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Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Sepsis Outcome Programme (GNSOP) Annual Report 2016

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Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Sepsis Outcome Programme (GNSOP) Annual Report 2016

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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 2016 survey was the fourth year to focus on blood stream infections, and included Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter* species.

Seven thousand five hundred and sixty-five species, comprising Enterobacteriaceae (6,750, 89.2%), *P. aeruginosa* (723, 9.6%) and *Acinetobacter* species (92, 1.2%), were tested using commercial automated methods (Vitek 2, BioMérieux; Phoenix, BD) and results were analysed using Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (January 2017). Of the key resistances, non-susceptibility to the third-generation cephalosporin, ceftriaxone, was found in 11.8%/11.8% of *Escherichia coli* (CLSI/EUCAST criteria) and 7.7%/7.7% of *Klebsiella pneumoniae*, and 11.1%/11.1% *K. oxytoca*. Non-susceptibility rates to ciprofloxacin were 12.8%/16.3% for *E. coli*, 3.8%/10.0% for *K. pneumoniae,* 0.8%/2.1% for *K. oxytoca,* 1.8%/5.6% for *Enterobacter cloacae* complex, and 5.5%/9.4% for *Pseudomonas aeruginosa*. Resistance rates to piperacillin-tazobactam were 3.1%/6.5%, 3.6%/7.1%, 14.1%/14.9%, 19.9%/22.3%, and 5.2%/11.8% for the same 4 species respectively. Twenty-eight isolates were shown to harbour a carbapenemase gene, 14 bla_{IMP}, five $bla_{\text{OXA-23,}}$ two $bla_{\text{OXA-48-like}}$, two $bla_{\text{NDM,}}$ one bla_{KPC}, one bla_{GES}, three $bla_{\text{IMP+OXA-23}}$.

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 Enterobacteriaceae is a worldwide phenomenon, and presents therapeutic problems for practitioners in both 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 (http://www.agargroup.org/surveys). 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, while *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 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 referred to as GNSOP.

Resistances of particular interest include resistance to ß-lactams due to ß-lactamases, especially extended-spectrum ß-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 2016 surveillance program were to:

1. monitor resistance in Enterobacteriaceae, *P. aeruginosa* and *Acinetobacter* species isolated from blood cultures taken from patients presenting to the hospital or already in hospital

2. examine the extent of co-resistance and multidrug resistance in the major species

3. detect emerging resistance to newer last-line agents such as carbapenems

4. characterise the molecular basis of resistance to third-generation cephalosporins, quinolones, amikacin and carbapenems

Methods

Study Design

From 1st January to 31st December 2016, 32 laboratories 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 System, or where available mass spectrometry (MALDI-TOF).

Susceptibility testing

Testing was performed by two commercial semi-automated methods, Vitek 2 (BioMérieux) or Phoenix (BD), which are calibrated to the ISO reference standard method of broth microdilution. Commercially available Vitek AST-N246 and AST-N247, or Phoenix NMIC-203 cards were utilized by all participants throughout the survey period. The CLSI M100[1] and EUCAST v7.0[2] breakpoints from January 2017 have been employed in the analysis. For analysis of cefazolin, breakpoints of ≤4 for susceptible, ≥8 for resistant were applied due to the restricted minimum inhibitory concentration (MIC) range available on the commercial cards, recognising that the January 2017 breakpoint is actually susceptible ≤2 mg/L.

Molecular 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 Enterobacteriaceae 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 molecular 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_{TEM} and bla_{SHV}, CTX-M-type genes (groups 1, 2, 9, 8/25), plasmid-borne AmpC (bla_{CIT}, bla_{DHA}, bla_{EBC}, bla_{ACC}, bla_{FOX}, bla_{MOX}), and carbapenemases genes (bla_{IMP}, bla_{NDM}, bla_{KPC}, $bla_{OXA-48-like}$, bla_{VIM}, bla_{GES}, bla_{SME}, bla_{IMI}).[3-5]

PCRs were also used to detect bla_{IMP} types, known plasmid-mediated quinolone resistance mechanisms (*qnr*, efflux [*qepA*, *oqxAB*] and *aac* (*6')-Ib-cr*), aminoglycoside ribosomal methytransferases (armA, rmtB, rmtC, rmtF), and mobile colistin resistance genes (mcr-1, mcr-2, cr-3).[6-11] All referred *E. coli* were examined for membership of the O25b-ST131 clone.[12] All isolates with demonstrated carbapenemase activity and any amikacin resistant isolates were also screened for OXA-23-like, -24, and -58 carbapenemases.[13]

