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Review

Management of infections in critically ill returning travellers in the intensive care unit—I: considerations on infection control and transmission of resistance☆

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SUMMARY

Depending on their destinations and activities, international travellers are at a significant risk of contracting both communicable and non-communicable diseases. On return to their home countries, such travellers may require intensive care. The emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), and more recently Ebola haemorrhagic fever, has highlighted the risks. Other well-known communicable pathogens such as methicillin-resistant *Staphylococcus aureus* and carbapenemase-producing *Enterobacteriaceae* have been described previously. However, malaria remains by far the most important cause of death. The issues related to imported antibiotic resistance and protection from highly contagious diseases are reviewed here. Surveillance strategies based on epidemiological data (country visited, duration of travel, and time elapsed since return) and clinical syndromes, together with systematic search policies, are usually mandatory to limit the risk of an outbreak. Single-bed hospital rooms and isolation according to symptoms should be the rule while awaiting laboratory test results. Because person-to-person contact is the main route of transmission, healthcare workers should implement specific prevention strategies.

1. Imported antibiotic resistance

Infections caused by multidrug-resistant (MDR) pathogens are typically associated with increases in morbidity, mortality, and healthcare-associated costs, and represent an increasing public health challenge of global dimensions.[1] The combination of a progressive loss of antibiotic efficacy due to the emergence and dissemination of resistance and the slow rates of discovery and development of new antibiotics active against MDR pathogens has led to what has been termed the 'antibiotic resistance crisis'. The situation has been further complicated recently by the emergence and dissemination of strains that remain susceptible to only a few antibiotics (extensively drug-resistant (XDR) strains), which are difficult to treat.[2]

The most challenging MDR pathogens include (1) methicillin-resistant *Staphylococcus aureus* (MRSA), (2) vancomycin-resistant enterococci (VRE), (3) *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBLs) or carbapenemases (CPE), (4) XDR *Pseudomonas aeruginosa* that remain susceptible only to polymyxins, and (5) carbapenem-resistant Acinetobacter (CRA). Among these, CPE and CRA are currently the most problematic due to their XDR phenotypes, their propensity for epidemic diffusion in

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healthcare settings, and the high mortality rates associated with invasive infections.[2]

In principle, any of these pathogens can be encountered, either as colonizers or as infecting agents, in travellers returning from areas of endemicity and in patients repatriated from foreign healthcare facilities. Acquisition may be the consequence of exposure to contaminated food or environments, of close contact with colonized individuals, or of admission to hospitals and exposure to medical practices either for unexpected reasons (e.g., trauma, acute diseases) or for medical tourism (e.g., specialized surgery, organ transplantation). As has been clearly documented, the transmission of MRSA has increased with the growth of international travel, resulting in either asymptomatic colonization or clinically significant MRSA infections.[3,4] Some evidence is also available for the international dissemination of VRE via transfer/repatriation of patients from hospitals located in endemic areas.[5] Concerning Gram-negative organisms, the impact of international travel has been firmly established in the dissemination of MDR *Enterobacteriaceae*, including high-risk clones producing ESBLs (especially enzymes of the CTX-M type) and/or carbapenemases of various types (e.g., KPC, OXA-48, NDM, VIM).[6–8] The risk of the spread of MDR strains of *Enterobacteriaceae* in this situation includes not only *Escherichia coli*, *Klebsiella spp*, and *Enterobacter spp*, but also classical enterobacterial pathogens such as *Salmonella enterica* and *Shigella spp*, with evidence of imported cases of typhoid fever and shigellosis caused by MDR strains.[8,9] The transmission of MDR Acinetobacter has been documented following the international transfer of patients from intensive care units (ICUs) in countries with high-level endemicity,[10] and the repatriation of evacuees involved in military operations in endemic areas.[11] Less evidence is available for the travel-related dissemination of MDR/XDR *P. aeruginosa* strains, but this is clearly a possibility following the transfer of colonized patients from ICUs where these strains are endemic or are causing outbreaks.[12]

The admission to the ICU of patients colonized or infected by MDR/XDR pathogens is a matter of concern, since it may be followed by cross-infections and outbreaks in the ICU setting unless suitable infection control practices are enforced immediately. Moreover, infections caused by MDR/XDR pathogens may require different antimicrobial treatments from those routinely used in the ICU, which are based on the local epidemiology; this may result in inappropriate empiric treatment and thus increased morbidity and mortality.

