, chills, headache, and nausea. He was a coffee roaster by trade, and his symptoms had started about 10 days after returning from a 3-week trip to buy coffee in Ethiopia. He said his fever would come and go, and the last episode was 2 days earlier. He denied any diarrhea, constipation, rash, or lymphadenopathy.

The patient appeared lethargic. Examination of his heart, lungs, and abdomen was unremarkable. His vital signs were:

- Temperature 38.9°C (102.0°F)
- Heart rate 80 beats per minute
- Respiratory rate 14 breaths per minute
- Blood pressure 142/80 mm Hg
- Oxygen saturation 97% on room air.

He had been treated for malaria in Tanzania when he fell sick there a few years earlier. He said he took chloroquine to prevent malaria every time he went abroad, as directed for his earlier trips. He had received the yellow fever virus vaccine because of his frequent travel to the tropics and was up-to-date on his routine childhood and pretravel immunizations. On his last trip, he had not been exposed to local domestic or wild animals, had not had any sexual encounters, had not drunk any unclean water, and had not eaten any raw or improperly cooked food.

DIFFERENTIAL DIAGNOSIS OF FEVER IN A RETURNING TRAVELER

1 What is the most likely cause of this patient's fever?

- ☐ Malaria
- ☐ Typhoid fever
- ☐ Influenza
- ☐ Yellow fever
- ☐ Meningococcemia
- ☐ Measles

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The differential diagnosis for fever with a medium to long incubation period in a returning traveler is broad. Providers should consider the infections endemic to the region where the patient traveled (wwwnc.cdc.gov/travel).

Thwaites and Day[1] proposed a risk-based approach using the Quick Sepsis-Related Organ Failure Assessment (qSOFA) score, signs of severe disease (cyanosis, meningism, peritonism, digital gangrene), and possibility of a highly transmissible infection (eg, Middle East respiratory syndrome-coronavirus [MERS-CoV], Ebola) as an initial assessment to identify and treat life-threatening causes of fever. A detailed history of exposure to unclean water, animals, insects, bites, or raw or improperly cooked food is crucial in building a robust differential diagnosis.[2]

The differential diagnosis is broad for fever with a medium to long incubation in a returning traveler

Malaria

Fever in a traveler returning from an area where malaria is endemic (see www.cdc.gov/malaria/travelers/country_table/) is an emergency. Major clinical features of malaria are fever (present in 92% of cases in 1 study), chills (78%), headache (64%), and nausea and vomiting (35%)—and our patient had all of these. Other possible symptoms such as myalgia (53%) and diarrhea (26%) are sometimes mistaken for symptoms of influenza or infectious gastroenteritis.[3]

In another study,[4] *Plasmodium falciparum* malaria was the most common cause of fever in US residents returning from sub-Saharan Africa (accounting for 12.78% of cases), followed by acute unspecified diarrhea (9%), acute bacterial diarrhea (5.59%), and giardiasis (4.23%).

TABLE 1

Incubation periods of common travel-related infections[a]

Short (< 10 days)	Medium (10–21 days)	Long (> 21 days)
Bacteria	Bacteria	Bacteria
Typhoid and paratyphoid	Typhoid and paratyphoid	*Rickettsia* species
Bacterial diarrhea	*Brucella* species	*Brucella* species
Bacterial pneumonia	*Rickettsia* species	Bartonellosis
Neisseria meningitidis		**Tuberculosis**
Brucella species	Spirochete	
Rickettsia species	Leptospirosis	Spirochetes
		Leptospirosis
Spirochetes	Viruses	Syphilis
Relapsing fever (*Borrelia recurrentis*)	Hemorrhagic fevers[b]	
Leptospirosis	Human immunodeficiency virus (acute)	Viruses
	Cytomegalovirus	HIV (acute)
Viruses	Hepatitis A	Hepatitis B, hepatitis C
Hemorrhagic fevers[b]	Rabies	Epstein-Barr virus
Respiratory viruses	**Measles**	Cytomegalovirus
Influenza, **Middle East respiratory syndrome coronavirus (MERS-CoV)**	**Chicken pox (varicella)**	Rabies
Measles	Protozoa	**Measles**
Protozoa	Malaria	Protozoa
Malaria	Giardia	Malaria
African trypanosomiasis	Toxoplasma	Leishmaniasis
Amoebic dysentery	African trypanosomiasis	African trypanosomiasis
Parasite	Parasite	Parasites
Fascioliasis	Babesia	Filariasis
		Leishmaniasis
		Amebic liver abscess
		Babesia

[a]Bold-face type indicates a serious transmissible infection; isolation precaution is mandatory when such infections are suspected.
[b]Viruses that cause hemorrhagic fevers in humans comprise 5 distinct families:
- Arenaviridae (lymphocytic choriomeningitis virus, Junin virus, Machupo virus, **Lassa virus**, Guanarito virus, Sabia virus, Chapare virus, Lujo virus)
- Bunyaviridae (orthobunyavirus, phlebovirus [eg, Rift Valley fever virus], nairovirus [eg, **Crimean-Congo hemorrhagic fever**], hantavirus)
- Flaviviridae (yellow fever, dengue fever, Japanese encephalitis, West Nile virus, Zika virus)
- Filoviridae (cuevavirus, **Marburgvirus**, **Ebolavirus**)
- Paramyxoviridae (measles, mumps, Newcastle disease virus, Hendra virus, Nipah virus).

Fever in a traveler returning from a malaria-endemic area is an emergency

Malaria is transmitted by the bite of a female *Anopheles* mosquito.[5] Most *Anopheles* mosquitoes are not exclusively anthropophilic (preferring to feed on humans). However, the primary malaria vectors, *A gambiae* and *A funestus*, are strongly anthropophilic and are the two most efficient malaria vectors worldwide.

