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REVIEW

Management of septic shock and severe infections in migrants and returning travelers requiring critical care

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Abstract During the past decade, global human movement created a virtually "borderless world". Consequently, the developed world is facing "forgotten" and now imported infectious diseases. Many infections are observed upon travel and migration, and the clinical spectrum is diverse, ranging from asymptomatic infection to severe septic shock. The severity of infection depends on the etiology and timeliness of diagnosis. While assessing the etiology of severe infection in travelers and migrants, it is important to acquire a detailed clinical history; geography, dates of travel, places visited, type of transportation, lay-overs and intermediate stops, potential exposure to exotic diseases, and activities that were undertaken during travelling and prophylaxis and vaccines either taken or not before travel are all important parameters. Tuberculosis, malaria, pneumonia, visceral leishmaniasis, enteric fever and hemorrhagic fever are the most common etiologies in severely infected travelers and migrants. The management of severe sepsis and septic shock in migrants and returning travelers requires a systematic approach in the evaluation of these patients based on travel history. Early and broad-spectrum therapy is recommended for the management of septic shock comprising broad spectrum antibiotics, source control, fluid therapy and hemodynamic support, corticosteroids, tight glycemic control, and organ support and monitoring. We here review the diagnostic and therapeutic routing of severely ill travelers and migrants, stratified by the nature of the infectious agents most often encountered among them.

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Introduction

Over the past century, international travel, commerce, and conflicts around the world caused mass human movements and created a "borderless world". In addition, according to the United Nations High Commissioner for Refugees (UNHCR) report released in January 2015, a huge population has become globally displaced [1]. Basically, the total population of concern was as high as 43 million at the start of 2015 and this population is likely to increase when the current situation, in many different regions but the Middle East in particular, is taken into consideration. Hence, the displaced populations in the world according to January 2015 data are presented in Table 1.

Traveling and population dynamics have resulted in an enhanced distribution of communicable diseases. Many infections can be diagnosed during and after travel and migration, and the clinical spectrum is diverse from innocent asymptomatic infection to severe septic shock. ICU admission may be high in immigrant populations since they are quite susceptible to infections for various reasons, such as living outdoors in the open, crowding, exposure to low temperatures, low standards of environmental hygiene, limited availability of potable water, declining nutritional status, interrupted immunization programs, and a lack of infection control and prevention in local health care settings [2–7].

The altered distribution of infections among displaced populations was obvious in African and Southeast Asian refugees especially when health infrastructures are broken, leading to outbreaks due to endemic infections like malaria, tuberculosis,

Table 1 The displaced populations in the world

Classification	Estimated number (million)
Refugees	11
People in refugee-like situation	0.7
People assisted by UNHCR	11
Asylum-seekers	1.2
Returned refugees	0.4
Internally displaced populations protected/assisted by UNHCR	24
Returned internally displaced populations	1.4
People under UNHCR's statelessness mandate	3.5
Others	0.8

vector-borne infections, meningitis, and hepatitis [3, 8–11]. Basically, diarrheal illnesses and upper respiratory tract infections were the predominating communicable diseases in many parts of the world among refugees [7, 12–15]. Accordingly, immigration led to the introduction of infectious diseases rarely encountered in developed nations anymore, e.g. louse-borne fevers in Europe [16]. Consequently, the 2015 migrant crisis originating mainly from the Middle East and North Africa increased the number of ICU admissions among migrants due to community acquired infections, comprising 25 % of all ICU admissions in routine medical practice [17]. Tuberculosis, malaria, lung infection, visceral leishmaniasis, enteric fever, and hemorrhagic fever are the most important common etiologies in severe infection of travelers and migrants [18–21]. Below, we will focus primarily on the management of these specific diseases.

