Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Sepsis Outcome Programme (GNSOP) Annual Report 2018

Jan M Bell, Thomas Gottlieb, Denise A Daley, Geoffrey W Coombs
Annual report

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Abstract

The Australian Group on Antimicrobial Resistance (AGAR) performs regular period-prevalence studies to monitor changes in antimicrobial resistance in selected enteric gram-negative pathogens. The 2018 survey was the sixth year to focus on bloodstream infections, and included Enterobacterales, Pseudomonas aeruginosa and Acinetobacter species.

Eight thousand three hundred and fifty isolates, comprising Enterobacterales (7,512, 90.0%), P. aeruginosa (743, 8.9%) and Acinetobacter species (95, 1.1%), were tested using commercial automated methods. The results were analysed using Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (January 2019). Of the key resistances, resistance to the third-generation cephalosporin, ceftriaxone, was found in 13.4%/13.4% of Escherichia coli (CLSI/EUCAST criteria), and 9.4%/9.4% of Klebsiella pneumoniae. Resistance rates to ciprofloxacin were 15.2%/15.2% for E. coli, 11.3%/11.3% for K. pneumoniae, 7.4%/7.4% for Enterobacter cloacae complex, and 3.6%/7.7% for P. aeruginosa. Resistance rates to piperacillin-tazobactam were 3.0%/6.0%, 4.3%/7.9%, 18.2%/22.0%, and 5.1%/11.1% for the same five species respectively. Thirty-one isolates from 27 patients were shown to harbour a carbapenemase gene: 14 bla\text{IMP-4} (11 patients), including one with bla\text{IMP-4+OXA-23}, four bla\text{KPC} (three patients), three bla\text{OXA-48}, three bla\text{NDM}, three bla\text{GES}, two bla\text{OXA-18}, and two bla\text{OXA-23}.

Keywords: Australian Group on Antimicrobial Resistance (AGAR); antibiotic resistance; bacteraemia; gram-negative; Escherichia coli; Enterobacter; Klebsiella

Introduction

Emerging resistance in common pathogenic members of the Enterobacterales is a world-wide phenomenon and presents therapeutic problems for practitioners, both in the community and in hospital practice. The Australian Group on Antimicrobial Resistance (AGAR) commenced surveillance of the key gram-negative pathogens, Escherichia coli and Klebsiella species, in 1992. Surveys have been conducted biennially until 2008 when annual surveys commenced, alternating between community- and hospital-onset infections. In 2004, another genus of gram-negative pathogens in which resistance can be of clinical importance, Enterobacter, was added. E. coli is the most common cause of community-onset urinary tract infection; Klebsiella species are less common but are known to harbour important resistances. Enterobacter species are less common in the community, but of high importance due to intrinsic resistance to first-line antimicrobials in the community. Taken together, the three groups of species surveyed are considered to be valuable sentinels for multi-resistance and emerging resistance in enteric gram-negative bacilli. In 2013 AGAR com-
menced the Enterobacteriaceae Sepsis Outcome Programme (EnSOP) which focused on the collection of resistance and some demographic data on all isolates prospectively from patients with bacteraemia. In 2015, *Pseudomonas aeruginosa* and *Acinetobacter* species were added, and the program has subsequently been identified as the Gram-negative Sepsis Outcome Program (GNSOP).

Resistances of particular interest include resistance to β-lactams due to β-lactamases, especially extended-spectrum β-lactamases, which inactivate the third-generation cephalosporins that are normally considered reserve antimicrobials. Other resistances of interest are to agents important for treatment of these serious infections, such as gentamicin; and resistance to reserve agents such as ciprofloxacin, meropenem and colistin.

The objectives of the 2018 surveillance program were to:

- Monitor resistance in Enterobacterales, *P. aeruginosa* and *Acinetobacter* species isolated from blood cultures taken from patients presenting to the hospital or already in hospital;
- Examine the extent of co-resistance and multidrug resistance in the major species;
- Detect emerging resistance to newer last-line agents such as carbapenems and colistin; and
- Examine the molecular basis of resistance to third-generation cephalosporins, quinolones and carbapenems.

