Antibiotic resistance and overseas travel

Souvenirs that are not in your suitcase

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Acquisition of highly resistant organisms during travel is common and subsequent infections may not respond to usual antibiotic therapy. Obtaining clinical samples from patients with symptoms of bacterial infection who have recently travelled overseas is essential.

Multidrug-resistant bacteria are a growing global public health threat.[1] The resistant Gram-positive organisms methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci have been circulating in Australia for more than a decade. More recently, resistance among Gram-negative bacteria including *Neisseria gonorrhoea* and *Enterobacteriaceae* (such as *Escherichia coli* and *Klebsiella pneumoniae*) have become of greater concern. In this article, we will focus on multidrug-resistant *Enterobacteriaceae* (MDRE), which are important because strains with very limited antimicrobial susceptibilities are now present in Australia and are increasingly reported as a cause of community-acquired infections.

It is now well recognised that international travel is a major risk factor for the acquisition of MDRE. The risk of gastrointestinal tract colonisation with MDRE varies according to the region of travel, but may exceed 90% for some destinations.[2] Factors associated with colonisation include having traveller's diarrhoea and taking antibiotics while travelling, but even those who remain well throughout their trip may acquire MDRE. Duration of carriage is variable, but may be many months. If during this time a patient develops an infection, such as a urinary tract infection (UTI), they are at higher risk of this infection being drug resistant.

This article discusses the risk of MDRE acquisition while travelling, risk factors associated with acquisition and considerations for investigation and management of patients presenting with symptoms of UTI after overseas travel. Two recent cases are presented to provide clinical context for this review and highlight some of the clinical challenges.

Organisms of concern

Enterobacteriaceae are present within normal bowel flora and are the predominant cause of UTIs. The ability of these organisms to develop and share antimicrobial resistance mechanisms enables resistant strains to emerge and spread readily. It has now been clearly established that increased community carriage of MDRE results in increased infections with these organisms.[3] Many isolates of MDRE carry extended-spectrum beta-lactamases, a group of enzymes that confer resistance to most beta-lactam antibiotics, except carbapenems.[1] Extended-spectrum beta-lactamases are frequently encoded on plasmids, which are transmissible genetic elements that allow bacteria to share resistance genes. Plasmids carrying extended-spectrum beta-lactamase genes frequently also carry genes encoding resistance to other drug classes (for example, quinolones). Transmission of the plasmid therefore leads

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to organisms with very limited susceptibility to antibiotic treatment.[3]

Increasing numbers of infections are also occurring with organisms carrying plasmid-mediated enzymes that confer resistance to carbapenems, our usual antibiotics of last resort. This has given rise to truly pan-resistant organisms, or organisms that only retain susceptibility to antimicrobials with reduced efficacy or significant patient toxicity.[4] Concerning new research has also suggested these resistance mechanisms may actually increase the ability of MDRE to be transmitted from person to person.[5]

Rates of transmission

Travel is now a well-established risk factor for gastrointestinal tract colonisation with MDRE. A study in Australia reported a significant increase in colonisation with antibiotic-resistant *E. coli* after international travel, with the highest rates seen in travellers to the Indian subcontinent.[6] These findings were supported by the findings of a larger study in France which demonstrated that 51% of short-term (less than three months, median three weeks) travellers to tropical regions acquired at least one MDRE isolate during travel. Travellers to Southeast Asia and the Indian subcontinent had the highest rates of acquisition, with MDRE gastrointestinal tract colonisation rates exceeding 90% for travellers to Vietnam or India (Box 1).[2] This is of particular importance to Australian clinicians given that more than three million people depart from Australia for short-term visits to India or Southeast Asia annually.[7]

A similar study in Dutch travellers reported highly comparable rates of acquisition.[8] On return from international travel, onward transmission of MDRE occurred in 8% of household contacts of the travellers.[8] Duration of carriage was variable. More than half the travellers cleared these organisms within one month of return, but 10% remained colonised at 12 months. Key risk factors for acquisition of MDRE while travelling are hospitalisation or use of other local healthcare services, diarrhoeal illness and antibiotic exposure (Box 2).[8]

Although these studies demonstrate the risks associated with travel to developing nations, more traditional travel destinations such as Western Europe are not without risk. In-hospital acquisition while overseas is a well-described risk factor for MDRE colonisation (Box 3).[9] Establishing not just a travel history but a history of healthcare contact while overseas is important for patient care.

Investigations and treatment for UTI

Although some Australian guidelines do not recommend urine culture in cases of clinically evident uncomplicated cystitis, the significant risk of MDRE acquisition in travellers should prompt clinicians to enquire about recent travel in patients presenting with symptoms of UTI and to obtain a culture in all cases.[10] Standard laboratory culture methods for midstream urine samples will usually identify MDRE if present, and additional tests are not routinely required.

1. CASE 1. PYELONEPHRITIS AFTER A TRIP TO INDIA

A university student without a history of previous urinary tract infections presented to her GP with fever and dysuria. She had returned eight weeks ago from a four-week holiday in India. She was well during her trip, aside from some intermittent diarrhoea that was self-managed with loperamide. Her GP collected a urine sample and prescribed oral trimethoprim.

