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# Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Sepsis Outcome Programme (GNSOP) Annual Report 2015

Jan M Bell, Thomas Gottlieb, Denise A Daley and Geoffrey W Coombs for the Australian Group on Antimicrobial Resistance

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# **Annual Report**

# Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Sepsis Outcome Programme (GNSOP) Annual Report 2015

Jan M Bell, Thomas Gottlieb, Denise A Daley and 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 2015 survey was the third year to focus on blood stream infections, and included Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter* species.

Seven thousand three hundred and thirty species, comprising Enterobacteriaceae (6,567, 89.6%), *P. aeruginosa* (660, 9.0%) and *Acinetobacter* species (103, 1.4%), were tested using commercial automated methods (Vitek<sup>®</sup> 2, BioMérieux; Phoenix<sup>™</sup>, BD) and results were analysed using Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (January 2016). Of the key resistances, non-susceptibility to the third-generation cephalosporin, ceftriaxone, was found in 10.6%/10.6% of *E. coli* (CLSI/EUCAST criteria) and 5.9%/5.9% of *Klebsiella pneumoniae*, and 8.4%/8.4% *K. oxytoca*. Non-susceptibility rates to ciprofloxacin were 12.6%/13.6% for *E. coli*, 3.9%/7.2% for *K. pneumoniae*, 0.4%/0.4% for *K. oxytoca*, 3.4%/4.0% for *Enterobacter cloacae*, and 6.3%/6.5% for *Pseudomonas aeruginosa*. Resistance rates to piperacillin-tazobactam were 2.8%/6.3%, 3.5%/6.4%, 8.9%/10.2%, 15.9%/20.6%, and 7.1%/13.9% for the same four species respectively. Twenty-two isolates were shown to harbour a carbapenemase gene, 14  $bla_{IMP}$ , four  $bla_{OXA-48}$ , one  $bla_{KPC}$ , one  $bla_{GES}$ , one  $bla_{NDM+OXA-48}$ , and one  $bla_{IMP+VIM}$ .

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 Gramnegative 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 used in the community. Taken together, the three groups of species surveyed are considered to be valuable sentinels for multiresistance 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 name was altered to GNSOP to reflect the additional species surveyed.

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 2015 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; and
- 4. characterise the molecular basis of resistance to third-generation cephalosporins, quinolones, amikacin and carbapenems.

## Methods

#### **Study Design**

From 1<sup>st</sup> January to 31<sup>st</sup> December 2015, 31 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<sup>®</sup>, Phoenix<sup>™</sup> Automated Microbiology System, or where available mass spectrometry (MALDI-TOF).

#### Susceptibility testing

Testing was performed by two commercial semiautomated methods, Vitek® 2 (BioMérieux) or Phoenix<sup>™</sup> (BD), which are calibrated to the ISO reference standard method of broth microdilution. Commercially available Vitek® AST-N246 and AST-N247, or Phoenix<sup>™</sup> NMIC-203 cards were utilized by all participants throughout the survey period. The CLSI M1001 and EUCAST v5.0<sup>2</sup> breakpoints from January 2016 have been employed in the analysis. For analysis of cefazolin, breakpoints of  $\leq 4$  for susceptible,  $\geq 8$ for resistant were applied due to the restricted minimum inhibitory concentration (MIC) range available on the commercial cards, recognising that the January 2016 breakpoint is actually  $\leq 2$ mg/L for susceptible isolates.

#### **Multidrug resistance**

For this survey, multidrug resistance was defined as acquired resistance to more than three antimicrobial classes. For each species, antimicrobials were excluded from the count if they were affected by intrinsic resistance mechanisms.

#### Molecular confirmation of resistances

*E. coli* and *Klebsiella* isolates with ceftazidime or ceftriaxone MIC > 1 mg/L, or cefoxitin MIC > 8 mg/L; *Enterobacter* spp. 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 (SA Pathology) for molecular confirmation of resistance.

All referred isolates were screened for the presence of the  $bla_{\text{TEM}}$ , and  $bla_{\text{SHV}}$  genes using a real-time polymerase chain reaction (PCR) platform (LC-480) and published primers.<sup>3,4</sup> A multiplex real-time TaqMan PCR was used to detect CTX-M-type genes.<sup>5</sup> Isolates were probed for plasmid-borne AmpC enzymes using the method described by Pérez-Pérez and Hanson<sup>6</sup>. and subjected to molecular tests for Metallo-Beta-Lactamase (MBL) ( $bla_{\text{VIM}}$ ,  $bla_{\text{IMP}}$ , and  $bla_{\text{NDM}}$ ),  $bla_{\text{KPC}}$ , and  $bla_{\text{OXA-48-like}}$  genes using real-time PCR.<sup>7,8</sup> Known plasmid mediated quinolone resistance (PMQR) mechanisms (Qnr, efflux [*qepA*, *oqxAB*]; aac(6')-Ib-cr) were examined by PCR on all referred isolates with

