Country-to-Country Transfer of Patients and the Risk of Multi-Resistant Bacterial Infection

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Management of patients with a history of healthcare contact in multiple countries is now a reality for many clinicians. Leisure tourism, the burgeoning industry of medical tourism, military conflict, natural disasters, and changing patterns of human migration may all contribute to this emerging epidemiological trend. Such individuals may be both vectors and victims of healthcare-associated infection with multiresistant bacteria. Current literature describes intercountry transfer of multiresistant Acinetobacter spp and Klebsiella pneumoniae (including Klebsiella pneumoniae carbapenemase– and New Delhi metallo-β-lactamase–producing strains), methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, and hypervirulent Clostridium difficile. Introduction of such organisms to new locations has led to their dissemination within hospitals. Healthcare institutions should have sound infection prevention strategies to mitigate the risk of dissemination of multiresistant organisms from patients who have been admitted to hospitals in other countries. Clinicians may also need to individualize empiric prescribing patterns to reflect the risk of multiresistant organisms in these patients.

Although the world may not be truly getting smaller, the increasing use of air transport could give this impression. The exponential growth of international air travel means almost 1 billion passengers are projected to take an international flight during 2011 [1]. An intercontinental journey now takes a matter of hours, rather than the weeks or months of old. Any medical practitioner could be faced with a person who may have been in the hospital in any part of the world in preceding days. Confounding this, practitioners are increasingly managing patients who have traveled vast distances primarily for the purpose of seeking medical or surgical treatment for an illness. This emerging and diverse category of patient has previously been described in various relevant contexts [2–5]. Collectively we term members of this group the “intercountry” patient. It includes the military and civilian aeromedical evacuee, the “medical tourist” who travels specifically to seek medical treatment internationally, and a larger, less well-defined group of informal medical tourists: those whose medical care is divided between countries for a variety of social, familial, or financial reasons.

Diseases such as malaria and arbovirus infection are classically described in returned travelers. The acquisition of blood-borne viruses such as the human immunodeficiency virus, hepatitis B, and hepatitis C has been associated with medical care in some developing healthcare systems [6]. The intercountry patient is also at high risk of the more prosaic infection, however. Healthcare-associated multiresistant bacterial infection is greatly heterogeneous, and not necessarily divided along lines of economic development and industrialization. Even ubiquitous nosocomial pathogens such as Staphylococcus aureus and Klebsiella pneumoniae will harbor vastly differing antimicrobial resistance patterns depending on the location of acquisition [7, 8]. Unsuspected resistance has implications on many levels. At an individual level, inadequate empirical
Factors Predisposing to Increased Risk of Infection and Carriage of Multiresistant Bacterial Organisms in Aeromedical Evacuees and Medical Tourists

### Facilities
- Hospital accreditation varies vastly between nations, providing variable levels of oversight for institutional infection control and antimicrobial use.
- Medical tourists may undergo procedures in unlicensed settings occasionally using unproven and experimental techniques.
- Evacuees may transit through multiple health facilities in a short space of time during the process of evacuation. For example, contemporary US military evacuees averaged 4 facilities in 7 days [16].
- Confined spaces and limited facilities of transport vehicles used for evacuation may make some regular infection control practices impossible.
- Barriers including language and differing clinical practice may limit the scope of information exchanged with a patient.

### Patients
- Common scenarios for evacuation such as road trauma and combat injuries have high background rates of secondary infection [17].
- High acuity of illness in transferred patients means they may be transferred directly from intensive care units, which traditionally have high rates of multiresistant organisms.
- Medical tourists undergoing solid-organ transplant or cancer therapy acquire the additional risk factor of immunosuppression while abroad.
- Medical tourism packages are frequently combined with a vacation, putting patients at risk for exposure to a broader range of community pathogens.

