Review Article

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The emergence of travel-related infections in critical care units

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ABSTRACT

Several tropical or geographically confined infectious diseases may lead to organ failure requiring management in an intensive care unit (ICU), both in endemic low- and middle-income countries where ICU facilities are increasingly being developed and in (nonendemic) high-income countries through an increase in international travel and migration. The ICU physician must know which of these diseases may be encountered and how to recognize, differentiate, and treat them. The four historically most prevalent "tropical" diseases (malaria, enteric fever, dengue, and rickettsiosis) can present with single or multiple organ failure in a very similar manner, which makes differentiation based solely on clinical signs very difficult. Specific but frequently subtle symptoms should be considered and related to the travel history of the patient, the geographic distribution of these diseases, and the incubation period. In the future, ICU physicians may also be more frequently confronted with rare but frequently lethal diseases, such as Ebola and other viral hemorrhagic fevers, leptospirosis, and yellow fever. No one could have foreseen the worldwide 2019–up to now coronavirus disease 2019 (COVID-19) crisis caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was initially spread by travel too. In addition, the actual pandemic due to SARS-CoV-2 reminds us of the actual and potential threat of (re)-emerging pathogens. If left untreated or when treated with a delay, many travel-related diseases remain an important cause of morbidity and even mortality, even when high-quality critical care is provided. Awareness and a high index of suspicion of these diseases is a key skill for the ICU physicians of today and tomorrow to develop.

Key words: travel-related infectious diseases, import pathology, critical illness, nonendemic

INTRODUCTION

The intensive care unit (ICU) harbors critically ill people with (multiple) organ failure (MOF), frequently caused by sepsis. Many once deadly infectious diseases with epidemic potential, such as typhoid fever, cholera, and plague, have virtually disappeared from industrialized countries and are currently restricted to tropical low-resource areas. Before the coronavirus disease 2019 (COVID-19) pandemic, imported infectious diseases were rarely encountered in the ICU in developed countries; however, the exponential growth of international tourism and migration[1] as well as the emergence of new pathogens will unavoidably expand the number and variety of critically ill patients in nonendemic settings.

The reality of critical care is also changing. Once restricted to high-income countries, intensive care is becoming available in most health-care systems around the world, including resource-constrained settings.[2] The number of ICUs is expected to further increase, and thus, local ICUs too will be increasingly confronted with the management of endemic tropical infections.[3] Through this article, we want to create awareness for tropical import and travel-related critical illness.

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DIFFERENTIAL DIAGNOSIS OF SEVERE TRAVEL-RELATED INFECTIOUS PATHOLOGY IS A COMPLEX PROBLEM

Travelers are at a significant risk of acquiring communicable and noncommunicable diseases.[4] Most tropical infectious diseases present with few specific symptoms, and thus, clinical awareness is key to optimizing the diagnosis and treatment of these diseases.

The etiological spectrum of imported fever is specific to the destination, but it also depends on other factors. Over 40% of returning travelers with acute undifferentiated febrile illnesses (AUFI) are later on diagnosed with malaria or dengue, infections that can be easily diagnosed by rapid diagnostic tests.[4,5] A prospective study reported on the causes of 1842 episodes of fever at the Institute of Tropical Medicine and the University Hospital of Antwerp (Belgium) in people returning from the tropics.[6] In approximately 40% of patients, tropical infectious diseases were identified as the main cause of fever, with malaria, dengue, and rickettsial infections identified most frequently.[6] The so-called "cosmopolitan respiratory and gastrointestinal infections" were observed in 34% of all cases. Only 2% required admission to the ICU. ICU admission and mortality was mainly associated with infection with *Plasmodium falciparum*,[6] which was also the only tropical cause of death.

Understanding the geographic and temporal trends in imported infections is key to the diagnosis and management of unwell travelers. Climate changes and global warming will have catastrophic effects on human, animal, and environmental ecosystems. Pathogens, especially neglected tropical disease agents, are expected to emerge and re-emerge in several countries, including those of Europe and North America.[7,8] The Global Burden of Diseases Study report provides detailed statistics on the incidence of communicable diseases endemic to tropical regions.[9] The most prevalent of these diseases were diarrheal diseases, malaria, dengue, viral hepatitis, schistosomiasis, typhoid/paratyphoid, tuberculosis, viral encephalitis, leishmaniosis, Chagas disease, and yellow fever. Data are also available from the GeoSentinel surveillance network that collects records from returning travelers and immigrants at 53 sites in 24 countries.[10,11] Leder *et al.*[12] reported illnesses in 42,173 returning travelers between 2007 and 2011. While malaria, dengue, hepatitis, and typhoid fever are currently endemic to most tropical regions across all continents, certain infections, such as Chagas disease, Japanese encephalitis (JE), certain viral hemorrhagic fevers (VHFs), sleeping sickness, and yellow fever, display a specific regional or continental distribution.[12] Of the travelers arriving from sub-Saharan Africa (SSA) with an illness requiring admission, 70% were diagnosed with a tropical infection.[12] Nontropical infections were more common than tropical infections (44.6%) among travelers to Asia, with enteric fever and dengue observed relatively commonly.[13] Nevertheless, physicians might also encounter ubiquitous pathogens, such as *Staphylococcus aureus* and carbapenemase-producing Enterobacteriaceae, strengthening hand hygiene and other universal precautions, and applying a low threshold for adding droplet and contact precautions are key infection prevention measures. Single-bed hospital rooms and isolation in the ICU according to symptoms should be the rule while awaiting laboratory test results. Most tropical diseases are vector borne, but person-to-person contact is a route of transmission for several tropical diseases. Therefore, health-care workers should implement specific prevention strategies.[14]