Our patient's symptoms were consistent with malaria. Moreover, although he was taking malaria chemoprophylaxis, he was not taking the right one, as there is a high incidence of chloroquine-resistant *P falciparum* malaria in Africa. The prolonged incubation period also points to malaria (**Table 1**).

Finally, although our patient's pulse rate of 80 beats per minute seems normal, it is actually lower than expected, given his fever. Assessing vital signs for relative bradycardia is a great tool to discern several medical conditions, and malaria is one of the causes (**Table 2**). However, the most common cause of relative bradycardia is the use of beta-blockers.[6,7]

Typhoid fever

Typhoid fever, caused by *Salmonella typhi*, is a common cause of travel-related fever. In 2002, an estimated 408,837 cases of typhoid fever occurred in Africa.[8] However, precise numbers are not available, since many hospitals in Africa do not have laboratories capable of performing the blood cultures essential for the di-

TABLE 2

Causes of relative bradycardia

Diseases that cause relative bradycardia[a]

Infections
- *Legionella*
- Psittacosis
- Q fever
- Typhus (*Rickettsia typhi, Orientia tsutsugamushi*)
- Typhoid fever (*Salmonella typhi*)
- Babesiosis
- Malaria
- Leptospirosis
- Yellow fever
- Dengue
- Viral hemorrhagic fevers
- Rocky Mountain spotted fever

Noninfectious causes
- Beta-blockers
- Drug fever
- Central nervous system lesions
- Lymphomas
- Factitious fever

Diseases not associated with relative bradycardia

Infections
- *Mycoplasma pneumoniae*
- *Streptococcus pneumoniae*
- Salmonella (nontyphoidal)

[a]A median increase in heart rate of less than 10 beats per minute for every increase of 1°C in body temperature.

agnosis of typhoid fever. In addition, typhoid fever is often mistaken for malaria.

Typhoid fever has an incubation period of about 1 week, which makes it less likely to be the cause of this patient's illness. However, in rare cases, the incubation period can be as long as 3 weeks.[9]

The patient said he had no diarrhea or constipation, which also makes typhoid fever less likely. Moreover, typhoid fever is more commonly associated with high unremitting fever, which is inconsistent with the patient's fever pattern.

Influenza

Influenza is uncommon in warm-weather months; however, the seasons are reversed in the Southern and Northern hemispheres. Also, physicians should suspect influenza at any time of year in travelers returning from the tropics, where influenza can occur year-round.[10] However, the incubation period of influenza is typically 1 to 4 days, which was inconsistent with our patient's history.

Influenza can occur year-round in the tropics

TABLE 3

Diseases that mosquitoes carry

Anopheles
Malaria (*Plasmodium* species)
O'nyong'nyong

Aedes
Dengue fever
Yellow fever (Africa)
West Nile fever
Chikungunya
Eastern equine encephalitis
Zika virus

Culex
West Nile virus
Japanese encephalitis
St. Louis encephalitis

Haemogogus
Yellow fever (South America)

Yellow fever

Yellow fever should be suspected if an unvaccinated traveler returns from sub-Saharan Africa or forested areas of Amazonia with fever, jaundice, hemorrhage, and renal failure.

The mosquito vectors of yellow fever are *Aedes* species in Africa and *Haemogogus* species in South America. *Aedes* mosquitoes are also vectors for dengue virus (symptoms: high fever, sudden-onset skin rash, myalgia, headache, and mild hemorrhagic manifestations), West Nile virus, Chikungunya (symptoms: high fever, headache, myalgia, and moderate to severe arthralgia), eastern equine encephalitis virus, and Zika virus (symptoms: low-grade fever, descending rash, myalgia, conjunctivitis, headache, edema, and vomiting) (**Table 3**).[11]

Our patient had relative bradycardia, which can be seen in yellow fever. However, the incubation period for yellow fever is short, 3 to 6 days (median 4.3 days) after the bite of an infected mosquito.[12] Moreover, he had been vaccinated against yellow fever.

