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Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Sepsis Outcome Programme (GNSOP) Annual Report 2019

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Annual report

Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Sepsis Outcome Programme (GNSOP) Annual Report 2019

Jan M Bell, Alicia Fajardo Lubian, Sally Partridge, Thomas Gottlieb, Jonathan Iredell, Denise A Daley, Geoffrey W Coombs

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 2019 survey was the seventh year to focus on bloodstream infections, and included Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter* species.

Eight thousand eight hundred and fifty-seven isolates, comprising Enterobacterales (7,983; 90.1%), *P. aeruginosa* (764; 8.6%) and *Acinetobacter* species (110; 1.2%), 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 2020). Of the key resistances, resistance to the third-generation cephalosporin ceftriaxone was found in 13.3%/13.3% (CLSI/EUCAST criteria) of *Escherichia coli* and 8.4%/8.4% of *Klebsiella pneumoniae*. Resistance rates to ciprofloxacin were 16.0%/16.0% for *E. coli*, 10.2%/10.2% for *K. pneumoniae* complex, 5.9%/5.9% for *Enterobacter cloacae* complex, and 4.1%/9.3% for *P. aeruginosa*. Resistance rates to piperacillin-tazobactam were 3.2%/5.7%, 4.7%/8.5%, 14.8%/21.4%, and 6.9%/12.5% for the same four species/complex respectively. Twenty-nine isolates from 29 patients were shown to harbour a carbapenemase gene: 15 $bla_{\text{IMP-4}}$, five $bla_{\text{OXA-181}}$, four $bla_{\text{OXA-23}}$ (one with $bla_{\text{OXA-58}}$ also), three $bla_{\text{NDM-4/5}}$, one $bla_{\text{GES-5}}$, and one $bla_{\text{IMP-1}}$.

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

Introduction

Emerging antimicrobial resistance (AMR) 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.[i] In 2004, another genus of gram-negative pathogens in which resistance can be of clinical importance, *Enterobacter* species, 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 impor-

i http://www.agargroup.org.au/agar-surveys.

tance due to intrinsic resistance to first-line antimicrobials used 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 commenced 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 been referred to since that date as the Gram-negative Sepsis Outcome Program (GNSOP).

Resistances of particular interest include resistance to ß-lactams due to ß-lactamases, especially extended-spectrum ß-lactamases (ESBLs), 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 2019 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 2019, 39 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, or Phoenix NMIC-404 and NMIC-422 cards were utilized by all participants throughout the survey period. The CLSI M100 and EUCAST v10.0 breakpoints from January 2020 have been employed in the analysis.[1,2]

Multidrug resistance

The definitions used by Magiorakos et al. were applied in this survey,[3] 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 are affected by natural resistance mechanisms.

PCR screening and whole genome sequencing

E. coli, *Klebsiella* spp., *Proteus* spp. and *Salmonella* spp. with ceftazidime or ceftriaxone minimum inhibitory concentration (MIC) > 1 mg/L, or cefoxitin MIC > 8 mg/L; any other Enterobacterales with cefepime MIC > 1 mg/L;

Enterobacterales with ciprofloxacin MIC > 0.25 mg/L; Enterobacterales with meropenem MIC > 0.25 mg/L; *P. aeruginosa* or *Acinetobacter* spp. with meropenem MIC > 4 mg/L; all isolates with amikacin MIC > 32 mg/L; and all isolates with colistin MIC > 4 mg/L were referred to a central laboratory (Centre for Infectious Diseases and Microbiology, The Westmead Institute for Medical Research) and underwent polymerase chain reaction (PCR) to detect selected resistance genes (Centre for Infectious Diseases & Microbiology Laboratory Services, ICPMR, Westmead Hospital) and/or whole genome sequencing (WGS) (Antimicrobial Resistance Laboratory, Microbial Genomics Reference Laboratory, CIDMLS, ICPMR, Westmead Hospital).

