Facing the challenge of multidrug-resistant gram-negative bacilli in Australia

Minimising the risk of MDR GNB becoming firmly established in Australian health care facilities will require a multifaceted approach

Summary

- Multidrug-resistant (MDR) gram-negative bacilli (GNB) are now globally widespread and present a major challenge to modern medical practice.
- Resistance to common antibiotics such as ceftriaxone is becoming more frequent in Australia, primarily mediated by extended-spectrum β-lactamase enzymes in common organisms such as *Escherichia coli*, and may occur in both hospital- and community-acquired infections.
- Carbapenem-resistant Enterobacteriaceae have emerged rapidly in recent years and are well established in many countries in the Asia–Pacific region. Although rare at present in Australia, they have caused significant nosocomial outbreaks.
- GNB have numerous mechanisms by which they can develop antibiotic resistance. Genes that encode extended-spectrum β-lactamases or carbapenemases are frequently co-located with multiple other resistance determinants on highly transmissible genetic structures such as plasmids.
- A key risk factor for infection with MDR GNB is travel to countries with high rates of resistance, especially with health care exposure.
- With limited prospects for new antibiotics in late-stage development that are active against MDR GNB, our national response to these challenges will require a multifaceted approach, including widespread implementation of antimicrobial stewardship, enhanced surveillance, targeted screening of at-risk patients and improved infection control practices.
- In the longer term, restriction of agricultural use of antibiotic classes critical to human medicine, removal of barriers to new drug development, and technological advances in rapid microbiological diagnostics will be required.

Antimicrobial resistance is a major challenge for current and future medical practice.[1,2] Yet the magnitude of the problem we face and its solutions are not obvious. It is estimated that at least 2 million people acquire infections with bacteria that are resistant to standard therapy each year in the United States alone.[3] The World Health Organization recently reported alarmingly high rates of bacterial resistance across all WHO regions.[2] This is not just a problem in hospitalised patients; community-acquired infections are now increasingly likely to be caused by resistant bacteria.[4]

The emerging phenomenon of multidrug-resistant (MDR) gram-negative bacilli (GNB) is a pressing contemporary concern. This challenge has been compounded by the paucity of new antibiotics in late-stage development for MDR GNB. Without effective antibiotics, many health care interventions (such as intensive care, transplantation or orthopaedic surgery) would be excessively risky. In this article, we aim to describe the current gram-negative resistance landscape in Australia and the implications for clinical care more broadly.

Antimicrobial resistance in gram-negative bacilli

Standardised definitions for multidrug resistance in GNB have recently been promulgated (Appendix 1).[5] Many bacterial species have been described with MDR or extensively drug-resistant phenotypes, but the greatest concern arises from this phenomenon occurring among Enterobacteriaceae. This family of bacteria includes common species such as *Escherichia coli* and *Klebsiella pneumoniae*. These bacteria are ubiquitous human gut commensals and frequent pathogens, causing the vast majority of gram-negative bacterial infections in community and health care settings. Other non-Enterobacteriaceae species such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* also have the propensity to develop multidrug resistance but tend to be problematic in defined patient groups (eg, cystic fibrosis) or clinical settings (eg, intensive care units).

The importance of β-lactams and β-lactamases

Beta-lactams are a broad group of antimicrobials, based on penicillin and its derivatives, including many essential antimicrobial classes: penicillins, cephalosporins, carbapenems and monobactams.

Beta-lactamases are bacterial self-defence enzymes capable of inactivating β-lactams.[6] They remain the primary mechanism of antibiotic resistance in gram-negative bacteria, with more than 1000 unique β-lactamase enzymes described. Although β-lactamases have been present in nature for millions of years,[7] their diversity and host range have flourished in response to antibiotic selection pressure in the contemporary world.

The genes encoding β-lactamases in MDR GNB often reside on plasmids (small mobile packages of DNA) associated with genes encoding resistance to other non-β-lactam antibiotics (co-resistance). Plasmids can be passed between different species of bacteria, leading to the rapid spread of multidrug resistance (Appendix 2).