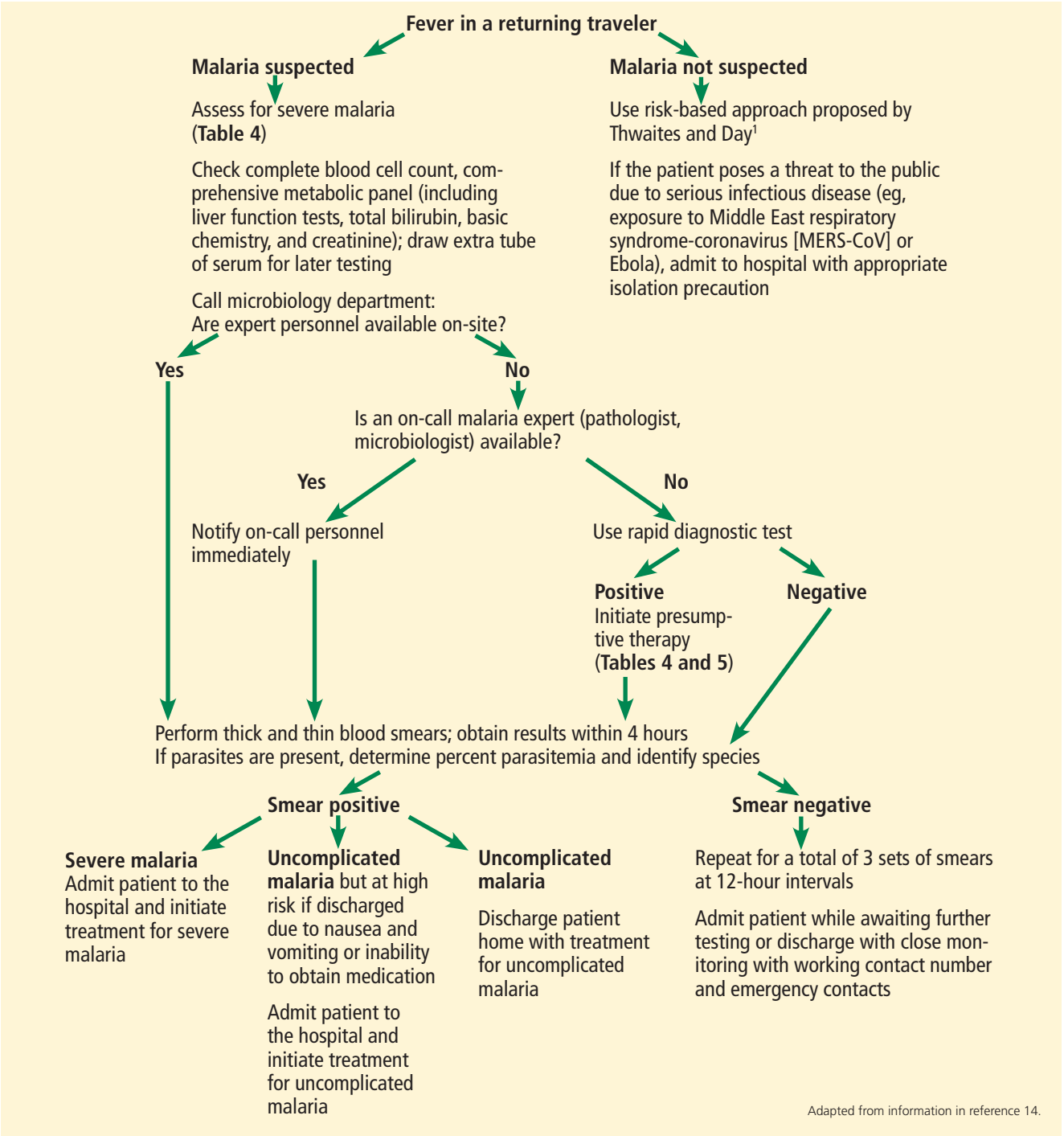

Figure 1. Workup of fever in a returning traveler.

Meningococcemia

Meningococcemia, caused by *Neisseria meningitides* serogroups A, B, C, W, X, and Y, is a life-threatening illness if not treated promptly. Travelers returning from the "meningitis belt" of sub-Saharan Africa who have symptoms consistent with this diagnosis should be suspected of having it, especially during the dry season (December–June). Symptoms generally surface 1 to 10 days after exposure (which is a short incubation period) and present as meningitis half of the time. The clinical

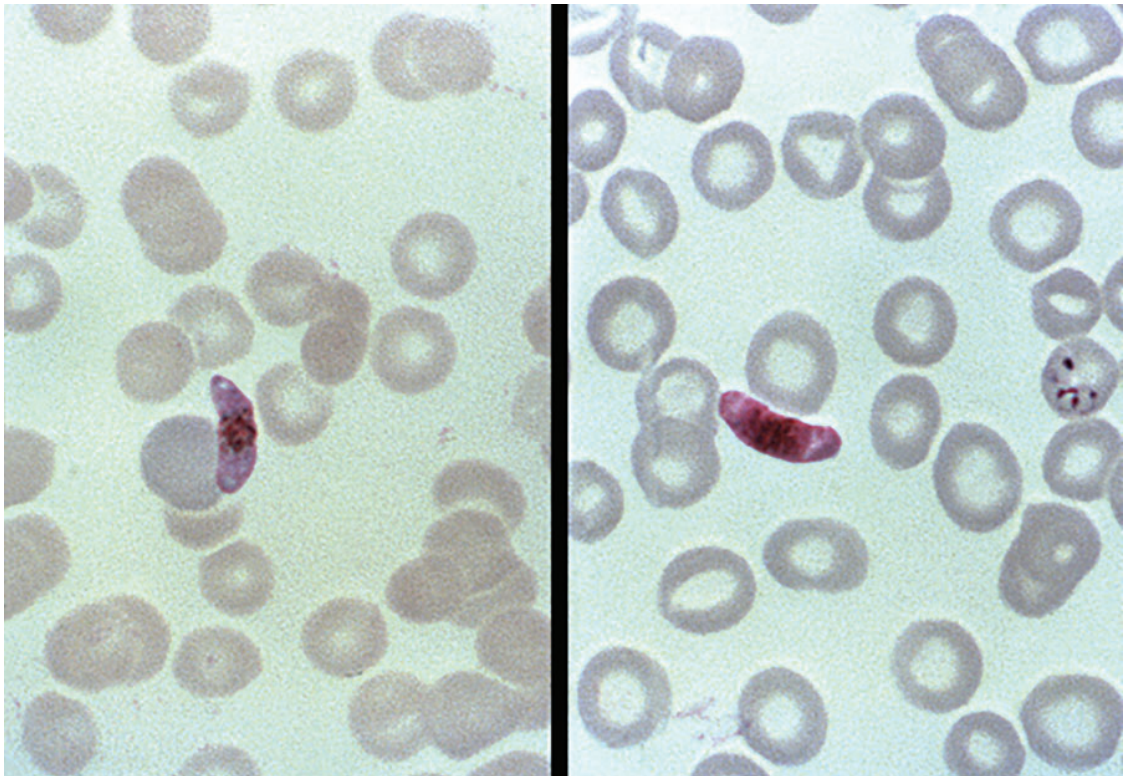

Figure 2. Two Giemsa-stained, thin-film blood smear photomicrographs. Left, a *Plasmodium falciparum* macrogametocyte; right, a microgametocyte. Image by US Centers for Disease Control and Prevention, Steven Glenn, Laboratory & Consultation Division 1979.

manifestations include sudden onset of headache, fever, neck stiffness, and petechial or purpuric rash, which did not fit our patient's presentation.