In endemic regions, tropical infections account for up to 20%–30% of ICU admissions in some published case series from Asia, South America, and Africa.[15] Another publication from the GeoSentinel database specifically addressed acute and potentially life-threatening tropical diseases in Western travelers. Of the 82,825 ill travelers returning from tropical and subtropical areas, 3655 (4.4%) received an acute, potentially life-threatening diagnosis.[10] The West African outbreak of Ebola virus disease (EVD; 2014–2016), has led to the export of cases to Europe and North America. However, clinicians encountering ill travelers arriving from regions with active Ebola and Lassa virus transmission must be aware of alternative diagnoses associated with fever and other nonspecific symptoms. The most common diagnosis identified among 770 nonimmigrant travelers from these "Ebola-endemic" countries (Sierra Leone, Liberia, and Guinea) was malaria (n = 310 [40.3%]), which should be promptly excluded.[16]

Several tropical diseases require management in a critical care environment, as they may also lead to hypotension, shock, respiratory distress, renal failure, hepatitis, coma, seizures, arrhythmias, or hemorrhage. Among others, diarrheal diseases, malaria, dengue, typhoid, rickettsial diseases, and leptospirosis may cause critical illness. However, overlapping clinical features make the initial diagnosis challenging. These severe life-threatening tropical illnesses characterized by organ failure and requiring critical care have been summarized extensively according to the taxonomy of the causative agent, the geographic region from which they originate, the incubation period, the clinical hallmarks, the vector, or consideration of either the traveler or migrant.[15] A systematic approach involving (1) a history of travel to a specific country, (2) exposure to specific environments (forests or farms, contaminated

Table 1: Some clues in the differential diagnosis of severe travel-related infectious diseases as highlighted in this review

Disease	Causative agent	When to consider this disease?
Malaria	*Plasmodium*	– Most frequent cause of febrile illness when returning from tropics (certainly after a stay in Africa) – Symptoms ranging from nonspecific (*i.e.*, fever) to life-threatening ARDS/MOF
Enteric fever (typhoid, paratyphoid)	*Salmonella* Typhi or Paratyphi	– Returning from India and Southeast Sea? – Fever, bradycardia, gastrointestinal symptoms, lung involvement – Second cause of life-threatening tropical disease in travelers – Rose spots in a pale skin?
Rickettsial diseases	Rickettsiae and related (*Rickettsia*-like) bacteria	– Common cause of fever when returning from African continent – Short incubation period – Maculopapular rash, fever, and "tache noir"
Dengue	Arbovirus	– Occurs in outbreaks, short incubation period – Frequent cause of fever with rash after returning from tropics (less frequent than malaria) – Hemorrhagic fever with rash; dengue shock, ARDS, and petechiae (thrombocytopenia) may occur
Rabies	Lyssavirus	– Not a major import disease; encephalitis
Yellow fever	Mosquito-borne flavivirus	– Biphasic illness with liver failure and shock
Viral hemorrhagic fever	Arenaviruses, filoviruses, bunyaviruses, flaviviruses	– Ebola-endemic countries are, among others, Sierra Leone, Liberia, and Guinea (West) Africa – Fever, collapse, MOF, and hemorrhage; purpura, petechiae, and ecchymosis
Melioidosis	*Burkholderia pseudomallei*	– Local cutaneous infection first symptom – Pneumonia rapidly progressing to ARDS
Zika virus	RNA flavivirus	– Similar to dengue, hardly MOF

ARDS: acute respiratory distress syndrome; MOF: multiple organ failure.

water, or consumption of exotic foods), (3) incubation period, and (4) a pattern of organ involvement and subtle differences in manifestations assist with the differential diagnosis and choice of initial empiric therapy.[15,17]

Even for an ICU physician who is familiar with the management of the patients with import and travel-related diseases, confirmation of the initial diagnosis and the subsequent choice of the appropriate treatment can be challenging. A stepwise approach with a careful interpretation of local disease patterns, possible exposure and risk factors, clinical features, and basic laboratory data can help clinicians recognize specific diseases (Table 1). At least a reliable and rapid test for malaria should be accessible 24/7[18] to have a targeted treatment with intravenous (IV) artesunate initiated quickly. A blood smear allows the identification and to know the parasitic load.

