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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,

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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.

References

1. UNHCR (2015) UNHCR Global Appeal 2015 Update. http://www.unhcr.org/ga15/index.xml . Accessed 19 Jan 2016
2. Healing TD, Pelly MD (2004) Refugees and disasters. In: Parry E, Godfrey R, Mabet D, Gill G (eds) Principles of medicine in Africa. Cambridge University Press, Singapore, pp 77–86
3. McGready R, Ashley EA, Wuthiekanun V, Tan SO, Pimanpanarak M, Viladpai-Nguen SJ, Jesadapanpong W, Blacksell SD, Peacock SJ, Paris DH, Day NP, Singhasivanon P, White NJ, Nosten F (2010) Arthropod borne disease: the leading cause of fever in pregnancy on the Thai-Burmese border. PLoS Negl Trop Dis 4(11):e888
4. Esteban-Vasallo MD, Dominguez-Berjon MF, Aerny-Perreten N, Astray-Mochales J, Martin-Martinez F, Genova-Maleras R (2012) Pandemic influenza A (H1N1) 2009 in Madrid, Spain: incidence and characteristics in immigrant and native population. Eur J Public Health 22(6):792–796
5. Pourkarim MR, Zandi K, Davani NA, Pourkarim HR, Amini-Bavil-Olyaee S (2008) An aberrant high prevalence of hepatitis B infection among Afghans residing in one of the Bushehr refugee camps (Dalaki camp) in the southwest of Iran. Int J Infect Dis 12(1):101–102
6. Fan CK, Liao CW, Wu MS, Hu NY, Su KE (2004) Prevalence of Pediculus capitis infestation among school children of Chinese refugees residing in mountainous areas of northern Thailand. Kaohsiung J Med Sci 20(4):183–187
7. Mateen FJ, Carone M, Al-Saedy H, Nyce S, Ghosn J, Mutuerandu T, Black RE (2012) Medical conditions among Iraqi refugees in Jordan: data from the United Nations Refugee Assistance Information System. Bull World Health Organ 90(6):444–451
8. WHO (2004) WHO Health Update for Darfur. WHO, Geneva, 31 August 2004
9. Yun K, Matheson J, Payton C, Scott KC, Stone BL, Song L, Stauffer WM, Urban K, Young J, Mamo B (2016) Health profiles of newly arrived refugee children in the United States, 2006–2012. Am J Public Health 106(1):128–135
10. Alawieh A, Musharrafieh U, Jaber A, Berry A, Ghosn N, Bizri AR (2014) Revisiting leishmaniasis in the time of war: the Syrian conflict and the Lebanese outbreak. Int J Infect Dis 29:115–119
11. Burki T (2013) Infectious diseases in Malian and Syrian conflicts. Lancet Infect Dis 13(4):296–297
12. Reports Related to Syrian Guests (2014) Turkish Public Health Agency, Ankara, February 2015
13. Ahmed JA, Katz MA, Auko E, Njenga MK, Weinberg M, Kapella BK, Burke H, Nyoka R, Gichangi A, Waiboci LW, Mahamud A, Qassim M, Swai B, Wagacha B, Mutonga D, Nguhi M, Breiman RF, Eidex RB (2012) Epidemiology of respiratory viral infections in two long-term refugee camps in Kenya, 2007–2010. BMC Infect Dis 12:7
14. Garg PK, Perry S, Dorn M, Hardcastle L, Parsonnet J (2005) Risk of intestinal helminth and protozoan infection in a refugee population. Am J Trop Med Hyg 73(2):386–391
15. Mohamed GA, Ahmed JA, Marano N, Mohamed A, Moturi E, Burton W, Otieno S, Fields B, Montgomery J, Kabugi W, Musa H, Cookson ST (2015) Etiology and incidence of viral acute respiratory infections among refugees 5 years and older in Hagadera Camp, Dadaab, Kenya. Am J Trop Med Hyg 93(6):1371–1376
16. Cutler S (2015) Refugee crisis and re-emergence of forgotten infections in Europe. Clin Microbiol Infect S1198-743X(15)00918-0