Measles

Measles is considered the most contagious viral disease known, and its incidence in Ethiopia is high, with 49 cases per million population in 2016.[13] The incubation period ranges from 7 to 21 days from exposure to onset of fever. A clinical diagnosis of measles can be made from the clinical features of generalized maculopapular rash lasting for 3 or more days, temperature of 38.3°C (100.9°F) or higher, and cough, coryza, and conjunctivitis.

These clinical features did not fit our patient's presentation; moreover, he had been vaccinated against measles.

All of the infections discussed above can be prevented with appropriate pretravel vaccinations and chemoprophylaxis.

DIAGNOSTIC TESTING FOR MALARIA

2 If a pathologist or microbiologist is not available on call, how is the diagnosis of malaria made?

- ☐ Blood culture
- ☐ *Plasmodium* species polymerase chain reaction (PCR)
- ☐ *Plasmodium* species rapid diagnostic test, then thick and thin blood films when an expert is available to look at them
- ☐ *Plasmodium* serologic study

The best choice in this situation is *Plasmodium* species rapid diagnostic test, followed by thick and thin blood films.

Light microscopy is the gold standard

Light microscopy of blood smears with Giemsa staining (to give parasites a distinctive appearance) remains the gold standard for malaria diagnosis if qualified staff are available to do it immediately (**Figure 1**). The thick film is used to screen for parasites using hypotonic

Measles is the most contagious viral disease known

saline to lyse red blood cells. The thin film is then used to identify the species of *Plasmodium*. Blood films should be prepared and read immediately by experienced personnel.

Rapid diagnostic tests

If expert personnel are not readily available to examine a blood smear, a rapid diagnostic test should be performed immediately (**Figure 2**).[14]

There are two types of rapid diagnostic tests for malaria. The first is based on detection of *Plasmodium* histidine-rich protein-2 (HRP-2), which is closely associated with the development and proliferation of the parasite. The only test of this type approved and available in the United States is BinaxNOW Malaria (www.alere.com/en/home/product-details/binaxnow-malaria.html), which has a reported sensitivity of 96% and specificity of 99% for *Plasmodium* infection compared with microscopy.[15] This test is approved for use by hospital and commercial laboratories, not by individual clinicians or by patients themselves.

However, HRP-2 tests have limitations. Common causes of false-negative results include:

- *P falciparum* strains that do not express HRP-2
- Nonfalciparum species (*P vivax*, *P ovale*, *P malariae*, *P knowlesi*)
- Low-level parasitemia (100–1,000/µL).

The second type of rapid diagnostic test, which is not available in the United States, is based on detection of *P falciparum*-specific lactate dehydrogenase and pan-*Plasmodium* lactate dehydrogenase. It has a sensitivity of 80% and a specificity of 98% for *Plasmodium* infection compared with microscopy.[15]

Rapid diagnostic tests take only 2 to 15 minutes and are highly specific; hence, a positive result should prompt immediate treatment. However, a negative result still requires a blood smear to detect low-level parasitemia or nonfalciparum species. Therefore, regardless of the rapid diagnostic test result, microscopy must always be performed afterward (**Figure 2**).[14]

Polymerase chain reaction

Although PCR testing for *Plasmodium* is available in commercial laboratories, the turn-around time may be unfavorable when an immediate medical decision is needed. It can, however, be beneficial in identifying the *Plasmodium* species (eg, *P vivax* and *P ovale*), which may further guide the need for presumptive antirelapse therapy (previously known as terminal prophylaxis).

Serologic testing

Serologic *Plasmodium* testing only assesses past exposure and has no utility in the acute setting.

Blood culture

Malaria diagnosis cannot be established through blood culture. Hence, that is not the correct answer to the question. However, if a provider suspects a bacterial coinfection with bacteremia (eg, *Salmonella* species or *Escherichia coli*), obtaining blood culture should be considered. In a small study of 67 adults hospitalized for *P falciparum*, 13% (95% CI 5.3%–21.6%) were bacteremic on admission.[16]

CDC malaria hotline 770-488-7788; after hours 770-488-7100

CASE CONTINUED: LABORATORY RESULTS

A rapid diagnostic test was ordered for our patient and was positive for *P falciparum*. On-call expert personnel were available to read the blood film. The level of parasitemia was 4% of red blood cells infected. Results of other blood tests were as follows:

- Hemoglobin 10 g/dL (reference range 13.0–17.0)
- White blood cell count 15.0 × 10^9/L (3.70–11.00)
- Platelet count 150 × 10^9/L (150–400)
- Glucose 60 mg/dL (65–100)
- Carbon dioxide 20 mmol/L (23–32)
- Creatinine 1.5 mg/dL (0.70–1.40)
- Total bilirubin 1.2 mg/dL (0.2–1.0).

The patient was immediately transferred to the emergency department to be treated and monitored.

TREATMENT OF MALARIA

3 What treatment should this patient receive?

- ☐ Chloroquine phosphate
- ☐ Hydroxychloroquine
- ☐ Primaquine
- ☐ Atovaquone-proguanil

TABLE 4

Severe malaria definition and treatment[a]

Definition	Treatment
Positive blood smear and at least one of the following criteria:	Intravenous artesunate is available under an expanded-access investigational new drug protocol (call the US Centers for Disease Control and Prevention)
Impaired consciousness or coma	and
Severe normocytic anemia (hemoglobin < 7 g/dL)	Artemether-lumefantrine, atovaquone-proguanil, doxycycline (clindamycin in pregnant women); if no other options, mefloquine
Acute kidney injury	
Acute respiratory distress syndrome	
Hypotension	
Disseminated intravascular coagulation	
Spontaneous bleeding	
Acidosis	
Hemoglobinuria	
Jaundice	
Repeated generalized convulsions	
Parasitemia ≥ 5%	

[a] Severe malaria is most often caused by *Plasmodium falciparum*.

Our patient appeared to have uncomplicated *P falciparum* infection from a chloroquine-resistant region. A patient who presents with symptoms of malaria and a positive malaria test without features of severe malaria is considered to have uncomplicated malaria (**Table 4**). Given this information, he should receive atovaquone-proguanil (**Table 5**).