The search for rapid, powerful, informative, and reliable diagnostic methods for infectious diseases is becoming urgent as ever.[19] Why? Conventional clinical tests (culture, polymerase chain reaction [PCR], serology, *etc.*) are being continually optimized, yet sometimes provide very limited data.[20] Indeed, many of these techniques suffer a number of limitations, including the need for a dedicated specialized staff and their intrinsic inefficiency in the propagation of fastidious bacteria and several major viruses. Could high-throughput sequencing (HTS) behave as the future gold standard in the molecular diagnostics of (viral) infections? [21] As in other medical fields, the availability of next-generation sequencing (NGS) techniques is capable of revolutionizing diagnostics of infectious diseases. Use of NGS has increased the depth of sequencing by several orders of magnitude and thereby the capacity to detect rare species and is more precise at profiling pathogens. Among many other applications, the rapidity and accuracy of differential diagnosis by NGS has been proposed to aid in the detection of arboviruses.[22] Due to recent technological advancement, NGS methods even have the potential to guide the choice, implementation, and use of effective antimalarial drugs in view of the emergence of artemisinin resistance in SSA.[23] Despite its obvious potency, it has currently not yet been widely accepted as a diagnostic tool for travel-related infections, owing primarily to its high cost and the complexity of sample preparation and data analysis.[23]

The combination of ceftriaxone and doxycycline is a good empiric treatment for an unstable patient suspected of having an imported infectious disease when malaria has been excluded (Table 2).[15] Additional antiviral, antifungal, or antiprotozoal medications may be required for some specific syndromes. Expertise in tropical infectious diseases must be sought for where necessary, particularly in nonendemic settings.[15,17]

Table 2: Recommendations for initial empiric therapy in the critically ill with undifferentiated sepsis returning from a (sub)tropical region*

Causative agent coverage	Treatment proposed	Specification
Antimalarial	IV artesunate	De-escalate if not confirmed
Antibacterial	IV third-generation cephalosporin	
	Ceftriaxone	Also covers bacterial sepsis, enteric fever
	Replace by ceftazidime?	If melioidosis is suspected, consider meropenem or ceftazidime
	IV doxycycline	Covers rickettsial diseases; is a companion drug against malaria
	Azithromycin	In children or pregnancy
Antiviral?	Acyclovir?	Is encephalitis present?
	Ribavirin?	Endemic with symptoms strongly suggestive of, that is, Lassa fever

Adapted from Karnad *et al*.[15] Consider initial empiric therapy: an antimalarial and one or more antibacterial drugs (ceftriaxone + doxycycline or azithromycin). Use a syndromic approach for differential diagnosis (consult Global Burden of Disease data https://www.healthdata.org/gbd/2019). *This should take into account the travel origin, the syndromic presentation, and the current epidemiological data to orient toward specific causes. IV: intravenous.

AWARENESS OF THE FOUR MOST FREQUENTLY ENCOUNTERED TROPICAL DISEASES: MALARIA, TYPHOID FEVER, INFECTIONS WITH *RICKETTSIA* SPP., AND DENGUE

Malaria is still the most important cause of import infectious pathology after a stay in Africa. It results from infection with one of five species of *Plasmodium* parasites, with *P. falciparum* being the most important and dangerous parasite. SSA still displays the greatest burden of malaria.[24] Globally, the incidence has decreased in the past decade, although stagnation has been observed in the last years. Global mortality has decreased; but an estimated 429,000 people still die from malaria each year, according to the World Health Organization (WHO).[25] Natural transmission of *P. falciparum* malaria (*Pf* malaria) depends on the presence of infected individuals and vectors, the *Anopheles* mosquito. In Europe, autochthonous acquisition of *Pf* malaria is the exception and is believed to be transmitted either through blood transfusion or by infected *Anopheles* imported from malaria-endemic areas, known as airport or baggage malaria.[26] Possible transmission of *Pf* malaria in Europe by the indigenous mosquito species *Anopheles plumbeus* has been suggested.[27]

The incubation time varies, but symptoms typically develop 4–28 days or longer after the initial transmission of the parasites. Uncomplicated malaria is characterized by nonspecific symptoms (intermittent high spiking fever and chills, accompanied by headaches and febrile delirium, diarrhea, vomiting), which may lead to a delay in the diagnosis. The inadequate intake of chemoprophylaxis is an observation in almost all patients with severe malaria treated in the ICU.[28,29] Severe malaria is not exclusively but most commonly due to *Pf* malaria infection.[28,29] Three variables independently predict death: advanced age, a low Glasgow Coma Scale score upon admission (which reflects cerebral malaria), and a parasitemia > 4%.[28] Factors associated with a poor outcome include shock, acute respiratory distress syndrome (ARDS), bacterial coinfection, a delay in starting antimalarial treatment, and lack of adequate intensive care facilities.[25]

Approximately 1% of the *Pf* malaria infections will progress to severe malaria.[30] Many patients with imported malaria from malaria-endemic countries who require admission to the ICU may not present with hyperparasitemia (greater than 2%).[31] In clinical studies conducted in nonendemic areas, up to 10% of *Pf* malaria cases are severe at diagnosis.[31,32]

