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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Emergency Medicine / Acil Tıp

How should Travel-Related Malaria Management in Emergency Departments of Non-endemic Countries? Single-center Study

Cem Gün[1], Hasan Aldinç[1], Orhan Çınar[1], Serpil Yaylacı[1], Gürdal Yılmaz[2], Süha Türkmen[3]

[1]Acibadem Mehmet Ali Aydinlar University, School of Medicine, Department of Emergency Medicine, Istanbul, Turkey

[2]Karadeniz Technical University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Trabzon, Turkey

[3]Hamad Medical Corporation, Emergency Department, Doha (Qatar

Cem GÜN
Hasan ALDİNÇ
Orhan ÇINAR
Serpil YAYLACI
Gürdal YILMAZ
Süha TÜRKMEN

Correspondence: Cem Gün
Acibadem Mehmet Ali Aydinlar University, School of Medicine, Department of Emergency Medicine, Istanbul, Turkey
Phone: +905058941654
E-mail: cem.gun@acibadem.edu.tr

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ABSTRACT

Purpose: Advancements in air travel enabled an increase in traveling to malaria-endemic countries such as those in sub-Saharan Africa. An increase in the incidence of imported malaria accompanied these advancements. This study aims to summarize how malaria patients who have imported the disease into non-endemic countries present to the emergency departments and to enlighten physicians in emergency departments by providing suggestions for practical approaches to handling such situations.

Methods: This study was conducted retrospectively in a university hospital, from January 1, 2014 to March 1, 2022. Eight years of emergency department records of patients who were examined in the emergency department with a suspected, or definitive diagnosis of malaria were included in the study. Epidemiological and clinical characteristics were evaluated.

Results: 892 patients were admitted to the emergency department with suspicion of malaria. Thirty of these patients were diagnosed with malaria, and 846 of the 892 patients were members of airline cabin crews. 94.3% (n=798) of the cabin crew did not use prophylactic medication for malaria. The mean age of the patients was 33.2±8.5. Twenty-five patients were diagnosed via peripheral blood smears, and the remaining three patients were diagnosed with polymerase chain reaction (PCR). Rapid diagnostic tests were positive in 26 out of 28 patients.

Conclusion: The risk of acquiring malaria is still high despite short-term visits and airport-limited stays. Travel history should be routinely asked of patients with fever by emergency physicians. Education of people traveling to malaria-endemic countries, including cabin crew, regarding malaria prophylaxis and protective measures to prevent mosquito bites plays a crucial role in preventing malaria.

Keywords: Malaria; Import Malaria; Emergency Department; Cabin Crew; Infection

Endemik Olmayan Ülkelerin Acil Servislerinde Seyahate Bağlı Sıtma Yönetimi Nasıl Olmalı? Tek Merkezli Çalışma

ÖZET

Amaç: Hava yolu ulaşımındaki gelişmeler ve artış, sıtmanın endemik olduğu Afrika ülkelerine olan seyahatlerinde artmasını sağladı. Bu gelişmelerle birlikte ithal sıtma vakalarının da dünya genelinde artmasına sebep oldu. Bu çalışma, hastalığı endemik olmayan ülkelere ithal eden sıtma hastalarının acil servislere nasıl geldiklerini özetlemeyi ve bu tür durumlarla başa çıkmak için pratik yaklaşımlar için önerilerde bulunarak acil servislerdeki hekimleri aydınlatmayı amaçlamaktadır.

Yöntemler: Bu çalışma 1 Ocak 2014-1 Mart 2022 tarihleri arasında bir üniversite hastanesi kayıtları incelenerek retrospektif olarak yürütülmüştür. Acil serviste sıtma şüphesi veya kesin tanısı ile başvuran hastaların yedi yıllık acil servis kayıtları çalışmaya dahil edilerek, epidemiyolojik ve klinik özellikler değerlendirildi. Sıtma tanısı alan hastalara tekrar ulaşılarak anket düzenlendi.