Therefore, the possibility of carriage or infection by an MDR/XDR pathogen should always be considered for critically ill returning travellers admitted to the ICU. A risk assessment should be performed, considering the area of provenance, the history of the patient, and the presence of additional risk factors for carriage or infection by similar resistant pathogens.[2,12]

The epidemiology of MDR/XDR pathogens may vary according to geographical area. The proportion of MRSA among *S. aureus* isolates remains very high in some European countries, the USA, Latin America, and the Far East, but is considerably lower in other European countries such as the Netherlands and the Scandinavian countries.[13] ESBL-producing *Enterobacteriaceae* are now disseminated worldwide, with very high rates detected among ICU patients in Latin America, the Asia-Pacific region, and the Middle East.[14] For their part, CPE have achieved a notable level of endemicity in some areas of Europe (e.g., Greece and Italy), the Middle East (e.g., Turkey, Israel), South America (e.g., Colombia), and China.[15] Travellers/patients from areas of high endemicity for MDR/XDR pathogens have a higher risk of exposure to these pathogens, and the possibility of being infected or colonized by these agents at the time of repatriation should always be considered. When consulting sources of information regarding resistance and endemicity (such as ProMED-mail, http://www.promedmail.org), clinicians should consider that (1) for several countries (especially low-income settings) epidemiological information is scarce or lacking, and (2) the epidemiology of MDR/XDR pathogens can change rapidly. So this information should be considered partial and should be updated regularly.

Exposure to medical practices in facilities from endemic areas, either unanticipated or scheduled, is an additional risk factor for carriage/infection by MDR/XDR pathogens.[16]

Recommendations for ICUs, based on the current evidence, include the following:

(1) Carrying out a risk assessment for carriage/infection by MDR/XDR pathogens for all ICU admissions of patients returning from international travel or transferred from foreign hospitals.
(2) Enforcing infection control precautions upon admission for all patients returning from international travel or transferred from foreign hospitals with known risk factors for carriage/infection by MDR/XDR pathogens. The infection control precautions should cover the various types of MDR/XDR pathogens for which a risk was assessed, and should be kept in place until carriage/infection by MDR/XDR pathogens has been ruled out by the proactive surveillance and clinical microbiology diagnostic workup.
(3) Carrying out proactive surveillance for MDR/XDR pathogens for which a risk was assessed by culture and/or molecular methods.

2. Protection from highly contagious disease in critically ill returning travellers in the ICU

2.1. Introduction to potentially life-threatening travel-associated infectious diseases

Depending on their destinations and activities, international travellers are at a significant risk of contracting both communicable and non-communicable diseases.[17] The emergence of severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and more recently Ebola haemorrhagic fever, has highlighted the risks. However, other well-known communicable pathogens such as MRSA[18] and CPE[19,20] have been described previously. ICU patients, because of the severity of illness, the workload, and the antibiotic selection pressure, are important potential reservoirs of dangerous microorganisms. The most important challenges for ICU practitioners are first to identify admissions with the highest risk of communicable disease, and second to rapidly implement preventive measures in order to avoid nosocomial transmission.

Surveillance strategies for the early detection of unusual infectious disease events should be the rule. Syndromic surveillance can help to reduce the identification time. All patients transferred from hospitals in high-risk countries (Table 1) should be considered as potential carriers of MDR or highly drug-resistant microorganisms. All of these patients should be screened for rectal carriage at admission and a few days after any antibiotic therapy.[21] While awaiting screening results, the patient should be hospitalized in a single-bed room. Contact and body fluid precautions should be added. All patients with fever and clinical or radiographic evidence of pneumonia or acute respiratory distress syndrome, and with a history of travel from countries in or near the Arabian Peninsula (Bahrain, Iraq, Iran, Israel, the West Bank and Gaza, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, the United Arab Emirates, and Yemen) within 14 days before symptom onset, or close contact with a symptomatic traveller who developed fever and acute respiratory illness within 14 days after travelling from countries in the region, should be considered as potentially infected by MERS-CoV.[22] Viral haemorrhagic fever