The superiority of artemisinin medication in treating malaria infections in adults and children, compared to quinine derivatives has been reported.[33,34] Artesunate is far more efficient and produces fewer side effects, resulting in a shorter length of both hospital and ICU stay and almost no fatalities.[33,34] A large randomized controlled trial (RCT; the SEAQUAMAT study) compared outcomes in 730 Southeast Asian patients with severe *Pf* malaria treated with IV artesunate and 731 patients treated with IV quinine.[33] The mortality rate in the former group (14.7%) was significantly lower than in the latter group (22.4%).[33] Another RCT conducted in African children (AQUAMAT study) reported similar results, and intravenous artesunate is now the recommended agent for severe malaria.[34] No dose adjustment of artesunate is required for patients with MOF.[25]

As of April 2019, artesunate, the WHO-recommended first-line treatment for severe malaria, has also become the first-line treatment for severe malaria in the USA, which was already true for most countries.[35]

Further supportive therapy consists of conservative fluid

therapy unless signs of hypovolemia are present. Red blood cell exchange transfusion has been used in the ICU to accelerate parasite clearance; however, its use remains controversial, and it is rarely used since the initiation of artesunate.[36,37] As concomitant bacterial infections are frequently present in patients with severe malaria, a low threshold for initiating antibacterial therapy, particularly in children, is recommended. ARDS should be managed with lung protective ventilation. Corticosteroids have never been shown to improve neurological outcomes in patients with cerebral malaria.

Enteric fever, which groups typhoid and paratyphoid fever, is a bacterial infection acquired through the consumption of contaminated food or water containing *Salmonella* Typhi or *Salmonella* Paratyphi species.[38] Currently, the most important regions from which enteric fever is imported appear to be India and Southeast Asia.[39] Typhoid fever is responsible for 200,000–600,000 deaths annually, predominantly in children younger than 5 years.[40] In industrialized countries, the disease has become very rare and is almost exclusively detected in travelers or migrants.[40] The mortality rate may be as high as 30% in endemic regions if patients are untreated. Due to early access of returning travelers to medical care, mortality is rarely observed in this group of patients, with the mortality rates being less than 1%, and hence, there is infrequent admission to the ICU.[40] High fever gradually occurs 6–30 days after transmission of the bacteria, accompanied by flu-like symptoms. Patients with light skin occasionally, but seldom show soft red spots on the thoracic region.[39,40] Bradycardia can accompany the fever, which is defined as the Faget sign, but is not always present and is not specific.[39] Enteric hemorrhage and/or perforation, neuropsychiatric symptoms, and metastatic infections (endocarditis or osteomyelitis) or abscesses may occur. These rare complications may be life-threatening and may require admission to the ICU.[40,41] Among the complications most frequently encountered, intestinal perforation, gastrointestinal (GI) bleeding, bronchitis, encephalopathy, and toxic myocarditis are the most relevant (reviewed in Banambar and Abhijeet[42]). Sepsis and septic shock are the most frequent indications for ICU admission; most of these patients require mechanical ventilation and inotropic cardiovascular, respiratory, renal, and other organ system support and ensuring its implementation adequately. Blood cultures are the way to diagnose, but have limited yield. Antibiotic therapy is very effective, but because resistance to fluoroquinolones is very common, a third-generation cephalosporin is advised.[12,39,40] ESBL *Salmonella* Typhi are on the rise in countries such as Pakistan and South India.[43]

Rickettsial diseases are transmitted through different vectors (lice, mites, or ticks). These Gram-negative, intracellular bacteria are responsible for a wide variety of clinical syndromes:[44] the "spotted fever" group (*e.g.*, African tick bite fever, Rocky Mountain spotted fever, and Mediterranean spotted fever) and the "typhus" group (*e.g.*, murine typhus and epidemic typhus), which also include the scrub typhus. The incidence of rickettsial diseases in travelers with fever ranges from 1.5% to 3.3%.[6,45] It is the second most common cause of imported tropical fever after malaria in travelers returning from the African continent. Scrub typhus, a zoonotic rickettsial infection, is an important cause of ICU admission in the Indian subcontinent. The classical clinical triad of fever, rash, and eschar ("tache noire") should raise suspicion,[44] although the eschar is frequently absent or overlooked. Other nonspecific symptoms include myalgia, headache, cough, leukopenia, thrombocytopenia, and hyponatremia.