The scientific terminology and classification systems used for β-lactamases can be confusing and are not always clinically useful. From a clinical perspective, β-lactamases associated with MDR GNB can be divided into two main groups: those that confer resistance to third-generation cephalosporins (3GCs; eg, ceftriaxone, cefotaxime), most commonly caused by extended-spectrum β-lactamases (ESBLs); and carbapenemases, which confer resistance

Patrick Harris
MB BS, FRACP, FRCPA[1]

David Paterson
PhD, FRCPA, FRACP[1]

Benjamin Rogers
MB BS, FRACP[2]

1 University of Queensland, Brisbane, QLD.

2 Monash Health, Melbourne, VIC.

p.harris@uq.edu.au

doi: 10.5694/mja14.01257

to carbapenems (eg, meropenem) (Appendix 1). Some species carry intrinsic, chromosomally encoded, broad-spectrum β-lactamases (AmpC enzymes) that may be expressed at a high level, leading to resistance against 3GCs and other β-lactams; these are also increasingly seen to spread via plasmids.

Carbapenems are some of the most broad-spectrum antimicrobials we have available and are often viewed as the last-line antimicrobial for treatment of MDR GNB. However, carbapenem-resistant Enterobacteriaceae (CRE) have emerged as a major concern in recent years, largely driven by the widespread dissemination of carbapenemase genes.[8] CRE almost invariably possess numerous other resistance mechanisms, drastically limiting treatment options.

Morbidity and mortality

High mortality rates have been reported for patients with bloodstream infections caused by antibiotic-resistant GNB,[8] in excess of those caused by susceptible isolates in otherwise comparable patients.[9] Rates of attributable mortality have ranged from 18.9% to 48.0% for CRE,[10] but this may also reflect significant confounding comorbidity. Even for non-severe infections, morbidity and cost may be incurred by the need for parenteral therapy because of the lack of oral options.

Epidemiology

The epidemiology of MDR GNB varies greatly by organism, resistance mechanism and geographical location.[2] For an Australian clinician, understanding a patient's risk of harbouring MDR GNB may pose a challenge. The proportion of the Australian population born overseas has been increasing since the 1950s, as has travel between Australia and other countries in our region. Increasingly, the exposure of Australian patients to MDR bacteria may occur overseas. This is particularly because of hospitalisation overseas, although in some situations community acquisition of MDR bacteria may occur.

Risk factors for becoming infected or colonised with MDR GNB have been described (Appendix 3). Risk-predictive tools have been developed for MDR pathogens but remain to be well validated in Australian populations.[11]

Third-generation cephalosporin-resistant Enterobacteriaceae

Within Australia, the rates of resistance to 3GCs in *E. coli* and other Enterobacteriaceae continue to rise, although they remain low by global standards. In 2012, a national survey suggested that about one in 25 community *E. coli* isolates (4.2%) were 3GC resistant, although the rate varied by state.[12] This is a considerable rise on previous data; a national survey in 2007 found that less than 2% of *E. coli* were 3GC resistant (coming from a mix of hospitals and community).[13] Perhaps the most comprehensive surveillance data are reported from the European Union, where an exponential rise in the prevalence of 3GC-resistant Enterobacteriaceae has been seen in recent years.[14] Such an outcome could be seen in Australia if timely action is not taken.