### PATIENTS AT RISK

#### Aeromedical Evacuation of Civilians

Aeromedical evacuation, defined as international patient transfer to a medical facility by long-distance air flight, is increasingly common. It is noteworthy that people with an increasing burden of comorbid disease are now traveling internationally and may have been hospitalized while abroad [10]. Collated statistics on civilian aeromedical evacuation are not readily available, although anecdotal reports indicate rising numbers [11]. A French insurer reported over 400 evacuations and repatriations in a single year [12]. The indications for transfer from a foreign hospital include a broad spectrum of medical and surgical conditions, occurring in both the military and civilian domains. Recently, mass mobilization of civilian evacuation services has been utilized in the setting of natural disasters such as the southeast Asian tsunami in 2004 and man-made disasters such as the Bali bombing terrorist attacks in 2002 [13, 14]. In both disasters, there were reports of transfer of multiresistant Gram-negative bacilli to institutions with low background rates of these organisms [4, 15].

There are factors in the dynamics of aeromedical evacuation that may increase the risk that such patients harbor multiresistant bacterial pathogens (Table 1). Two European studies have investigated rates of carriage of multiresistant organisms (MROs) in patients repatriated via air transfer. Although one study showed rates of methicillin-resistant *S. aureus* (MRSA) and multiresistant Gram-negative bacilli colonization in patients undergoing aeromedical evacuation to be similar to rates at their receiving institutions [18], a second study showed far higher rates [19]. The risk of MRSA was found to be highest in those with a prolonged intensive care unit (ICU) stay prior to transfer [18] while risk of multiresistant Gram-negative bacilli was found to be highest in patients transferred from Asia and Eastern Europe [19].

#### Aeromedical Evacuation of Military Personnel

Military patient movements are frequent, with the United States Air Force Aeromedical Evacuation system reporting over 40,000 patient movements globally during an 18-month period [20]. Recent military operations reveal a contemporary view of evacuees from the theater of war. High rates of infection caused by multiresistant Gram-negative bacilli have been reported in injured military personnel evacuated from Iraq and Afghanistan [21, 22]. Some studies estimate bacterial infection complicating 15% to 25% of admissions [17, 23]. Etiological investigation of infections has implicated both environmental contamination of field hospitals and frequent nosocomial transmission within the military health system [16, 24]. Risk factors for infection during evacuation included abdominal injuries, soft tissue injuries, and a high overall injury severity score. Additionally, the occurrence

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Table 1. Factors Predisposing to Increased Risk of Infection and Carriage of Multiresistant Bacterial Organisms in Aeromedical Evacuees and Medical Tourists

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of such infection increased the likelihood of the evacuee requiring ICU management [17]. At receiving institutions in North America, increasing MRO infection has led to a marked escalation in the use of broader spectrum and higher cost antimicrobials in the military healthcare system [21].

**Medical Tourists**

Medical tourism has been defined as “organized travel outside one’s natural health care jurisdiction for the enhancement or restoration of the individual’s health through medical intervention” [25]. With increasing globalization, such travel is now increasingly common [26]. For many years, patients have traveled internationally to access new and advanced treatment unobtainable in their home country. Patients are now increasingly traveling from developed countries to centers in South and Central America, South Africa, and Asia where treatment may be obtained at a lower cost, without the delay incurred by publicly funded health systems in their home location, or with greater privacy for cosmetic and other procedures [27, 28]. Destinations for medical tourists now encompass most corners of the globe. Patients travel internationally for procedures ranging from cosmetic surgery to fertility treatment, major joint replacement, and even life-saving cardiac surgery and organ transplant. Some health insurers in North America utilize foreign medical care in order to defray cost [26]. The American Medical Association and the American College of Surgeons have recently issued position statements pertaining to medical tourism [29, 30]. The exact numbers of medical tourists has not been documented. Recent estimates suggest that by 2012, 1.6 million patients per year will travel from North America to receive healthcare in another country [26–28]. Thailand, Hungary, India, and Singapore are all expected to receive 1 million or more medical tourists by 2012 [31].