The diagnosis is based on serial serological tests. PCR on eschar swabs or tissue samples may provide a species-specific diagnosis.[46] The different species have some more or less specific symptoms.[44,45,47] These intracellular bacteria invade the vascular endothelial cells in various organs, causing vascular damage with leakage, edema, hypoalbuminemia, and hypotension,[47] which can induce MOF. Scrub typhus is notorious for causing serious and permanent neurological damage. It is the most fatal type of all the rickettsial infections, showing mortality rates of up to 24% in ICU series.[48] MOF is also observed in patients with severe Rocky Mountain spotted fever, in addition to the development of GI symptoms. Complications related to other spotted fevers and murine typhus are much less frequent, but have been reported.[47] Multiple eschars on one site seem to be pathognomonic for African tick bite fever because of the aggressive nature of the specific vector. If the infections are untreated, mortality rates can be high.[48] If treatment is not delayed, mortality remains low.[47] Because of a diagnostic delay (serology is not immediately positive), empiric treatment with doxycycline is important for suspected cases, for example, a patient with a deteriorating condition who presents with fever and has recently returned from a trip to an endemic country. The treatment for all rickettsial species is identical (antibiotic therapy, particularly doxycycline or azithromycin), and thus, differentiation only has a scientific or epidemiological purpose.[49] Of note, cephalosporins (such as ceftriaxone) are not very effective, and fluoroquinolones appear to exert deleterious effects.[50] In patients presenting with organ failure, adequate supportive therapy should be initiated.

AN IMPORTANT FOURTH DISEASE: DENGUE

Dengue, the most common arbovirosis of which the incidence increased by 30-fold over the last 50 years,[51] is transmitted through mosquito bites. Evolution to severe

disease may occur because of a secondary infection with a different serotype in people who had a primary infection, according to the "antibody-dependent enhancement" hypothesis.[52] The problem is truly global, as dengue is endemic in over 100 countries, generally restricted to the tropics in South and Central America, including the Caribbean, Southeast Asia, Kenya, and Tanzania.[53]

Symptoms may vary from mild fever, hemorrhagic fever to dengue shock syndrome (DSS).[54,55] The mortality rate is not as high as in the other VHFs (*e.g.*, Ebola), but the mortality rate due to DSS still reaches up to 5%.[55] Thrombocytopenia, elevated liver enzymes, mucosal bleeding, hypovolemic shock, and edema following the febrile phase are signs of deterioration and evolution to DSS. When a major bleeding event does occur, it is almost invariably associated with profound shock, since this symptom, in combination with thrombocytopenia, hypoxia, and acidosis, can lead to MOF and death. Diagnosis has improved with the availability of a PCR test and a nonstructural protein 1 (NS1) antigen-based rapid diagnostic test.[56] No approved drugs or any efficient vaccines are currently available, and the mainstay of management continues to be careful fluid resuscitation. Supportive care in the ICU is necessary for severe cases.[54] Blood component therapy is indicated in patients with major hemorrhage.

The in-ICU and in-hospital mortality rates of DSS have been reported to be 18.6% and 19.6%, respectively.[57] Nonsurvivors were older and exhibited lower serum albumin concentrations and higher total leukocyte counts and serum creatinine levels.[57]

RARE BUT FREQUENTLY DEADLY DISEASES (YELLOW FEVER, RABIES, AND EBOLA)

Infections with mosquito-borne viruses (chikungunya, dengue, JE, Rift Valley fever, West Nile, and yellow fever) can all potentially lead to organ failure, some of which are accompanied by severe brain damage. Most of the imported cases of yellow fever, which is caused by a mosquito-borne flavivirus, are observed among unvaccinated travelers from SSA or South America.[52,58] Reported dramatic import cases highlight the importance of persons to be vaccinated against yellow fever before they travel to countries where the disease is endemic, even if the country, such as Gambia in the past, does not require travelers to be vaccinated.[59] The live-attenuated vaccine is efficient and safe. Most of the real cases present as a nonspecific, viral, febrile illness after an incubation period of 3–6 days; 15% of symptomatic patients progress to severe disease.[60] Liver failure with GI bleeding, intracranial bleeding and encephalitis, renal failure, shock, and death can occur. The mortality rate ranges from 20% to 60%.[59,61] A specific treatment is unavailable. ICU admission is advised, and supportive therapy should be initiated as soon as possible.[52]

Rabies is an important public health problem with a high mortality in low-income countries,[62] but it is not a major import disease.[63,64] This viral disease (lyssavirus) is transmitted through the saliva from infected animals, not from human to human.[62] Clinical rabies presents as a so-called furious or encephalitic form in the majority of patients (80%). Death is almost certain once symptoms appear.[62] Treatment in the ICU most often relies on symptom control and comfort care, and an aggressive treatment has been proposed (the so-called "Milwaukee protocol").[65] Unfortunately, this protocol failed to generate the same result in subsequent cases.[62] The long-term maintenance of the rabies-free status will be challenging, as many bordering non-EU countries are still infected.[66]

ARE WE PREPARED FOR THE CRITICALLY ILL PATIENT INFECTED WITH VHF IN THE ICU?