Origins of diseases leading to ICU admission

Migrants may experience a variety of mental and physical tortures along with inconveniences and hardship related to migration [22], and infected injuries requiring ICU support are the major concern in emergency medicine. Pyogenic bacteria such as *Clostridium perfringens*, enteric gram-negative rods, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Acinetobacter baumannii* have driven the increasing number of wound infections needing ICU support worldwide [23]. In addition, the geographic region of origin is a very important limiting factor for the correct identification of the etiologies of community acquired infectious syndromes in the ICU. In most of the developing countries, particularly in Africa and Asia, tuberculosis is highly endemic. Tuberculosis basically affects poor and vulnerable populations, and migrants are likely to contract tuberculosis [24]. In addition, lung infections other than tuberculosis are observed frequently upon migration from high risk areas [4, 24, 25]. Malaria is frequent in sub-Saharan Africa, and hemorrhagic fevers are more common in selected parts of Africa, Southeast Asia, the Caribbean and Central and South America. Actually, malaria is known to have a strong impact on displaced populations during human history and deserves particular attention [26, 27]. As a horrible example, sepsis and severe *Plasmodium falciparum* malaria contributed to 40 % of pregnancy-related deaths in migrants in north-western Thailand when the 25-year period data of antenatal clinics were analyzed [28]. Enteric fever is the clinical syndrome caused by *Salmonella typhi* and *paratyphi* and sometimes results in severe gastrointestinal symptoms and sepsis [29]. Enteric fever is mostly seen in overcrowded impoverished areas (e.g. south Asia and sub-Saharan Africa) with limited access to sanitation [26]. Leishmania parasites are transmitted by the bite of free-roaming phlebotomine sand flies and leishmaniasis is mostly seen across the Mediterranean coast, the Middle East, Central Asia, and South and Central America. Visceral leishmaniasis, known as kala-azar, is the most severe and potentially fatal form of the disease also among refugees [21, 25, 30].

Initial assessment of the patient

Most of the travel-related infections are acute and present within 6 months of return, and the severity of infection depends on the etiology and the timeliness of diagnosis. Diseases with long latent periods or chronic infections are rare after short-term travels and are usually seen in those who have lived abroad or were born overseas [31]. While assessing the etiology of severe infection in travelers and migrants, it is important to have a detailed clinical history at hand; the geographic region of travel, dates of travel, places visited, type of transportation, lay-overs and intermediate stops, potential exposure to exotic diseases or bites/vectors/animals, and activities that have been undertaken during the travel along with the prophylaxis and vaccines administered preceding the travel. Likewise, the timing of the onset of symptoms, and any predispositions to infection should be noted [32–34]. Incubation period will aid the physician in the differential diagnoses (Table 2) [31, 33]. The age of the traveler is also relevant for

Table 2 Common severe infections seen in immigrants and returned travellers

Infection	Geographic region	Incubation period	Diagnosis	Antimicrobial treatment
Malaria	Sub-Saharan Africa	10–>21 days	Giemsa-stained blood films PCR-based methods	Quinine Quinidine Artesunate Artemether
Lung infection (influenza)	Sub-Saharan Africa North Africa South and East Asia Middle East Central-South America	<10 days	PCR-based methods	Oseltamivir Zanamivir
Tuberculosis	Africa Asia	>21 days	Tuberculin skin test Culture PCR-based methods	Isoniazide Rifampicin Pyrazinamide Ethambutol Alternative drugs for MDR pathogens
Visceral leishmaniasis	Mediterranean cost Middle East Central Asia South and Central America	>21 days		
Enteric fever	Sub-Saharan Africa South Asia	<10–21 days	Culture	Ampicillin Trim-sulfa Chloramphenicol Fluoroquinolone
Hemorrhagic fever	Africa, Southeast Asia Caribbean Central and South America	10–21 days	Serology PCR-based methods	–
Hepatitis A,B,C,E		>21 days	Serologic diagnosis	Lamivudine or Entecavir for hep B

Trim-sulfa Trimethoprim-sulfamethoxazole

differential diagnosis, as younger travelers are more likely to have an exotic infection, whereas older travelers are more likely to have severe infection due to underlying disease including pneumonia [18, 19]. Besides, migrants' overall health status, availability and access to health-care systems, overall socio-economic conditions, consumption of contaminated water and food, contact with animals and occurrence of insect bites, and any disease epidemics determine their infectious etiology [35]. On the other hand, migrants are considered at increased risk for HIV and hepatitis, possibly due to sexual violence and improper medical instrumentation [35, 36].

