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General review

Travel and acquisition of multidrug-resistant Enterobacteriaceae

Voyages et acquisition d'entérobactéries multirésistantes

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Abstract

Bacterial resistance to antibiotics is considered a major threat to health. Enterobacteriaceae have increasingly become resistant to antibiotics through the acquisition and dissemination of extended-spectrum beta-lactamases (ESBL) that confer resistance to most beta-lactams. While ESBL-producing Enterobacteriaceae were formerly restricted to hospitals, they have now spread to community settings, especially in developing countries. The tremendous expansion of international travels contributed to the importation of multidrug-resistant Enterobacteriaceae (MRE) to low prevalence countries. Several studies reported that 21 to 51% of healthy travelers acquire a MRE when travelling abroad, depending on the visited region (Asia, and especially South Asia being associated with the highest risk – up to 85%). Traveling to Africa or the Middle East is associated with lower but still disturbing rates (13–44%). In addition, the occurrence of digestive disorders and/or diarrhea and antibiotic intake increase the risk of MRE acquisition by 2–3 folds. After traveling though, the length of MRE carriage seems to be short (< 1 month) and the risk of transmission within the household appears to be low. Nonetheless and beyond the intestinal carriage of MRE, traveling to endemic areas has also been pointed as a risk factor for infections involving MRE, mainly urinary tract infections.

Keywords: Enterobacteriaceae; Extended-spectrum beta-lactamase (ESBL); Multidrug resistance; Travel

Résumé

La résistance aux antibiotiques est considérée comme une menace majeure. Les entérobactéries sont de plus en plus résistantes au fil du temps en raison de l'acquisition et de la dissémination des BLSE qui confèrent la résistance à la majorité des bêtalactamines. Après avoir été principalement isolées dans les hôpitaux, ces entérobactéries multirésistantes (EMR) disséminent dans la communauté, particulièrement celle des pays en voie de développement. L'augmentation des voyages internationaux a favorisé l'importation des EMR dans les pays à faible prévalence. Les taux d'acquisition d'EMR au cours d'un voyage varient de 21 à 51 % chez les voyageurs sains, selon les études et les zones géographiques visitées. Après un voyage en Asie, particulièrement en Asie du Sud, les taux d'acquisition peuvent atteindre 85 %. Un voyage en Afrique ou au Moyen-Orient est associé à des taux plus faibles mais inquiétants (13–44 %). Outre la destination de voyage, les facteurs de risque associés à l'acquisition d'EMR sont troubles digestifs, diarrhées, prise d'antibiotiques. La durée de portage des EMR suite à un voyage semble toutefois courte (< 1 mois) et le risque de transmission aux personnes vivant sous le même toit est également faible. Au-delà du portage sain, les voyages en zone d'endémie ont également été identifiés comme facteur de risque d'infection à EMR, notamment d'infections urinaires.

Mots clés : Entérobactérie ; Bêtalactamase à spectre étendu (BLSE) ; Multirésistance ; Voyage

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The rise in bacterial resistance to antibiotics has become one of the major threats to public health worldwide. The French Burden study conducted by the French National Public Health Agency (Santé Publique France) reported that more than 150,000 patients per year contract a multidrug-resistant infection and nearly 12,500 of them die [1]. Jim O'Neil compiled a report commissioned by the British government and predicted that antimicrobial resistance will be responsible for 10 million deaths per year if nothing is done. Such figure would be higher than cancer-related deaths [2]. Bacterial resistance has always been observed, and bacteria have always managed to circumvent antibiotics aimed to kill them. Research also always led to the development of new antibiotics active against these resistant bacteria. However, the launch of new molecules has been slowing down over the past years and an imbalance between the emergence of multidrug-resistant bacteria and the availability of new drugs may be observed. The most worrying increase can be observed among Enterobacteriaceae strains. With *Escherichia coli* as their leading bacterium, Enterobacteriaceae's natural habitat is the digestive tract of humans and animals. They are frequently observed in hospital-acquired and community-acquired infections such as urinary tract infections, bacteremia, intraabdominal infections, and pneumonia (especially ventilator-associated pneumonia). The selection pressure caused by the extensive use of antibiotics in humans and animals led to the substantial increase in bacterial resistance among this antibiotic class [3]. Multidrug-resistant Enterobacteriaceae (MRE) include extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E), plasmid-mediated cephalosporinase-producing Enterobacteriaceae (pAmpC-E), and carbapenemase-producing Enterobacteriaceae (CPE). The dissemination of ESBL strains among Enterobacteriaceae was the starting point of the pandrug resistance among these strains. ESBL confer resistance against almost all beta-lactam antibiotics, which is the most frequently prescribed antibiotic class apart from carbapenems (and other inconstantly active antibiotics such as cefoxitin, piperacillin-tazobactam, and temocillin) [4]. ESBL-E are also frequently resistant to antibiotic classes prescribed as an alternative to beta-lactam antibiotics such as fluoroquinolones, co-trimoxazole, aminoglycosides, or tetracycline [4]. Carbapenems are considered the treatment of choice for ESBL-E severe infections [5]. With the increased incidence of ESBL-E infections, carbapenem consumption automatically increased over the past 10 years thus contributing to the emergence and spread of carbapenem resistance, especially through the acquisition of carbapenemases [6]. These enzymes affect all beta-lactam antibiotics. Physicians are left with very few therapeutic alternatives such as colistin and tigecycline [7]. The recent identification of a resistance mechanism that could be transferred to colistin (*mcr* gene) among Enterobacteriaceae strains thus poses the threat of a new post-antibiotic era [8,9].