VHFs, characterized by increased vascular permeability, are caused by arenaviruses, filoviruses, bunyaviruses, and flaviviruses.[52] Ebola virus, the best-known filovirus, causes this frequently fatal intravascular damage. Once the more virulent forms enter the human population, transmission primarily occurs through direct human-to-human transmission following contact with infected body fluids, resulting in outbreaks. Since the devastating outbreak of 2013–2016 in West Africa, the very contagious Ebola virus has regained his infamous name of a difficult-to-contain disease.[67] As this outbreak of EVD in West Africa continues, clinical preparedness is needed in countries at risk of encountering EVD (*e.g.*, Western Europe, the USA), and more fully equipped clinical teams are needed in those countries with an epidemic spread. The clinical staff must approach the patient with a very deliberate focus on providing effective care while ensuring personal safety, certainly if they require admission to the ICU.[68]

The incubation period is 2–21 days, which is followed by fever, headache, diarrhea, vomiting, and dehydration. The patient may recover or deteriorate with collapse, neurological manifestations, and bleeding. These sequelae lead to hypovolemia, metabolic acidosis, electrolyte imbalance, renal failure, and MOF.[69] None of the pharmacological interventions have produced a conclusive benefit; yet, things are changing: several compounds have

shown promise to various degrees in interfering with the filovirus life cycle (including monoclonal antibodies [mAbs] such as ZMapp, mAb114, and REGN-EB3 and inhibitors of viral RNA synthesis such as remdesivir and TKM-Ebola).[70] Future management of epidemics should also center around prevention and containment.

A few imported cases have been published and all patients had contact with infected patients in Africa or nursed and treated patients evacuated from Africa in their homeland.[71-74] During the West Africa outbreak, 890 health-care workers were among the infected patients. The mortality rate in this subgroup was 57%.[75] These numbers underscore proper use of personal protective equipment and training in using and, more importantly, doffing of these suits.

The effect of ICU-level supportive care interventions (fluid resuscitation, vasoactive medications, blood transfusions, hydrocortisone, and ventilator support) on the pathophysiology of EVD in rhesus macaques infected with a lethal dose of Ebola strain Makona C07 was studied.[76] The animals developed progressive MOF and shock before death. While the overall impact of supportive care on the observed pathophysiology in this highly lethal model was limited, some time-dependent positive responses were observed.[76] Although an Ebola virus-specific therapy has not been proven to be effective in clinical trials, the mortality rate has been dramatically decreased among patients with EVD who are managed with supportive intensive care in settings with large amounts of resources, enabling the avoidance of hypovolemia, correction of electrolyte imbalance, and provision of oxygen, ventilation, vasopressors, and dialysis. This experience emphasizes that in addition to evaluating specific medical treatments, improvements in the global capacity to provide supportive critical care to patients with EVD may be the greatest opportunity to outcome.

Treatment with ribavirin is warranted for patients with a confirmed diagnosis of Lassa fever; in addition, empiric treatment with ribavirin is reasonable for treatment of patients in endemic areas with symptoms strongly suggestive of Lassa fever[77] before diagnostic confirmation. The combination of three mAbs that targets three nonoverlapping epitopes on the Ebola virus surface glycoprotein (atoltivimab, maftivimab, and odesivimab) (REGN-EB3) and a monoclonal antibody ansuvimab (mAb114) are two antibody-based therapies that are both approved for use by the US Food and Drug Administration, providing virus neutralization.[78]

The provision of efficient intensive care by itself has proven to reduce the mortality in endemic settings.[79] Mortality in the West Africa outbreak appeared to decrease from 70% to 40% due to improvements in supportive intensive care.[80] The creation and evaluation of the context-appropriate ICU capacity is a knowledge translation priority. For comparison, the cumulative percentage of deaths in airlifted patients with a laboratory-confirmed Ebola virus infection who were treated in Western Europe and the USA from 2014 to 2015 was less than 20%.[69,73] Of these 27 patients, only three (11%) acquired EVD in the USA or Europe. During the clinical course, the predominant findings included diarrhea, hypoalbuminemia, and electrolyte disturbances; 14 patients (52%) presented with hypoxemia and nine (33%) with oliguria, of whom five had anuria. Nearly all the patients received intravenous fluids and electrolyte supplementation, nine (33%) received noninvasive or invasive mechanical ventilation, five (19%) received continuous renal replacement therapy, and 23 (85%) received investigational therapies (19 [70%] received at least two experimental interventions). Ebola viral blood RNA levels peaked at a median of 7 days after the onset of illness, and the median time from the onset of symptoms to clearance of viremia was 17.5 days. Five patients died, including three who experienced respiratory and renal failure.[73] An adequate staffing ratio is advised because of fatigue and inadequate self-protection during long shifts in the uncomfortable personal protective equipment.[80]

OTHER EMERGING OR RARE TRAVEL-RELATED DISEASES

Tropical and low-income countries also experience the worst cases of pneumonia and tuberculosis, also due to a lack of access to health care.