**Methods**

**Study design**

From 1 January to 31 December 2018, a total of 36 institutions across Australia collected either all or up to 200 isolates from different patient episodes of bacteraemia.

**Species identification**

Isolates were identified using the routine method for each institution: Vitek®, Phoenix™ automated microbiology systems, or where available matrix assisted laser desorption/ionisation – time of flight (MALDI-ToF) mass spectrometry.

**Susceptibility testing**

Testing was performed by two commercial semi-automated methods, Vitek 2 (BioMérieux, France) or Phoenix (Becton Dickinson, USA), which are calibrated to the ISO reference standard method of broth microdilution. Commercially available Vitek AST-N246 and AST-N247, or Phoenix NMIC-404 and NMIC-422 cards were utilised by all participants throughout the survey period. The CLSI M100 and EUCAST v9.0 breakpoints from January 2019 have been employed in the analysis. For analysis of ceftazolin, breakpoints of ≤ 4 mg/L for susceptible, ≥ 8 mg/L for resistant were applied due to the restricted minimum inhibitory concentration (MIC) range available on the commercial cards, recognising that the January 2019 breakpoint is actually susceptible ≤ 2 mg/L.

**Multidrug resistance**

The definitions defined by Magiorakos et al. were applied in this survey, where multidrug resistance was defined as resistance to one or more agent in three or more antimicrobial categories. For each species, antimicrobials were excluded from the count if they were affected by natural resistance mechanisms.

**Confirmation of resistances**

*E. coli*, *Klebsiella* spp., *Proteus* spp. and *Salmonella* spp. with ceftazidime or ceftriaxone MIC > 1 mg/L, or cefoxitin MIC > 8 mg/L; any other Enterobacterales with cefepime MIC > 1 mg/L; all isolates with ciprofloxacin MIC > 0.25 mg/L; all isolates with meropenem MIC > 0.25 mg/L; all isolates with amikacin MIC > 32 mg/L, and all isolates with colistin MIC > 2 mg/L were referred to a central laboratory (University of Adelaide) for confirmation of resistance.
All referred isolates were screened using real-time polymerase chain reaction (PCR) platform (LC-480) and published primers for the presence of bla\textsubscript{TEM} and bla\textsubscript{SHV}, CTX-M-type genes (groups 1, 2, 9, 8/25), plasmid-borne AmpC (bla\textsubscript{GTT}, bla\textsubscript{DHA}, bla\textsubscript{ABC}, bla\textsubscript{ACC}, bla\textsubscript{FOX}, bla\textsubscript{MOX}), and carbapenemases genes (bla\textsubscript{IMP}, bla\textsubscript{NDM}, bla\textsubscript{MPC}, bla\textsubscript{OXA-48}-like, bla\textsubscript{VIM}, bla\textsubscript{GEO}, bla\textsubscript{SMR}, bla\textsubscript{IMI}).

The RT-PCR technique was also used to detect plasmid-mediated quinolone resistance mechanisms (qnr, efflux [qepA, oqxAB] and aac (6’)-lb-cr), aminoglycoside ribosomal methyltransferases (armA, rmtB, rmtC, rmtF), and mobile colistin resistance genes (mcr-1, mcr-2, mcr-3).

All referred E. coli were examined for membership of the O25b-ST131 clone. All isolates with demonstrated carbapenemase activity and any amikacin resistant isolates were also screened for OXA-23-like, -24, and -58 carbapenemases.

All isolates with carbapenemase activity were subjected to whole genome sequencing using the Illumina NextSeq 500 platform. Data were analysed using a modification of the Nullarbor bioinformatic pipeline. The pipeline was used to identify the multi-locus sequence type and the resistome.