Risk factors for community-onset 3GC-resistant *E. coli* infection in Australia have been defined. Health care contact and antimicrobial use still constitute the greatest risks. New risk groups include recent travellers to countries with high rates of resistance, and birth on the Indian subcontinent, independent of travel.[15] Nursing homes may also act as a reservoir for resistant infections.[16] Globally, fluoroquinolone use is a strong risk factor for infection with ESBL producers, due to co-selection. While these are used sparingly in Australia, in instances where fluoroquinolone use is common (eg, prophylaxis for transrectal prostate biopsy), subsequent infection by ESBL producers is of considerable concern.[16]

From a regional perspective, our Asia–Pacific neighbours have some of the highest rates of 3GC-resistant *E. coli* in the world. Current publications suggest in excess of 25% of *E. coli* are 3GC resistant in many Asia–Pacific countries; in mainland China and the Indian subcontinent, the rate is over 50%. Alarmingly, the vast majority of these infections are community acquired.[17]

Carbapenem-resistant Enterobacteriaceae

CRE of various types have been identified in Australia for many years. After a sustained outbreak in the 1990s, CRE are now endemic in some intensive care units and other high-acuity settings (eg, burns units) on Australia's east coast.[18] Until recently, CRE were infrequently isolated from Australian patients unless they had exposure to these endemic settings. Dramatic changes in global epidemiology of CRE are changing this picture.

Although CRE infections remain infrequent in Australia by global standards, patients with overseas health care contact in countries of high incidence for CRE[2] are increasingly identified with colonisation or infection on return. The type of overseas health contact has ranged from minor procedures to receipt of a commercial organ transplant.[19] Consequences of CRE importations have included secondary transmission leading to deaths within Australian hospitals[20] and secondary spread to family members of carriers.[21]

Clinical management

The key investigation for detecting MDR GNB remains adequate clinical samples for culture. Screening rectal swabs, although potentially limited by imperfect sensitivity, may be necessary to identify carriers in certain high-risk groups.[22] For patients with suspected infection with MDR bacteria or prior risk factors, early communication between the laboratory, infection control services and infectious disease services is essential. The inherent delay in laboratory identification and susceptibility testing has proved an obstacle to providing real-time notification of bacterial resistance. Evolving technological advances in this area have the potential to reduce this lag time, although they remain some years from routine use.

1 Strategies for managing infections caused by multidrug-resistant gram-negative bacilli

	Third-generation cephalosporin-resistant Enterobacteriaceae	Carbapenem-resistant Enterobacteriaceae (CRE)
Treatment		
Severe illness and/or requiring intravenous therapy (includes pyelonephritis)	Discuss with an infectious diseases physician or clinical microbiologist. Typically treated with a carbapenem (eg, meropenem). Occasionally aminoglycosides or fluoroquinolones are a suitable alternative if susceptible. Piperacillin–tazobactam may be effective but clinical experience is limited.	Highly specialised therapy required. Always discuss with an infectious diseases physician or clinical microbiologist. Often requires combination therapy.
Non-severe illness (eg, cystitis)	Fluoroquinolone or trimethoprim–sulfamethoxazole can be used if susceptible. For cystitis, amoxicillin–clavulanate or nitrofurantoin can be used if susceptible. Fosfomycin and pivmecillinam are commonly available overseas but not easily obtained in Australia. Agents that test resistant in vitro using minimum inhibitory concentration break points calibrated for systemic infection may still be effective in uncomplicated urinary infection. Even for non-severe infection outside of the urinary tract, intravenous therapy may be required owing to a lack of suitable oral therapies.	Always discuss with an infectious diseases physician or clinical microbiologist. Frequently no oral options are available for therapy. In non-severe and potentially self-limiting illnesses, occasional observation without treatment is appropriate.
Infection control[22,23]		
Universal	Practices aimed at preventing patient infection including: • minimising the use of invasive devices (eg, urinary catheters, short-term intravenous catheters and long-term vascular access devices such as peripherally inserted central catheters or central venous catheters) and their rapid removal when not required • antimicrobial stewardship • hand hygiene • care with environmental cleaning • surveillance of infection rates and antimicrobial resistance patterns (these should be tailored to the clinical setting and resources available and may range from a simple audit to a broad-based integrated program) • education of health care workers, patients and the public about multidrug-resistant bacteria.	
Acute care hospitals	Current National Health and Medical Research Council guidelines recommend use of contact precautions (although with consideration given to local circumstances). Data suggest a low risk of transmission of extended-spectrum β-lactamase *Escherichia coli* in an acute care setting. Practice among Australian hospitals varies widely from full contact precautions to use of only standard precautions.	Covered by Australian Commission on Safety and Quality in Health Care guidelines, which recommend active case finding with screening of high-risk patients and contact precautions for all patients harbouring CRE.
Nursing homes and subacute settings	Transmission may be higher in these settings owing to longer cohabitation and greater sharing of facilities. However, contact precaution use is very problematic due to staff levels, cost and impact on patients, hence it is used infrequently. Careful attention should be paid to the universal measures above.	Guidelines suggest risk-based stratification dependent on factors such as patient continence and clinical site of CRE. Use of contact precautions in high-risk patients is recommended.
Outpatient and clinic settings	Risk of transmission likely low; no precautions recommended.	No specific recommendations from guidelines. Gloves for examination and cleaning of examination bed recommended by some authorities overseas. ◆