Diagnosis

The initial signs and symptoms of sepsis can be non-specific and at the early stages sepsis can be easily misdiagnosed. However, rapid diagnosis and the administration of suitable antimicrobials along with supportive therapy are important for the survival of patients with sepsis and septic shock. Blood cultures and cultures of the possible peripheral sources are needed for the diagnosis of bacterial infections. However, the sensitivity of culture is generally low and it takes time for positive results to become available. For the early diagnosis of sepsis, several biomarkers have been developed, including procalcitonin, C-reactive protein (CRP) and circulating cell-free DNA (cfDNA). Among these biomarkers, PCT has useful diagnostic accuracy. However, there is no ideal test for diagnosis of sepsis and all tests currently available may yield both false-positive and -negative results [37]. Sepsis screening tools can be used for early diagnosis but comprehensive clinical evaluation together with laboratory tests, cultures, biomarkers and lactate levels should be used to decrease sepsis-related mortality [38]. In the next section, diagnostic tests for the most common etiologies in severe infection in travelers and migrants will be discussed.

Malaria Any patient with severe sepsis who just returned from a malaria endogenous region should be tested for malaria promptly. There are five species of Plasmodia (*P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae, P. knowlesi*) causing disease. However, *P. falciparum* generates the highest risk for the development of septic shock. Falciparum malaria can progress rapidly to severe forms and it is a potentially lethal, but still treatable infection. The median incubation period for *P. falciparum* is 12 days (ranging from 6 to 14 days) whereas for *P. vivax* and *P. ovale* these are longer, ranging from 8 days to several months. Although malaria generates no clear

pathognomonic signs and symptoms, severe *P. falciparum* infection may present with renal failure, jaundice, respiratory failure, and central nervous system involvement. Laboratory diagnosis is performed by the examination of Giemsa-stained blood films and wherever possible with supplementary diagnostic tests (rapid diagnostic tests, PCR, etc.) [25, 39, 40].

Dengue fever Another common tropical infectious disease that is transmitted by mosquitos is dengue fever. Dengue hemorrhagic fever and dengue shock syndrome are serious forms of this arboviral infection. The incubation period is short (4 to 8 days) and progression to the more serious state is marked by hemorrhagic manifestations, coagulopathy and increased vascular permeability (edema, effusions and circulatory collapse). Laboratory features suggestive of dengue infection include thrombocytopenia, leucopenia, and elevated levels of liver enzymes. Serologic diagnosis and PCR methods are used for laboratory diagnosis. Chikungunya is the other viral infection transmitted to humans by the bites of mosquitos and characterized by a febrile illness with conspicuous polyarthralgia which may be severe. Laboratory diagnosis is generally skilled by testing serum to detect virus, viral nucleic acid, or virus-specific IgM and neutralizing antibodies [31, 41].

Ebola virus disease Ebola virus disease (EVD) is a severe, often fatal disease in humans and transmitted to people from wild animals and it spreads in the human population by close contact with the blood, secretions, organs or other bodily fluids of infected people and animals. It is difficult to distinguish EVD from other exotic infections, but having traveled to a country (e.g. recently to Central and West Africa) with widespread and recent Ebola transmission is a clear indicator for having to be tested. Symptoms usually develop within 21 days (headache, weakness, muscle pain, vomiting, diarrhea, abdominal pain or hemorrhage) and provide further clues for diagnosis; patients at this stage should also be tested for the virus. Reverse transcriptase polymerase chain reaction (RT-PCR) is the most common recommended test for the diagnosis of EVD. Antibody-capture enzyme-linked immune-sorbent assay (ELISA), antigen-capture detection tests, serum neutralization test, electron microscopy and virus isolation by cell capture are the other diagnostic tests for EVD [42]. All these tests have their own issues with sensitivity, specificity, robustness and reproducibility and the ideal tests do not yet exist.