All referred isolates, except *P. aeruginosa*, *Acinetobacter* spp., *Salmonella* spp., and Enterobacterales with meropenem MIC > 0.25 mg/L which underwent WGS, were screened using real-time multiplex PCR using published primers to detect ESBLs ($bla_{\text{SHV-ESBL}}$ with G→A substitution at position 700 and/or 703, $bla_{\text{CTX-M}}$ groups 1 and 9, bla_{VEB}), plasmid-borne AmpC ($bla_{\text{CMY-2-like}}$, bla_{DHA}) and carbapenemase (bla_{IMP}, bla_{NDM}, bla_{VIM}) genes.[4]

Assays for other ESBL targets ($bla_{\text{ACT/MIR,}}$ bla_{KPC}, $bla_{\text{OXA-48-like}}$, bla_{GES}, bla_{SME}, $bla_{\text{SPM,}}$ $bla_{\text{AIM,}}$ $bla_{\text{GIM,}}$ $bla_{\text{SIM,}}$ $bla_{\text{OXA-23/24/58}}$); aminoglycoside ribosomal methytransferases (*armA*, *rmtA*, *rmtB*, *rmtC*, *rmtD*, *rmtE*, *rmtF*, *rmtG*, *rmtH*); and mobile colistin resistance genes (*mcr-1*, *mcr-2*, *mcr-3*, *mcr-4*, *mcr-5*) were detected using in-house, NATA-accredited primers and probes in routine use by the Centre for Infectious Diseases & Microbiology Laboratory Services, ICPMR, at Westmead Hospital.

Genomic DNA for WGS was extracted using the DNeasy® Blood & Tissue Kit (Qiagen) according to the manufacturer's instructions for gram-negative bacteria. WGS was performed by the Antimicrobial Resistance Laboratory, Microbial Genomics Reference Laboratory, CIDMLS, ICPMR, Westmead Hospital using the Illumina NextSeq 500 platform. Data were analysed using a modification of the Nullarbor bioinformatic pipeline,[5] incorporating searching contigs against the NCBI AMRFinder database[ii] using ABRicate[6] and AMRFinder[7], followed by a custom AMR-specific pipeline which includes a read-based search using ARIBA[8] against the CARD[9] and NCBI databases.

Results

The species isolated, and the numbers of each by onset setting, are listed in Table 1. Enterobacterales accounted for 90.1%, followed by *P. aeruginosa* (8.6%) and *Acinetobacter* species (1.2%). Of the Enterobacterales, three genera—*Escherichia* (61.6%), *Klebsiella* (19.8%) and *Enterobacter* (5.5%)—contributed 86.9% 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. Multiresistance was detected in 26.0% of *E. coli* isolates, 11.8% of *K. pneumoniae* complex, and 7.3% 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 (54.4%/56.3%, CLSI/EUCAST criteria), with lower rates for amoxicillin-clavulanic acid (14.8%/– intermediate, 7.8%/– resistant). Non-susceptibility to third generation cephalosporins was maintained at similar levels to the 2018 survey (ceftriaxone 13.4%/13.4%, ceftazidime 7.1%/13.0%). Moderate levels of resistance were detected to cefazolin (17.0%/24.0%) and trimethoprim–sulfamethoxazole (30.9%/30.9%). Ciprofloxacin non-susceptibility was found in 19.5%/19.5% of *E. coli* isolates. Resistance to

ii https://www.ncbi.nlm.nih.gov/bioproject/PRJNA313047.

Table 1. Number and proportion of species isolated, by onset setting, blood cultures, 2019

