Clinical Microbiology and Infection 23 (2017) 673.e1–673.e8

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Patients hospitalized abroad as importers of multiresistant bacteria—a cross-sectional study

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ARTICLE INFO

Article history:
Received 22 November 2016
Received in revised form
30 January 2017
Accepted 4 February 2017
Available online 11 February 2017

Editor: A. Huttner

Keywords:
Antimicrobial drug resistance
Hospitalization
Infection control
Multidrug resistance
Travel

ABSTRACT

Objectives: The pandemic spread of multidrug-resistant (MDR) bacteria poses a threat to healthcare worldwide, with highest prevalence in indigent regions of the (sub)tropics. As hospitalization constitutes a major risk factor for colonization, infection control management in low-prevalence countries urgently needs background data on patients hospitalized abroad.

Methods: We collected data on 1122 patients who, after hospitalization abroad, were treated at the Helsinki University Hospital between 2010 and 2013. They were screened for methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-PE), vancomycin-resistant enterococci, carbapenemase-producing *Enterobacteriaceae* (CPE), multi-resistant *Pseudomonas aeruginosa* and multiresistant *Acinetobacter baumannii*. Risk factors for colonization were explored by multivariate analysis.

Results: MDR colonization rates were higher for those hospitalized in the (sub)tropics (55%; 208/377) compared with temperate zones (17%; 125/745). For ESBL-PE the percentages were 50% (190/377) versus 12% (92/745), CPE 3.2% (12/377) versus 0.4% (3/745) and MRSA 6.6% (25/377) versus 2.4% (18/745). Colonization rates proved highest in those returning from South Asia (77.6%; 38/49), followed by those having visited Latin America (60%; 9/16), Africa (60%; 15/25) and East and Southeast Asia (52.5%; 94/179). Destination, interhospital transfer, short time interval to hospitalization, young age, surgical intervention, residence abroad, visiting friends and relatives, and antimicrobial use proved independent risk factors for colonization.

Conclusions: Post-hospitalization colonization rates proved higher in the (sub)tropics than elsewhere; 11% (38/333) of carriers developed an MDR infection. We identified several independent risk factors for contracting MDR bacteria. The data provide a basis for infection control guidelines in low-prevalence countries **T. Khawaja, Clin Microbiol Infect 2017;23:673.e1–673.e8**

Introduction

Antimicrobial resistance is rapidly increasing in regions with poor hygiene and uncontrolled use of antimicrobials. Multidrug-resistant (MDR) bacteria, particularly multiresistant *Enterobacteriacae*, spreading from there across the globe constitute a universal threat to health care [1,2]. The great number of international arrivals presumably has a major effect on this spread, since travellers act as transporters of the strains [3]: 20%–60% of visitors to these regions become colonized by MDR bacteria, such as extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-PE) [3–10]. The colonization rates are highest among those returning from South Asia and Southeast Asia, followed by Africa and South America [3,5–10].

The rapid growth of international travel, with over one billion international arrivals annually, is driven by visits to developing

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http://dx.doi.org/10.1016/j.cmi.2017.02.003

countries: African and Asian travel have more than doubled during the last 15 years [11]. Hospitalization per se is known to predispose to colonization, and those heading to poor regions are more likely to be hospitalized than those opting for high-income countries [12,13]. The elderly, those visiting friends and relatives (VFR), and those with co-morbidities constitute separate risk groups for travel-related morbidity [4,14,15]. Medical tourism, a growing business, involves elective admittance to a foreign hospital. Of the roughly 500 million annual visitors to developing countries, over a million are likely to be hospitalized there [11,16]. Despite the multitude of reports on ordinary travellers [3–10], we found surprisingly limited data, only seven small studies, of multiresistant bacteria in patients hospitalized abroad [17–23]. Most of them examine only repatriated patients and centre on merely a few MDR types; none provides a detailed geographic distribution or risk factor analysis.

Although patients hospitalized abroad are recognized as a special risk group at hospitals in low-prevalence countries, establishing sound infection control guidelines is difficult in the absence of larger studies that would contain comprehensive risk factor analyses. Most low-prevalence countries only screen for methicillin-resistant *Staphylococcus aureus* (MRSA) and possibly vancomycin-resistant enterococci (VRE), but recently some countries have also begun testing for multiresistant Gram-negative bacteria (MRGN).

A revised screening programme for MRSA and a variety of intestinal MDR strains was implemented in 2010 at our hospital in Helsinki, Finland, which is a low-prevalence country. Since then, we have accumulated data about thousands of patients. The current study focuses on the extent of MDR colonization among patients hospitalized abroad in various geographic regions. Other aims of our investigation were to identify patient-level risk factors for MDR colonization and examine the incidence of symptomatic MDR infection among those colonized.