Lung infections Lung infection or pneumonia, mainly caused by influenza, is the next most frequent cause of severe infection in migrants and returning travelers, especially from East Asia. Overall, the viral and bacterial pathogens affecting travelers are similar to those in the general population. The classical viral pathogens are rhinovirus, respiratory syncytial virus, influenza virus, parainfluenza viruses, human metapneumovirus, measles, mumps, adenovirus, and several coronaviruses. Well-known bacterial pathogens are *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenza, Chlamydia pneumoniae*, *Coxiella burnettii*, and *Legionella pneumophila*. However, novel viral pathogens [Middle East Respiratory Syndrome (MERS), additional coronaviruses, swine flu H1N1, avian influenza H5N1, avian influenza H7N9, etc.] should be considered in returning travelers and migrants. Molecular methods including PCR provide rapid and sensitive tests to sometimes even simultaneously identify several infectious agents. Furthermore, rapid serological tests are available for some pathogens, like *L. pneumophila* and group A Streptococcus. Microbiological culture of sputum and blood has low sensitivity, but high specificity for bacterial pathogens [31, 43]. Pulmonary tuberculosis and miliary tuberculosis are other causes of severe infection especially in migrants, including multiple organ dysfunction and septic shock. The tuberculin skin test can be a surrogate diagnostic modality if testing positive; however, a negative skin test result is frequently seen in miliary forms of tuberculosis. Acid-fast smears and cultures of infected tissues and fluids or drainage from an infected tissue are the standard diagnostic tests for the diagnosis of tuberculosis. Molecular tests, if available, are also useful for rapid diagnosis and several simple formats have been proposed in recent years [44].

Salmonellosis Typhoid and paratyphoid fever are characterized by sustained fever and abdominal pain and are diagnosed by culture of the causative microorganism. Blood cultures are positive in 40–80 % of patients and stool culture is positive in up to 30–40 % of cases. Bone marrow culture should be considered in complicated cases or when there is an uncertainty in the diagnosis. Serologic tests (Widal test) have limited clinical value in endemic areas, as positive test results may originate from previous infection [45].

Visceral leishmaniasis For the diagnosis of visceral leishmaniasis, routine laboratory analyses are useful. However, for specific diagnosis, serology (enzyme-linked immunosorbent assay (ELISA)), agglutination, indirect fluorescent antibody (IFA), parasitological examination and molecular tests are used [46].

Patient management

The resuscitation of a patient with septic shock should begin as soon as the syndrome is recognized well enough. Management of septic shock includes provision of broad spectrum antimicrobials, source control, fluid therapy and hemodynamic support, corticosteroids, tight glycemic control, and organ support and monitoring [47, 48]. Most patients are admitted to hospitals with undifferentiated and non-localizing systemic febrile syndromes. Malaria, dengue fever, enteric fever, and rickettsial disease were the most common and likely diseases among such patients. Moreover, non-exotic infectious diseases such as

pneumonia, urinary tract infection, skin and soft tissue infections, meningitis, and endocarditis should obviously be taken into consideration as well [31–33]. Early administration of appropriate antimicrobials reduces mortality of patients. Initial empiric antimicrobial therapy should include one or more antibiotics that show activity against the probable pathogens (bacterial, viral, fungal or parasites) and that penetrate into the expected source of septic shock [49]. Unfortunately, distinguishing between bacteria, parasites and viruses causing septicemia is difficult and as stated before there is not a single Gold Standard test available.

Drug susceptibility Antimicrobial susceptibility profiles of identified bacterial pathogens and carriage of multidrug resistant pathogens should be taken into consideration in decision making for empirical antimicrobial therapy [50–52]. Drug resistance in tuberculosis should be detected rapidly, and appropriate treatment options with the alternative second and third line anti-tuberculosis drugs (fluoroquinolones, ethionamide, cycloserine, amikacin, linezolid) is crucial in the management of multidrug resistant tuberculosis [53].

