

An Approach to a Patient with Tropical Infection in the Intensive Care Unit

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Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-23867

INTRODUCTION

Tropical diseases are often defined as diseases that are prevalent in, or unique to, tropical and subtropical regions of the world.¹ Infections form a large proportion of the burden of tropical diseases. These infections may sometimes require intensive care and tropical infections account for about 20% of all intensive care unit (ICU) admissions in published data from Asia, South America, and Africa.² In the INDICAPS study that included data from 4038 patients from 124 ICUs in India, 231 (5.7%) patients had tropical infections and 50 (21.7%) of these died.³ In another study, Parikh et al. found that almost 24% of 1116 patients admitted to the ICU of a public hospital in Mumbai were for tropical infections.⁴ Yeolekar et al. mention that in the monsoon months, almost 80% of ICU beds in public hospitals may be occupied by patients with tropical infections.⁵

Tropical infections are common in the geographic regions of the world that are close to the equator because they have a warmer climate with less seasonal variation in temperatures, higher rainfall, and greater coverage of land by vegetation,⁶ all of which favor the multiplication of insects like mosquitoes, ticks, mites and flies which are vectors for several tropical infections.⁷ Some pathogens survive only in such warm, humid environments. Many infections tend to peak in monsoon months. Increasing interactions between humans closer to animals⁶ may increase the risk of acquiring zoonoses, like leptospirosis, Japanese B encephalitis, brucellosis, and Q fever.^{2,7} Poor sanitation and consumption of contaminated drinking water or uncooked food may cause infections like typhoid, amebiasis, viral hepatitis, travelers' diarrhea, and neurocysticercosis.^{2,7} This supplement of the *Indian Journal of Critical Care Medicine* features several articles on intensive care of tropical infections. Many of these common infections have overlapping clinical and laboratory features and also a wide spectrum of presentations of the same infection.² In this situation, a systematic approach to the diagnosis and treatment of tropical infections is very important, especially before the diagnosis is confirmed by specific laboratory tests. This article describes a systematic approach to diagnosis and empiric treatment in a newly admitted patient in the ICU (Table 1).^{2,7,8}

TRAVEL HISTORY

Travel history forms the first step in the diagnosis. The epidemiology of tropical infections varies in different continents and countries (Table 2).⁷⁻¹³ Two books, the CDC Yellow Book 2020, published by the Centers for Disease Control, USA,⁸ and the International travel and health: situation as on 1 January 2012, published by the World Health Organization,⁷ are excellent

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How to cite this article: Karnad DR, Amin P. An Approach to a Patient with Tropical Infection in the Intensive Care Unit. *Indian J Crit Care Med* 2021;25(Suppl 2):S118-S121.

Source of support: Nil

Conflict of interest: None

references regarding diseases that can be acquired by travelers after visiting specific geographic areas.

Although travel history may not apply to patients residing in endemic areas in the tropics, even in tropical countries, specific regions are endemic for infections like visceral leishmaniasis in certain districts of Bihar, West Bengal, Uttar Pradesh, and Jharkhand,¹⁴ scrub typhus in rural areas of Tamil Nadu, northeast states, and northwest India,¹⁵ Japanese B encephalitis in Gorakhpur and Basti districts of Uttar Pradesh.¹⁶

Two important publications from GeoSentinel database describe real world experience on tropical infections in travelers.^{17,18} GeoSentinel is a global network (<https://www.istm.org/geosentinel>) established in 1995 by the International Society of Travel Medicine and the Centers for Disease Control and Prevention with the goal of monitoring travel-related morbidity. There are 60 GeoSentinel travel and tropical medicine clinics, located in >26 countries on six continents, that contribute clinician-based anonymous information on ill travelers. The spectrum of critical illness due to tropical infections across the world is described in a publication on infections in 82,825 symptomatic western travelers who sought medical care at a GeoSentinel site from 1996 to 2011.¹⁹ Of these, 3655 (4.4%) patients had an acute and potentially life-threatening disease.¹⁹ The most common diseases seen were falciparum malaria, typhoid and paratyphoid fever, leptospirosis, rickettsial infections, dengue hemorrhagic fever/dengue shock syndrome, melioidosis, East African trypanosomiasis, and Japanese encephalitis.¹⁹

The spectrum of severe tropical infections in Indian ICUs is available from a recent multicenter study from 34 ICUs across India. Singhi et al. found that dengue ($n = 105$; 23%), scrub typhus ($n = 83$; 18%), encephalitis/meningitis ($n = 44$; 9.6%), malaria ($n = 40$; 9%),