Certain aspects of medical tourism may increase the risk of acquisition and complicate the management of MRO infection (Table 1). There have been no prospective studies of the infections associated with medical tourism, likely due to the difficulty in prospectively capturing this group. Available data come from retrospective case series and surveys of patients and physicians [32]. The largest published experiences arise from solid-organ transplantation owing to the obligate need for medical contact in the recipient’s home country [33–36]. Illustrating the difficulty of such studies, a single-center experience from North America found fewer bacterial infections in those who received transplants abroad compared with local recipients. The authors felt this was significantly confounded by the inability to measure the incidence of early transplant infection in the patients who received transplants abroad [35]. Few series have specified the infecting bacterial pathogens. Canadian experience reported 8 of 20 patients with bacterial infection after renal transplant abroad, although the location of the transplant procedure was not specified. Four of these patients suffered infection with bacteria likely producing an extended-spectrum β-lactamase (ESBL) [36].

**Care Shared Across Countries**

Similar in nature is a broader group of informal medical tourists: patients for whom care of an acute or chronic condition is spread across multiple nations. Factors influencing the country of care may include the proximity to friends and family, financial factors, and access to advanced facilities. The term “diaspora” has been used in reference to large permanent expatriate populations from many nations. Recently this term has been applied to thriving expatriate Indian and Pakistani communities, which likely number more than 24 million and 7 million individuals, respectively [37, 38]. A nation’s diaspora may maintain strong familial and cultural links to their nation of origin, including frequent return travel and potentially medical treatment for acute and chronic conditions spread across multiple nations [39–41]. This group is likely more numerous than medical tourists or aeromedical evacuees.

**INFECTIONS OF CURRENT CONCERN**

**Gram-Negative Bacilli**

*A. baumannii* in a Belgian hospital, the 2 index patients were evacuated from a Greek ICU after road trauma. Despite increased infection prevention precautions, 17 subsequent cases of a clonal isolate were identified over the next 6 months [42]. A smaller outbreak was also described in northern Italy, also secondary to evacuees from Greece [43].

A widespread carbapenem-resistant *Acinetobacter* outbreak in medical facilities involved in the treatment of aeromedical evacuees from military operations in Iraq and Afghanistan has been reported [22, 44]. More than 100 cases of bacteremia over an 18-month period occurred within military hospitals in the United States and Germany [44]. Although *Acinetobacter* is associated with traumatic injury in many settings, molecular and clinical studies have shown that the majority of infection in this outbreak was due to nosocomial acquisition [16, 24]. The United Kingdom has also reported the introduction of new strains of *Acinetobacter* from evacuees from Iraq [22]. In the setting of traumatic burns and blast injuries after the 2002 terrorist attacks in Bali, frequent *Acinetobacter* infection was noted in patients evacuated to Australia. Subsequent nosocomial spread in receiving hospitals was again reported [15].

**Bacteria Harboring KPC and NDM Carbapenem Resistance Genes**

Epidemiological investigation suggests that introduction of the *Klebsiella pneumoniae* carbapenemase (KPC) gene into several
regions has been due to carriage by the intercountry patient. Israel was the first nation outside the United States to report a large outbreak of KPC-harboring *K. pneumoniae*. Widespread healthcare-associated transmission occurred of a strain identified as of North American origin [45]. Greece has identified widespread clonal KPC-producing *K. pneumoniae* indistinguishable from contemporary Israeli clones [46]. In neither case was a single point of introduction identified. The likely index case in a single-center outbreak in Germany was a patient who had been previously hospitalized in Greece [47]. Many additional countries including the United Kingdom and France have reported episodes of colonization or infection of patients transferred from endemic countries [48, 49] (Figure 1).