Species	Percentage (n)	Onset setting percentage (n)	
		Community onset	Hospital onset
Escherichia coli	55.5 (4,914)	83.3 (4,093)	16.7 (821)
Klebsiella pneumoniae complex	13.5 (1,193)	73.0 (871)	27.0 (322)
Pseudomonas aeruginosa	8.6 (764)	56.2 (429)	43.8 (335)
Enterobacter cloacae complex	4.8 (427)	57.4 (245)	42.6 (182)
Proteus mirabilis	3.0 (267)	84.3 (225)	15.7 (42)
Klebsiella oxytoca	2.7 (239)	72.4 (173)	27.6 (66)
Serratia marcescens	2.4 (214)	48.1 (103)	51.9 (111)
Klebsiella aerogenes	1.5 (129)	62.0 (80)	38.0 (49)
Salmonella species (non-typhoidal)	1.4 (127)	96.1 (122)	3.9 (5)
Morganella morganii	1.1 (96)	68.8 (66)	31.3 (30)
Salmonella species (typhoidal)	0.9 (82)	100.0 (82)	0.0 (0)
Citrobacter freundii complex	0.9 (77)	68.8 (53)	31.2 (24)
Acinetobacter baumannii complex	0.7 (62)	56.5 (35)	43.5 (27)
Citrobacter koseri	0.7 (62)	72.6 (45)	27.4 (17)
Raoultella ornithinolytica	0.2 (20)	90.0 (18)	10.0 (2)
Klebsiella species	0.2 (19)	73.7 (14)	26.3 (5)
Acinetobacter species	0.2 (14)	64.3 (9)	35.7 (5)
Acinetobacter ursingii	0.1 (13)	69.2 (9)	30.8 (4)
Providencia rettgeri	0.1 (13)	76.9 (10)	23.1 (3)
Acinetobacter lwoffii	0.1 (12)	75.0 (9)	25.0 (3)
Pantoea agglomerans	0.1 (12)	83.3 (10)	16.7 (2)
Enterobacter species	0.1 (11)	90.9 (10)	9.1 (1)
Other species (total n = 33)	1.0 (90)	72.2 (65)	27.8 (25)
Total	**8,857**	**76.5 (6,776)**	**23.5 (2,081)**

gentamicin (9.0%/9.5%), piperacillin-tazobactam (3.2%/5.7%) and cefepime (3.2%/4.1%) was low. Fifteen isolates (0.3%) had elevated meropenem MICs (≥ 0.5 mg/L). For the strains with ESBL phenotype, ciprofloxacin and gentamicin resistance was found in 64.8%/64.8% and 34.2%/34.9% respectively.

Most of the referred *E. coli* with an ESBL phenotype (580/674, 86.1%) harboured Ambler class A ESBL (489/580, 84.3%), plasmid borne class C (pAmpC) (76, 13.1%) or both ESBL and pAmpC (15, 2.6%) genes. Almost all with an ESBL gene (497/504, 98.6%) had $bla_{\text{CTX-M}}$ types: $bla_{\text{CTX-M}}$ group 9 (n = 249), $bla_{\text{CTX-M}}$ group 1 (n = 246) or both (n = 2). *E. coli* with pAmpC harboured mostly bla_{DHA} (51/91, 56%) or $bla_{\text{CMY-2}}$-like (37/91, 41%) genes or both (n = 3).

Klebsiella pneumoniae complex

K. pneumoniae complex showed slightly higher levels of resistance to piperacillin-tazobactam than did *E. coli*, but lower rates of resistance to

Table 2. Non-susceptibility and resistance rates for the top six ranked species tested, 2019