**Results**

The species isolated, and the numbers of each, are listed in Table 1. Enterobacterales accounted for 90.0%, followed by P. aeruginosa (8.9%) and Acinetobacter species (1.1%). Of the Enterobacterales, three genera—Escherichia (61.0%), Klebsiella (20.4%) and Enterobacter (5.6%)—contributed 87.0% of all isolates. Major resistances and non-susceptibilities for the top six ranked species are listed in Table 2. Non-susceptibility (which includes both intermediate and resistant isolates) has been included for some agents because these figures provide information about important emerging acquired resistances. Multiple acquired resistances by species are shown in Table 3. Multi-resistance was detected in 26.9% of E. coli isolates, 12.2% of K. pneumoniae, and 8.2% of E. cloacae complex. A more detailed breakdown of resistances and non-susceptibilities by state and territory is provided in the online AGAR report.

**Escherichia coli**

Moderately high levels of resistance to ampicillin (and therefore amoxicillin) were maintained (54.7%/56.8%, CLSI/EUCAST criteria), with lower rates for amoxicillin-clavulanic acid (13.6%--intermediate, 8.8%--resistant). Non-susceptibility to third generation cephalosporins was low (ceftriaxone 13.5%/13.5%, ceftazidime 6.6%/12.7%).

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**Table 1. Number and proportion of species isolated, blood cultures, 2018**

| Species                                      | Percentage (n) |
|----------------------------------------------|----------------|
| Escherichia coli                            | 54.8 (4,577)   |
| Klebsiella pneumoniae                       | 13.3 (1,107)   |
| Pseudomonas aeruginosa                      | 8.9 (743)      |
| Enterobacter cloacae complex                | 5.0 (420)      |
| Proteus mirabilis                           | 3.1 (261)      |
| Klebsiella oxytoca                          | 2.8 (230)      |
| Serratia marcescens                         | 2.4 (199)      |
| Klebsiella aerogenes                        | 1.5 (125)      |
| Salmonella species (non-typhoidal)          | 1.3 (107)      |
| Citrobacter freundii complex                | 1.1 (91)       |
| Morganella morganii                         | 1.0 (81)       |
| Klebsiella variicola                        | 0.8 (65)       |
| Acinetobacter baumannii complex             | 0.8 (63)       |
| Citrobacter koseri                          | 0.8 (63)       |
| Salmonella species (typhoidal)              | 0.6 (46)       |
| Raoultella ornithinolytica                  | 0.3 (22)       |
| Providencia rettgeri                        | 0.2 (17)       |
| Acinetobacter species                       | 0.2 (13)       |
| Raoultella planticola                       | 0.1 (11)       |
| Hafnia alvei                                | 0.1 (10)       |
| Pantoea species                             | 0.1 (10)       |
| Proteus vulgaris                            | 0.1 (10)       |
| Other species (total n = 27)                | 0.9 (79)       |
| **Total**                                   | **8,350**      |
Table 2. Non-susceptibility and resistance rates for the top six ranked species tested, 2018

