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Review

Review

Travel-acquired ESBL-producing *Enterobacteriaceae*: impact of colonization at individual and community level

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Abstract

Background: Antibiotic resistance is a rapidly increasing global emergency that calls for action from all of society. Intestinal multidrugresistant (MDR) bacteria have spread worldwide with extended-spectrum beta-lactamase (ESBL) -producing *Enterobacteriaceae* (ESBL-PE) as the most prevalent type. The millions of travelers annually visiting regions with poor hygiene contribute substantially to this spread. Our review explores the underlying data and discusses the consequences of the colonization.

Methods: PubMed was searched for relevant literature between January 2010 and August 2016. We focused on articles reporting (1) the rate of ESBL-PE acquisition in a group of travelers recruited before/after international travel, (2) fecal carriage of ESBL-PE as explored by culture and, for part of the studies, (3) analysis of factors predisposing to colonization.

Results: We reviewed a total of 16 studies focusing on travel-acquired ESBL-PE. The acquisition rates reveal that 2070% of visitors to (sub)tropical regions get colonized by ESBL-PE. The main risk factors predisposing to colonization during travel are destination, travelers diarrhea, and antibiotic use.

Conclusions: While most of those colonized remain asymptomatic, acquisition of ESBL-PE may have consequences both at individual and community level. We discuss current efforts to restrict the spread.

Key words: Extended-spectrum β-lactamase, ESBL, Escherichia coli, ESBL-PE, multi-drugresistant bacteria, MDR, travel, traveller, colonization, antibiotics, travellers' diarrhea, TD

Introduction

The multi-drugresistant (MDR) bacteria constitute a global emergency,[1] with factors such as international travel and trade contributing to its worldwide spread. The MDR bacteria, of which extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* (ESBL-PE) has become the most common type, are highly prevalent in developing regions of the (sub)-tropics. A substantial proportion of visitors to these destinations get colonized by ESBL-PE. Back home, they may spread the bacteria to their close contacts and local hospitals—and contribute to further dissemination of MDR bacteria worldwide.

ESBL-PE in Outline

ESBL are plasmid-borne β-lactamases belonging to the Ambler class A.[2] These enzymes confer to the strain an ability to hydrolyze the most commonly used β-lactam antibiotics including penicillins and oxyimino-β-lactams (e.g. cefotaxime, ceftazidime, aztreonam). The only β-lactam families that ESBL-PE remain fully susceptible to are cephamycins and carbapenems. Combinations with β-lactam inhibitors partly restore the activity of several β-lactams. However, severe ESBL-PE infections often require treatment with carbapenems, highly effective drugs[3] which should be used very prudently.

The spread of ESBL-PE has occurred as two successive waves. The first included dissemination of strains producing TEM and SHV-derived β-lactamases. These ESBL-PE mostly belonged to the *Klebsiella* and *Enterobacter* genus and spread almost exclusively within hospitals. During the 1980s and 1990s, they caused small outbreaks relatively easily contained by infection control measures.[4,5]. This first ESBL-PE wave declined after the turn of the century, only to be replaced during the last decennium by the second wave involving CTX-M-type ESBL-PE, which mainly differ by two features. First, CTX-M ESBL are mostly seen in the *Escherichia coli* species, probably because of the remarkable fit between this species and the type of plasmid.[6] Second, the spread was not restricted to hospitals but occurred also in community settings.[7]

As a result, the proportions of ESBL-PE infections have increased everywhere, consistent with the well-known parallel between colonization and infection.[8] Increasing rates have been seen in both community-acquired and nosocomial infections. According to a recent meta-analysis, colonization rates in American and European communities range from 2 to 4%, whereas those in the eastern Mediterranean, Southeast Asia and Africa reach 15, 22 and 22%, respectively, and exceed even that in the West Pacific region, with an estimated 46% carriage.[9] These regional differences are clearly seen in hospitals, especially in areas with the highest carriage rates, as shown by recent studies carried out in India[10] and Cambodia,[11] where approximately half of the bacteria isolated from blood cultures at hospitals were identified as ESBL-PE.