A particular type of "tropical" pneumonia is melioidosis, which is caused by infection with the Gram-negative bacterium *Burkholderia pseudomallei*, which resides in superficial water, mud, and soil. *B. pseudomallei* is hyperendemic to Southeast Asia reaching to Northern Australia and has been found to be endemic in other parts of (South) Asia, Africa, and Latin America. Because of increased international travel and immigration, melioidosis might become more important in the future in nonendemic countries,[81] particularly in vulnerable travelers, for example, people with diabetes, steroid use, or other immune depression. The mortality rate in Australia, where ICUs are well equipped, is approximately 10%.[82] In countries in which antibiotics and supportive therapies are not readily available, the mortality rate ranges from 50% to 90%.[81,82] The incubation time after inhalation ranges from 1 to 21 days. A local cutaneous infection is often the first symptom. Patients with risk factors can deteriorate rapidly with the formation of disseminated abscesses, pneumonia, septicemia, and shock.[81–83] The causal bacterium has been detected in sputum, urine, tissue samples, or

blood, but culture requires specific biosafety measures. Repetitive cultures should be taken because negative results are frequently observed in septic patients.[81] Only specific broad-spectrum antibiotics such as ceftazidime, meropenem, and, to a lesser extent, amoxicillin–clavulanic acid and co-trimoxazole are effective.[84]

The Zika virus (ZIKV), an RNA flavivirus, is transmitted by bites from *Aedes aegypti* and *Aedes albopictus* species, sexual activity, blood transfusion, and from the mother to the fetus. Fifty territories and countries in the Americas have reported ZIKV infections. The presentation is similar to dengue fever, with body aches, joint pain, fatigue, malaise, fever, and conjunctivitis lasting up to 7 days. ZIKV infection is rarely a cause of severe disease requiring ICU admission. Catastrophic neurological complications are well documented and include Guillain–Barré syndrome (GBS) and congenital ZIKV syndrome, and less frequently, acute myelitis and meningoencephalitis. Most patients are managed conservatively. Intravenous immunoglobulins have been used, similar to conventional GBS. Of the ill travelers returning with a confirmed, probable, or clinically suspected diagnosis of ZIKV disease between January 2013 and February 29, 2016 who were exposed in the Americas, two of 93 patients developed GBS and three of four pregnancies resulted in adverse outcomes (microcephaly, major fetal neurologic abnormalities, and intrauterine fetal death).[85]

OTHER RARE/FULMINANT INFECTIONS AFTER MIGRATION AND TRAVEL

There are many other emergency/rare infections which may cause fever and even MOF, such as trypasonomiasis, *Strongyloides* hyperinfestation, leptospirosis, *Borrelia duttonii* infection, or severe dysentery due to *Entamoeba histolytica*, among many others.[15,86,87] We reported the case of a boy who fled from Chechnya to Belgium and died due to organ failure caused by a human immune deficiency virus (HIV)/visceral leishmaniasis (VL) coinfection.[88] In both countries, VL is not an endemic tropical disease. This case again illustrates that the migration of people results in confrontations with diseases that are not frequently encountered in the countries of destination.[89,90] Sporadic cases of diphtheria are very rare throughout Europe, but not worldwide. A 3-year-old incompletely vaccinated girl was admitted to our ICU with pharyngotonsillitis caused by diphtheria. Renal and cardiac failure with a third-degree atrioventricular (AV) block occurred. Unfortunately, she died within 36 h of admission, despite pacemaker placement and the administration of antibiotics and diphtheria antitoxin. The delayed antitoxin administration was related to a lack of availability and knowledge of its availability in Europe, which likely contributed to the unfavorable outcome.[91]

Do you ever consider JE or West Nile fever, the latter emerging in Europe too? JE should be suspected among travelers from endemic regions who are suffering from severe and unexplained neurological symptoms.[92,93] JE is caused by infection with mosquito-borne flavivirus and is maintained in a transmission cycle with pigs and bird species as the main amplifying hosts. The diagnosis is challenging and requires a specialized laboratory. The case fatality rate of symptomatic JE can be as high as 30%, and the residual disabilities might be considerable. Recent studies have shown that one-third of travel-associated JE cases acquired it during short-term travel and suggested that the risk of this enzootic disease is potentially underestimated.

COVID-19 OVERWHELMED AND WILL OVERWHELM THE ICUS WORLDWIDE

The Health Commission of Hubei province, China, first reported a cluster of unexplained cases of pneumonia on Dec 31, 2019 in Wuhan.[94] No one could have foreseen that the world would have been in a worldwide crisis mode because of COVID-19 caused by a novel coronavirus labeled severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[95]

The surveillance network and laboratory capability of China were able to recognize this outbreak and announced the virus genome sequences that would allow the development of rapid diagnostic tests and epidemiological control. The disease is highly transmitted.[94,95] Human-to-human transmission occurs primarily *via* respiratory droplets from coughs and sneezes and contaminated surfaces. SARS-CoV-2 has spread rapidly worldwide, triggered by traveling too, and on March 11, 2020, the WHO had already declared COVID-19 a pandemic. Since then, COVID-19 is a public health emergency of international concern. Evidence related to transmissibility and mortality inform the clinical community in the ICU of the importance of vigilance, preparation, active management, and protection. Early recognition of cases will allow clinicians to ensure adequate clinical monitoring, institution of supportive interventions, and preventing further transmission by implementing infection control measure.[96,97]

Symptoms overlap greatly with other severe acute respiratory infections.[98] Initially, clinicians had to rely on the epidemiological link as outlined in the current COVID-19 case definition, such as travel history to affected areas, although this has completely changed as spread continues. Avoiding travel and crowds may, of course, still

decrease the risk of infection. ICU may be required for approximately 20% of polymorbid, COVID-19-infected patients, and hospitalization is associated with a high case fatality rate of over 13%. Meanwhile, the pressure on the global health-care workforce and the ICU community continues to intensify.