17. Erdem H, Inan A, Altindis S, Carevic B, Askarian M, Cottle L, Beovic B, Csomos A, Metodiev K, Ahmetagic S, Harxhi A, Raka L, Grozdanovski K, Nechifor M, Alp E, Bozkurt F, Hosoglu S, Balik I, Yilmaz G, Jereb M, Moradi F, Petrov N, Kaya S, Koksal I, Aslan T, Elaldi N, Akkoyunlu Y, Moravveji SA, Csato G, Szedlak B, Akata F, Oncu S, Grgic S, Cosic G, Stefanov C, Farrokhnia M, Muller M, Luca C, Koluder N, Korten V, Platikanov V, Ivanova P, Soltanipour S, Vakili M, Farahangiz S, Afkhamzadeh A, Beeching N, Ahmed SS, Cami A, Shiraly R, Jazbec A, Mirkovic T, Leblebicioglu H, Naber K (2014) Surveillance, control and management of infections in intensive care units in Southern Europe, Turkey and Iran–a prospective multicenter point prevalence study. J Infect 68(2):131–140
18. Al-Abri SS, Abdel-Hady DM, Al Mahrooqi SS, Al-Kindi HS, Al-Jardani AK, Al-Abaidani IS (2015) Epidemiology of travel-associated infections in Oman 1999–2013: a retrospective analysis. Travel Med Infect Dis 13(5):388–393
19. Wilson ME, Freedman DO (2007) Etiology of travel-related fever. Curr Opin Infect Dis 20(5):449–453
20. Gushulak BD, MacPherson DW (2004) Globalization of infectious diseases: the impact of migration. Clin Infect Dis 38(12):1742–1748
21. Jacobson RL (2011) Leishmaniasis in an era of conflict in the Middle East. Vector Borne Zoonotic Dis 11(3):247–258
22. Asgary R, Charpentier B, Burnett DC (2013) Socio-medical challenges of asylum seekers prior and after coming to the US. J Immigr Minor Health 15(5):961–968
23. Whitman TJ (2007) Infection control challenges related to war wound infections in the ICU setting. J Trauma 62(6 Suppl):S53
24. Liu Y, Posey DL, Cetron MS, Painter JA (2015) Tuberculosis incidence in immigrants and refugees. In response. Ann Intern Med 163(2):150–151
25. Wilson ME, Weld LH, Boggild A, Keystone JS, Kain KC, von Sonnenburg F, Schwartz E (2007) Fever in returned travelers: results from the GeoSentinel surveillance network. Clin Infect Dis 44(12):1560–1568
26. Erdem H, Tetik A, Arun O, Besirbellioglu BA, Coskun O, Eyigun CP (2011) War and infection in the pre-antibiotic era: the Third Ottoman Army in 1915. Scand J Infect Dis 43(9):690–695
27. Sonden K, Castro E, Tornnberg L, Stenstrom C, Tegnell A, Farnert A (2014) High incidence of Plasmodium vivax malaria in newly arrived Eritrean refugees in Sweden since May 2014. Euro Surveill 19(35):20890
28. McGready R, Boel M, Rijken MJ, Ashley EA, Cho T, Moo O, Paw MK, Pimanpanarak M, Hkirijareon L, Carrara VI, Lwin KM, Phyo AP, Turner C, Chu CS, van Vugt M, Price RN, Luxemburger C, ter Kuile FO, Tan SO, Proux S, Singhasivanon P, White NJ, Nosten FH (2012) Effect of early detection and treatment on malaria related maternal mortality on the north-western border of Thailand 1986–2010. PLoS One 7(7):e40244
29. Hoffman TA, Ruiz CJ, Counts GW, Sachs JM, Nitzkin JL (1975) Waterborne typhoid fever in Dade County, Florida. Clinical and therapeutic evaluation of 105 bacteremic patients. Am J Med 59(4):481–487
30. Boussery G, Boelaert M, van Peteghem J, Ejikon P, Henckaerts K (2001) Visceral leishmaniasis (kala-azar) outbreak in Somali refugees and Kenyan shepherds, Kenya. Emerg Infect Dis 7(3 Suppl):603–604

31. Looke DF, Robson JM (2002) 9: infections in the returned traveller. Med J Aust 177(4):212–219
32. Kotlyar S, Rice BT (2013) Fever in the returning traveler. Emerg Med Clin North Am 31(4):927–944
33. Connolly E, Eppes SC (2014) Fever in a returning traveler: the importance of a good history, physical examination, and focused laboratory testing. Clin Pediatr (Phila) 53(2):201–203