Infection prevention and control

Two national Australian guidelines pertain to the prevention of infection with MDR GNB in health care settings. Guidelines published by the National Health and Medical Research Council cover all pathogens[23] and the 2013 guidelines by the Australian Commission on Safety and Quality in Health Care pertain to CRE specifically.[22] Several states have also published local guidelines or directives. Recommendations are summarised in Box 1.

In addition to standard precautions, typical interventions include microbiological screening to actively identify carriers of MDR GNB and the use of contact precautions (placement in a single room with gown and glove use for contact) for known or suspected carriers.[23] In all settings, a key factor in reducing transmission and optimising treatment of these patients is clear communication within and between facilities and care teams.[18]

A guiding tenet of infection control is to ensure that a patient is never denied quality care as a result of harbouring a resistant pathogen. The potential negative effects of contact precautions on patient care and the burden on resources needs to be balanced against the consequences of transmission. In low-acuity settings the consequences of transmission may be less significant than in an acute-care hospital. Australian guidelines stress the importance of individualising policies for the health service involved.

Minimising the risk of MDR GNB becoming firmly established in Australian health care facilities will require a multifaceted approach. Essential key strategies include antimicrobial stewardship, hand hygiene adherence, attention to environmental decontamination, and enhanced local and national microbiological surveillance. Limitation of antibiotic exposure — especially to 3GCs, quinolones and carbapenems — has been shown to reduce rates of subsequent resistance.[24] Broader measures across the

community as a whole will also be required to help preserve the future of our current antimicrobials (Box 2).[25]

Therapy

On receipt of a culture result reporting MDR GNB, the first decision is whether antibiotic therapy is warranted. Typical specimens where treatment may not necessarily be warranted include urine from an asymptomatic patient with an indwelling urinary catheter and wound or respiratory tract specimens without convincing clinical signs to suggest infection rather than colonisation.

Significant cultures growing organisms that are ceftriaxone resistant (eg, ESBL producers) have historically been treated with carbapenems when intravenous therapy is required. However, there is increasing recognition that carbapenems should be not be used as workhorse antibiotic therapy. Beta-lactam–β-lactamase inhibitor combination drugs (eg, piperacillin–tazobactam) have generally been avoided for the treatment of serious infections caused by ESBL producers, despite in-vitro susceptibility. However, recent studies would suggest they may be safe and effective treatment for ESBL producers in many circumstances.[26] In all cases, source control (adequate surgical debridement of the nidus of infection) should be performed if appropriate.[27] Urinary tract infections with ceftriaxone-resistant organisms may be resistant to all orally available antibiotics, although amoxicillin–clavulanate, nitrofurantoin and fosfomycin may be useful if the organisms show susceptibility on testing. However, the application of minimum inhibitory concentration break points calibrated for systemic infections to urinary infections may explain why patients can respond to antibiotics despite apparent resistance in vitro.