Therefore, ensuring routine droplet barrier precautions, environmental hygiene, and overall sound infection prevention practice in the ICU is indicated. To ensure minimal risk of infection when treating patients with COVID-19, the Centers for Disease Control and Prevention (CDC)[99] recommended the use of personal protective equipment including a gown, gloves, and either an N95 respirator plus a face shield/goggles or a powered, air-purifying respirator (PAPR).[100] Caring for infected patients represents a substantial exposure risk for the ICU staff because of high and prolonged exposure to critically ill patients who presumably have higher viral shedding. Severe infections and deaths have occurred among the health-care workers too from COVID-19, exerting significant psychosocial stress on the staff.[100]

As COVID-19 spreads across the world, policymakers, ICU practitioners, and hospital administrators had to prepare for a substantial increase in critical care bed capacity, with a focus not just on infrastructure and supplies, but also on staff management. Critical care triage to allow the rationing of scarce ICU resources was needed. Researchers still have to address unanswered questions, including the role of repurposed and experimental therapies. Indeed, this outbreak has led to a significant increase in the need for ICU beds in many countries, simultaneously reducing the available beds. Hence, hospitals should always have plans to augment ICU bed capacity, which may include transforming general wards into ICUs.[101–103] This substantial increase in the number of critically ill patients has exceeded the total ICU capacity in many countries, without even considering other critical admissions, such as for trauma, stroke, and other emergencies. Surge capacity organization as reflected by ICU overflow or the creation of COVID-19–specific supplementary ICU beds was found to negatively impact ICU patient outcomes.[102] Incidence and hospitalization rates were consistently highest for unvaccinated persons and lowest for fully vaccinated persons with a booster. Being up-to-date with COVID-19 vaccination is critical to protecting against SARS-CoV-2 infection and associated hospitalization, although hospitalization in the ICU is still necessary, despite the emergence of other variants making people less sick, that is, the omicron variant.[103]

DISCUSSION AND CONCLUSIONS

Due to a global increase in the number of travelers (including migrants and refugees), travel-related pathology may further increase as a cause of severe infectious disease in the ICU.[1,4,5]

When confronted with patients admitted in ICU and with a recent history of traveling abroad or migration from low-income countries, the inclusion of an infectious/tropical pathology in the differential diagnosis is of paramount importance. There is considerable overlap in the manifestations of many of the acute infections, and even for an ICU physician familiar with the management of such patients in the ICU, confirmation of the diagnosis initially and thereafter choosing the appropriate treatment can be challenging.[11,17] Common and serious pathology should be considered, according to their geographic spread. The incubation time and presence of specific symptoms, such as a rash, stupor, GI symptoms, eschars, elevated liver enzyme levels, thrombocytopenia, and so on, should be taken into account and they guide further diagnosis.[15] Finally, clinicians should take advantage of targeted diagnostic tests. To educate and motivate the ICU community, the Task Force of the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM) compiled a group of experts in this field who have written important review articles in 2018 on more than 10 key import and travel-related tropical diseases, as well as some general aspects related to the provision of critical care for these patients in low-income countries, where many of these conditions are endemic.[2]

Over 40% of returning travelers with AUFI are diagnosed with malaria or dengue, infections that can be easily diagnosed by rapid diagnostic tests.[4,15,17] Other diseases may require blood cultures, PCR/antigen tests, and/or time-consuming serology tests for confirmation.[11] PCR, which is increasing in importance for the detection of several pathogens, is readily available in specialized centers. Of course, diagnostic testing (including PCR) plays a critical role in addressing COVID-19 pandemic, which is caused by SARS-CoV-2. Rapid and accurate diagnostic tests are imperative for identifying and managing infected individuals, contact tracing, epidemiologic characterization, and public health decision-making.

A delay in the initiation of therapy can be dangerous, and thus, empiric therapy should be administered as soon as possible if one of these diseases is considered (Table 2). A systematic approach is useful in making a diagnosis in patients with fever due to tropical diseases, and the steps would include obtaining history of travel and the type of exposure, defining the incubation period, and then fitting these clinical features into the syndromic approach. Empiric treatment using a combination of artesunate, ceftriaxone, and either doxycycline or azithromycin should cover a majority

of patients with these syndromes. Not every disease has a tropical origin, and therefore, the most obvious cosmopolitan infections should also be considered, and physicians should be aware at not only COVID-19, but *i.e.* increased bacterial resistance is a global problem.

Authors Contributions

Herten PJ initially wrote the manuscript. All other authors (Vlieghe E, Bottieau E, Florence E, Jorens PG) provided substantial contributions to the consecutive and final versions.

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Conflict of Interest

None declared.

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