Narrative review

What is the impact of international leisure travel on the acquisition of multi-drug resistance in healthy persons?

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Abstract

There is gradually occurring a worldwide rise in antibiotic resistance. Several risk factors, such as antibiotic use, geographical areas and travelling, have been identified. The aim of this narrative review is to focus on the risk factor of travelling by summarizing the current literature on the impact of international leisure travel on the acquisition and colonization of multi-drug resistance (ESBL). The infection incidence resulting from acquisition and additional travel-associated risk factors will be discussed. Further research is needed to assess the actual severity and to develop guidelines to contaminate the resistance crisis.

Key words: Antibiotics; ESBL; acquisition and colonization; international travel; infection rate.

Introduction

Antibiotics are chemical substances that can either kill bacteria or inhibit further growth and in this way fight infections. These substances can distinguish the difference between a bacterial cell and an animal cell (e.g. cell wall) and because of this the animal cells will be not be affected. The characteristics of the bacterial cell will be modified by the antibiotic. The different types of antibiotics all have their own mechanism for killing the bacteria. An example of such a mechanism is the inhibition of certain enzymes to prevent cell division, as is used in fluoroquinolone antibiotics. But the most common is the group that interferes with the cell wall synthesis, which are mostly the beta-lactam antibiotics. Penicillin is an example of such a beta-lactam antibiotics that interferes with bacteria synthesis. These beta-lactam antibiotics are worldwide the most frequently used antibiotics in the fight against bacterial infections due to their wide range. However, there is a drawback to the excessive use of the antibiotics since there is a worldwide increase in antibiotic resistance, which abolishes the effects of antibiotics. Some bacteria are naturally resistant but bacteria can also become resistant via a genetic mutation or by acquiring resistance from another bacterium. This resistance can make bacteria insensitive to a certain type of antibiotic for which it first
was sensitive. The bacteria continue to multiply even in the presence of a therapeutic amount of antibiotics. In the United States the Center for Disease Control and Prevention estimated in 2013 that antibiotic resistance was responsible for more than two million infections and 23,000 deaths each year at $20 billion of direct costs. In Europe, an annual 25,000 deaths are attributable to antibiotic resistance infections.\textsuperscript{2} Of particular concern are those bacteria that are multi-drug resistant, i.e. that are insensitive to more than one type of antibiotic, such as the extended-spectrum beta-lactamase producing (ESBL) bacteria. These ESBL producing bacteria can inactivate the effect of most β-lactam antibiotics by cleaving off the β-lactam ring. The produced enzymes mediate resistance to all penicillins, first, second third generation cephalosporins and aztreonam. However, ESBL do not yet mediate resistance to cephemycins and carbapenems.\textsuperscript{3}

The rise in the prevalence of single and multi-drug resistance is a worldwide phenomenon. Even if resistance emerges only in one country, it can spread easily to other countries and put others at risk. For example the ESBL producing \textit{Enterobacteria} (ESBL-PE) are rising and scattering in an alarming rate throughout Europe. Even though there may be great differences in degree between the European countries, still almost every European country has experienced an outbreak of an ESBL producing organism.\textsuperscript{4} However, outside Europe the antibiotic resistant problems are even of a greater scale, especially in developing countries such as India, Pakistan and China but also in the African continent possibly because of overcrowding and bad hygiene (figure 1).\textsuperscript{5} In these countries the antibiotic use is also often unregulated and therefore frequently misused and overused. On the one hand patients do not have access to life-saving antibiotics when needed while on the other hand patients are treated with antibiotics in situations where these are not the standard treatment such as a common cold or uncomplicated cases of diarrhea.\textsuperscript{6}

A situation analysis about resistance in India provided some possible reasons for overuse, which are similar to the reasons in other countries.\textsuperscript{7} These reasons include:

- Lack of microbiology facilities.
- Doctors prescribing antibiotics to any patients with a fever, taking it as a sign of bacterial infection.
- Doctors satisfying patient expectations.
- The public’s lack of knowledge about the (in)appropriate use of antibiotics.