All isolates with carbapenemase activity were subjected to whole genome sequencing using the Illumina MiSeq platform. Data were analysed using the Nullarbor bioinformatic pipeline.[14] 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. Enterobacteriaceae accounted for 89.2%, followed by *P. aeruginosa* (9.6%) and *Acinetobacter* species (1.2%). Of the Enterobacteriaceae, three genera - *Escherichia* (60.9%), *Klebsiella* (18.2%) and *Enterobacter* (8.2%) - contributed 87.2% of all isolates. Major resistances and non-susceptibilities for the top six ranked species are listed in Table 2. Non-susceptibility, (which includes both intermediately resistant and resistant strains), 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 21.2% of *E. coli* isolates, 9.9% of *K. pneumoniae*, and 17.1% of *E. cloacae* complex. A more detailed breakdown of resistances and non-susceptibilites by state and territory is provided in the online report from the group (http://www.agargroup.org/surveys).

Table 1. Species, blood cultures, 2016

Species	Total	
Escherichia coli	4,106	54.3%
Klebsiella pneumoniae	955	12.6%
Pseudomonas aeruginosa	723	9.6%
Enterobacter cloacae complex	396	5.2%
Klebsiella oxytoca	243	3.2%
Proteus mirabilis	226	3.0%
Serratia marcescens	175	2.3%
Enterobacter aerogenes	127	1.7%
Salmonella species (non-typhoidal)	116	1.5%
Citrobacter freundii	77	1.0%
Morganella morganii	69	0.9%
Citrobacter koseri	51	0.7%
Acinetobacter baumannii complex	48	0.6%
Salmonella species (typhoidal)	32	0.4%
Klebsiella variicola	19	0.3%
Raoultella ornithinolytica	16	0.2%
Acinetobacter species	16	0.2%
Enterobacter species	14	0.2%
Providencia rettgeri	13	0.2%
Other species (total n = 45)	143	1.9%
Total	7,565	

Escherichia coli

Moderately high levels of resistance to ampicillin (and therefore amoxycillin) were maintained (53.6%/55.2%, CLSI/EUCAST criteria), with lower rates for amoxycillin-clavulanate (12.6%/- intermediate, 8.3%/- resistant). Non-susceptibility to third-generation cephalosporins was low ceftriaxone 11.8%/11.8%, ceftazidime 6.7%/10.8%). Moderate levels of resistance were detected to cefazolin (24.2%/24.2%) and trimethoprim (32.1%/32.3%). Ciprofloxacin non-susceptibility was found in 12.8%/16.3% of *E. coli* isolates. Resistance to gentamicin (7.4%/7.6%), piperacillin-tazobactam (3.1%/6.5%), cefepime (5.5%/9.1%) were low. Thirteen isolates (0.3%) had elevated meropenem MICs (≥ 0.5 mg/L).

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Table 2. Non-susceptibility and resistance rates for the top six ranked species tested, 2016