Malaria Anti-malarial therapy should be considered for the patients with a history of fever who have returned from malaria-endemic regions. Antimalarial medication should be started only for patients with a definitive malaria diagnosis. However, death from severe malaria is basically a rule rather than an exception (mortality is defined 100 %, particularly in cerebral malaria) and falls to 10–20 % with appropriate antimalarial therapy. Therefore, empiric treatment might be initiated when either severe *P. falciparum* infection is suspected or there is no clearly identified alternative diagnosis. Parenteral antimalarial therapy is essential in the initial treatment of severe malaria. The cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives (artesunate and artemether) are two major classes of drugs for parenteral treatment. Artemisinin derivatives clear parasitemia more rapidly, and they are effective against a broader range of parasitic stages and species. However, artemisinin-based combination therapy is not widely available and the CDC recommends parenteral quinidine for severe malaria in these cases. Intravenous or intramuscular artesunate should be administered at least for 24 h until the patient can tolerate oral medications. Once the patient has received 24 h of parenteral therapy at the minimum and can tolerate oral therapy, the treatment must be completed with 3 days of oral artemisin-based combination therapy [39, 40].

Leishmaniasis In the treatment of visceral leishmaniasis, liposomal amphotericin B is the most active and safe drug. However, pentavalent antimonial drugs, paromomycin and miltefosine are the other alternative agents [46]. Costs and availability of drugs remain issues in developing countries and hence for regional refugees in particular.

Viral infections In managing viral infections, supportive therapy and infection prevention and control measures are essential. No antiviral drugs are available for coronaviruses or hemorrhagic viruses. Basically, oseltamivir and zanamavir are used effectively for severe influenza cases [41–43].

Enteric fever In the management of enteric fever, antimicrobial resistance endemic to the region of travel should be kept in the mind. Important multidrug resistant strains are reported from the Indian subcontinent, Southeast Asia including China, Mexico, the Arabian Gulf and Africa. For uncomplicated enteric fever monotherapy is usually appropriate and parenteral therapy with ampicillin, trimethoprim-sulfamethoxazole, chloramphenicol and fluoroquinolone are primary choices. For the resistant pathogens, alternative therapies including azithromycin, carbapenems, the newer fluoroquinolones, higher doses of fluoroquinolones, and combination therapies can be considered [45].

Hemodynamic support Initiating aggressive fluid resuscitation is the other vital management strategy. Fluid resuscitation may employ colloids or crystalloids. Crystalloids are generally the first line fluids and colloids are administered in addition to crystalloids. In some illnesses, shock develops suddenly and the administration of colloids is theoretically more effective. Dengue shock syndrome is a good example for this case. The main characteristic of Dengue shock syndrome is a sudden marked increase in vascular permeability, and large volumes of intravenous fluid is needed. To overcome the risk of overload, colloids might be preferred for acute resuscitation [54]. However, because of the lack of convincing evidence and the higher cost of colloids, the choices are still controversial [55]. When an appropriate fluid challenge fails to restore hemodynamic stability, vasopressor therapy should be initiated. In hemorrhagic fevers, disseminated intravascular coagulation can be observed, and transfusion of coagulation factors and platelets is needed for patients who are bleeding [55]. In general, norepinephrine and dopamine are the preferred first-line vasopressor agents. Epinephrine, phenylephrine or vasopressin can be considered when the first-line agents fail. Glycemic control (<150 mg/dL), renal replacement therapy and corticosteroid therapy are important adjunctive therapies in sepsis [56]. Human recombinant activated protein C (APC) has been used to reduce the high rate of death by severe sepsis or septic shock. However, no evidence suggesting APC should be used in treating patients with severe sepsis or when septic shock is known to exist. Additionally, APC is associated with a higher risk of bleeding [57]. Furthermore, source control is the most important issue in the management of septic shock. Drainage of infected fluids, debridement of infected soft tissues and removal of infected devices or foreign bodies are the main elements of source control [56].

Conclusions

The management of severe sepsis and septic shock in migrants and returning travelers should involve a systematic approach to the evaluation of these patients and should include basic information about the geographic distribution of infections in the visited regions and concurrent activities. Early goal directed therapy is mandatory and lifesaving after the diagnosis of septic shock. It should be noted that in travelers and refugees the spectrum of infectious agents is likely to be broader than in regular autochtones.

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