Figure 1. Worldwide map with the percentage of resistance per country
Limited access to basic medical care also plays an important role in the overuse of second-line antibiotics such as carbapenems (β-lactam antibiotic). For the greater part, the citizens of India live in rural areas where hospitals are often understaffed and lack basic equipment and medication. This leads to the rural patients turning to local pharmacists which can be confirmed by fact that the retail sales of carbapenems increased nearly six times, from 0.21 units per million in 2005 to 1.23 in 2010. This was compared to the United States, which seem to have a stable retail sale (figure 2).

*French West Africa includes Benin, Burkina Faso, Cameroon, Congo, Gabon, Guinea, Ivory Coast, Mali, Senegal and Togo.

Another comparison was made, this time between the Netherlands, the USA, French West Africa, India and Pakistan, in which India and Pakistan had the highest rise in retail sales while the other three stayed quite stable or increased in smaller degree (figure 3).

The acquisition of antibiotic resistance bacteria also happens mainly in these foreign countries which can make international travelling a risk factor which needs to be examined. It is important to understand in which degree travelers acquire ESBLs during their international stay as this information can be used to establish guidelines, e.g. screening before entering a country. This is important because the antibiotic resistance problem keeps rising and without effective antibiotics, more simple infections such as food poisoning can be fatal. Furthermore are there many routine medical procedures that rely on antibiotics to prevent infection and these will also become more and more difficult to safely perform. The countries themselves have a higher prevalence of ESBL which contributes to the acquisition but also the fact that there are more and more people travelling to these places causes a rise in the acquisition.

The aim of this review is to summarize the current literature on the impact of international leisure travel on the acquisition and colonization of multi-drug resistance. A further focus will be made on infection incidence resulting from acquisition and additional travel-associated risk factors.

**Method**

For this narrative review several databases were consulted. An overview of these database, the key words searched in the database, the number of hits and the number of works included are shown in table 1 (table 1). The main databases used were Pubmed and Google Scholar. A time-frame was set as one of the criteria and thus papers that were published 15 years ago or earlier (<2002) were excluded. As for language as a criteria, articles in Dutch, English and German were searched and included. In Pubmed an additional inclusion criteria for species was taken into account and only articles about humans were included. The databases were used to retrieve
information on international travelling and resistance bacteria, especially the association between travelling and resistance by ESBL. Furthermore a search was conducted for articles on the infection rate and prevalence after ESBL acquisition.

**Results**

**Colonization of antibiotic resistant bacteria in travellers**

The colonization of antibiotic resistant bacteria does fundamentally not cause issues in healthy subjects, however when the bacteria starts to cause an infection it can give problems as it becomes difficult to treat. The infection always comes after colonization but a colonized person does not necessarily have to become infected. One of the risk factors for the acquisition of ESBL producing bacteria that is seen more and more often is the aspect of international travel. However the incidence rates may vary considerably due to geography. The colonization and acquisition rate in travelers after

<table>
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For articles on the infection rate and prevalence after ESBL acquisition.

With regards to colonization rate, a prospective study with Swedish volunteers examined the pre- and post-travel prevalence of ESBL-producing *Escherichia coli* strains in fecal samples.\textsuperscript{10} From the 100 included participants (excluding five due to pre-travel acquisition or non-completion) 24 (24%) were colonized with the ESBL-producing *E. coli* after the trip. While comparing the colonization rate before travel to the rate after travel, a statistically significant difference (p < 0.001) was found. The colonization even turned out to be persistent in five from the 21 volunteers (three persons
were excluded due to not providing a follow-up sample) after a follow-up of six months. Besides that, three participants, which did not have persistent E. coli colonization, developed an infection. Another prospective study investigated the acquisition rate after travelling and the persistence during follow up. From the 1847 travelers that had no ESBL-E pre-travel 633 returned with acquired ESBL-E strains, resulting in an average acquisition rate of 34%.\textsuperscript{11} The highest acquisition rate resulted from Southern Asia (75%) and East and Central Asia (48%). During the follow up, the sustained colonization with multidrug resistant bacteria decreases from 42.9% after the first month to 11.3% after twelve months of return. Rúppe et al also conducted a study in which 574 subjects were followed pre and post travel to the tropics (sub-Saharan, Africa, Latin America and Asia).\textsuperscript{12} From these 574 subjects at least one multidrug-resistant Enterobacteria (MRE) was acquired by 292 participants (50.9%). In terms of persistence, the first follow up after one month consisted of 83 subjects (33.9%) that were still positive for MRE from the 245 that provided a follow-up sample. During the following months participants were lost or became negative for MRE and after twelve months five (2%) of the original 245 that provided a follow-up sample were still positive.