Bacterial multidrug resistance has long been restricted to hospital settings, with Enterobacteriaceae outbreak known as "hospital outbreak" and with TEM- or SHV-type ESBL-producing *Klebsiella pneumoniae* or *Enterobacter* sp. [10,11]. As of the year 2000, a new type of ESBL known as CTX-M started to disseminate [12]. An epidemiological switch was then observed as this enzyme's preferential host was *E. coli*, a species carried by all subjects while other Enterobacteriaceae strains are inconstantly carried by subjects. Multidrug resistance can now be observed in community settings, and one may observe the progressive increase in community carriage of ESBL-E and related infections [13,14], for which the emergence and dissemination of CTX-M-type ESBL worldwide are the main causes [15,16]. However, the prevalence of ESBL-E community carriage differs by country. The highest prevalence of ESBL-E community carriage is observed in low-income countries. In 2010, Woerther et al. estimated the community carriage of ESBL-E at 70%, 35%, and 15% in Asia, Eastern Mediterranean Basin, and Africa, respectively (Fig. 1) [13]. The poor hygiene and the uncontrolled antibiotic consumption observed in low-income countries most certainly contributed to the dissemination of these enzymes through fecal transmission. By contrast, the prevalence of ESBL-E carriage in European and North American community settings remains quite low (< 10%) even though steadily increasing [13,17,18]. It is thus expected that people traveling from a low-prevalence area to an endemic area are at risk of acquiring multidrug-resistant bacteria.

This issue is hardly new. As of 1990, Murray et al. reported the acquisition of multidrug-resistant *E. coli* strains in healthy subjects who did not take any antibiotics after returning from Mexico [19]. However, these observations did not raise any concerns at that time because even though multidrug-resistant (to ampicillin, chloramphenicol, co-trimoxazole, tetracycline, and/or streptomycin) these strains were still susceptible to many antibiotics, including to third-generation cephalosporins that had been commercialized in the early 1980s [19].

Interest in this issue was renewed at the end of the years 2000s with the marked increase in ESBL-E infections in community settings (especially in tropical countries), but also with the constant rise in air traffic and international travels. The number of international tourists kept on increasing each year (Fig. 2), reaching 1.2 billion in 2015 while it was estimated at only 527 million 20 years earlier [20]. A total of 23.8 million of French people traveled abroad in 2015, including 1.7 million in America, 1.6 million in Africa, and 1.3 million in Asia [21].

1. Travels – a source of multidrug-resistant bacteria acquisition

The first studies on ESBL-E acquisition when traveling abroad were performed in Sweden. Almost 10 years ago, Tham et al. already reported that among 242 Swedish patients consulting for diarrhea after traveling abroad, 24% presented with ESBL-E colonization. The authors also reported differences across visited countries as 37% of patients traveling outside Europe had been colonized with ESBL-E versus 3% of those traveling within Europe. The highest rate of colonization was observed among patients traveling back from India (79% of acquisition) [22].

The first study of ESBL-E acquisition among healthy travelers was then published in 2010. Rectal swabs were collected from 100 Swedish travelers before and after the trip, and results