Bulgular: 892 hastanın acil serviste sıtma ön tanısıyla değerlendirildiği tespit edildi. Bu hastaların 30'u sıtma teşhisi aldı ve 892 hastanın 846'sı havayolu kabin ekibi üyesiydi. 28 hasta ithal sıtma tanısı aldı. Kabin ekibinin %94,3'ünün (n = 798) sıtma için koruyucu ilaç kullanmadığı saptandı. Hastaların yaş ortalaması 33.2±8.5 idi. Yirmi beş hastaya periferik kan yayması, kalan üç hastaya PCR ile tanı konuldu. 28 hastanın 26'sında hızlı tanı testleri pozitifti.

Sonuç: Kısa süreli ziyaretlere ve havaalanında sınırlı kalışlara rağmen sıtmaya yakalanma riski hala yüksektir. Acil hekimleri tarafından ateş şikayeti olan hastalara rutin olarak seyahat öyküsü sorulmalıdır. Kabin ekibi de dahil olmak üzere sıtmanın endemik olduğu ülkelere seyahat eden kişilerin sıtma profilaksisi ve sivrisinek ısırıklarını önlemeye yönelik koruyucu önlemler alması, sıtmayı önlemede çok önemli bir rol oynamaktadır.

Anahtar Kelimeler: Sıtma; İthal Sıtma; Acil Servis; Kabin Ekibi; Enfeksiyon

The number of people who travel to Africa has increased enormously in recent years, and travel-acquired infections have also increased (1). Malaria is one of the most critical infections among these. Authorities estimate that around 229 million cases were present in 2019 in 87 malaria-endemic countries (2). Malaria is an infectious disease with high mortality and is caused by Plasmodium parasites. It is endemic in many countries throughout the world and threatens approximately 40% of their populations (3). People most at risk for malaria infection and malaria-related death are those traveling to Sub-Saharan African Countries (4). Prophylaxis and protective measures are of great importance and included in the World Health Organization's 2030 goals (5).

The malaria cases that are imported into non-endemic countries are frequently associated with delayed diagnosis and treatment and are thus accompanied by increased mortality rates (6). These cases also cause the rates of drug resistance to rise and have an overall negative effect on the long-term goals for eradicating this disease (7). Therefore, malaria prophylaxis should be initiated for people who travel to high-risk malaria-endemic countries, and measures need to be taken to avoid mosquito bites (8). However, people who are staying in the malaria-endemic countries for short-term periods without getting started on malaria prophylaxis constitute a severe problem. This is a particularly important issue among the members of airline cabin crews, who represent a clear example of short-term visitors who make multiple visits to malaria-endemic countries and do not initiate the malaria prophylaxis before traveling.

The number of infections acquired during international travels that arise in different settings may vary throughout the world. People who visit endemic countries for a short time and become infected with malaria may present to the emergency department (ED) with nonspecific symptoms. Most emergency physicians rarely encounter such diseases; therefore, malaria may not be among the preliminary diagnoses of emergency physicians. Any delay in recognizing or treating a possible malaria infection may increase both morbidity and mortality rates (9).

This study aims to summarize how malaria patients who have imported the disease into non-endemic countries present to the EDs and to inform physicians in EDs by providing suggestions for practical approaches to handling such situations. The second goal of the study is to investigate the prophylaxis statuses of patients and the reasons why they do not get the prophylactic treatments in cases where this was not initiated.