Table 1
Distribution of the most common organisms by region and reservoir

Infectious agents	Geographical origin	Reservoir	Main type of transmission	Main type of protection
Viruses				
MERS-CoV	Middle East	Dromedary camels	Droplet contact	Droplet precautions
SARS-CoV	South China	Chinese horseshoe bats	Droplet contact, airborne	Droplet precautions
H7N9	Eastern China, Hong Kong, Taiwan, Malaysia	Poultry, wild birds	Droplet?	Droplet precautions
Influenza virus			Droplet	Droplet precautions
Haemorrhagic fever			Droplet, contact	Droplet precautions
Ebola	Africa, Guinea, Sierra Leone	Bats	Droplet, contact	
Bacteria				
Carbapenemase-producing *Enterobacteriaceae*	Southern Asia, India, Middle Eastern Countries; Maghreb countries, Israel, Romania, Italy, Turkey, Greece	Human	Contact	Contact precautions
XDR-TB and MDR-TB	Russia, eastern Europe, southern Africa	Human	Airborne	Airborne precautions
Meningococci		Human	Droplet	Droplet precautions

MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; XDR-TB, extensively drug-resistant tuberculosis; MDR-TB, multidrug-resistant tuberculosis.

should be suspected in selected patients coming from Sub-Saharan Africa with fever and bleeding disorders, depending on the geographical origin and local epidemiological situation. A general syndromic approach to tropical infections in the ICU is described in Table 2.[23]

Although many imported infectious diseases may require ICU admission, the most frequent ones are relatively few in number. In a descriptive analysis of acute and potentially life-threatening tropical diseases among 82 825 ill Western travellers reported to GeoSentinel from 1996 to 2011, 3655 patients (4.4%) with 13 diseases were identified; falciparum malaria (76.9%), enteric fever (18.1%), and leptospirosis (2.4%) were the most frequent. Ninety-one percent of patients had fever. The median time from travel to presentation was 16 days. Thirteen (0.4%) patients died: 10 with falciparum malaria, two with melioidosis, and one with severe dengue. Falciparum malaria was mainly acquired in West Africa, enteric fever on the Indian subcontinent, and leptospirosis, scrub typhus, and murine typhus in Southeast Asia.[24]

2.2. Transmission risks of highly contagious tropical infectious diseases associated with healthcare settings

Emergency departments at general hospitals are the first units to deal with an unknown highly contagious tropical infectious disease and they should be prepared for this eventuality (a heavy price was paid during the SARS outbreak). In an endemic area, MERS-CoV infection is more likely to be acquired in healthcare facilities than in the community: in the 2014 outbreak in Jeddah, Saudi Arabia, more than four out of five exposures were at healthcare facilities, mainly due to poor and insufficient isolation measures at admission.[25]

Patients with suspected highly contagious tropical infectious diseases should be placed directly in an emergency department isolation room (if available) and should be examined and assessed as soon as possible. Standard precautions and cough and respiratory etiquette should be applied systematically. During admission, these patients should avoid any contact with other patients, and unprotected healthcare workers should avoid contact with them. If possible, point-of-care bedside laboratory tests should be used for sampling, or all analyses should be done in a biosafety level 3/4 laboratory. Samples should be inactivated (with formalin) before testing in a routine laboratory. Transfer to the ICU or to a high-level isolation unit must be carried out in a secure manner.

Many organisms are present in the ICU, but only a few are involved in person-to-person transmission. An overview of the precautions recommended for selected tropical infections and conditions is shown in Table 3.