		E. coli (%)		*K. pneumoniae* (%)		*P. aeruginosa* (%)		*E. cloacae* complex (%)		*K. oxytoca* (%)		*P. mirabilis* (%)	
Antimicrobial	***Category****	**CLSI**	**EUCAST**	**CLSI**	**EUCAST**	**CLSI**	**EUCAST**	**CLSI**	**EUCAST**	**CLSI**	**EUCAST**	**CLSI**	**EUCAST**
Ampicillin	I	1.6	–	†	†	na	na	†	†	†	†	1.3	-
	R	53.6	55.2	†	†	na	na	†	†	†	†	16.9	18.2
Amoxycillin-clavulanate (2:1) ‡	I	12.6	na	4.6	–	na	na	†	†	5.0	–	6.4	–
	R	8.3	–	4.9	–	na	na	†	†	9.9	–	2.7	–
Piperacillin-tazobactam	R	3.1	6.5	3.6	7.1	5.2	11.8	19.9	22.3	14.1	14.9	0.0	0.9
Cefazolin	R	24.2	24.2	11.2	11.2	na	na	†	†	66.7	66.7	17.4	17.4
Cefoxitin	R	3.7	/	4.4	/	na	na	†	†	0.4	/	0.4	/
Ceftriaxone	NS	11.8	11.8	7.7	7.7	na	na	27.0	27.0	11.1	11.1	0.4	0.4
Ceftazidime	NS	6.7	10.8	5.4	8.0	7.9	7.9	24.2	26.5	1.6	2.1	0.0	0.4
Cefepime	NS	5.5	9.1	3.3	6.1	2.9	6.2	6.1	12.9	1.2	1.2	0.4	0.4
Meropenem	NS	0.1	0.1	0.5	0.4	8.0	8.0	2.5	2.3	0.4	0.4	0.0	0.0
Ciprofloxacin	NS	12.8	16.3	3.8	10.0	5.5	9.4	1.8	5.6	0.8	2.1	1.8	3.6
Gentamicin	R	7.4	7.6	4.3	4.3	1.7	4.2	5.6	5.6	1.2	1.2	0.4	2.2
Trimethoprim	R	32.1	32.3	15.8	16.6	na	na	15.2	15.4	2.9	2.9	20.9	20.9
Nitrofurantoin	R	0.8	0.8	23.2	/	na	na	13.5	/	2.9	/	†	†

* R = resistant, I = intermediate, NS = non-susceptible (intermediate + resistant), using criteria as published by the CLSI [2017] and EUCAST [2017].

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

‡ 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, 2016

Species	Total	Number of acquired resistances (EUCAST breakpoints)															
		Non-multi-resistant				Cumulative%	Multi-resistant										Cumulative%
		0	1	2	3		4	5	6	7	8	9	10	11	12	13	
E. coli	3,944	1,552	540	648	367		239	157	117	148	76	58	30	11	1	0	
	%	39.4	13.7	16.4	9.3	78.8%	6.1	4.0	3.0	3.8	1.9	1.5	0.8	0.3	0.0	0.0	21.2%
K. pneumoniae[*]	919	676	99	35	18		17	12	15	12	12	21	1	1			
		73.6	10.8	3.8	2.0	90.1%	1.8	1.3	1.6	1.3	1.3	2.3	0.1	0.1			9.9%
E. cloacae complex[†]	339	216	29	7	29		32	9	4	6	6	1					
		63.7	8.6	2.1	8.6	82.9%	9.4	2.7	1.2	1.8	1.8	0.3					17.1%
P. mirabilis	212	117	50	21	13		9	1	0	1	0	0	0	0	0		
		55.2	23.6	9.9	6.1	94.8%	4.2	0.5	0.0	0.5	0.0	0.0	0.0	0.0	0.0		5.2%
S. marcescens[†]	138	124	4	4	0		1	1	3	0	1	0					
		89.9	2.9	2.9	0.0	95.7%	0.7	0.7	2.2	0.0	0.7	0.0					4.3%
K. oxytoca[*]	234	61	130	2	14		20	2	2	1	2	0	0	0			
		26.1	55.6	0.9	6.0	88.5%	8.5	0.9	0.9	0.4	0.9	0.0	0.0	0.0			11.5%
E. aerogenes[†]	124	78	6	4	27		7	0	2	0	0	0					
		62.9	4.8	3.2	21.8	92.7%	5.6	0.0	1.6	0.0	0.0	0.0					7.3%
Salmonella species (non-typhoidal)	109	101	4	1	3		0	0	0	0	0	0					
		92.7	3.7	0.9	2.8	100%	0.0	0.0	0.0	0.0	0.0	0.0					0.0%

[*] Antibiotics included: amoxycillin-clavulanate, piperacillin-tazobactam, cefazolin, cefoxitin, ceftriaxone, ceftazidime, cefepime, gentamicin, amikacin, ciprofloxacin, nitrofurantoin, trimethoprim, meropenem;
Antibiotics excluded: ampicillin (intrinsic resistance), tobramycin, norfloxacin, nalidixic acid, sulfamethoxazole-trimethoprim (high correlation with antibiotics in the included list)

[†] Antibiotics included: piperacillin-tazobactam, ceftriaxone, ceftazidime, cefepime, gentamicin, amikacin, ciprofloxacin, trimethoprim, meropenem
Antibiotics excluded: ampicillin, amoxycillin-clavulanate, cefazolin, and cefoxitin, (all four due to intrinsic resistance); also excluded were ticarcillin-clavulanate, tobramycin, norfloxacin, nalidixic acid, sulfamethoxazole-trimethoprim (high correlation with antibiotics in the included list).