Antimicrobial	Category[a]	*E. coli* (%)		*K. pneumoniae* complex (%)		*P. aeruginosa* (%)		*E. cloacae* complex (%)		*P. mirabilis* (%)		*K. oxytoca* (%)	
		CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST
Ampicillin	I	1.9	–	*b*	*b*	na	na	*b*	*b*	0.0	–	*b*	*b*
	R	54.4	56.3	*b*	*b*	na	na	*b*	*b*	14.7	14.7	*b*	*b*
Amoxicillin-clavulanic acid (2:1)[c]	I	14.8	c	5.2	c	na	na	*b*	*b*	3.4	c	3.3	c
	R	7.8	c	6.7	c	na	na	*b*	*b*	2.1	c	6.0	c
Piperacillin-tazobactam	R	3.2	5.7	4.7	8.5	6.9	12.5	14.8	21.4	0.0	0.0	7.9	9.2
Cefazolin	R	17.0	24.0	11.4	13.0	na	na	*b*	*b*	2.1	16.8	24.7	56.3
Cefoxitin	R	3.4	/	5.9	/	na	na	*b*	*b*	0.4	/	0.4	/
Ceftriaxone	NS	13.4	13.4	8.7	8.7	na	na	24.1	24.1	1.5	1.5	7.6	7.6
Ceftazidime	NS	7.1	13.0	7.2	9.7	9.0	9.0[d]	21.5	24.1	0.4	0.8	1.3	3.0
Cefepime	NS	5.3	10.7	3.7	7.0	5.8	5.8[d]	4.5	10.0	1.1	1.1	0.4	1.3
Meropenem	NS	0.2	0.1	1.1	0.9	7.2	7.2	2.6	2.1	0.8	0.4	0.0	0.0
Ciprofloxacin	NS	19.5	19.5	11.5	11.5	9.3	9.3[d]	7.1	7.1	2.3	2.3	1.7	1.7
Gentamicin	R	9.0	9.5	5.1	5.4	0.9	na	4.9	6.1	1.1	11.7	0.4	0.4
Trimethoprim–sulfamethoxazole	R	30.9	30.9	16.3	16.1	na	na	16.9	16.9	15.8	15.8	5.0	5.0
Nitrofurantoin	R	0.9	0.9	30.5	/	na	na	11.9	/	*b*	*b*	0.9	/

– no intermediate category; / no breakpoints defined; na = not applicable (testing not recommended).

a R = resistant, I = intermediate, NS = non-susceptible (intermediate + resistant), using criteria as published by CLSI [2020] and EUCAST [2020].

b Considered largely intrinsically resistant.

c For EUCAST interpretation, the clavulanic acid concentration is fixed at 2 mg/L, rather than the 2:1 ratio of amoxicillin to clavulanic acid used in CLSI guidelines. As all susceptibility test cards used have a 2:1 ratio of amoxicillin to clavulanic acid no EUCAST category has been applied.

d Percent resistant.

Table 3. Multiple acquired resistances by species, 2019

Species	Number of acquired resistances (EUCAST breakpoints)[a]													
	Total	Non-multi-resistant			Cumulative %	Multi-resistant								
		0	1	2		3	4	5	6	7	8	9	10	Cumulative %
Escherichia coli	4,358	1,720	762	744		312	274	290	159	64	26	6	1	
	%	39.5	17.5	17.1	74.0	7.2	6.3	6.7	3.6	1.5	0.6	0.1	0.0	26.0
Klebsiella pneumoniae complex[b]	1,064	794	91	53		23	28	31	20	12	8	4	na	
	%	74.6	8.6	5.0	88.2	2.2	2.6	2.9	1.9	1.1	0.8	0.4		11.8
Enterobacter cloacae complex[c]	358	234	41	57		5	12	6	3	na	na	na	na	
	%	65.4	11.5	15.9	92.7	1.4	3.4	1.7	0.8					7.3
Proteus mirabilis	235	162	40	15		8	5	2	2	0	1	0	0	
	%	68.9	17.0	6.4	92.3	3.4	2.1	0.9	0.9	0.0	0.4	0.0	0.0	7.7
Klebsiella oxytoca[b]	215	90	94	15		5	7	3	0	0	1	0	na	
	%	41.9	43.7	7.0	92.6	2.3	3.3	1.4	0.0	0.0	0.5	0.0		7.4
Salmonella species (non-typhoidal)[d]	119	109	7	2		0	0	0	1	0	0	0	na	
	%	91.6	5.9	1.7	99.2	0.0	0.0	0.0	0.8	0.0	0.0	0.0		0.8
Serratia marcescens[e]	159	49	76	28		1	4	1	0	0	na	na	na	
	%	30.8	47.8	17.6	96.2	0.6	2.5	0.6	0.0	0.0				3.8
Klebsiella aerogenes[c]	115	71	3	39		1	1	0	0	na	na	na	na	
	%	61.7	2.6	33.9	98.3	0.9	0.9	0.0	0.0					1.7