Table 1: An approach to the diagnosis of tropical infections

1. History of travel to endemic areas
 - a. Places visited—consider geographic variation and endemicity of diseases
 - b. Activities done—swimming in lake or river water, wading through monsoon floods
 - c. Food consumed—exotic foods, uncooked food
 - d. Contact with animals—farm animals and wild animals
 - e. History of insect bites—ticks, fleas, sandfly, mosquito
2. Interval between exposure and onset of symptoms (incubation period)
3. Prophylactic measures followed during travel
 - a. Vaccines—typhoid, cholera, yellow fever, meningococcal vaccine
 - b. Chemoprophylaxis—malaria, leptospirosis
4. Spectrum of organ involvement (syndromic presentation)—presence of fever and:
 - a. Thrombocytopenia, coagulation disturbances (hemorrhagic fever)
 - b. Liver involvement
 - c. Renal syndrome
 - d. Neurological involvement
 - e. Rash
 - f. Pulmonary syndrome
 - g. Gastrointestinal syndrome

Based on Karnad et al.,² World Health Organization,⁷ and Wilson⁸

Table 2: Infections endemic in various geographic regions of the world

<i>Geographical region</i>	<i>Common tropical infections</i>
Caribbean	Chikungunya, dengue, malaria, enteric fever, Zika, acute histoplasmosis, leptospirosis
Central America	Chikungunya, dengue, malaria (mainly vivax), Zika, leptospirosis, coccidioidomycosis
South America	Chikungunya, dengue, enteric fever, malaria (mainly vivax), Zika, bartonellosis, leptospirosis, histoplasmosis
South Asia (including India)	Dengue, enteric fever, malaria (vivax and falciparum), chikungunya, scrub typhus, Japanese B encephalitis, lymphatic filariasis
Southeast Asia	Dengue, malaria, chikungunya, leptospirosis
Africa	Malaria (mainly falciparum), rickettsia, acute schistosomiasis, dengue, yellow fever, African trypanosomiasis, filarial infections
Northern Australia and Oceania	Necator americanus (hookworm), strongyloidiasis, lymphatic filariasis, balantidiasis, trachoma, treponematoses, dengue, Japanese encephalitis.

Based on World Health Organization,⁷ Wilson,⁸ Hotez et al.,⁹ Hotez et al.,¹⁰ Kline et al.,¹¹ Hotez and Damania,¹² and Mitra and Mawson¹³

leptospirosis ($n = 7$; 1.5%), viral hepatitis ($n = 5$; 1.1%), and typhoid ($n = 5$; 1.1%) were the common tropical infections seen.²⁰ In an older single-center study from Mumbai, Parikh et al. reported that in 1116 patients admitted to the ICU during a 12-month study period, malaria ($n = 137$; 13.8%), tetanus ($n = 61$; 6.1%), bacterial meningitis ($n = 28$; 2.8%), tuberculosis and its complications ($n = 17$; 1.7%), and leptospirosis ($n = 13$; 1.3%) were the predominant tropical infections requiring ICU admission.⁴

INCUBATION PERIOD AND ACTIVITIES DURING TRAVEL

The interval between travel and onset of symptoms is a valuable clue in the diagnosis (Table 3).^{2,7,21–24}

Migrant workers employed in large cities may acquire infections when they travel to their villages in endemic areas and develop symptoms on return to large cities. Unusual tropical infections may be acquired during recreational, leisure, or business foreign travel to countries in Southeast Asia, Africa, South America, or northern Australia.^{7,23} It is also important to ask for specific activities performed. For example, swimming in lakes or rivers

may predispose to schistosomiasis or leptospirosis.^{7,13,23} Drinking unclean water may predispose to Hepatitis A or E infections, enteric or nonenteric salmonellosis, or cholera.⁷ Eating exotic uncooked food may predispose to tissue parasitic infestations.⁷

SYNDROMIC APPROACH TO DIAGNOSIS

A syndromic approach to the diagnosis of tropical infections has been recommended.^{1,2,7,8,21,23,24} A recent comprehensive review discusses in detail the various syndromes commonly seen in tropical diseases.² Common syndromes and their causes are listed in Table 4.

It is important to note that most ICU patients will have more than one of these syndromes with fever, thrombocytopenia, leucopenia, elevated serum creatinine, and elevated liver transaminases being the commonest combination.^{1,2,21} These features are very commonly seen in malaria, dengue, scrub typhus, leptospirosis, and enteric fever.^{2,21} Myalgia and arthralgia are also common symptoms. The predominance of one feature usually points to the diagnosis, e.g., severe thrombocytopenia suggests a diagnosis of dengue or malaria, rash suggests rickettsial infections, arthritis suggests

Table 3: Incubation period of common tropical infections

<i>Incubation period</i>	<i>Common tropical infections</i>
<2 weeks	Malaria Dengue Rickettsial typhus fevers Leptospirosis Typhoid fever Viral hemorrhagic fevers East African trypanosomiasis Acute diarrheal disorders Arboviral encephalitis Angiostrongyliasis Histoplasmosis Coccidioidomycosis Q fever Zika virus
2–6 weeks	Malaria Typhoid fever Hepatitis A and E Amebic liver abscess Leptospirosis East/West African trypanosomiasis Q fever
>6 weeks	Malaria Tuberculosis Visceral leishmaniasis Lymphatic filariasis Schistosomiasis West African trypanosomiasis