METHODS

This study was conducted retrospectively in a university hospital, from January 1, 2014 to March 1, 2022. This study was approved by Acibadem Mehmet Ali Aydinlar University Medical Research Evaluation Committee (ATADEK) (Decision number: 2020-12/2). The University hospital is not a primary referral center for tropical diseases but because it is located close to an international airport and may be more frequently visited by airline cabin crews, airport personnel, and travelers. Eight years of ED records of patients who were examined in the ED with a suspected, or definitive diagnosis of malaria were included in the study. From an epidemiologic perspective, the ages of the patients were recorded, along with their genders, occupations, primary complaints, the countries they had visited, the duration of their visits, their statuses regarding prophylaxis usage, and any previous malaria diagnoses. The lengths of time between their returns to the countries and the beginning of symptoms, the symptoms they had when they were admitted to the ED, and the duration of the time when their symptoms began to when they applied to our clinic were also evaluated. Any histories of mosquito bites, ongoing fevers, and accompanying symptoms such as nausea, vomiting, diarrhea, jaundice, or muscle pain were recorded. Findings from physical examinations including hepatomegaly and splenomegaly were also noted. Laboratory examination results were collected for parasitic loads, leukocytes, hemoglobin, thrombocytes, lactate dehydrogenase, aspartate transaminase, alanine transaminase, total and direct bilirubin, urea, creatinine, C-reactive protein, and international normalized ratios. Also, rapid diagnostic tests, blood smears, and polymerase chain reactions test results were noted. Clinical features regarding treatment were recorded using the hospital's electronic medical system. Telephone numbers were obtained from the hospital records of the patients diagnosed with malaria, and the patients were called. An explanation was given about the study, and verbal consent was obtained from those who agreed to participate in the study, 6 questions were asked; 1- Before you got malaria, did you know about malaria disease while traveling to a risky area? 2- Did you take any precautions (using chemical-topical repellent; wearing long pants, socks, and long-sleeved shirts; staying indoors) to protect yourself from malaria disease while traveling to the risky area? 3- Did you use any prophylaxis? if you did not take any prophylaxis, what is the reason? 4- When the

symptoms started? did you think you might have malaria? 5-When you applied to the emergency service, did the triage nurse or doctor question whether you went to a risky area from malaria? 6- After receiving treatment for malaria, did you go to the risk area for malaria again? If you went, did you take any precautions to protect yourself from malaria? Approval for the study was obtained from the university's ethics committee, to which the university hospital is linked.

Data were analyzed using IBM SPSS version 18 for Windows. Descriptive statistics were used to determine the frequencies and percentages for biodemographic variables. The median Malaria Mortality Score (MMS) was used as the measure of the severities of the disease

RESULTS

It was determined that 892 patients had been admitted to the ED with suspicion of malaria in a 8-year period. Flowchart 1 is shown in Figure 1. Thirty of these patients were diagnosed with malaria, and 846 of the 892 patients were members of airline cabin crews. A full 94.3% (n = 798) of the cabin crew members did not use prophylactic medication for malaria. In addition, malaria prophylaxis had not been initiated in any of our patients before or during their travel. 30 people diagnosed with malaria were identified. As we aimed to evaluate imported malaria, we included 28 patients in the study. The other two patients lived in South Africa.

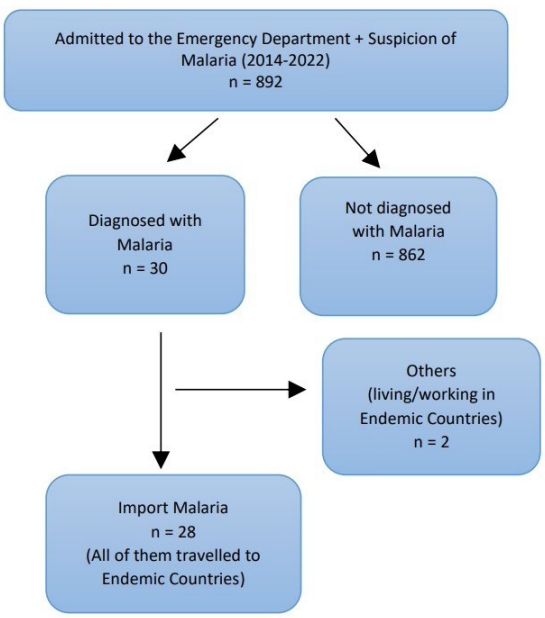

Figure 1. *Flowchart of Study Population*

Table 1 presents the general characteristics of those who were diagnosed with malaria. The mean age of these patients was 33.2±8.5 (24-48), with 17 male patients and 11 female patients. All infected patients had a history of visiting Sub-Saharan Africa. The mean duration of their layover in Africa was 2.3±1.6 (1-8) days; the mean delay before the onset of their symptoms after return from travel was 9.0±6.0 (0-35) days, and the mean symptom duration before presentation to the ED was 3.6±2.0 (1-10) days.