Östholm-Balkhed et al conducted an observational prospective cohort study and showed the incidence of ESBL acquisition in Swedish individuals.\textsuperscript{13} In their results 30% (68 participants) of the participants that had no ESBL-PE in their stool samples prior to travel, acquired ESBL-PE during travel. As regards to international travel as risk factor, the geographical area visited was the most important one as shown in their univariate analysis. The highest risk was present in the Indian subcontinent in which travelers have an almost 25 times as high odds of getting colonized by ESBL-PE (OR 24.8 P<0.001). However the study found that the duration of the visit did not have an effect on the risk of becoming colonized. Thus a longer travel duration does not necessarily increase the risk of acquiring multidrug resistant bacteria which could mean that the colonization happens during the early stages of travelling.

\textbf{Infections caused by ESBL}

It is becoming more and more clear that international travel can be linked to higher acquisition rates. However it is not just associated with an asymptomatic acquisition but also with an increased risk for community-acquired infections with for example ESBL-producing enterobacteriaceae.\textsuperscript{14} Due to this increased risk, infection analyses may be useful to identify the actual severity of the multidrug resistance bacteria rise. Infections caused by these multidrug-resistant organisms pose challenges for treatment since therapeutic options are limited and hospitalization is prolonged. With regard to the infection rate an American case-case control study was conducted in patients (children 0 – 18 years) with ESBL and patients with non-ESBL infections.\textsuperscript{15} Of the 1258 patients that were positive for either E.coli or Klebsiella there were 76 with ESBL (6%). Within these 76 patients 85 separate ESBL infections occurred, of which 9 were episodes of recurrence. Among the ESBL group 11% had travelled internationally in the previous 6 months and with the multivariate analysis international travel was the only aspect that had a significant difference. As for infection in Europe, several studies conducted in eight European countries between 2003 and 2006 showed that from 1,941 E.coli strains a total of 148 displayed reduced susceptibility to ciprofloxacin and caused uncomplicated urinary tract infections.\textsuperscript{16} Ciprofloxacin is a broad-spectrum fluoroquinolone antibiotic that inhibits certain enzymes to prevent cell division. Even though it is not a beta-lactam antibiotic the research is of importance in illustrating the size of the problem. The majority of these microorganisms even carried resistance to two or more additional drugs, besides the ciprofloxacin. In this study international travel was not taken into account, however a strain of ESBL-negative ST131 was described which has emerged internationally as a multidrug-resistant pathogen.

A matched cohort study from 2010 till 2013 compared 60 patients with urinary tract infections (UTI) due to ESBL producing E.coli to 60 patients with UTI due to non-ESBL producing E.coli.\textsuperscript{17} This was done in order to estimate the costs that infections by ESBL-PE bring along. The infections caused by the ESBL E.coli are associated with inadequate prescribed antibiotic treatment and increased use of health care resources, which in turn raise the costs. The results show that the ESBL-E.coli infection costs more than the non-ESBL-E.coli infection (€4980 respectively €2612).