Most severe malaria cases are caused by *P falciparum*. Fortunately, our patient appeared to have uncomplicated *P falciparum* malaria. This could be thanks to acquired immunity from earlier infection, which does not provide sterilizing immunity against parasitemia but may inhibit the development of symptomatic and severe disease. This immunity increases with age, cumulative number of malarial infections, and time spent living in a malaria-endemic area.[17] Nevertheless, acquired immunity is usually short-lived without continuous exposure. It is a misconception that prior infection causes lifelong immunity against malaria; in fact, immigrants visiting friends and relatives constitute the most significant group for malaria importation in developed countries.[18] **Table 6** lists other risk factors for malarial acquisition.

If chloroquine phosphate, hydroxychloroquine, quinine, atovaquone-proguanil, or mefloquine is used to treat *P vivax* or *P ovale* infection, either primaquine or tafenoquine must be given as presumptive antirelapse therapy (also known as terminal prophylaxis) to prevent late-onset or relapsing disease due to hypnozoites (the liver stage of the parasite) of *P vivax* or *P ovale*, which can occur 17 to 255 days after the initial infection.[19]

The patient was treated with atovaquone-proguanil and recovered.

Most severe malaria cases are caused by *P falciparum*, which is widely resistant to chloroquine in Africa

STAYING HEALTHY ABROAD

4 What can clinicians do to prevent malaria at the present time?

- ☐ Give chemoprophylaxis that is appropriate to the area the traveler will visit
- ☐ Instruct patients to take measures to avoid being bitten by mosquitoes
- ☐ Give the malaria vaccine
- ☐ Release genetically modified *Anopheles* to reduce the mosquito population

TABLE 5

Treatment of uncomplicated malaria

Plasmodium species	Region	Recommended medication
P falciparum **or species not identified**	Chloroquine-resistant (all areas except Central America or the Caribbean) or unknown	Atovaquone-proguanil
		Artemether-lumefantrine
		Quinine sulfate + doxycyline, clindamycin, or tetracycline
		Mefloquine[a]
	Chloroquine-sensitive (Central America or the Caribbean)	Chloroquine phosphate
		Hydroxychloroquine
P malariae **or** ***P knowlesi***	All	Chloroquine phosphate
		Hydroxychloroquine
P vivax **or** ***P ovale***	Chloroquine-sensitive	Chloroquine phosphate + primaquine phosphate or tafenoquine
		Hydroxychloroquine + primaquine phosphate or tafenoquine
P vivax	Chloroquine-resistant (Papua New Guinea or Indonesia)	Quinine sulfate + doxycyline or tetracycline + primaquine phosphate or tafenoquine
		Atovaquone-proguanil + primaquine phosphate or tafenoquine
		Mefloquine + primaquine phosphate or tafenoquine
Alternatives for pregnant women	Chloroquine-sensitive	Chloroquine phosphate
		Hydroxychloroquine
	Chloroquine-resistant *P falciparum* and *P vivax*	Artemether-lumefantrine (2nd or 3rd trimester only)
		Quinine sulfate + clindamycin (all trimesters)
		Mefloquine (all trimesters)[a]

[a]Do not use in mefloquine-resistant areas (eg, Thailand, Myanmar, Cambodia, Vietnam).

Malaria prevention

It is essential to give appropriate chemoprophylaxis, taking into account the regions where malarial organisms are resistant to chloroquine, and to instruct patients to take measures to avoid being bitten by mosquitoes.

Risk assessment of travelers to malaria-endemic areas is important (**Table 6**).[20,21] Education of travelers and physicians about chloroquine-resistant areas is essential. Failure to take appropriate precautions may result in death due to severe malaria.[22]

The US Centers for Disease Control and Prevention (CDC) website provides information on areas with malaria, estimated relative risk of malaria for US travelers, drug resistance, malaria species, and recommended chemoprophylaxis (**Table 7**). Some chemoprophylaxis regimens need to be started 1 to 2 weeks before travel to malaria-endemic areas.

Other measures to prevent malaria infection are use of mosquito repellent containing 20% to 35% *N*,*N*-diethyl-meta-toluamide (DEET), wearing permethrin-treated clothes, sleeping under insecticide-treated bed nets, and staying in air-conditioned buildings.

TABLE 6

Risk factors for acquiring malaria

Risk factors	Not risk factors
Rural setting	Urban setting
Camping	Air-conditioned environment
Longer duration of stay	Shorter duration of stay
Altitude of destination (< 2,000 m above sea level)	High altitude (≥ 2,000 m above sea level)
Inappropriate chemoprophylaxis	Appropriate chemoprophylaxis with good adherence
Visiting friends and relatives (eg, immigrants who return to home country to visit friends and relatives)	

Vaccinations

The CDC provides information about vaccinations according to the destination country at wwwnc.cdc.gov/travel. For example, for a traveler going to Ethiopia, vaccinations against cholera, hepatitis A, hepatitis B, meningococcal disease, polio, rabies, typhoid, and yellow fever are recommended.

Certain countries require proof of vaccination against yellow fever to enter, especially if traveling from a country where yellow fever is endemic. Due to limited availability of yellow fever vaccine in the United States, travelers may need to schedule appointments well in advance and visit a nonlocal travel clinic.

Saudi Arabia requires visitors and Hajj and Umrah pilgrims to be vaccinated against meningococcal disease.

Obtaining care abroad

Medical evacuation insurance can be helpful when traveling to a remote destination or to a place where medical care is not up to US standards. Supplemental travel health insurance is recommended as well if the current travel and medical insurance has inadequate coverage.

The US embassy in the destination country (www.usembassy.gov/) can assist in locating medical services and notifying friends and family in the event of an emergency. Other sources such as the International Association for Medical Assistance to Travelers (www.iamat.org/medical-directory; requires free membership login) or International Society of Travel Medicine (www.istm.org/AF_CstmClinicDirectory.asp) can also help you find travel clinics around the globe.