All 28 malaria patients had fever, 22 reported accompanying chills, and 21 mentioned sweating. Sixteen had nausea and/or vomiting, and eight reported diarrhea. In addition, 21 patients had histories of mosquito bites. Splenomegaly was detected in 17 patients, hepatomegaly in 15, and jaundice in six. Nine patients had signs of central nervous system involvement. Table 1 presents the laboratory parameters of the patients at the time of their applications. Among the 28 patients, 25 were diagnosed through peripheral blood smears and the remaining three patients were diagnosed through PCR. Rapid diagnostic tests were positive in 26 out of the 28 patients; 27 patients were determined to be infected with Plasmodium Falciparum and one patient with Plasmodium Ovale. In addition, 13 patients had parasitic loads of over 5% and seven had over 10%. In terms of treatment, 20 patients were given artemether-lumefantrine, five received artemether-lumefantrine and primaquine, and three patients who were critically ill were given artemether-lumefantrine following intravenous artesunate. The mean duration of the hospitalizations of the patients was 6.1±4.5 (3–18) days. Nine patients received a transfusion of red blood cells or platelets, and 27 were discharged after treatment completion. One patient, who had a 20% parasitic load, died during their hospitalization. Three patients experienced recurrence during the two-month follow-up.

All patients diagnosed with malaria were called by phone and a 6-question survey was conducted except one patient. The one patient, that we couldn't reach was deceased. In this survey, all of the participants express that they had information on malaria before their visit to the malaria-endemic country. The survey questions and results are in Table 2.

Table 1. General characteristics and Laboratory parameters of Cabin Crews diagnosed with Malaria

	Frequency (n)	Percentage (%)
Gender		
Male	17	60.7
Female	11	39.3
Symptoms		
Jaundice	7	25
Fever	28	100
Diarrhea	8	28.5
Nausea/vomiting	16	57.1
Neurological	9	32.1
History of a mosquito bite	21	75
Splenomegaly	17	60.7
Hepatomegaly	15	53.5
	Median ±SD	
Time to treatment	7.18±6.7 days	
Age	33.2±8.5 years	
Duration of travel	2.3±1.6 days	
Beginning of the symptoms	3.6±2.0 days	
Laboratory Parameters		
Leucocyte (mm^3)	5228±3210	
Hemoglobin (gr/dL)	13.0±2.2	
Thrombocyte (mm^3)	83935±68432	
ALT (U/L)	76.82±54.5	
AST (U/L)	72.61±50	
Total bilirubin (mg/dL)	1.95±2.18	
Direct bilirubin (mg/dL)	1.19±1.49	
Creatinine (mg/dL)	1.20±1.24	
Lactate Dehydrogenase (U/L)	497±579	
C-Reactive Protein (mg/dL)	10.5±8.0	
International Normalized Ratio (INR)	1.97±0.2	

Table 2. The questionnaire asked to patients diagnosed with malaria

The questions	Yes (n)	No (n)
1- Before you got malaria, did you know about malaria disease while traveling to a risky area?	27	0
2- When the symptoms started, did you think you might have malaria?	5	22
3- When you applied to the emergency service, did the triage nurse or doctor question whether you went to a risky area from malaria?	20	7
4- After receiving treatment for malaria, did you go to the risk area for malaria again?	24	3
-If you went, did you take any precautions to protect yourself from malaria?	9	15
5- Did you take any precautions to protect yourself from malaria disease while traveling to the risky area?	8	19
6- Did you use any prophylaxis?	0	27
-Reasons for not using prophylaxis	**n**	**%**
•Inspite of short trips to risky areas, they had never been sick. So they feel safe without using prophylaxis.	19	70.3
•They closely follow their health condition and symptoms, they apply to the health institution quickly in case of any problem	4	14.8
•They are concerned about the side effects of drugs	3	11.1
•For allergic reasons	1	3.7

DISCUSSION

United States emergency physicians rarely encounter internationally acquired travel ill-nesses in emergency departments(9). However, malaria is one of the more frequent of these. Symptoms of malaria are nonspecific, and few have abnormal physical findings. The most common of these is fever, which our study supports (10). However, fever is a general symp-tom and could represent non-malarial infections. The symptom of fever in the setting of travel, even with layovers of short duration was key to prompting suspicion of malaria in our cohort.