The New Delhi metallo-ß-lactamase gene (NDM-1) also confers almost complete ß-lactam resistance. NDM-1 has been identified in a broad range of Gram-negative bacteria including *K. pneumoniae*, *Escherichia coli*, and *Citrobacter freundii*. Almost all isolates are also resistant to aminoglycosides, fluoroquinolones, and other classes of antimicrobials. Of concern, some isolates exhibited resistance to the agents of last resort, tigecycline and colistin [50]. The NDM-1 gene was first described in Sweden [51] and the United Kingdom [52], and was strongly associated with healthcare received on the Indian subcontinent. In the United Kingdom, 9 of 19 patients had recently been hospitalized in India or Pakistan for treatment ranging from solid-organ transplantation to cosmetic surgery. Subsequently, imported cases associated with healthcare contact in India and Bangladesh have been reported in other regions including the United States, Australia, Canada, Japan, and several European nations [39, 53, 54]. Cases have also been identified among patients repatriated to locations in Western Europe from hospitals in Balkan nations, and a cluster of cases was identified in Kenya [41, 55]. These epidemiological observations require further elucidation (Figure 1).

**Bacteria Harboring ESBL Enzymes**

Carriage of bacteria harboring ESBL enzymes by the intercountry patient is well established and still remains a significant risk [56]. Early reports include international transfer of common nosocomial ESBL-producing bacteria such as *K. pneumoniae* [57]. Current literature reflects the emergence of *E. coli* harboring CTX-M ESBLs, with healthcare-associated acquisition responsible for approximately 15% of travel-related infections due to ESBL producers in some studies [58, 59].

**Gram-Positive Organisms**

**Methicillin-Resistant S. aureus**

Almost 50 years after its emergence, the spread of MRSA by the intercountry patient still poses a threat to institutions that have maintained low MRSA prevalence. The prevalence among hospital-acquired *S. aureus* isolates in the Netherlands and Scandinavia remains <1%, contrasting with levels in other European nations and North America (6%–63%) [7]. Two outbreaks in the Netherlands were directly linked to the transfer of patients from institutions in France and Turkey where MRSA is endemic [60]. A study in Sweden demonstrated that one-quarter of 1733 MRSA cases reported between 2000 and 2003 were likely acquired abroad; over half of these were healthcare associated [61]. The potential intercountry spread of MRSA via healthcare workers, rather than patients, is illustrated by the report of a Swiss physician found to have a new nasopharyngeal colonization with a North American clone of MRSA after returning from a clinical fellowship in North America [62].

**Vancomycin-Resistant Enterococci (VRE)**

Reports of intercountry spread of VRE come primarily from molecular epidemiologic assessments. VRE clonal complex-17 (CC-17), a group consisting of a number of closely related VRE sequence types, has been responsible for VRE dissemination in countries including the UK, Australia, and North America [63]. Investigators linked a sharp rise in the rate of VRE in southwest Germany to the likely importation of CC-17 VRE to their hospital system [64]. An outbreak due to CC-17 has also been reported in Turkey [65]. Neither report identified a single point of introduction.

Clinical reports of VRE transfer between nations have been prevalent in Europe [66]. Low-incidence Nordic countries (where VRE accounts for <1% of enterococcal isolates) have had sporadic importation and outbreaks from other nations since the early 1990s [66]. Molecular studies were strongly suggestive of intercountry spread of a distinctive VRE clone from North America to Norway and also to Ireland [67]. In a prospective study from the Netherlands, VRE was identified in approximately 3% of patients repatriated from a number of countries, with Asian origin being a significant risk [19].

**Hypervirulent Clostridium Difficile**

Since the initial description of hypervirulent ribotype O27, there have been repeated descriptions of transfer of the strain via the intercountry patient [68, 69]. A retrospective study in 2007 identified the transfer of a patient infected with the hypervirulent strain from the United Kingdom to Ireland very soon after the initial descriptions in 2005; fortunately, no outbreak occurred [68]. Introduction of the strain into France in 2006, which now has sustained transmission, was speculated to be due to transfer with patients from neighboring Belgium [70]. Australia has reported a single case of importation in a patient recently hospitalized in North America [69].