Risk Factors for ESBL-PE Acquisition Among Travellers

Numerous studies conducted more than a decade ago have shown that, in addition to classic risk factors,[12,13] overseas travel is associated with the acquisition of infections caused by ESBL-PE.[14] At the same time, a series of community patients with CTX-M - *E. coli* urinary tract infections (UTI) was published.[15] Although the classic risk factors for ESBL-PE were lacking, all had a recent history of travelling to the Indian subcontinent. In 2010, Tham *et al.* published an investigation among 242 travellers with travellers' diarrhea (TD), 24% of whom were found colonized by ESBL-PE.[16] In the first prospective study undertaken to quantify the rate of ESBL-PE acquisition, which was reported in 2010 by Tängden *et al.*, ESBL-PE were found in 24% of the cohort of 105 travellers.[17] The highest risk destination was India (88%), followed by Asia (32%) and the Middle East (29%). These findings were confirmed by later investigations[16–31] (Table 1), many of which also looked at risk factors predisposing travellers to ESBL-PE acquisition. Although the accumulated data are somewhat heterogeneous regarding study designs, risk factors tested or traveller populations, certain conclusions are evident: ESBL-PE acquisition is driven at least by three independent factors: (i) country visited, (ii) occurrence of TD and (iii) use of antibiotics during travel.

Travel to tropical regions like South Asia and Southeast Asia are one of the most frequently identified risk factors.[17,18,21,23,25–29,31] Acquisition rates as high as 93 and 91% have been found among subjects visiting Vietnam and India, respectively.[28] The main factors accounting such rates in high-risk regions include massive uncontrolled use of antibiotics to treat both humans and animals, high percentage of ESBL-PE carriage among the population, inadequate hygiene, and vast contamination of local environment, drink and food.[32–35]

Association with TD is also clearly shown in risk factor studies[17,18,21,22,25,26,28] (Table 1). It appears reasonable to think that uncontrolled conditions in TD lead to intestinal dysbiosis that decreases resistance to colonization by exogenous bacteria, among these MDR in the surroundings. The finding of antibiotic exposure as a risk factor[25,28,29] accords with reports on antibiotics predisposing to ESBL-PE carriage within community and at hospitals.[36,37] Individual antibiotic classes have not been explored separately among travellers due to inadequate numbers of cases, but data exist both for fluoroquinolones[25,30] and β-lactams[28] as factors predisposing to ESBL-PE acquisition. By altering the intestinal microbiota, antibiotics disrupt its ability to resist colonization by new intruders, a phenomenon well known as colonization resistance.[38] The substantial impact of TD and antibiotics is well exemplified by a recent study: among travellers to Indian subcontinent, ESBL-PE was contracted by 23% of those staying healthy, 47% of those with TD but not using antibiotics, and 80% of those with TD who took antibiotics.[25,39]

Other predisposing factors (Table 1) are reported more infrequently, either because they are only rarely tested or the specifics varying among the study populations, such as age,[21,25,31] type of travel[24,28] and consumption of ice cream and pastries.[24] Data on the duration of exposure are not consistent.[22,24,25,28] Malaria prophylaxis appears not to have an impact,[25] yet further studies are needed. Only one report has addressed loperamide intake,[40] finding no association with increased risk of ESBL-PE acquisition unless combined with antibiotics.

Consequences for Travellers, Contacts and Community

In a vast majority of cases, ESBL-PE colonization remains asymptomatic and does not lead to infection. The consequences, even at the individual level, can be substantial if the bacteria succeed in causing an infection, since MDR infections have a higher risk of treatment failures, longer hospitalization stays and greater mortality.[41] Data on the actual risk of a colonized traveller developing an infection are scarce. Even though international travel is confirmed as a risk factor for contracting ESBL-PE UTI,[42,43] the actual risk appears only low.[25,27] In a recent study drawing on a survey of laboratory databases, none of 90 colonized travellers had laboratory-verified pyelonephritis or any other severe ESBL-PE infections in a 1-year follow-up;[25] still, the most common *E. coli* infection, lower UTI, was not addressed since urine cultures are not taken from patients with cystitis symptoms. Another study explored ESBL-PE prevalence rates among patients attending an Infectious Diseases ward and found an increased risk of ESBL-PE carriage and symptomatic ESBL-PE infection among patients with a history of international travel during the past 12 months: 23/191 (23%) patients with travel history were colonized and out of these, 4/23 (17%) had UTI and one had bacteremia (4%) with a culture-verified ESBL-PE.[27] The low risk among healthy travellers concurs with a recent study showing the vast majority of travel-acquired ESBL-PE to lack virulence factors of uropathogenic strains.[44]

Table 1. Studies of acquisition of extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-PE) by travellers