In our study, some cases in which the patient may have had no fever and therefore not sus-pected of malaria. This could have resulted in undiagnosed cases that were not selected for study, leading to selection bias. Emergency physicians or triage nurses should inquire about whether patients have been to endemic areas for malaria in emergency departments. This raises the following question: Which countries are at risk from malaria disease? Figure 2 shows coun-tries with indigenous cases and their status from 2000 to 2019 (2). Any patient with a travel history to any of the countries in Figure 2 should be investigated as a potential malaria case.

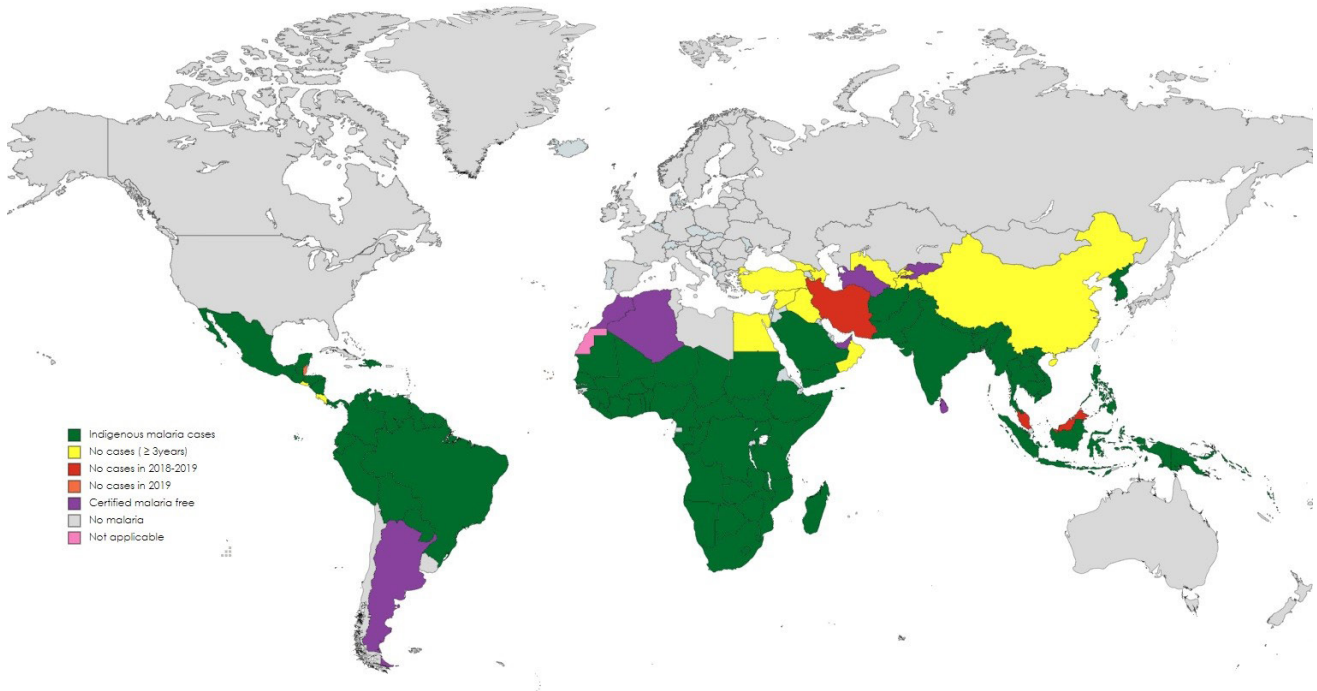

Figure 2. *World Map; Countries with indigenous cases and their status*

Although malaria is mostly deemed preventable for those traveling from non-endemic to endemic countries, numerous studies have reported that if prophylaxis is not initiated or there is reduced compliance to the recommended dosage, malaria is commonly encountered in this group (11). Travel has become more frequent to endemic areas, and as indicated in our study, even exposure of 2-3 days is enough to contract malaria.

This short duration layover may be incorrectly perceived as safe, since 82.8% (798/846) of cabin crews did not have prophylaxis, and of these, 3.5% (28/798) became infected. Of the 28 infected cases, none were prophlaxed (12,13). Travel timing reported local resistance, and drug side effects should guide physicians in chemoprophylaxis selections for malaria. Table 3 summarizes the drugs recommended by the Centers for Disease Control and Prevention (CDC) for malaria prophylaxis and gives a review for each drug (14).