| Antimicrobial                  | Category | CLSI (%) | EUCAST (%) | CLSI (%) | EUCAST (%) | CLSI (%) | EUCAST (%) | CLSI (%) | EUCAST (%) | CLSI (%) | EUCAST (%) | CLSI (%) | EUCAST (%) | CLSI (%) | EUCAST (%) |
|--------------------------------|----------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|
| Ampicillin                     | R        | 54.7     | 56.8       | b        | b          | na       | na         | b        | 17.1       | 18.2     | b          | b        |            |          |
| Amoxicillin-clavulanic acid (2:1) | I        | 13.6     | na         | 6.3      | –          | na       | na         | b        | b          | 5.8      | –          | 3.5      | –          |          |            |
| Piperacillin-tazobactam        | R        | 3.0      | 6.0        | 4.3      | 7.9        | 5.1      | 11.1       | 18.2     | 22.0       | 0.0      | 0.8        | 9.6      | 10.5       |          |            |
| Cefazolin                      | R        | 24.8     | 24.8       | 14.5     | 14.5       | na       | na         | b        | b          | 18.7     | 18.7       | 62.1     | 62.1       |          |            |
| Cefoxitin                      | R        | 4.1      | /          | 5.6      | /          | na       | na         | b        | b          | 0.8      | /          | 0.4      | /          |          |            |
| Ceftaxone                      | NS       | 13.5     | 13.5       | 9.6      | 9.6        | na       | na         | 25.6     | 25.6       | 2.0      | 2.0        | 8.7      | 8.7        |          |            |
| Ceftazidime                    | NS       | 6.6      | 12.7       | 7.4      | 10.4       | 8.1      | 8.1        | 22.2     | 24.6       | 1.6      | 2.0        | 0.4      | 0.8        |          |            |
| Cefepime                       | NS       | 4.6      | 10.5       | 4.5      | 8.0        | 5.6      | 5.6        | 8.6      | 13.4       | 0.8      | 1.6        | 0.0      | 0.4        |          |            |
| Meropenem                      | NS       | 0.1      | 0.1        | 1.0      | 1.0        | 7.7      | 7.7        | 3.1      | 2.7        | 0.4      | 0.0        | 0.0      | 0.0        |          |            |
| Ciprofloxacin                  | NS       | 19.1     | 19.1       | 12.7     | 12.7       | 7.7      | 7.7        | 8.4      | 8.4        | 2.7      | 2.7        | 0.8      | 0.8        |          |            |
| Gentamicin                     | R        | 8.2      | 8.4        | 4.3      | 4.4        | 0.7      | 2.2        | 6.0      | 6.9        | 1.2      | 1.9        | 0.0      | 0.4        |          |            |
| Trimethoprim–sulfamethoxazole  | R        | 32.1     | 32.0       | 20.5     | 19.6       | na       | na         | 17.2     | 17.2       | 14.3     | 14.3       | 3.0      | 3.0        |          |            |
| Nitrofurantoin                 | R        | 0.9      | 0.0        | 35.8     | /          | na       | na         | 17.3     | /          | b        | b          | 1.8      | /          |          |            |

a R = resistant, I = intermediate, NS = non-susceptible (intermediate + resistant), using criteria as published by the CLSI [2019] and EUCAST [2019].

b Considered largely intrinsically resistant due to natural β-lactamases; – no intermediate category; / no breakpoints defined; na = not applicable (testing not recommended)

c For EUCAST interpretation, the clavulanate is fixed at 2 mg/L, rather than a 2:1 ratio used in CLSI guidelines. As all susceptibility test cards used have a 2:1 ratio of clavulanate no EUCAST category has been applied.
### Table 3. Multiple acquired resistances by species, 2018