# Table 1. Number and proportion of speciesisolated, blood cultures, 2015

Species	Total	
Escherichia coli	4,006	54.7%
Klebsiella pneumoniae	977	13.3%
Pseudomonas aeruginosa	658	9.0%
Enterobacter cloacae complex	326	4.4%
Klebsiella oxytoca	238	3.2%
Proteus mirabilis	223	3.0%
Serratia marcescens	189	2.6%
Enterobacter aerogenes	131	1.8%
Salmonella species (non-typhoidal)	115	1.6%
Morganella morganii	79	1.1%
Acinetobacter baumannii complex	59	0.8%
Citrobacter koseri	55	0.8%
Citrobacter freundii	45	0.6%
Salmonella species (typhoidal)	26	0.4%
Acinetobacter species	20	0.3%
Pantoea agglomerans	13	0.2%
Enterobacter species	12	0.2%
Raoultella ornithinolytica	12	0.2%
Providencia rettgeri	11	0.2%
Proteus vulgaris	11	0.2%
Other species (total n=40)	124	1.7%
Total	7,330	

ciprofloxacin MIC >0.25 mg/L using published methods.<sup>9,10</sup> All *E. coli* were examined for presence of the O25b-ST131 clone and its *H30-* and *H30-*Rx subclones.<sup>11-13</sup>

#### Results

The species isolated, and the numbers of each are listed in Table 1. Enterobacteriaceae accounted for 89.6%, followed by P. aeruginosa (9.0%) and Acinetobacter species (1.4%). Of the Enterobacteriaceae, three genera - Escherichia (61.0%), Klebsiella (18.5%) and Enterobacter (7.4%) - contributed 86.9% of all isolates. Major resistances and non-susceptibilities for the top six ranked species are listed in Table 2. Nonsusceptibility, (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. Multidrug resistance was detected in 20.0% of Escherichia coli isolates, 8.6% of Klebsiella pneumoniae, and 15.2% of Enterobacter cloacae. 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).

#### Escherichia coli

Moderately high levels of resistance to ampicillin (and therefore amoxycillin) were maintained (53.1%/55.1%, CLSI/EUCAST criteria), with lower rates for amoxycillin-clavulanate (13.7%/- intermediate, 8.7%/- resistant). Nonsusceptibility to third-generation cephalosporins was low ceftriaxone 10.6%/10.6%, ceftazidime 6.1%/9.9%). Moderate levels of resistance were detected to cefazolin (21.8%/21.8%) and trimethoprim (31.0%/31.4%). Ciprofloxacin nonsusceptibility was found in 12.6%/13.6% of E. coli isolates. Resistance to gentamicin (7.8%/7.9%), piperacillin-tazobactam (2.8%/6.3%), cefepime (3.7%/4.8%) were low. Four isolates had elevated meropenem MICs ( $\geq 0.5 \text{ mg/L}$ ). For the extended-spectrum  $\beta$ -lactamase (ESBL)-

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		E. COI (%)	E. coli (%)	K. pneu (9	K. pneumoniae (%)	P. aerugi (%)	P. aeruginosa (%)	E. cloa (%)	E. cloacae (%)	К. <b>о</b> х (9	K. oxytoca (%)	P. mi	P. mirabilis (%)
Antimicrobial	Category*	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST
Ampicillin	_	2.1	1	+	+			+	÷	+	+	0.0	1
	Я	53.1	55.1	÷	+			+	+	+	+	17.1	17.1
Amoxycillinclavulanate <sup>‡</sup>	_	13.7	1	4.8	ı			+	+	4.2	ı	8.6	ı
	Я	8.7	ı	4.2	ı			+	+	7.6	ı	1.8	ı
Piperacillintazobactam	Я	2.8	6.3	3.5	6.4	7.1	13.9	15.9	20.6	8.9	10.2	0.5	0.9
Cefazolin	Я	21.8	21.8	10.9	10.9			÷	÷	62.3	62.3	25.4	25.4
Cefoxitin	ж	3.4	/	4.8	~			÷	÷	2.5	/	0.5	/
Ceftriaxone	NS	10.6	10.6	5.9	5.9			25.8	25.8	8.4	8.4	2.3	2.3
Ceftazidime	NS	6.1	9.9	4.9	6.9	10.4	10.4	22.4	24.2	1.3	2.1	1.4	1.8
Cefepime	NS	5.7	8.7	2.6	4.7	2.6	8.0	5.8	12.9	0.8	1.3	1.4	1.4
Meropenem	NS	<0.1	0.0	0.3	0.3	8.1	8.1	3.4	3.1	0.4	0.4	0.0	0.0
Ciprofloxacin	NS	12.6	13.6	3.9	7.2	6.3	6.5	3.4	4.0	0.4	0.4	4.1	4.5
Gentamicin	NS	7.8	7.9	4.2	4.5	2.4	3.4	6.7	7.4	0.8	1.3	0.5	1.8
Trimethoprim	В	31.0	31.3	15.4	16.1			16.0	16.0	3.4	3.4	18.1	19.0
Nitrofurantoin	Я	1.3	1.3	32.4	/			20.6	/	2.1	/	÷	+