Table 3. Prophylactic Regimens for Malaria and Special Considerations by CDC (Centers for Disease Control and Prevention)

	Dosing	Pregnancy	Special Considerations
Primaquine	- Daily dosing - 1–2 days before through 7 days after	Contraindicated	- Used in areas where P. vivax is seen intensely - Not used in G6PD deficiency
Chloroquine	- Weekly dosing - 1–2 weeks before through 4 weeks after	Trustworthy for pregnants	- Many areas with resistance
Doxycycline	- Daily dosing - 1–2 days before through 4 weeks after	Likely safe but second line	- Inexpensive - Photosensitivity
Atovaquone-proguanil	- Daily dosing - 1–2 days before through 7 days after	Contraindicated	- More expensive
Tafenoquine	- Daily dosing for 3 days before travel and transitions to weekly through 1 week after return	Contraindicated	- Not used in G6PD deficiency
Mefloquine	- Weekly dosing - 2 weeks before to 4 weeks after	Trustworthy for pregnants	- Not recommended for seizures, psychiatric disorders, cardiac dysfunctions

There is a definite association between international air travel to malaria-endemic countries and the possibility of contracting the disease. Overall, the degree of endemicity in the region of travel, period of stay, the health status of the person during travel, precautions taken, and the person's behavior determine the risk (15,16). It is estimated that for aircraft cabin crews, the contagion rate of malaria is 0.5 per 1,000 people per night in malaria-endemic countries (13). Although our patients had traveled to malaria-endemic countries, malaria prophylaxis was not initiated in any of them. Prophylaxis has been neglected because of some reasons, most of the patients (70%) stated that they travel to the malaria-endemic country and do not use prophylactic medication because they are not sick. Other patients answered that they keep track of their symptoms closely and did not take prophylactic medication because they were concerned about the adverse effects. They had tried to protect themselves from mosquito bites. The literature cites cabin crews may mitigate the risk of mosquito bites and thus malaria, by wearing long-sleeves shirts and pants, using bed netting, and by minimizing night-time out-door activities (13,17). However, 28 of our malaria patients had no prophylaxis, suggesting that prophylaxis may be important for cabin crews even for short layovers in endemic coun-tries. Unfortunately, in the current study, 21 of the patients (75%) recalled being bitten by a mosquito.

Fatal malaria cases among members of cabin crews have been reported, and even non-lethal cases have resulted in a significant loss in the workforce (13). We were informed that the deceased patient, a 34-year-old female cabin crew member, spent two days in Africa at the airport hotel. It was found that most of our patients had stayed in malaria-endemic countries for only two or three days. These cases show that the risk is still high for short-term travels. Our study identified two important clues in suspecting patients having malaria: it only requires 2-3 days exposure in an endemic area to acquire malaria, and a delay of symptom onset of 9 days after return from travel is common in patients presenting to the ED (18,19). Before her death, our deceased patient reported that she had returned from Africa 40 days ago. Her symptoms had started 15 days before application to our clinic, and she had received non-specific treatment for an upper airway infection at another hospital. However, she applied to our clinic because of persistent fever and fatigue despite the treatment. Her parasitic load in the peripheral blood smear was detected to be 20%. Delayed diagnosis of imported malaria cases is a common occurrence, emphasized in a meta-analysis by Tatem et al (7). In addition to contributing to global eradication plans, scrutinizing imported malaria cases in non-endemic countries could decrease complications and mortality rates by increasing the awareness level of clinicians, which can prevent these cases from being overlooked.