WHAT'S NEW IN MALARIA?

No more quinidine

On March 28, 2019, the CDC issued new guidance for the treatment of severe malaria in the United States. The change in treatment protocol was necessary because quinidine, the only approved intravenous antimalarial drug in the United States, was discontinued by its sole manufacturer, Lilly USA. Previously available lots have now passed their expiration date of March 2019.

Artesunate

Artesunate, the first-line treatment for severe malaria recommended by the World Health Organization, is now the first-line treatment for severe malaria in the United States. However, US clinicians must call the CDC malaria hotline (770-488-7788) to obtain intravenous artesunate.

Malaria vaccine

In 2019, public health programs in Ghana, Kenya, and Malawi began vaccinating young children against *P falciparum* malaria using the RTS,S/AS01 (RTS,S) vaccine, the first malaria vaccine provided to young children through routine immunization. In an intention-to-treat analysis of a controlled clinical trial, children 6 weeks to 17 months old who received this vaccine had an infection rate of 1.9% compared with 2.8% in a control group that received a nonmalaria comparator vaccine ($P < .001$), with a number needed to treat of 111 to prevent 1 case of severe malaria.[23]

In 2019, public health programs in Ghana, Kenya, and Malawi began vaccinating young children against *P falciparum* malaria

TABLE 7

Chemoprophylaxis for malaria

Drug	Adult dosage	Adverse effects and cautions	Price[a]
Chloroquine phosphate[b]	500 mg (300 mg base) once every week Start 1–2 weeks before travel; stop 4 weeks after leaving malaria-endemic area	Hypoglycemia, potential retinopathy from prolonged use Only in chloroquine-sensitive areas (Central America and Caribbean)	$23.11–$55.60 (7 tablets)
Atovaquone-proguanil	250 mg/100 mg daily Start 1–2 days before travel; stop 1 week after leaving malaria-endemic area	Diarrhea, dreams, oral ulcers, headache Take with food or whole milk Contraindicated in severe renal impairment (creatinine clearance < 30 mL/min)	$64.10–$86.02 (30 tablets)
Doxycycline	100 mg daily Start 1–2 days before travel; stop 4 weeks after leaving malaria-endemic area	Drug-induced esophagitis, photosensitivity Do not use in children < 8 years old or in pregnant women	$13.65–$52.23 (30 tablets)[c]
Mefloquine[b,d]	250 mg once every week Start 2 or more weeks before travel; stop 4 weeks after leaving malaria-endemic area	Do not use in individuals with cardiac conduction abnormalities, history of seizures, or serious psychiatric illnesses Do not use in first trimester of pregnancy	$30–$46.97 (8 tablets)
Primaquine phosphate	30 mg daily Start 1–2 days before travel; stop 1 week after leaving malaria-endemic area	Contraindicated in glucose-6 phosphate dehydrogenase (G6PD) deficiency and women who breastfeed G6PD-deficient infants	$37.68–$47.73 (28 tablets)
Tafenoquine	Loading: 200 mg daily starting 3 days before travel Maintenance: 200 mg/week while in malaria-endemic area, starting 7 days after the last loading dose Terminal prophylaxis: 200 mg once, 7 days after the last maintenance dose	Contraindicated in G6PD deficiency and women who breastfeed G6PD-deficient infants Contraindicated in patients with history of psychotic disorders or current psychotic symptoms	$37.52–$42.41 (2 Krintafel 150-mg tablets)

[a]Drug price obtained from www.goodrx.com on 10/25/19 at 11:33 AM.
[b]Can be used in pregnancy.
[c]Doxycyline monohydrate.
[d]Do not use if traveling to mefloquine-resistant areas (eg, Thailand, Myanmar, Cambodia, Vietnam).

Plasmodium and the intestinal microbiome

The intestinal microbiome may influence the development and treatment of malaria. Ippolito et al,[24] in a systematic review, discussed how *Plasmodium* infection may cause intestinal dysbiosis, which correlates with more severe disease outcomes and frequent bacterial coinfection. Moreover, intestinal microbiota may also influence the metabolism of antimalarial agents, susceptibility to *Plasmodium* infection, and skin microbiome determinants of mosquito attraction.[24]

'Gene-driving' mosquitoes to be less of a threat

On July 1, 2019, the first release of genetically modified *Anopheles* mosquitoes in Africa took place in Burkina Faso. This "gene drive" approach, under development at the nonprofit consortium Target Malaria (tar-

getmalaria.org/), is designed to spread mutations through the wild population that knock out key fertility genes or reduce the proportion of female insects that transmit the disease. Researchers released about 10,000 genetically sterilized males to observe their survivability and dispersion in the wild and to introduce the concept of genetically modified mosquitoes to regulators and community members.

Tafenoquine

Tafenoquine was recently approved for treating malaria of all species. It can be used for chemoprophylaxis against all *Plasmodium* species and, as a single dose, for presumptive antirelapse therapy.[25,26] Patients must be tested for glucose-6-phosphate dehydrogenase deficiency before receiving tafenoquine.

CASE CONCLUDED

Our patient recovered from his illness and received education about the importance of malaria chemoprophylaxis when he travels to malaria-endemic areas in the future. The most recent event did not deter him from further travel to buy coffee in South America or Africa; however, he is now an advocate for malaria prevention.

TAKE-HOME POINTS

- Fever in a traveler returning from a malaria-endemic area is an emergency.
- Clinical features of malaria are nonspecific and include fever, headache, weakness, and profuse night sweats.
- *P falciparum* is chloroquine-sensitive in some areas of Central America and the Caribbean and resistant in all other areas.
- A blood smear is the gold standard for diagnosing malaria. However, a rapid diagnostic test can be used if a microbiologist or pathologist is not readily available.
- Treatment of malaria depends on the severity and the sensitivity or resistance of the organism in the malaria-endemic area.