Based on Karnad et al.,² World Health Organization,⁷ Kothari et al.,²¹ Rudolph et al.,²² Fairley,²³ and Wood-Morris et al.²⁴

Table 4: Common syndromes of tropical infections requiring an ICU treatment^{1,2,8,21}

<i>Clinical syndrome</i>	<i>Common causes</i>
Fever with rash	Dengue, chikungunya, rickettsial fevers, meningococemia, viral hemorrhagic fevers
Fever with respiratory manifestations	Leptospirosis, malaria, scrub typhus, melioidosis, military TB, hantavirus infection, Q fever, acute schistosomiasis
Fever with jaundice	Acute viral hepatitis, leptospirosis, severe malaria, scrub typhus, yellow fever
Fever with encephalopathy/seizures	Viral encephalitis, cerebral malaria, leptospirosis, typhoid, meningitis, African trypanosomiasis (sleeping sickness), scrub typhus
Hemorrhagic fever	Dengue, Ebola, yellow fever, malaria, leptospirosis
Fever and shock	Cholera, algid malaria, dengue shock syndrome, Chagas disease, typhoid fever with intestinal hemorrhage or myocarditis

chikungunya, severe jaundice is seen in leptospirosis and malaria, and subconjunctival hemorrhage in leptospirosis.^{2,21}

LABORATORY DIAGNOSIS

Initial laboratory evaluation includes complete blood count to look for leukocytosis or leukopenia, anemia, thrombocytopenia, and eosinophilia.^{2,21,23} Serum electrolytes, renal and liver function tests, and coagulation profile should be done on admission in all

ICU patients with tropical fever.^{2,21} In most tropical diseases, making a specific diagnosis is challenging.² The peripheral blood smear may show the causative parasite in malaria, trypanosomiasis, or leishmaniasis.^{2,7} Rapid diagnostic tests to detect pathogen-specific antigens in peripheral blood are available (NS1 antigen for dengue, parasite LDH in falciparum, and vivax malaria).^{2,7} Blood culture can confirm the diagnosis of Salmonella infections, melioidosis, and other bacterial infections.² The diagnosis of most viral infections and leptospirosis is possible by the detection of specific nucleic acids by reverse transcriptase-polymerase chain reaction but these tests may be positive only in the initial stages of the illness.² Diagnosis in later stages is by demonstrating the presence of specific IgG and IgM antibodies; these tests become positive only in the second week of the disease.²⁵ In some patients, a four-fold rise in specific IgG titer during convalescence is confirmatory.² Thus, for some viral infections like dengue, there may be a window period when neither antigen nor antibody tests are negative.²⁵ Stool examination for ova and parasites is helpful in some patients with diarrhea as the presenting manifestation.^{2,7} Specific tests are needed to diagnose individual infections and are discussed in elsewhere in this journal issue.

EMPIRIC TREATMENT

While awaiting confirmation of the diagnosis, empirical therapy is usually initiated. Initial empiric therapy should include an antimalarial and one or more antibacterial drugs.^{1,2,21} Intravenous artesunate is administered in a dose of 2.4 mg/kg/dose; a higher dose is required in children.^{1,2} An injectable third generation cephalosporin like ceftriaxone (2 g IV q12 hours) is added to treat common tropical infections like typhoid and paratyphoid fever, cholera, bacillary dysentery, and bacterial meningitis.^{1,2,21} Intravenous or oral doxycycline is also an important drug for empiric therapy and is the drug of choice in scrub typhus and other rickettsial infections like spotted fevers and Q-fever.^{1,2} It is also active against leptospira, atypical pathogens causing pneumonia (chlamydia, legionella, and mycoplasma), brucellosis, and acute bacterial diarrhea due to cholera and shigella.^{1,2,7} It is also recommended by the WHO as a partner drug to artesunate as combination therapy for severe falciparum malaria.^{1,2,7} Azithromycin may be used instead of doxycycline in children and pregnant women where tetracyclines are contraindicated.^{1,2} The initial empiric combination of artesunate, ceftriaxone, and doxycycline or azithromycin should be deescalated as soon as a definitive diagnosis is made and specific anti-infective treatment is continued.

CONCLUSION

In this article, we discuss the clinical basis of making a diagnosis of tropical infections in the ICU. A systematic approach is important to make a diagnosis and includes travel history, details of diet and recreational activities during travel, attention to the incubation period, and a syndromic approach to narrow down the list of possibilities. Confirmatory tests for various tropical diseases are discussed in detail in another article in this issue of the journal. Empiric treatment is often initiated on admission; a combination of artesunate, ceftriaxone, and doxycycline or azithromycin is preferred, and then treatment is tailored to the specific condition once the diagnosis is confirmed. Specific treatment of common tropical infections is discussed in the accompanying articles in this issue.



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