First author (year)	Origin of travellers; prospective (P), retrospective (R)	Number of subjects, years data collected	Pre-travel ESBL-PE cases/all (%)	Post-travel ESBL-PE cases/all (%)	Risk factors in uniariate/multivariable analysis
Tham *et al.*, 2010[16]	Sweden (R)	242 with TD, 2007–08	NA	58/242 (28)	NA
Tängden *et al.*, 2010[17]	Sweden (P)	100, 2007–10	1/105 (1)	24/100 (24)[a]	India, TD
Kennedy *et al.*, 2010[18]	Australia (P)	102 2008–09	2/106 (2)	22/102 (22)[a]	Asia, South America, Middle-East, Africa, TD, AB use[b]
Peirano *et al.*, 2011[19]	Canada (R)	113 with TD, 2009	NA	26/113 (23)	NA
Weisenberg *et al.*, 2012[20]	USA (P)	28, 2009–10	1/28 (4)	7/28 (25)[a]	NA
Östholm-Balkhed *et al.*, 2013[21]	Sweden (P)	231, 2008–09	6/251 (2)	68/226 (30)[a]	Asia, Africa, Indian subcontinent, TD, Age
Lausch *et al.*, 2013[22]	Denmark (R)	88, 2011	NA	11/88 (13)	TD, duration of travel
Paltansing *et al.*, 2013[23]	The Netherlands (P)	370, 2011	32/370 (9)	113/338 (33)[a]	South and East Asia
Kuenzli *et al.*, 2014[24]	Switzerland (P)	175, 2012–13	5/175 (3)	118/170 (69)[a]	Duration of travel, type of travel, ice cream and pastry
Kantele *et al.*, 2015[25]	Finland (P)	430, 2009–10	5/430 (1)	90/430 (21)[a]	Destination, TD, AB use, age
Lübbert *et al.*, 2015[26]	Germany (P)	205, 2013	14/205 (7)	58/191 (30)[a]	India, South-East Asia, TD
Epelboin *et al.*, 2015[27]	France (R)	191 admitted to ID ward[c], 2012–13	NA	23/191 (12)	Asia, visiting friends and relatives or migrants
Ruppé *et al.*, 2015[28]	France (P)	574, 2012–13	81/700 (12)	292/574 (51)[a]	Asia, Sub-Saharan Africa, TD, AB use, type of travel
Angelin *et al.*, 2015[29]	Sweden (P)	107, 2010–14	7/99 (7)	35/99 (35)[a]	South-East Asia, AB use
Reuland *et al.*, 2016[30]	The Netherlands (P)	445, 2012–13	27/445 (6)	98/418 (23)[a]	Combination of TD and AB use
Barreto Miranda *et al.*, 2016[31]	Germany (R)	211 with TD, 2013–14	NA	107/211 (51)	South-East Asia, Indian subcontinent, age

[a]Cases with newly acquired ESBL-PE.
[b]Risk factors analyzed for a variety of resistant *Enterobacteriaceae* (not only ESBL-PE).
[c]Infectious Diseases ward.

On the other hand, in other investigations, a pandemic spread of the uropathogenic ST131 ESBL *E. coli* has been reported.[45]

Travel-acquired ESBL-PE tends to disappear fairly quickly after returning home: only 5–35% of those with travel-acquired ESBL-PE were carriers 6 months later.[17,23,26,28] In one study, a cohort of 245 travellers with travel-acquired ESBL-PE were subjected to monthly monitoring. The strain was found in one-third of the cohort (33.9%, 83/245) after 4 weeks, but only 5% at 6 months.[28] Thus, the risk of ESBL-PE transmission or infection may not be a concern beyond a few months post return. Interestingly, one study identified antibiotic use[46] and another reported vegetarian diet and owning a cat[31] as risk factors for prolonged intestinal carriage by resistant bacteria.

The consequences at the community level refer to sequelae of bacterial transmission to new hosts in the home country. Household contacts of ESBL-PE carriers have been shown to be at risk of colonization.[47,48] In a study among ESBL-PE positive travellers, 18% (2/11) of close contacts acquired the same ESBL-PE[23]—and possibly ran the risk of an ESBL-PE infection comparable to that of the initially colonized traveller. Such transmission may not only affect household contacts; eventually, the bacteria can reach local hospitals. Travellers' role in spreading this bacteria should not be neglected, as there are hundreds millions of annual visitors to regions with poor hygiene,[49] a continuous flux of air traffic with three billion annual passengers, and large-scale migration exemplified by the recent wave of refugees into Europe. A recent investigation identified refugees from Syria to Germany as potential sources for transmission of MDR bacteria,[50] showing their ESBL-PE carriage rate to be around 35%, thus exceeding the 5% rate estimated in Germany. Even if the number of refugees has recently increased considerably, it is far lower, however, than that of returning travellers with similar colonization rates.