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.

amoxicillin-clavulanic acid, cefazolin, ceftriaxone, ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole. Twenty-one *K. pneumoniae* complex isolates (1.8%) had elevated meropenem MICs (see below). A substantial majority of the referred *K. pneumoniae* complex with an ESBL phenotype (92/118; 78.0%) harboured ESBL (76; 82.6%), pAmpC (15; 16.3%) or both ESBL and pAmpC (1; 1.1%) genes. The vast majority with an ESBL gene (72/77; 93.5%) had $bla_{\text{CTX-M}}$ types, mostly $bla_{\text{CTX-M}}$ group 1 (62/72; 86.1%). A substantial majority of the *K. pneumoniae* complex with pAmpC harboured bla_{DHA} (13/16; 81%).

Enterobacter cloacae complex

Acquired resistance was common among *E. cloacae* complex isolates, to piperacillin-tazobactam (14.8%/21.4%) ceftriaxone (23.4%/23.4%), ceftazidime (21.3%/21.5%) and trimethoprim–sulfamethoxazole (16.9%/16.9%). Cefepime, ciprofloxacin and gentamicin resistance remain at less than 10%. Seventeen (4.0%) *E. cloacae* complex isolates had elevated meropenem MICs.

Carbapenemases

Overall, 29 isolates (29 patients) in fourteen institutions from four states/territories were found to harbour a carbapenemase gene. $bla_{\text{IMP-4}}$ was detected in 15 isolates: *K. pneumoniae* (five), *E. cloacae* (five), *E. hormaechei* (three), one *K. variicola*, and one *E. coli*. $bla_{\text{OXA-181}}$ was detected in five *K. pneumoniae*. $bla_{\text{NDM-4}}$ was detected in two *K. pneumoniae* and $bla_{\text{NDM-5}}$ in one *E. coli*. $bla_{\text{OXA-23}}$ was detected in three *A. baumannii*, one of which also harboured $bla_{\text{OXA-58}}$, and one *Proteus mirabilis*. Among *Pseudomonas aeruginosa*, one $bla_{\text{GES-5}}$ and one $bla_{\text{IMP-1}}$ were detected. Just over one quarter of the carbapenemase-producing organisms were from one institution.

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.[10] In 2013, the first survey of antimicrobial resistance among Enterobacterales isolates from bacteraemic patients throughout Australia was conducted using an approach similar to that conducted by the European EARS-Net program. 2019 was the seventh survey of antimicrobial resistance among Enterobacterales, and the fifth for *P. aeruginosa* and *Acinetobacter* spp. from bacteraemic patients through Australia.

Relative to 2018, the percentage resistance in *E. coli* declined for almost two-thirds (7/11; 60%) of the antimicrobial agents tested, and for *K. pneumoniae* complex by half (5/10). AGAR data show a longitudinal trend of increasing *E. coli* resistance to key anti-gram-negative antimicrobial agents, such as ceftriaxone and ciprofloxacin. The steady rise in resistance to fluoroquinolones is more striking in hospital-onset bacteraemia, with a change from 13.7% to 21.3% between 2013 and 2019.

Carbapenem resistance attributable to acquired carbapenemase genes is still uncommon in patients with bacteraemia in Australia, although five different types (IMP, NDM, OXA-48-like, OXA-23, and GES-5) were detected in isolates from fourteen of the participating institutions. Compared with many other countries in our region, resistance rates in Australian gram-negative bacteria are still relatively low,[11] but similar to those observed in 2018 in many Northern European countries.[12] Resistance to third generation cephalosporins in *E. coli* from bacteraemic patients in Australia is similar to the European Union and European Economic Area average.[12]

One quarter of *E. coli* and 12% of *K. pneumoniae* complex were multi-resistant. This is likely to drive more broad-spectrum antibiotic use and increase the resistance selection pressure for important reserve classes, especially the carbapenems.

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