34. O'Brien D, Tobin S, Brown GV, Torresi J (2001) Fever in returned travelers: review of hospital admissions for a 3-year period. Clin Infect Dis 33(5):603–609
35. Poulakou G, Bassetti M, Timsit JF (2015) Critically ill migrants with infection: diagnostic considerations for intensive care physicians in Europe. Intensive Care Med. 2015 Oct 14. [Epub ahead of print]
36. Hernando V, Alvarez-Del Arco D, Alejos B, Monge S, Amato-Gauci AJ, Noori T, Pharris A, Del Amo J (2015) HIV infection in migrant populations in the European union and European economic area in 2007–2012: an epidemic on the move. J Acquir Immune Defic Syndr 70(2):204–211
37. Marik PE (2014) Don't miss the diagnosis of sepsis! Crit Care 18(5):529
38. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 41(2):580–637
39. WHO (2015) Guidelines for the treatment of malaria. World Health Organization, Italy
40. Esu E, Effa EE, Opie ON, Uwaoma A, Meremikwu MM (2014) Artemether for severe malaria. Cochrane Database Syst Rev 9: CD010678
41. Kularatne SA (2015) Dengue fever. BMJ 351:h4661
42. West TE, von Saint Andre-von Arnim A (2014) Clinical presentation and management of severe Ebola virus disease. Ann Am Thorac Soc 11(9):1341–1350
43. Leder K, Sundararajan V, Weld L, Pandey P, Brown G, Torresi J (2003) Respiratory tract infections in travelers: a review of the GeoSentinel surveillance network. Clin Infect Dis 36(4):399–406
44. Ryu YJ (2015) Diagnosis of pulmonary tuberculosis: recent advances and diagnostic algorithms. Tuberc Respir Dis (Seoul) 78(2):64–71
45. Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL (2015) Typhoid fever. Lancet 385(9973):1136–1145
46. Neghina R, Neghina AM (2010) Leishmaniasis, a global concern for travel medicine. Scand J Infect Dis 42(8):563–570
47. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, Jahan R, Harvey SE, Bell D, Bion JF, Coats TJ, Singer M, Young JD, Rowan KM (2015) Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 372(14):1301–1311
48. Green JM (2015) Essentials of sepsis management. Surg Clin N Am 95(2):355–365
49. Rhodes A, Bennett ED (2004) Early goal-directed therapy: an evidence-based review. Crit Care Med 32(11 Suppl):S448–S450
50. Bochud PY, Bonten M, Marchetti O, Calandra T (2004) Antimicrobial therapy for patients with severe sepsis and septic shock: an evidence-based review. Crit Care Med 32(11 Suppl):S495–S512
51. Rogers BA, Kennedy KJ, Sidjabat HE, Jones M, Collignon P, Paterson DL (2012) Prolonged carriage of resistant E. coli by returned travellers: clonality, risk factors and bacterial characteristics. Eur J Clin Microbiol Infect Dis 31(9):2413–2420
52. Paltansing S, Vlot JA, Kraakman ME, Mesman R, Bruijning ML, Bernards AT, Visser LG, Veldkamp KE (2013) Extended-spectrum beta-lactamase-producing enterobacteriaceae among travelers from the Netherlands. Emerg Infect Dis 19(8):1206–1213
53. Jeon D (2015) Medical management of drug-resistant tuberculosis. Tuberc Respir Dis (Seoul) 78(3):168–174
54. Dung NM, Day NP, Tam DT, Loan HT, Chau HT, Minh LN, Diet TV, Bethell DB, Kneen R, Hien TT, White NJ, Farrar JJ (1999) Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous-fluid regimens. Clin Infect Dis 29(4):787–794
55. Funk DJ, Kumar A (2015) Ebola virus disease: an update for anesthesiologists and intensivists. Can J Anaesth 62(1):80–91
56. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R (2013) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39(2):165–228
57. Marti-Carvajal AJ, Sola I, Lathyris D, Cardona AF (2012) Human recombinant activated protein C for severe sepsis. Cochrane Database Syst Rev 3:CD004388