**APPRAOCH TO THE PATIENT**

All hospitals should have a predefined approach to management of patients transferred from other institutions, including
1. Maintain vigilance.
   Ask specifically about healthcare contact whenever a patient reports international travel within the previous 12 months.

2. Preemptive isolation and screening should be used in patients with a history of international hospitalization and who have a high risk of carriage of multiresistant organisms.
   Isolate patients who have had direct hospital-to-hospital transfer or recent international hospitalization involving prolonged hospital stay, intensive care or critical care admission, major trauma, burns, or receipt of chemotherapy or immunsuppression (eg, solid-organ or stem-cell transplant).

3. Screening needs to be customized to the receiving institution: Focus screening on organisms that are not already endemic at your site.
   Basic screening may include axillary, inguinal, and nose/throat swabs PLUS rectal swab or stool sample PLUS clinical specimens including catheter urine, surgical drain, or wound discharges—screen for MRSA-, VRE-, and ESBL-producing or carbapenem-resistant GNB. Only screen for Clostridium difficile if diarrhea is present.

4. Receive transferred patients in an area of the hospital equipped to manage isolation for multiresistant organisms.
   Patients may initially require management in an area of higher acuity than required for their medical care (eg, patients for rehabilitation may need to go to an acute ward until screened).

5. All receiving institutions should have a readily accessible infection prevention policy defining at-risk patients, screening procedures, and preemptive isolation criteria.
   If your institution frequently receives patients from a particular location, a customized protocol should be developed and maintained for this location: Including an outline of the current pathogens of concern and empirical therapy is recommended in the case of infection.

NOTE. ESBL, extended-spectrum β-lactamase; GNB, Gram-negative bacilli; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant enterococci.

those in other countries (Table 2). Preemptive contact isolation may be considered when there is a risk of introduction of an MRO not currently found in the institution receiving the patient. In institutions with few or no endemic MROs, there will likely be a greater willingness to institute preemptive contact isolation. In some institutions, there may already be a high prevalence of MROs and it may seem to matter little that a patient has come from another institution which also has endemic MROs. However, introduction of new mechanisms of antibiotic resistance or new “hospital adapted” bacterial strains may pose risks of amplifying antibiotic resistance. An example may be the receipt in a hospital in the United States with endemic KPC producers of a patient from a hospital in India or Pakistan where NDM producers are endemic.

In the setting of management of an individual patient with suspected bacterial infection we suggest a considered approach to the use of empirical therapy (Table 3).

Healthcare staff must adopt a pragmatic and nonjudgmental approach to the management of the intercountry patient who has acquired an MRO infection. This may be challenging in the setting of a patient who has sought a healthcare intervention believed inappropriate or unethical by the home treating clinician, such as commercial organ transplantation, or experimental or cosmetic procedures. This attitude is crucial in order to avoid the patient feeling stigmatized and to facilitate open

Table 2. Recommendations for the Management of Patients Who Have Been Hospitalized Internationally

| 1. Ensure appropriate microbiology samples for the clinical presentation (eg, blood cultures, urine culture, respiratory tract cultures) if required. Notify the microbiology laboratory of the patients’ origin. They may broaden their testing beyond their normal scope (eg, detection of NDM-1, Clostridium difficile ribotype). |
| 2. If screening has identified MROs: These bacteria must be targeted in empirical therapy. If susceptibilities are available use these to guide antimicrobial selection. If susceptibilities are not available, empirical therapy may include agents such as linezolid or daptomycin (for VRE and MRSA) and polymyxin B, colistin, or amikacin for multidrug-resistant gram-negative bacilli. If available, consultation with an infectious disease physician or clinical microbiologist may be helpful in selecting the optimal agent for identified pathogens. |
| 3. If no screening results are available: Therapy must target the prevalent pathogens at the transferring institution. When possible, ascertain these by direct discussion with this institution as recent outbreaks may not be publicized. See suggestions above for empirical therapy. |
| 4. If screening does not detect an MRO: Treat as per local guidelines. However, screening is not 100% sensitive. If the patient fails to improve on empirical therapy then reassess for occult sites of infection and reculture as extensively as possible. Consider empirical therapy for organisms prevalent at the transferring institution as outlined above. |