Materials and methods

Study design

Helsinki University Hospital (HUCH) provides secondary and tertiary care for 1.6 million inhabitants of southern Finland. In April 2010 HUCH implemented a screening programme for MDR infections accompanied by guidelines of mandatory contact isolation precautions for all inpatients hospitalized (24 h or longer) or operated upon outside the Nordic countries (within 12 months). These patients are screened for MRSA, VRE, ESBL-PE, carbapenemase-producing *Enterobacteriaceae* (CPE), multiresistant *Acinetobacter baumannii* (MRAB) and multiresistant *Pseudomonas aeruginosa* (MRPA). According to the guidelines, MRSA samples should be taken from nares, throat and either groin or perineum. Rectal swab or stool samples are used for screening for MRGN and VRE. Secreting wounds, indwelling catheters and other spots with increased risk are also sampled.

Using the HUCH laboratory database, we compiled a list of patients with both MRSA and MRGN samples taken between 1 January 2010 and 31 December 2013. We only included patients who had been sampled at least once for both MRSA and all the multiresistant Gram-negative bacteria; VRE cultures were not used as an inclusion criterion, and patients were selected even if the sample was missing. We only included patient charts showing (a) a history of hospitalization or invasive procedure outside the Nordic countries during the past 12 months (henceforth called hospitalization); (b) country of hospitalization; and (c) approximate time frame of travel. Patients treated in more than one geographic region and those having visited another longer than 5 days after hospitalization were excluded.

According to the Finnish Medical Research Act, a review by an ethics committee is only required in research involving intervention. The study protocol was approved by the research board of the Department of Internal Medicine of Helsinki University Hospital.

Collection of patient data, classifications and definitions

Our patient data covered the factors listed in Table S1 (see Supplementary material). Charlson co-morbidity index was calculated. The results of bacterial cultures (blood, urine, stools) were recorded. Countries were grouped into seven geographic regions (see Supplementary material, Table S1, Fig. S1). Patients treated in two countries were categorized by the one last visited.

To enable a rough comparison between emerging and advanced economies, the regions were further grouped by climate zones into temperate (North America, Oceania and Europe) and (sub)tropical (others).

The patients were classified by purpose of travel: (a) ordinary travellers (tourist and business journeys; mostly Finnish citizens), (b) VFR, and (c) those living abroad for more than 6 months a year.

Multidrug resistance detected in clinical specimens within 30 days of presentation was considered to indicate an MDR infection only if the findings were viewed as relevant by the clinicians. To keep the definition strict, patients given empiric MDR treatment and those with microbiological samples taken abroad were not classified as having a clinical MDR infection.

Microbiological methods

Methicillin-resistant *S. aureus* was screened after overnight enrichment on chromID™ MRSA (bioMérieux, Marcy-l'Étoile, France), or CHROMagar™ MRSA (CHROMagar, Paris, France), and confirmed with *S. aureus*-specific nuclease and *mecA* gene quantitative PCR. VRE was screened using enrichment Enterococcosel broth (BBL, Cockeysville, MD, USA) followed by in-house selective media as previously described [24], or CHROMagar™ VRE media. Positive findings were confirmed by in-house PCR as described by Suppola *et al.* [24].

Extended spectrum β-lactamase-PE and CPE were analysed by plating directly on CHROMagar™ ESBL and CHROMagar™ KPC, respectively. ESBL species identification was confirmed by matrix-assisted laser desorption/ionization time-of fight (MALDI-TOF; Vitek-MS, bioMérieux) and resistance was confirmed by standard CLSI method [3]. CPE species were confirmed with in-house carbapenemase gene PCR [25].

Multidrug resistant *P. aeruginosa* (strain is resistant to both ceftatzidime and meropenem) and MRAB (resistant to meropenem) were screened from ESBL and KPC plates. Cultures were tested by C-390, VITEK-GN or MALDI-TOF for species identification. Isolates resistant to meropenem for *Acinetobacter*, and both meropenem and ceftatzidime for *Pseudomomas*, were analysed by PCR for carbapenemase genes as previously described [25].

The ESBL and CPE isolates of the same species were considered separate strains if their susceptibility profiles differed substantially.

Statistics

Univariate analyses were conducted using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). For categorical variables, we used chi-squared test or one-sample binomial test, for continuous variables the Mann–Whitney *U* test or binary logistic regression was used. All tests were two-sided. Factors with a p value <0.2 in the univariate analysis were chosen for further analysis by the multivariable model with binary logistic regression; of the strongly correlating risk factors only one was picked. When selecting the