Carbapenem-resistant organisms pose a greater therapeutic problem because they are typically resistant not just to carbapenems but also β-lactam–β-lactamase inhibitor combination drugs, fluoroquinolones and sometimes to all aminoglycosides. Much Australian research has been conducted into the optimal use of colistin.[28] This older antibiotic (first used in the 1950s) may be the only active antibiotic against CRE, but potential nephrotoxicity has been a major concern. Increasingly, colistin is used in combination with other antibiotics. Tigecycline, amikacin and fosfomycin are rarely used antibiotics that may be given under specialist advice for CRE infections.

Conclusions

Discussion of antimicrobial resistance can often seem a lost cause. Yet there may be reasons for optimism. The US Food and Drug Administration has initiated revised strategies to facilitate new antibiotic development.[29] There are several promising antimicrobial agents (eg, ceftolozane–tazobactam, ceftazidime–avibactam) against MDR GNB currently undergoing clinical trials,[30] and further compounds in earlier stages of development. Antimicrobial stewardship is now an essential part of Australian hospital accreditation. The public is increasingly aware of the risks of health care-associated infection and the overuse of antibiotics. Although most health care providers understand these risks, applying this awareness to daily practice is a challenge that we all have to confront.

2 Long-term strategies to reduce the burden of antibiotic resistance*

- Establish a central database of national antimicrobial use
- Restrict agricultural use of antibiotic classes used in human medicine
- Prevent nosocomial infections using a systematic implementation plan
- Strong advocacy and implementation of antimicrobial stewardship
- Improve microbiological diagnostics, including rapid testing
- Reduce legislative barriers to drug development
- Facilitate public–private partnerships to help bring new drugs to market

* Adapted from Bartlett and colleagues.[25] ◆

Competing interests: David Paterson has participated in advisory boards for AstraZeneca, MSD, Pfizer, Bayer, Cubist Pharmaceuticals and LEO Pharma.

Provenance: Not commissioned; externally peer reviewed. ■

References are available online at www.mja.com.au.

1 Looke DF, Gottlieb T, Jones CA, et al. Gram-negative resistance: can we combat the coming of a new "Red Plague" [editorial]? *Med J Aust* 2013; 198: 243-244.

2 World Health Organization. Antimicrobial resistance: global report on surveillance. Geneva: WHO, 2014. http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf (accessed Jan 2015).

3 Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. Atlanta: CDC, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf (accessed Jan 2015).

4 Doi Y, Park YS, Rivera JI, et al. Community-associated extended-spectrum -lactamase-producing *Escherichia coli* infection in the United States. *Clin Infect Dis* 2013; 56: 641-648.

5 Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; 18: 268-281.

6 Jacoby GA, Munoz-Price LS. The new beta-lactamases. *N Engl J Med* 2005; 352: 380-391.

7 Bhullar K, Waglechner N, Pawlowski A, et al. Antibiotic resistance is prevalent in an isolated cave microbiome. *PLOS One* 2012; 7: e34953.

8 Tzouvelekis LS, Markogiannakis A, Psichogiou M, et al. Carbapenemases in *Klebsiella pneumoniae* and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clin Microbiol Rev* 2012; 25: 682-707.

9 Tumbarello M, Spanu T, Sanguinetti M, et al. Bloodstream infections caused by extended-spectrum-beta-lactamase-producing *Klebsiella pneumoniae*: risk factors, molecular epidemiology, and clinical outcome. *Antimicrob Agents Chemother* 2006; 50: 498-504.

10 Akova M, Daikos GL, Tzouvelekis L, Carmeli Y. Interventional strategies and current clinical experience with carbapenemase-producing gram-negative bacteria. *Clin Microbiol Infect* 2012; 18: 439-448.

11 Lim CJ, Cheng AC, Kong DC, Peleg AY. Community-onset bloodstream infection with multidrug-resistant organisms: a matched case-control study. *BMC Infect Dis* 2014; 14: 126.

12 Australian Group on Antimicrobial Resistance. Gram-negative survey: 2012 antimicrobial susceptibility report. Canberra: AGAR, 2013. http://www.agargroup.org/files/AGAR%20GNB12%20Report%20FINAL.pdf (accessed Jan 2015).