NOTE. MRO, multiresistant organism; MRSA, methicillin-resistant Staphylococcus aureus; NDM-1, New Delhi metallo-β-lactamase; VRE, vancomycin-resistant enterococci.

Table 3. Approach to Suspected Bacterial Sepsis in Patients Previously Hospitalized in Another Country

1. Ensure appropriate microbiology samples for the clinical presentation (eg, blood cultures, urine culture, respiratory tract cultures) if required. Notify the microbiology laboratory of the patients’ origin. They may broaden their testing beyond their normal scope (eg, detection of NDM-1, Clostridium difficile ribotype).

2. If screening has identified MROs: These bacteria must be targeted in empirical therapy. If susceptibilities are available use these to guide antimicrobial selection. If susceptibilities are not available, empirical therapy may include agents such as linezolid or daptomycin (for VRE and MRSA) and polymyxin B, colistin, or amikacin for multidrug-resistant gram-negative bacilli. If available, consultation with an infectious disease physician or clinical microbiologist may be helpful in selecting the optimal agent for identified pathogens.

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NOTE. MRO, multiresistant organism; MRSA, methicillin-resistant Staphylococcus aureus; NDM-1, New Delhi metallo-β-lactamase; VRE, vancomycin-resistant enterococci.
communication of information between the patient, family, and clinician. International institutions may operate with constraints and resource limitations that are not present in the patient’s country of residence. Furthermore, the patient may have felt they had no option but to utilize the facilities available in a foreign country due to the urgency of care required or the financial cost of care at home.

Local, national, and international regulations may pertain to the notification, transit, and control of patients harboring MROs [71]. This is a complex and evolving area that varies between jurisdictions.

CONCLUSION

The management of patients transferred from other institutions is a daily reality for almost all healthcare practitioners. The patient with international healthcare contact may present to healthcare institutions in a variety of forms, ranging from the overt (eg, aeromedical evacuee) to the unsuspected (eg, elective surgical day case). In some settings, ready identification of a patient’s origin in foreign hospitals is difficult and requires specific questioning. Similarly, a multitude of communication barriers may lead to difficulty obtaining information pertaining to a patient’s medical care in another country.

Contemporary molecular epidemiological techniques have allowed us considerable insight into the origins and movement of healthcare-associated MROs. The range of potential MROs acquired by the intercountry patient is broad. We have outlined a small number with current significance. A key concept is the dynamic nature of such outbreaks. These may emerge and disseminate before reaching the general medical literature. At times, outbreaks may go undetected in their country of origin until exported with the intercountry patient [46, 50].

Figure 1. Schematic representation of epicenters (black) and reported/potential importations (gray) of *Klebsiella pneumoniae* carbapenemase (A) and New Delhi metallo-β-lactamase-1 (B) β-lactamase-producing organisms [39, 41, 45–49, 53–55].
Furthermore, emerging data now suggest that the risk of acquisition of some MROs may extend to those without healthcare contact during travel to countries of high endemicity [72, 73]. Given the large pool of international travelers, this area requires further exploration to better define risk factors and the potential magnitude of this problem.

For an individual patient, the significance of an MRO infection will largely depend on his or her current medical condition and may range from an incidental finding to a life-threatening infection. For an institution, the significance of importation of MROs depends on the preexisting milieu of MROs and the likelihood of spread, determined by infection prevention practices.

In conclusion, there are many factors that may complicate the identification and management of infections with MROs in the intercountry patient. Clinical vigilance in the form of sensitive prevention practices.

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