Treatment depends on four main factors, which are as follows: the *Plasmodium* species by which the patient was infected; the patient's symptoms and clinical severity; the sensitivity of the *Plasmodium* species in the geographical region where infection occurs to anti-malarial drugs; and previous use of antimalarials, including those taken for malaria chemoprophylaxis. The CDC recommends that a blood smear be performed if the patient has a fever and has traveled to a risky area for malaria in the last 2 months or is clinically suspected of having ma-laria. If a blood smear is negative, repeat blood smears should be conducted every 12–24 hours (a total of three times). If the blood smear is positive, the instructions in flowchart 2 should be followed (Figure 3) (20). Malaria treatment usually takes 3–7 days. Most of the pa-tients in our study received only artemether-lumefantrine; four received artemether-lumefantrine and primaquine, one received quinine and primaquine, and three patients re-ceived artemether-lumefantrine following intravenous artesunate. The utilization of the anti-malarial medication artesunate in conjunction with exchange transfusion demonstrated effica-cy and safety in patients suffering from severe malaria and neurological complications (21). An exchange blood transfusion and artesunate treatment were applied to two malaria patients. One patient was deceased. The obvious difference between the deceased patient and the oth-ers was that she was diagnosed approximately 40 days later.

When patients present to the ED with fever, it is prudent for emergency physicians or tri-age nurses to ask about their travel history in the prior two months. Or if the patient presents to the ED with a history of recent travel it is prudent to ask about fevers, chills or night sweats. When there is suspicion of malaria, then testing should be considered regardless of the dura-tion of their endemic exposure or whether a mosquito bite has been observed. Blood smears, rapid diagnostic testing (antigen), or polymerase chain reaction testing are commonly used to make malaria diagnoses in suspected cases (9). Rapid diagnostic tests for malaria represent a fast, cheap, simple, and field-deployable way to accurately identify a malarial infection at the point of care, and these tests are especially useful in low-resource and rural settings. Blood smears were the most widely used method to confirm the entity of Plasmodium parasites until the appearance of malaria rapid diagnostic tests; they are still useful and reliable. Polymerase chain reaction assays can determine low parasitemia and have great analytical performance, but they are costly and impractical for use (22).

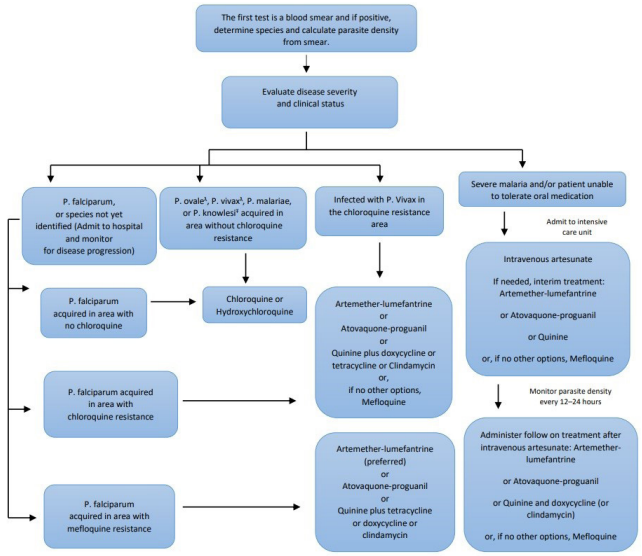

Figure 3. *Algorithm for Treatment of Malaria*[Ɣ]
Footnotes:
Ɣ Algorithm for treatment not for children and pregnant women
Ŧ If species later identified P. knowlesi admit to hospital and monitor for disease progression.
λ If species later identified as P. vivax or P. ovale, add primaquine if not G6PD deficient by quantitative testing. Tafenoquine can only be used if chloroquine or hydroxychloroquine used for acute infection.

Limitations

There are some limitations in the current study. The fact that the study is single-centered is one of them. Since the university hospital where the study was conducted is a hos-pital close to the airport, airline employees may have applied more frequently. Although the number of patients examined with a prediagnosis of malaria is sufficient, the low number of patients diagnosed with malaria is low.

CONCLUSION

Traveled malaria-endemic country, fever and mosquito bite are factors that should raise emergency physician suspicion of malaria. Blood smears, rapid diagnostic testing (antigen), or polymerase chain reaction testing are commonly available to confirm the diagnosis. Unprophylaxed cabin crews who have even one or two days duration layover in endemic areas may be at risk for acquiring malaria. Although wearing long-sleeved shirts and pants, using bed netting, and minimizing night-time outdoor activities may mitigate the risk of acquiring the condition, prophylaxis may be especially important.

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