13 Pearson J, Turnidge J, Franklin C, et al. Prevalence of antimicrobial resistances in common pathogenic Enterobacteriaceae in Australia, 2004: report from the Australian Group on Antimicrobial Resistance. *Commun Dis Intell Q Rep* 2007; 31: 106-112.

14 European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2013. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC, 2014. http://www.ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-surveillance-europe-2013.pdf (accessed Jan 2015).

15 Rogers BA, Ingram PR, Runnegar N, et al. Community-onset *Escherichia coli* infection resistant to expanded-spectrum cephalosporins in low-prevalence countries. *Antimicrob Agents Chemother* 2014; 58: 2126-2134.

16 Stuart RL, Kotsanas D, Webb B, et al. Prevalence of antimicrobial-resistant organisms in residential aged care facilities. *Med J Aust* 2011; 195: 530-533.

17 Lu PL, Liu YC, Toh HS, et al. Epidemiology and antimicrobial susceptibility profiles of Gram-negative bacteria causing urinary tract infections in the Asia-Pacific region: 2009-2010 results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). *Int J Antimicrob Agents* 2012; 40 Suppl: S37-S43.

18 Kumar Y, Sood S, Sharma A, Mani KR. Antibiogram and characterization of resistance markers among *Escherichia coli* isolates from urinary tract infections. *J Infect Dev Ctries* 2013; 7: 513-519.

19 Chua KY, Grayson ML, Burgess AN, et al. The growing burden of multidrug-resistant infections among returned Australian travellers. *Med J Aust* 2014; 200: 116-118.

20 Espedido BA, Steen JA, Ziochos H, et al. Whole genome sequence analysis of the first Australian OXA-48-producing outbreak-associated *Klebsiella pneumoniae* isolates: the resistome and in vivo evolution. *PLOS One* 2013; 8: e59920.

21 Blyth CC, Pereira L, Goire N. New Delhi metallo-beta-lactamase-producing enterobacteriaceae in an Australian child who had not travelled overseas. *Med J Aust* 2014; 200: 386.

22 Australian Commission on Safety and Quality in Health Care. Recommendations for the control of multi-drug resistant gram-negatives: carbapenem resistant enterobacteriaceae. Sydney: ACSQHC, 2013. http://www.safetyandquality.gov.au/wp-content/uploads/2013/12/MRGN-Guide-Enterobacteriaceae-PDF-1.89MB.pdf (accessed Jan 2015).

23 Australian Commission on Safety and Quality in Health Care. Australian guidelines for the prevention and control of infection in healthcare. Canberra: Australian Government, 2010. http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cd33_exec_summary.pdf (accessed Jan 2015).

24 Davey P, Brown E, Charani E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2013; (4): CD003543.

25 Bartlett JG, Gilbert DN, Spellberg B. Seven ways to preserve the miracle of antibiotics. *Clin Infect Dis* 2013; 56: 1445-1450.

26 Rodríguez-Baño J, Navarro MD, Retamar P, et al. β-Lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase-producing *Escherichia coli*: a post hoc analysis of prospective cohorts. *Clin Infect Dis* 2012; 54: 167-174.

27 Patel G, Huprikar S, Factor SH, et al. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. *Infect Control Hosp Epidemiol* 2008; 29: 1099-1106.

28 Li J, Nation RL, Turnidge JD, et al. Colistin: the re-emerging antibiotic for multidrug-resistant gram-negative bacterial infections. *Lancet Infect Dis* 2006; 6: 589-601.

29 Shlaes DM, Sahm D, Opiela C, Spellberg B. The FDA reboot of antibiotic development. *Antimicrob Agents Chemother* 2013; 57: 4605-4607.

30 Butler MS, Blaskovich MA, Cooper MA. Antibiotics in the clinical pipeline in 2013. *J Antibiot (Tokyo)* 2013; 66: 571-591. ■