| Species                          | Total   | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Cumulative % |
|----------------------------------|---------|---|---|---|---|---|---|---|---|---|---|----|-------------|
| **Escherichia coli**             | 4,508   | 1,746 | 763 | 786 | 321 | 315 | 309 | 159 | 69 | 27 | 10 | 3 | 26.9 |
| %                                | 38.7 | 16.9 | 17.5 | 73.1 | 7.1 | 7.0 | 6.9 | 3.5 | 1.5 | 0.6 | 0.2 | 0.1 |
| **Klebsiella pneumoniae**        | 1,088   | 768 | 137 | 50 | 27 | 21 | 36 | 20 | 16 | 6 | 7 | na | 12.2 |
| %                                | 70.6 | 12.6 | 4.6 | 87.8 | 2.5 | 1.9 | 3.3 | 1.8 | 1.5 | 0.6 | 0.6 | 0.1 |
| **Enterobacter cloacae complex** | 402     | 251 | 52 | 66 | 8 | 9 | 11 | 5 | na | na | na | na | 8.2 |
| %                                | 62.4 | 12.9 | 16.4 | 91.8 | 2.2 | 1.9 | 3.6 | 1.8 | 1.5 | 0.6 | 0.1 | 0.0 |
| **Proteus mirabilis**            | 257     | 179 | 32 | 23 | 17 | 2 | 0 | 2 | 2 | 0 | 0 | 0 | 8.9 |
| %                                | 69.6 | 12.5 | 8.9 | 91.1 | 6.6 | 0.8 | 0.0 | 0.8 | 0.8 | 0.0 | 0.0 | 0.0 |
| **Klebsiella oxytoca**           | 226     | 82 | 115 | 6 | 5 | 16 | 2 | 0 | 0 | 0 | 0 | na | 10.2 |
| %                                | 36.3 | 50.9 | 2.7 | 89.8 | 2.2 | 1.9 | 0.9 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Salmonella species (non-typhoidal)** | 100    | 86 | 11 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | na | 3.0 |
| %                                | 86.0 | 11.0 | 0.0 | 97.0 | 1.0 | 1.0 | 1.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Serratia marcescens**          | 165     | 45 | 104 | 11 | 3 | 2 | 0 | 0 | 0 | na | na | na | 3.0 |
| %                                | 27.3 | 63.0 | 6.7 | 97.0 | 1.8 | 1.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Klebsiella aerogenes**          | 123     | 76 | 10 | 27 | 6 | 3 | 1 | 0 | na | na | na | na | 8.1 |
| %                                | 61.8 | 8.1 | 22.0 | 91.9 | 4.9 | 2.4 | 0.8 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |

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**Notes:**

- **a** Antimicrobial categories (agents) included: aminoglycosides (gentamicin or tobramycin or amikacin), antipseudomonal penicillins + β-lactamase inhibitor (piperacillin–tazobactam), carbapenems (meropenem), non-extended cephalosporins (cefazolin), extended-spectrum cephalosporins (ceftriaxone or ceftazidime or cefepime), cephamycins (cefoxitin), fluoroquinolones (ciprofloxacin), folate pathway inhibitors (trimethoprim–sulfamethoxazole), penicillins (ampicillin), and penicillins + β-lactamase inhibitor (amoxicillin–clavulanic acid, CLSI), na = not applicable
- **b** Antimicrobial categories excluded: penicillins
- **c** Antimicrobial categories excluded: penicillins, non-extended cephalosporins, cephamycins, penicillins + β-lactamase inhibitor
- **d** Antimicrobial categories excluded: aminoglycosides
- **e** Antimicrobial categories excluded: penicillins, non-extended cephalosporins, penicillins + β-lactamase inhibitor
Moderate levels of resistance were detected to cefazolin (24.8%/24.8%) and trimethoprim–sulfamethoxazole (32.1%/32.0%). Ciprofloxacin non-susceptibility was found in 19.2%/19.2% of E. coli isolates. Resistance to gentamicin (8.2%/8.4%), piperacillin-tazobactam (3.0%/6.0%) and cefepime (2.9%/3.7%) was low. Nine isolates (0.2%) had elevated meropenem MICs (≥ 0.5 mg/L). For the strains with extended-spectrum β-lactamase (ESBL) phenotype, ciprofloxacin and gentamicin resistance was found in 58.4%/58.4% and 30.4%/30.7% respectively.

Most of the E. coli strains with ESBL genes harboured genes of the CTX-M type (525/609 = 86%). Fifty-one percent of E. coli with CTX-M group 1 types were found to belong to sequence type 131 (O25b-ST131). ST131 accounted for 63% of E. coli ESBL phenotypes that were ciprofloxacin resistant (MIC > 1 mg/L), and only 4% of ciprofloxacin-susceptible ESBL phenotypes.

Klebsiella pneumoniae

K. pneumoniae showed slightly higher levels of resistance to cefazidime and piperacillin-tazobactam than did E. coli, but lower rates of resistance to amoxicillin-clavulanic acid, cefazolin, ceftiraxone, ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole. Fourteen (1.3%) K. pneumoniae isolates had elevated meropenem MICs (see below). ESBLs were present in 108 of 120 (90%) presumptively ESBL-positive isolates of K. pneumoniae, 89 (82%) of which were confirmed to be of the CTX-M type.