Malaria resources

Treatment should be in collaboration with an infectious disease physician and an infectious disease pharmacist

US Centers for Disease Control and Prevention (CDC)

Vaccines. Medicines. Advice
wwwnc.cdc.gov/travel

Malaria information and prophylaxis, by country
www.cdc.gov/malaria/travelers/country_table/

CDC malaria hotline
770-488-7788 (M–F, 9 AM–5:00 PM, Eastern time)
770-488-7100 (after hours; ask to speak with a CDC malaria expert)

Malaria treatment (United States)
www.cdc.gov/malaria/diagnosis_treatment/treatment.html

Dosing details
www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf

United States embassies
www.usembassy.gov/

International Association for Medical Assistance to Travelers
www.iamat.org/medical-directory

International Society of Travel Medicine
www.istm.org/AF_CstmClinicDirectory.asp

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A young man with hypertension and hypokalemia

A 20-year-old man with a 1-year history of untreated hypertension presented to the emergency department for evaluation and management of a hypertensive emergency. During the past 3 weeks, he had progressively worsening headaches, and on the day of presentation, his blood pressure was 184/154 mm Hg. Results of initial laboratory testing were as follows:

- Sodium 132 mmol/L (reference range 136–144)
- Potassium 3.1 mmol/L (3.7–5.1)
- Chloride 86 mmol/L (97–105)
- Bicarbonate 34 mmol/L (22–30)
- Blood urea nitrogen 14 mg/dL (9–24)
- Creatinine 1.2 mg/dL (0.73–1.22)
- Albumin 4.9 g/dL (3.4–4.9).

Urinalysis showed no hematuria or proteinuria. Plasma aldosterone was elevated at 49 ng/mL (reference range 3.0–35.4), as was plasma renin activity, at 115 ng/mL/hour. His 24-hour urine aldosterone secretion was quite elevated at 61.8 µg/24 hours (2.3–21). Thyroid-stimulating hormone, serum cortisol, and plasma catecholamine levels were normal. His urine normetanephrine level was mildly elevated at 399 µg/g creatinine (91–365), with a normal urine metanephrine level.

In light of the hypertension with elevated renin activity, hypokalemia, and metabolic alkalosis, the patient underwent computed tomographic angiography of the chest, abdomen, and pelvis with intravenous contrast. Aortic coarctation was ruled out, and the adrenal glands were unremarkable. The right kidney was small, measuring 9.6 cm (vs 11.1 cm for the left kidney), and the right renal artery had multiple midvessel stenoses (**Figure 1**). Subsequent renal artery duplex ultrasonography revealed a markedly elevated distal peak systolic velocity of 743 cm/second in the right renal artery (normal is < 150).

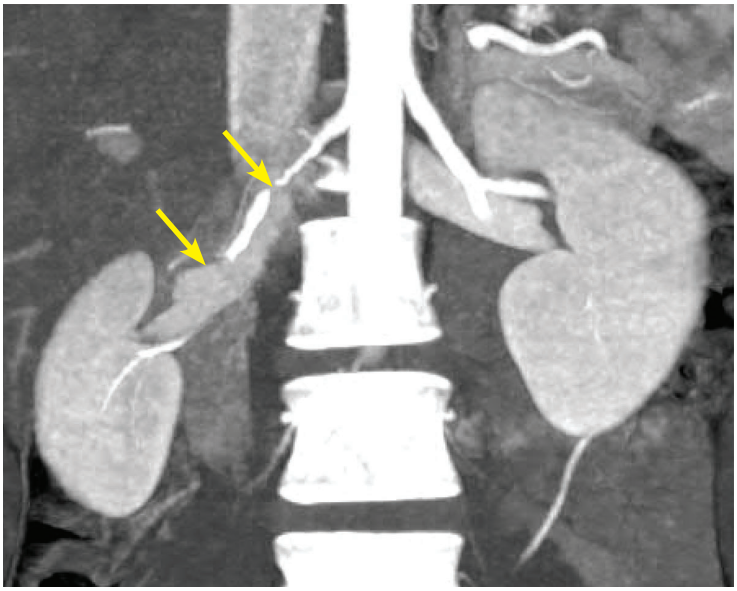

Figure 1. Coronal computed tomographic angiography demonstrated a small right kidney with multifocal fibromuscular dysplasia of the right renal artery (arrows).

The imaging characteristics were most consistent with multifocal fibromuscular dysplasia leading to secondary hyperreninemia with hyperaldosteronism. The patient underwent percutaneous transluminal angioplasty to 3 critical stenoses of the right renal artery, with less than 30% residual stenosis (**Figure 2**). Pressure wire measurements of the left renal artery did not demonstrate significant stenosis. Magnetic resonance angiography of the head and neck was normal, with no evidence of fibromuscular dysplasia in the cervical or intracranial circulation.