\textbf{Travel-associated risk factors on acquisition}
Next to the geographical area visited there are travel-associated factors that might also contribute to an increase in acquisition rate. In the previously mentioned Swedish prospective study by Tängdén et al, risk factors that were associated with travelling were also examined.\textsuperscript{10} The region visited was one factor, in which the rate of acquisition was once more the highest in travelers visiting India (88%) followed by Asia, with India excluded (32%) and the Middle East (29%). The other regions were quite lower (<13%) and in some regions the rate was even 0%. Another factor that turned out to be of significance was the idea that participants who acquired ESBL-producing \textit{E. coli} were more likely to have had gastroenteritis during the trip than participants who did not acquire the \textit{E. coli}. In the Swedish observational prospective cohort study mentioned previously, there were more risk factors besides the region that was visited during the travel. Symptoms during travel such as fever, diarrhea and other gastrointestinal symptoms also turned out to be significant as these increased the risk of acquisition. However in the final model, only diarrhea and other gastrointestinal symptoms increased the odds of becoming a carrier at a significant level (OR=2.46 respectively OR=2.99).

The study from Rüppe also examined other variables associated with MRE acquisition.\textsuperscript{12} In a univariate analysis the factors of diarrhea during travel and the type of travel (e.g. all-inclusive, family visits, backpacking) were identified. The presence of diarrhea during travel increased the odds of acquiring MRE with a significant level of $p < 0.001$ (OR=1.89). Regarding the type of travel an all-inclusive resort posed the lowest threat (OR = 1) while family visit, backpacking and organized tour again increased the odds (OR=2.23, OR=2.96 and OR=3.07 respectively).

**Discussion**

**Limitations**

Research on international travel is of high importance since as a risk factor only a few studies have evaluated its impact. Especially prospective studies would be ideal since now most articles have conducted a retrospective study. Another gap is the travel-associated risk factors, since little is known about for example the type of travel, the accommodation and the duration of the travel. The duration of the colonization is also an important aspect, as a decrease in colonization is present. However the factors that might increase or decrease the duration still need to be investigated. An important limitation of this review is the fact that the acquisition in children and/or elderly after international travel are not taken into account. Only the study by Strysko eventually names international travel as a risk factor for the acquisition of ESBL in children.\textsuperscript{15} Also there have been studies other regarding ESBL \textit{E.coli} or/and \textit{Klebsiella} acquisition in children and whether these bacteria cause infections. However most of these corresponding studies do not take international travel into account. Concerning elderly, the same observation can be made. There have been studies focused on ESBL in elderly, with for example regard to living at home or in a nursing home. However, in these studies none of the elderly travelled and thus international travel was not taken into account.

Another limitation of this review itself is the focus on the size of the problem and its impact but not on what needs to happen next. There are no guidelines or ideas mentioned about what can be done. In future reviews, the focus should be on the guidelines and solutions to contaminate the resistance crisis. For this it is also important to conduct studies among several populations (e.g. children/elderly/adult, male/female, per nationality) to determine which groups have the highest risk. To obtain these results, every country should perform a study, preferably a prospective one, in different age categories to assess the different risk groups. Especially since data on the acquisition and carriage of ESBL producing bacteria in healthy individuals are lacking for most countries. However it is also not realistic to expect every country to perform a study, thus perhaps instead of countries regions can be taken (e.g. The UK, the Netherlands, Belgium, Luxemburg, France, Spain and Portugal as Western Europe). This research is required for healthcare facilities, physicians and even the tourists themselves.

**Conclusion**

While comparing all studies on acquisition, colonization, infection rate and related risk factors, it becomes clear that international travel has an impact on the colonization with multidrug resistant bacteria in healthy tourists. These tourist have an increased risk of acquiring antibiotic resistance bacteria. This risk is shown to be geographical dependent and especially the region of India has often the highest acquisition rates (as high as 88%). The infection rates indicate the
severity of the colonization and up until now a mean was found, in which 7.6% of the ESBL colonized participants actually developed one or more infections. In terms of travel-associated risk factors besides geographical region, the symptoms of traveler’s diarrhea and other gastrointestinal symptoms stand out. The factor of travel type has been examined modestly but seems related to the acquisition rate. However more research in the form of prospective longitudinal studies, is needed to assess the actual severity and to develop guidelines to contaminate the resistance crisis.

Literature