The risk of colonization by ESBL-PE and other MDR bacteria has been shown to be particularly high among travellers hospitalized abroad,[51,52] especially if treated on high-risk wards like intensive care units. This health risk includes not only an increased colonization rate but also a greater likelihood of infection complications related to surgery and other medical care. Data on the rate of MDR acquisition during hospitalization abroad are scarce. One study of patients repatriated or recently hospitalized overseas reported ESBL-PE a carriage rate of 48% and, alarmingly, carbapenemase-producing *Enterobacteriaceae* or glycopeptid-resistant enterococci were identified in 11% of the subjects.[53] Another investigation carried out among 235 patients transferred from overseas or high-risk regions in Switzerland during 2012–13 identified as risk factors for MDR-acquisition an active infection and recent hospitalization outside Europe, especially in South and South-East Asia.[51] Hospitalization after return may entail a substantial risk of spreading MDR to local hospitals in low-prevalence countries, especially if the patients are not flagged upon admission into a home country hospital.

Efforts to Decrease ESBL-PE Transmission by Travellers

While there is no single way of halting the worldwide emergence of antibiotic resistance, all reasonably possible means should be used

to combat it. Preventing colonization offers one logical approach to restricting travel-related spread and, therefore, current travel advice should focus on identified risk factors (Table 1). Avoiding travel to high risk regions is not within the scope of this paper. Those heading there should be actively advised by travel medicine practitioners about two main risk factors, TD and antibiotic use.[39] While prevention of TD by taking hygiene and food precautions has proved unsuccessful,[54,55] antibiotic use during travel can be restricted. After all, these drugs are for the most part used against TD, a disease with mainly spontaneous recovery.

Accordingly, apart from specific groups, a UK guideline advises about antibiotic use for self-treatment as follows: 'If diarrhea is severe or associated with blood and mucous in the stool, medical attention must be sought. If no medical treatment is readily available antibiotic self-treatment may be used'.[56] Similarly, a Finnish guideline only recommends antibiotics for treating patients with a high fever, bloody stools, an exceptionally severe illness or deteriorating condition, and for specific groups with an underlying disease which might deteriorate because of TD or lead to particularly serious symptoms.[57] Antibiotics are not recommended for the prevention of TD at all[57] or only in special circumstances.[56] Instead of antibiotics, medications with impact on gastrointestinal functions have been recommended for mild/moderate TD.[56,57] Interestingly, a recent review on loperamide found only meager data comparing the efficacy of loperamide with that of antibiotics, and reported a lack of studies that would adequately show the superiority of one of these over the other.[58] In a recent analysis, antibiotics, both when taken alone and together with loperamide, were found to predispose to ESBL-colonization (40 vs. 70%), while loperamide used singly showed rates similar to a group taking no medications (20 vs. 21%).[40]

It is not possible to screen all travellers upon return. However, when admitted to hospitals, a risk evaluation is needed, and to prevent secondary cases, contact precautions should be taken to contain the spread of MDR bacteria. Special emphasis should be put on patients with the highest probability to spread the bacteria (i.e. those treated abroad at ICU, those with urinary catheter, wounds or a history of antibiotic intake). Currently, hospitals do not have risk-based guidelines, but many use contact precautions for travellers hospitalized abroad, and screen them for colonization by various MDR bacteria. Since these guidelines vary considerably between hospitals and countries, consensual guidelines would be valuable.

Conclusion

As ESBL-PE have become highly prevalent in developing (sub)-tropics regions, a substantial proportion of visitors to these destinations get colonized—and remain carriers for several months. Major risk factors for colonization include destination, TD and antibiotic use. ESBL-PE carriage mostly remains asymptomatic. The risk of clinical ESBL-PE infection is small, but the disease tends to entail treatment failures and even increased mortality. Travellers may spread the bacteria to their household contacts and, eventually, hospitals in their home countries. Further studies of travellers are needed to address the impact of various antibiotic classes and the risks at individual and community levels. The bottom line is that hundreds of millions of people visit tropical regions annually—and a substantial proportion of them do contribute to the transport of ESBL-PE worldwide.

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