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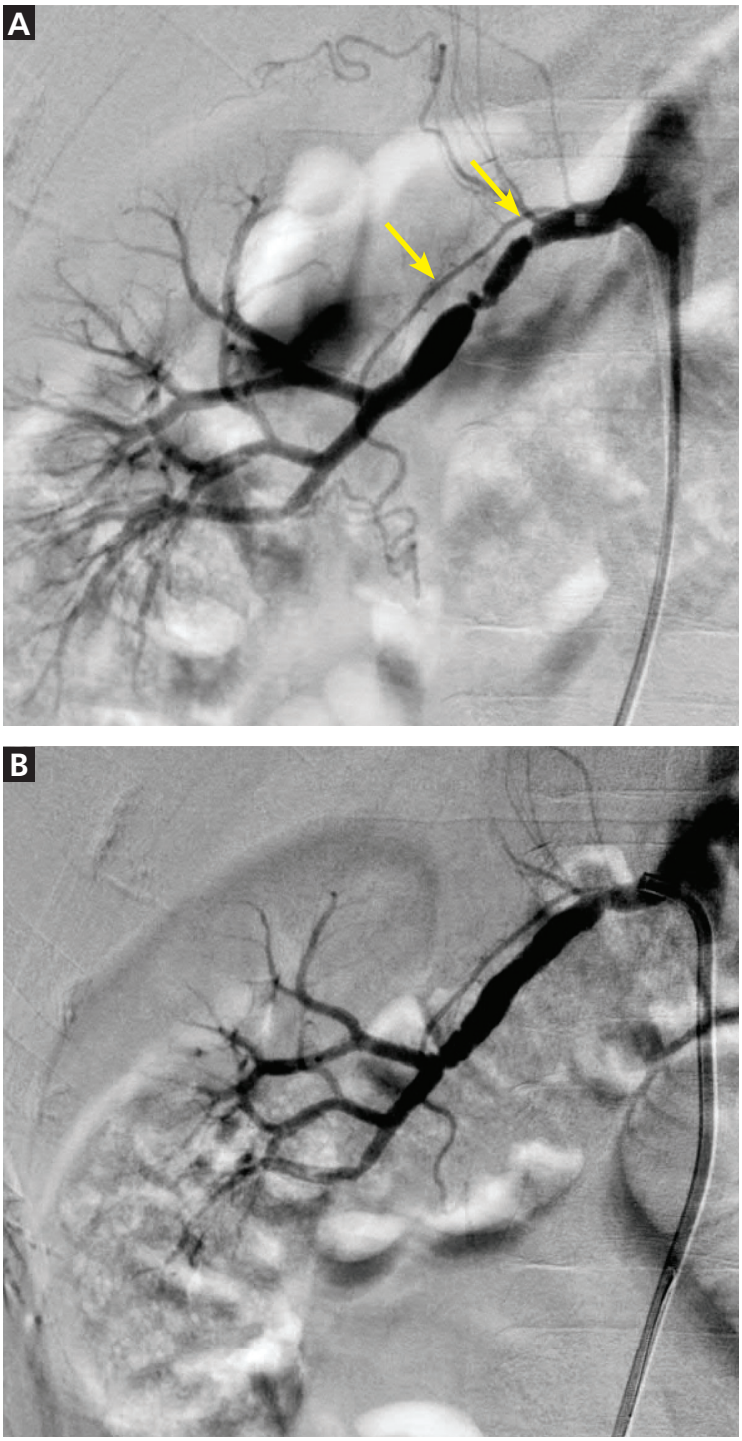

Figure 2. The right renal artery (arrows) before (A) and after (B) percutaneous transluminal angioplasty.

At follow-up 2 years later, his blood pressure was normal without medication; peak systolic velocity of the right renal artery was 203 cm/second.

RENAL ARTERY FIBROMUSCULAR DYSPLASIA

Fibromuscular dysplasia, a noninflammatory vasculopathy of medium-sized arteries, is diagnosed primarily in women (80%–90% of cases), although it can occur in men.[1] The renal arteries are most frequently involved, followed by the extracranial internal carotid, vertebral, visceral, and iliac arteries.[1] Aneurysm or dissection or both occur in 40% of patients.[2] Renal artery fibromuscular dysplasia, when symptomatic, usually manifests with renovascular hypertension, dissection, infarction, and sometimes ischemic renal atrophy.

Diagnosis and treatment

Hypertensive disorders associated with elevated renin activity, hypokalemia, and metabolic alkalosis include renal artery disease and reninoma. Fibromuscular dysplasia is diagnosed radiographically and classified as multifocal (2 or more stenoses) or focal (single focal or tubular stenosis).[1,3]

Focal and multifocal fibromuscular dysplasia have different epidemiologies and histologies. The focal type is not well correlated with a specific histology, is more common in men, presents at a younger age, and is more often associated with both higher blood pressure and evidence of ischemic nephropathy.[3,4] Multifocal fibromuscular dysplasia is classically described as resembling a "string of beads" and correlating with medial fibroplasia on histology. Our patient's multiple, serial stenoses were clinically more similar to focal than to multifocal disease. Nevertheless, some investigators consider multiple focal, serial stenoses, as seen in this case, to be multifocal fibromuscular dysplasia.

Key to the diagnosis of fibromuscular dysplasia is to exclude vasculitis and other recognized vascular syndromes (eg, Ehlers-Danlos type IV, Loeys-Dietz syndrome) by history, laboratory evaluation, and imaging. Features of such diseases were not present in our patient.

Because disease is found in multiple arterial beds in as many as two-thirds of patients, it is recommended that all patients with fibromuscular dysplasia undergo baseline skull-to-pelvis cross-sectional imaging by computed tomographic angiography or magnetic resonance angiography.[1,5]

Although percutaneous transluminal angioplasty is not always curative, it is more likely to be successful when performed within 5 years of the onset of hypertension.[6] Assessment for restenosis every 6 to 12 months by duplex ultrasonography is common, although velocity data specific to fibromuscular dysplasia are not well established.

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CORRECTION

The article "Fever in a traveler returning from Ethiopia" by Ken Koon Wong, MD (Cleve Clin J Med 2020; 87(1):31–42, doi:10.3949/ccjm.87a.19017) contained an error. In Table 7, "Chemoprophylaxis for malaria" on page 40, the entry for doxycycline incorrectly carried a footnote that states this drug can be used in pregnancy. This footnote has been removed. According to the US Food and Drug Administration, "While there are no controlled studies of doxycycline use in pregnant women to show safety, an expert review of published data on experiences with doxycycline use during pregnancy by TERIS—the Teratogen Information System—concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data = limited to fair), but the data are insufficient to state that there is no risk" (https://www.fda.gov/drugs/bioterrorism-and-drug-preparedness/doxycycline-use-pregnant-and-lactating-women).