"R = resistant, I = intermediate, NS = non-susceptible (intermediate + resistant), using criteria as published by the CLSI [2014] and EUCAST [2014]. <sup>†</sup>Considered largely intrinsically resistant due to natural β-lactamases; - no intermediate category; / no breakpoints defined <sup>‡</sup> For EUCAST interpretation, 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.

#### Annual Report

Table 3. Number and proportion of acquired resistances (EUCAST) in Enterobacteriaceae, blood cultures, 2015

						Numbe	r of acqu	Number of acquired resistances (EUCAST breakpoints)	istance	s (EUCA:	ST breal	(points					
		No	Non-multidrug resistant	ug resista	ant					Mu	ltidrug	Multidrug resistant					
Species	Total	0	1	2	m	Cumulative%	4	5	9	7	∞	6	10	11	12	13	Cumulative%
E. coli	3,743	1,497	580	561	358		217	149	93	144	53	53	26	12	0	0	
	%	40.0	15.5	15.0	9.6	80.0%	5.8	4.0	2.5	3.8	1.4	1.4	0.7	0.3	0.0	0.0	20.0%
K. pneumoniae*	606	667	101	42	21		25	5	6	12	6	16	-	-			
		73.4	11.1	4.6	2.3	91.4%	2.8	0.6	1.0	1.3	1.0	1.8	0.1	0.1			8.6%
<i>E. cloacae</i> complex <sup>†</sup>	277	187	17	7	24		15	11	6	7	0	0	0				
		67.5	6.1	2.5	8.7	84.8%	5.4	4.0	3.2	2.5	0.0	0.0	0.0				15.2%
P. mirabilis	205	109	56	11	14		6	ĸ	-	0	0	2	0	0	0		
		53.2	27.3	5.4	6.8	92.7%	4.4	1.5	0.5	0.0	0.0	1.0	0.7	0.0	0.0		7.3%
S. marcescens $^{\star}$	142	127	9	4	m		-	-	0	0	0	0	0				
		89.4	4.2	2.8	2.1	98.6%	0.7	0.7	0.0	0.0	0.0	0.0	0.0				1.4%
K. oxytoca*	217	72	111	4	12		15	2	0	-	0	0	0	0			
		33.2	51.2	1.8	5.5	91.7%	6.9	0.9	0.0	0.5	0.0	0.0	0.0	0.0			8.3%
E. aerogenes $^{ au}$	130	68	9	4	43		e	2	-	m	0	0	0				
		52.3	4.6	3.1	33.1	93.1%	2.3	1.5	0.8	2.3	0.0	0.0	0.0				6.9%
<i>Salmonella spp</i> . (non Typhi)	106	97	5	1	-		0	0	2	0	0	0	0	0	0		
		91.5	4.7	0.9	0.9	98.1%	0.0	0.0	1.9	0.0	0.0	0.0	0.0	0.0	0.0		1.9%
* Antibiotics included: amoxycillin-clavulanate, piperacillin-tazobactam, cefazolin, cefoxitin, ceftriaxone, ceftazidime, cefepime, gentamicin, amikacin, ciprofloxacin, nitrofurantoin, trimethoprim, meropen Antibiotics excluded: ampicillin (intrinsic resistance), ticarcillin-clavulanate, tobramycin, norfloxacin, nalidixic acid, sulfamethoxazole-trimethoprim, due to high correlation with antibiotics in the included list	lin-clavular (intrinsic re	nate, piper sistance), t	acillin-tazo icarcillin-cla	bactam, ce avulanate,	fazolin, ce tobramyci	n, cefoxitin, ceftriaxone, ceftazidime, cefepime, gentamicin, amikacin, ciprofloxacin, nitrofurantoin, trimethoprim, meropenem; nycin, norfloxacin, nalidixic acid, sulfamethoxazole-trimethoprim, due to high correlation with antibiotics in the included list.	ie, ceftazi idixic acio	dime, cef d, sulfame	epime, g thoxazol	entamicir e-trimeth	ı, amikac oprim, dı	in, ciprof le to high	loxacin, r n correlat	iitrofurar ion with	ntoin, trin antibiotic	nethopri the	m, meropenem; included list.
† Antibiotics included: piperacillin-tazobactam, ceftriaxone, ceftazidime, cefepime, gentamicin, amikacin, ciprofloxacin, nitrofurantoin, trimethoprim, meropenem Antibiotics excluded: ampicillin, amoxycillin-clavulanate, cefazolin, and cefoxitin, (all four due to intrinsic resistance); also excluded were ticarcillin-clavulanate, tob	in-tazobaci amoxycillir	tam, ceftria n-clavulane	ixone, cefta ite, cefazoli	izidime, cei n, and cefc	fepime, ge vxitin, (all f	e, gentamicin, amikacin, ciprofloxacin, nitrofurantoin, trimethoprim, meropenem (all four due to intrinsic resistance); also excluded were ticarcillin-clavulanate, tobramycin, norfloxacin, nalidixic acid, sulfameth-	in, ciproflo c resistan	oxacin, ni ice); also ∈	trofurant	oin, trime were tica	thoprim, cillin-cla	meropen /ulanate,	em tobramy	cin, norfl	oxacin, n	alidixic a	cid, sulfameth-
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producing strains, ciprofloxacin and gentamicin resistance was found in 60.7%/61.5% and 32.4%/32.4% respectively.