For the strains with ESBL phenotype, ciprofloxacin and gentamicin resistance was found in 58.2%/60.9% and 27.8%/28.0% respectively.

Most of the *E. coli* strains with extended-spectrum β-lactamase (ESBL) genes harboured genes of the CTX-M type (368/423 = 87%). Fifty-five percent of *E. coli* with CTX-M group 1 types were found to belong to sequence type 131 (O25b-ST131). ST131 accounted for 62% of *E. coli* ESBL phenotypes that were ciprofloxacin resistant (MIC >1 mg/L), and only 3% of ciprofloxacin susceptible ESBL phenotypes.

Klebsiella pneumoniae

K. pneumoniae showed slightly higher levels of resistance to piperacillin-tazobactam and ceftazidime compared with *E. coli*, but lower rates of resistance to amoxycillin-clavulanate, cefazolin, ceftriaxone ciprofloxacin, gentamicin, and trimethoprim. Ten *K. pneumoniae* isolates had elevated meropenem MICs (see below). ESBLs were present in 66 of 82 (80%) presumptively ESBL-positive isolates of *K. pneumoniae*, 48 (73%) of which confirmed to be of the CTX-M type.

Enterobacter species

Acquired resistance was common to piperacillin-tazobactam (19.9%/22.3% and 25.0%/29.0%), ceftriaxone (27.0%/27.0% and 33.1%/33.1%), ceftazidime (24.2%/26.5% and 29.1%/31.5%) and trimethoprim (15.2%/15.4% and 3.9%/3.9%) for *E. cloacae* complex and *E. aerogenes*, respectively. Cefepime resistance was less than 13%; ciprofloxacin and gentamicin resistance were both less than 10%. Twenty-three *E. cloacae* complex strains had elevated meropenem MICs.

Carbapenemase resistance

Overall, 28 isolates (25 patients) in 15 institutions from six states/territories were found to harbour a carbapenemase gene. $bla_{\text{IMP-4}}$ was detected in *E. cloacae* complex (7, from 6 patients), and in *E. coli* (one), *K. pneumoniae* (two), *E. aerogenes* (one), *Morganella morganii* (one), and *Serratia marcescens* (one); $bla_{\text{IMP-14}}$ was detected in *Pseudomonas aeruginosa* (one); $bla_{\text{IMP-4+OXA-23}}$ was detected in *Acinetobacter baumannii* (three, from two patients); $bla_{\text{OXA-23}}$ was detected in *A. baumannii* (5, from 4 patients); $bla_{\text{NDM-4}}$ was detected in one *P. aeruginosa*; $bla_{\text{NDM-1}}$ was detected in one *K. pneumoniae*; $bla_{\text{OXA-181}}$ was detected in one *K. pneumoniae;* $bla_{\text{OXA-48}}$ was detected in one *K. pneumoniae;* $bla_{\text{KPC-2}}$ was detected in one *K. pneumoniae*; $bla_{\text{GES-5}}$ was detected in one *P. aeruginosa*.

Discussion

The Australian Group on Antimicrobial Resistance 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.[15] In 2013, the first survey of antimicrobial resistance among Enterobacteriaceae isolates from bacteraemic patients through Australia was conducted using an approach similar to that conducted by the European EARS-Net program. 2016 was the fourth survey of antimicrobial resistance among Enterobacteriaceae, and the second 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 are still uncommon in patients with bacteraemia in Australia, although six different types (IMP, KPC, NDM, OXA-48-like, VIM, and GES) were detected from 15 of the participating institutions. Compared with many other countries in our region, resistance rates in Australian Gram-negative bacteria are still relatively low[16], but similar to those observed in 2016 in many Western European countries http://ecdc.europa.eu/sites/portal/files/documents/AMR-surveillance-Europe-2016.pdf.

Multi-resistance is being increasingly observed, especially in *E. coli* and *E. cloacae* complex, both of which have multi-resistance rates (as defined by AGAR) above 17%. This is likely to drive more broad-spectrum antibiotic use, and increase the resistance selection pressure for important reserve classes, especially the carbapenemases.

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