Table 2
Syndromic approach to tropical infections in the ICU

Syndrome	Diseases
Fever and toxic appearance	Dengue fever, malaria, typhoid fever, early shigellosis, leptospirosis, and anicteric hepatitis. The presence of a
Fever and rash	haemorrhagic rash may indicate arboviral, rickettsial, and meningococcal aetiologies. Aetiologies of VHF that have been known to cause person-to-person transmission are Lassa virus, Ebola virus, Marburg virus, and Crimean-Congo haemorrhagic fever virus
Fever and thrombocytopenia	Malaria, dengue, leptospirosis, rickettsiosis
Fever with eosinophilia	Schistosomiasis (Katayama fever or acute neurological sequelae of myelitis or encephalitis), visceral larva migrans, tropical pulmonary eosinophilia, acute fascioliasis, acute trichinosis
Severe pneumonia or ARDS	*Streptococcus pneumoniae*, *Legionella pneumophila*, bacterial sepsis with other pathogens, tuberculosis, *Burkholderia pseudomallei* (melioidosis), plague, histoplasmosis, malaria, typhoid fever, leptospirosis, scrub typhus, hantaviruses, coronaviruses, highly pathogenic avian influenza A (H5N1)
Pulmonary renal syndrome	Falciparum malaria, leptospirosis, hantavirus infection, scrub typhus, severe pneumonia
Hepatorenal dysfunction	Falciparum malaria, leptospirosis, scrub typhus, hepatitis E or A with fulminant hepatic failure and the hepatorenal syndrome, yellow fever virus
Acute abdomen	Appendicitis, cholecystitis, diverticulitis, perforated peptic ulcer, enteric fever, amoebic liver abscess
Dysentery and severe gastrointestinal fluid losses	Amoebic (*Entamoeba histolytica*) and bacillary (*Shigella spp*, especially *S. dysenteriae* and *S. flexneri*, *Campylobacter jejuni*, non-typhoidal *Salmonella spp*, *Yersinia enterocolitica*, enteroinvasive *Escherichia coli*, and enterohaemorrhagic *E. coli* (EHEC))
Altered sensorium	Cerebral malaria, meningitis, typhoid fever, viral encephalitis (Japanese encephalitis virus, Rift Valley fever virus, Murray Valley encephalitis virus, West Nile virus, St. Louis encephalitis virus, rabies virus, Nipah virus). Eosinophilic meningoencephalitis (*Angiostrongylus cantonensis*, *Gnathostoma spinigerum*, migrating ascarids, and schistosomiasis)

ICU, intensive care unit; VHF, viral haemorrhagic fever; ARDS, acute respiratory distress syndrome.

Table 3
Precautions recommended for selected tropical infections and conditions

Infection/condition	Precautions[a]	Comments
Amoebiasis	Standard	Person-to-person transmission is rare (care when handling diapered infants and mentally challenged persons)
Chagas disease (*Trypansoma cruzi*)	Standard	Not transmitted from person to person (only vertical transmission and organ/blood donation)
Coronavirus: SARS-CoV, MERS-CoV	Airborne High-level isolation unit	Aerosol-generating procedures and 'super-shedders' present highest risk for transmission
Dengue virus Chikungunya virus	Standard	Not transmitted from person to person Install screens in windows and doors in endemic areas; use DEET-containing mosquito repellents and clothing to cover extremities
Echinococcosis (hydatidosis)	Standard	Not transmitted from person to person
Encephalitis, arthropod-borne viral Japanese encephalitis Central European tick-borne Venezuelan equine Murray Valley encephalitis St. Louis encephalitis West Nile virus Nipah virus Hendra virus	Standard	Not transmitted from person to person, except rarely by transfusion and for West Nile virus by organ transplant, breast milk, or transplacentally Install screens in windows and doors in endemic areas; use DEET-containing mosquito repellents and clothing to cover extremities Airborne precautions for Hendra and Hendra-like virus, as human-to-human spread is unknown
Gastroenteritis Cholera Enteropathogenic O157:H7 and other shiga toxin-producing strains *Salmonella* species (including *Salmonella* Typhi) *Shigella* species (bacillary dysentery)	Standard	Use contact precautions for diapered or incontinent persons
Hantavirus pulmonary syndrome Haemorrhagic fever with renal syndrome, and other Puumala, Seoul, and Sin Nombre viruses	Droplet	Rarely transmitted from person to person
Histoplasmosis	Standard	Not transmitted from person to person
Influenza, avian (H5N1, H7, H9 strains)	Droplet	
Leptospirosis	Standard	Not transmitted from person to person
Malaria	Standard	Not transmitted from person to person except through transfusion rarely and through a failure to follow standard precautions during patient care Install screens in windows and doors in endemic areas; use DEET-containing mosquito repellents and clothing to cover extremities
Melioidosis	Standard	Not transmitted from person to person
Meningitis: meningococcal disease	Droplet	Post-exposure chemoprophylaxis for household contacts and healthcare workers exposed to respiratory secretions Eosinophilic meningitis (*Angiostrongylus cantonensis, Gnathostoma spinigerum*, migrating ascarids, and schistosomiasis) is not transmitted from person to person
Rabies	Standard	Person-to-person transmission is rare (has been reported in corneal, tissue, and organ transplants). If the patient has bitten another individual or saliva has contaminated an open wound or mucous membrane, wash the exposed area thoroughly and administer post-exposure prophylaxis
Relapsing fever	Standard	Not transmitted from person to person
Rickettsial fevers, tick-borne (boutonneuse fever, Rocky Mountain spotted fever, tick-borne typhus fever, scrub typhus)	Standard	Not transmitted from person to person
Schistosomiasis (bilharziasis)	Standard	Not transmitted from person to person
Strongyloidiasis	Standard	Could hypothetically be transmitted by skin contact with secretions of patients with hyperinfestation syndrome
Viral haemorrhagic fevers Yellow fever Rift Valley fever virus	Standard	Not transmitted from person to person
Viral haemorrhagic fevers (2) Kyasanur Forest disease virus Omsk haemorrhagic fever virus Crimean-Congo haemorrhagic fever virus Ebola virus Marburg virus Lassa fever virus Junin virus (Argentine haemorrhagic fever) Guanarito virus (Venezuelan haemorrhagic fever) Machupo virus (Bolivian haemorrhagic fever) Sabiá virus (Brazilian haemorrhagic fever)	High-level isolation unit	Crimean-Congo haemorrhagic fever virus, Ebola virus, Marburg virus, Lassa fever virus, Guanarito virus, and Machupo virus can be transmitted from person to person. Unknown for Kyasanur Forest virus, Omsk virus, Junin virus, and Sabiá virus Emphasize: (1) use of sharp safety devices and safe work practices; (2) hand hygiene; (3) barrier protection against blood and body fluids upon entry into room (single gloves and fluid-resistant or impermeable gown, face/eye protection with masks, goggles, or face shields); and (4) appropriate waste handling. Use N95 or higher respirators when performing aerosol-generating procedures. Largest viral load in final stages of illness when haemorrhage may occur; additional PPE, including double gloves, leg and shoe coverings may be used, especially in resource-limited settings where options for cleaning and laundry are limited

SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; DEET, *N*,*N*-diethyl-*meta*-toluamide; PPE, personal protective equipment.

[a] Standard precautions include hand hygiene, use of PPE, prevention of needlestick injuries, environment cleaning, and the appropriate handling of waste. Droplet precautions include standard precautions and the use of a single room, surgical masks for healthcare workers when working within 1–2 m of the patient, and a surgical mask on the patient if transport is necessary. Airborne precautions include standard precautions and a single monitored negative-pressure room, closed door, special high-filtration particulate respirators (N95 or FFP2 mask) for healthcare workers, and movement of the patient, wearing a surgical mask, only when essential.

2.3. Infection prevention and control recommendations for hospitalized patients with a suspected highly contagious tropical infectious disease in the ICU

ICUs attend patients who are severely ill and in some way immunocompromised because of underlying diseases and the use of invasive medical devices and technology in their care. Consequently, person-to-person transmission of pathogens may be frequent. Intensive care therapy should be performed in collaboration with the infectious disease team. The unit should be subjected to negative pressure if available. The duration of manual ventilation during resuscitation procedures should be kept to a minimum. Non-invasive positive pressure ventilation should be used instead of facial mask aerosol therapy when possible. Endotracheal intubation and cardiopulmonary resuscitation have been associated with increased SARS-CoV transmission among physicians and nurses in the ICU. Endotracheal intubation should be performed with rapid sequence induction by the most skilled person available, who should wear personal protective equipment. Meticulous infection control measures must be followed.

Invasive procedures should be avoided unless absolutely essential. Chest radiography, ultrasonography, bronchoscopy, and gastrointestinal endoscopy should be performed at the bedside, avoiding moving the patient unnecessarily; if not possible, these procedures should be performed in an air-controlled environment. Patients who require dialysis at their bedside should receive either peritoneal dialysis or haemodialysis, and dedicated haemodialysis machines and decontaminated dialysate should be designated as infectious waste.

Detailed tutorials and guidelines have been produced by the US Centers for Disease Control and Prevention (CDC),[26] the European Centre for Disease Prevention and Control (ECDC),[27] and the European Network for Infectious Diseases (EUNID).[28] There are also other guidelines focused on specific diseases such as Ebola virus disease (CDC) and Crimean-Congo haemorrhagic fever.[29,30]

New definitions of sepsis have different implications when applied in low-income and middle-income countries,[31] and a new paradigm for management should be developed. A research agenda highlighting the differences in approach between high-income and poor-resource scenarios is required.

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