Most of the *E. coli* strains with ESBL genes harboured genes of the CTX-M type (349/408 =86%). Over 65% of *E. coli* with CTX-M group 1 types were found to belong to sequence type 131 (O25b-ST131). ST131 accounted for 74% of *E. coli* ESBL phenotypes that were ciprofloxacin resistant (MIC >1 mg/L), and only 6% of ciprofloxacin susceptible ESBL phenotypes. Ninety-five percent and 64% of O25b-ST131 with an ESBL phenotype were associated with the H30 and *H30-Rx* subclones, respectively, consistent with their reported association with more antibiotic resistances and greater virulence potential.<sup>12</sup>

#### 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. Nine *K. pneumoniae* isolates had elevated meropenem MICs (see below). ESBLs were present in 53 of 71 (75%) presumptively ESBL-positive isolates of *K. pneumoniae*, 44 (83%) of which proved to be of the CTX-M type.

## Enterobacter species

Acquired resistance was common to piperacillin-tazobactam (15.9%/20.6% and 27.7%/40.0%), ceftriaxone (25.8%/25.8% and 42.0%/42.0%), ceftazidime (22.4%/24.2% and 37.4%/39.7%) and trimethoprim (16.0%/16.0% and 6.2%/6.2%) for *E. cloacae* and *E. aerogenes*, respectively. Cefepime, ciprofloxacin, and gentamicin resistance were all less than 10%. Twenty-one *E. cloacae* strains had elevated meropenem MICs.

## Carbapenemase resistance

Overall, 22 isolates (20 patients) in eleven institutions from five states/territories were found to harbour a carbapenemase gene.  $bla_{IMP-4}$ was detected in *E. cloacae* (8 isolates, from 7 patients), *Citrobacter freundii* (2), and in one *K. pneumoniae*, *K. oxytoca*, *Raoultella ornithinolytic*a and *Serratia marcescens*;  $bla_{OXA-48}$  was detected in *K. pneumoniae* (4 isolates, from 3 patients);  $bla_{KPC}$  was detected in one *K. pneumoniae*;  $bla_{GES-5}$  was detected in one *P. aeruginosa*;  $bla_{NDM+OXA-48}$  was detected in one *K. pneumoniae*; and  $bla_{NDM-4+VIM-2}$  in one *P. aeruginosa*.

#### 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.<sup>14</sup> 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 Antimicrobial Resistance Surveillance Network (EARS-Net) program. 2015 was the third survey of antimicrobial resistance among Enterobacteriaceae, and the first to include *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 ST131 H30-Rx subclone, and its recognised association with greater antibiotic resistance, in particular to ciprofloxacin, and greater virulence potential.<sup>12</sup> Carbapenem resistance attributable to acquired carbapenemases is still uncommon in patients with bacteraemia in Australia, although six different types of carbapenemase (IMP, KPC, NDM, OXA-48, VIM, and GES) were detected from eleven of the participating institutions. Compared with many other countries in our region, resistance rates in Australian Gramnegative bacteria are still relatively low<sup>15</sup>, but similar to those observed in 2015 in many Western European countries.<sup>22</sup>

Multidrug resistance is being increasingly observed, especially in *E. coli* and *E. cloacae*,

both of which now have multidrug resistance rates (as defined by AGAR) above 15%. Despite national efforts to improve antimicrobial stewardship, increasing multi-resistance is likely to be a driver for broad-spectrum antibiotic use, and will increase the resistance selection pressure for important reserve classes, especially the carbapenemases.

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