Enterobacter cloacae complex

Acquired resistance was common to piperacillin-tazobactam (18.5%/22.0%) ceftiraxone (25.1%/25.1%), cefazidime (21.7%/22.2%) and trimethoprim–sulfamethoxazole (17.2%/17.2%) among E. cloacae complex isolates. Cefepime, ciprofloxacin and gentamicin resistance were all less than 10%. Twenty-seven E. cloacae complex strains (6.5%) had elevated meropenem MICs.

Carbapenemase resistance

Overall, 31 isolates (27 patients) in sixteen institutions from six states/territories were found to harbour a carbapenemase gene. bla\textsubscript{IMP-4} was detected in 14 isolates from 11 patients: E. cloacae (eight from five patients), K. pneumoniae (two), K. aerogenes (one), K. variicola (one), C. freundii (one), and one A. radioresistens which also harboured bla\textsubscript{OXA-23}, bla\textsubscript{OXA-48} was detected in two E. coli and one K. pneumoniae; bla\textsubscript{OXA-181} was detected in two K. pneumoniae. bla\textsubscript{NDM-5} was detected in two E. coli and bla\textsubscript{OXA-48} in one K. pneumoniae; bla\textsubscript{KPC-2} was detected in two K. pneumoniae and bla\textsubscript{KPC-3} in two K. pneumoniae from one patient. bla\textsubscript{GES-5} was detected in three P. aeruginosa; and bla\textsubscript{OXA-23} was detected in one A. baumannii and one A. pittii.

Discussion

AGAR has been tracking resistance in sentinel enteric gram-negative bacteria since 1992. From 2008, surveillance was segregated into hospital-versus community-onset infections. The last year of hospital-onset only surveillance was 2011.\textsuperscript{16} In 2013, the first survey of antimicrobial resistance among Enterobacterales isolates from bacteraemic patients through Australia was conducted using an approach similar to that conducted by the European EARS-Net program. 2018 was the sixth survey of antimicrobial resistance among Enterobacterales, and the fourth for P. aeruginosa and Acinetobacter spp. from bacteraemic patients through Australia.

CTX-M-producing E. coli and Klebsiella species and gentamicin- and ciprofloxacin-resistant E. coli continued to be a problem in patients with bacteraemia. Of concern is the high proportion of E. coli that belong to the O25b-ST131 clone. Carbapenem resistance attributable to acquired carbapenemases is still uncommon in patients with bacteraemia in Australia, although six different types (IMP, KPC, NDM, OXA-48-like, OXA-23, and GES) were detected from sixteen of the participating institutions. Compared with many other countries in our region, resistance
rates in Australian gram-negative bacteria are still relatively low, but similar to those observed in 2018 in many Western European countries.

Multi-resistance is being increasingly observed, especially in *E. coli*, with multi-resistance rates above 25%. This is likely to drive more broad-spectrum antibiotic use, and increase the resistance selection pressure for important reserve classes, especially the carbapenemases.

**Acknowledgments**

This study was funded by a grant from the Australian Commission on Safety and Quality in Health care.

AGAR acknowledges the Antimicrobial Resistance Laboratory, Centre for Infectious Diseases and Microbiology, Westmead Institute for Medical Research, for performing whole genome sequencing on carbapenemase-producing isolates.

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Rodney Givney and Kimberly Ross, John Hunter Hospital

James Branley and Linda Douglass, Nepean Hospital

Peter Huntington, Royal North Shore Hospital

Sebastiaan van Hal and Alicia Beukers, Royal Prince Alfred Hospital

Jock Harkness and David Lorenz, St Vincent’s Hospital Sydney

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Denis Spelman and Chris Lee, Alfred Hospital

Marcel Leroi and Elizabeth Grabsch, Austin Health

Tony Korman and Despina Kotsanas, Monash Health, Monash Medical Centre and Monash Children’s Hospital

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