Twenty-four hours later, the patient presented to a hospital emergency department with significant malaise, rigors and tachycardia. Blood cultures were drawn and both these and her original urine sample grew *Escherichia coli*, confirming a diagnosis of pyelonephritis. The isolate was resistant to all penicillins and cephalosporins, as well as second-line agents such as ciprofloxacin and trimethoprim/sulfamethoxazole.

The patient was initially treated in hospital with intravenous meropenem. With no oral options available, after discharge from hospital she received 10 days of intravenous ertapenem via a hospital-in-the-home service.

2. KEY RISK FACTORS FOR MULTIDRUG-RESISTANT *ENTEROBACTERIACEAE* COLONISATION DURING TRAVEL[8]

- Hospitalisation or local healthcare utilisation
- Diarrhoeal illness
- Antibiotic exposure

3. CASE 2. RESISTANT *ESCHERICHIA COLI* CAUSING A URINARY TRACT INFECTION

A high-school student presented to the emergency department with ongoing dysuria after recent amoxicillin therapy for presumed cystitis (no urine sample was obtained). She had recently returned from a three-week trip to Western Europe, during which she contracted influenza and required admission to hospital for 36 hours. She had a history of a single previous uncomplicated urinary tract infection 18 months previously, when a fully sensitive *Escherichia coli* was cultured from urine.

A urine sample was obtained and biochemical test results were highly suggestive of a urinary tract infection. *E. coli* was cultured and susceptibility testing revealed significant resistance. Treatment with meropenem was initiated in hospital. Further susceptibility testing revealed sensitivity to fosfomycin, which was given to successfuly complete the patient's antibiotic therapy.

Treatment of UTI caused by MDRE must be guided by microbiological information. Although the urgent initiation of empirical treatment for UTI is recommended in most cases, it is crucial that a urine sample is obtained before initiating antibiotic therapy.[11] Both of the cases presented (Boxes 1 and 3) highlight the need to educate patients about possible failure of empiric therapy and the need to re-present should they deteriorate or fail to respond appropriately. Reported resistance patterns are very diverse, with many isolates retaining sensitivity to only a limited number of oral medications. This may include trimethoprim and nitrofurantoin, which can be very useful in uncomplicated cystitis caused by MDRE, and may prevent the need for intravenous therapy. Clinical microbiologists at accredited laboratories supply reports that include a selected susceptibility pattern deemed appropriate to the specimen in the context of the clinical notes provided. Additional antimicrobial susceptibility tests will usually be performed and may be available on request. Isolates that are more resistant should be discussed with a clinical microbiologist or infectious diseases physician for advice regarding a patient-specific approach.

Fosfomycin is a cell-wall-active antibiotic that works via a different mechanism to beta-lactams. Potentially, activity of fosfomycin against MDRE that are resistant to all other oral agents can be retained.[12] Fosfomycin has recently been registered by the TGA for use in Australia for the treatment of uncomplicated cystitis in females over the age of 12 years caused by susceptible *Enterobacteriaceae* (including *E. coli*) and *Enterococcus faecalis*. Although fosfomycin is not on the PBS, it is relatively inexpensive and is available to all prescribers. It appears to be an attractive option to clinicians given the evidence for efficacy of a single dose in uncomplicated *E. coli* cystitis in women.[11] However, some evidence suggests that fosfomycin may be less effective than other agents, such as nitrofurantoin, in the treatment of cystitis.[13] Its efficacy in complicated UTIs (e.g. pyelonephritis) and against *Enterobacteriaceae* other than *E. coli* has not been established and use in these circumstances is not generally recommended.

There is significant concern about widespread use of fosfomycin, as there is evidence of rapid resistance developing in vitro. If fosfomycin is used empirically, or for isolates that retain sensitivity to alternative agents, there may be a rapid reduction in its efficacy.[11] We recommend its use only in cases of demonstrated resistance to other oral agents, preferably in consultation with an infectious diseases physician to discuss optimal dosing and duration as this can vary based on the patient's specific clinical circumstances.

Screening for MDRE

There is no evidence to support the routine use of screening in the community to detect carriage of MDRE in patients returning from travel. This is predominantly because no treatment to remove these organisms is available, and screening is not needed if there is colonisation without a clinically significant infection. Exposure to antibiotics in patients who have asymptomatic colonisation with MDRE is unlikely to remove these organisms, and in fact has the potential to cause the acquisition of further drug-resistant organisms.[14]

Screening is often performed in hospital so that appropriate infection control measures can be instituted to limit horizontal spread to vulnerable patients.[15] It is also considered if patients are scheduled for an invasive procedure or biopsy (e.g. cystoscopy, transrectal ultrasound-guided prostate biopsy) soon after return from travel so that, if necessary, appropriate prophylactic antibiotic therapy can be instituted. In patients presenting with signs or symptoms of bacterial infection after return from travel (especially travel within the past six to 12 months), the most important management consideration is to obtain appropriate clinical specimens before initiating antibiotic therapy.

Conclusion

The acquisition of MDRE in travellers is very common. Colonisation increases the risk that a subsequent UTI will be due to an MDRE. Management of returned travellers presenting with symptoms of UTI should include obtaining microbiological samples before treatment to avoid delayed initiation of optimal antibiotic therapy, as delays may increase morbidity and, potentially, mortality. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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