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Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Sepsis Outcome Programme (AESOP) Annual Report 2019

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Annual report

Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Sepsis Outcome Programme (AESOP) Annual Report 2019

Geoffrey W Coombs, Denise A Daley, Shakeel Mowlaboccus, Stanley Pang

Abstract

From 1 January to 31 December 2019, thirty-nine institutions around Australia participated in the Australian Enterococcal Sepsis Outcome Programme (AESOP). The aim of AESOP 2019 was to determine the proportion of enterococcal bacteraemia isolates in Australia that were antimicrobial resistant, and to characterise the molecular epidemiology of the *E. faecium* isolates. Of the 1,361 unique episodes of bacteraemia investigated, 95.2% were caused by either *E. faecalis* (51.4%) or *E. faecium* (43.8%). Ampicillin resistance was not detected in *E. faecalis* but was detected in 91.1% of *E. faecium*. Vancomycin non-susceptibility was detected in 0.1% of *E. faecalis* and in 41.8% of *E. faecium*. Overall, 45.4% of *E. faecium* harboured *vanA* and/or *vanB* genes. For the *vanA*/*vanB* positive *E. faecium* isolates, 49.1% harboured *vanA* genes only and 50.6% *vanB* genes; 0.3% harboured both *vanA* and *vanB* genes. The percentage of *E. faecium* bacteraemia isolates resistant to vancomycin in Australia is substantially higher than that seen in most European countries. *E. faecium* consisted of 78 multilocus sequence types (STs), of which 75.0% of isolates were classified into six major STs containing ten or more isolates. All major STs belong to clonal cluster (CC) 17, a major hospital-adapted polyclonal *E. faecium* cluster. The predominant STs (ST1424, ST17, ST796, ST80, ST1421, and ST78) were found across most regions of Australia. The most prevalent clone was ST1424, which was identified in all regions except the Northern Territory and Western Australia. Overall, 51.4% of isolates belonging to the six predominant STs harboured *vanA* or *vanB* genes. In 2019, AESOP has shown that enterococcal bacteraemias in Australia are frequently caused by polyclonal ampicillin-resistant high-level gentamicin-resistant *vanA* or *vanB E. faecium* which have limited treatment options.

Keywords: Australian Group on Antimicrobial Resistance (AGAR); antimicrobial resistance surveillance; *Enterococcus faecium*; *Enterococcus faecalis*; vancomycin-resistant enterococci (VRE); bacteraemia

Background

Globally, *Enterococcus* is thought to account for approximately 10% of all bacteraemias, and in North America and Europe is the fourth and fifth leading cause of sepsis respectively.[1,2] Although in the 1970s healthcare-associated enterococcal infections were primarily due to *Enterococcus faecalis*, there has been a steadily-increasing prevalence of *E. faecium* nosocomial infections.[3–5] Worldwide, the increase in nosocomial *E. faecium* infections has primarily been due to the expansion of polyclonal hospital-adapted clonal complex (CC) 17 strains. While innately resistant to many classes of antibiotics, *E. faecium* has demonstrated a remarkable capacity to evolve new antimicrobial resistances. In 2009, the Infectious Diseases Society of America highlighted *E. faecium* as one of the key problem bacteria or ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species*) pathogens requiring new therapies.[6]

The Australian Group on Antimicrobial Resistance (AGAR) is a network of laboratories located across Australia that commenced surveillance of antimicrobial resistance in *Enterococcus* species in 1995.[7] In 2011, AGAR initiated the Australian Enterococcal Sepsis Outcome Programme (AESOP).[8,9] The objective of AESOP 2019 was to determine the proportion of *E. faecalis* and *E. faecium* bacteraemia isolates demonstrating antimicrobial resistance, with particular emphasis on:

1. Assessing susceptibility to ampicillin;

2. Assessing susceptibility to glycopeptides; and

3. Ascertaining the molecular epidemiology of *E. faecium*.

Methodology

Participants

Thirty-nine laboratories from all Australian states and mainland territories.

Collection period

From 1 January to 31 December 2019, the 39 laboratories collected all enterococcal species isolated from blood cultures. Enterococci with the same species and antimicrobial susceptibility profiles isolated from a patient's blood culture within 14 days of the first positive culture were excluded. A new enterococcal sepsis episode in the same patient was recorded if it was confirmed by a further culture of blood taken more than 14 days after the initial positive culture. Data were collected on age, sex, dates of admission and discharge (if admitted), and mortality at seven and 30 days from date of blood culture collection. To avoid interpretive bias, no attempt was made to assign attributable mortality. Each episode of bacteraemia was designated as 'hospital-onset' if the first positive blood culture(s) in an episode was collected > 48 hours after admission.

Laboratory testing

Enterococcal isolates were identified to the species level by the participating laboratories using matrix-assisted laser desorption ionization, MALDI (MALDI Biotyper [Bruker Daltonics, Germany] or Vitek-MS® [bioMérieux, France]), or by the Vitek2® (bioMérieux). Antimicrobial susceptibility testing was performed using the Vitek2® (bioMérieux) or the Phoenix™ (Becton Dickinson, USA) automated microbiology systems according to the manufacturer's instructions. Minimum inhibitory concentration (MIC) data and isolates were referred to the Antimicrobial Resistance and Infectious Diseases (AMRID) Research Laboratory at Murdoch University. Breakpoints as identified by the Clinical and Laboratory Standards Institute (CLSI)[10] and European Committee on Antimicrobial Susceptibility Testing (EUCAST)[11] were utilised for interpretation. Linezolid- and daptomycin-non-susceptible isolates and vancomycin-susceptible isolates which harboured *vanA* or *vanB* genes were retested by Etest® (bioMérieux) using the Mueller-Hinton agar recommended by the manufacturer. *E. faecalis* ATCC® 29212 was used as the control strain. Molecular testing was performed by whole genome sequencing (WGS) using the NextSeq® platform (Illumina, USA). Sequencing results were analysed using the Nullarbor pipeline.[12]

A chi-square test for comparison of two proportions was performed and 95% confidence intervals (95% CI) were determined using MedCalc for Windows, version 12.7 (MedCalc Software, Belgium).

Approval to conduct the prospective data collection was given by the research ethics committee associated with each participating laboratory.

Results

From 1 January to 31 December 2019, a total of 1,361 unique episodes of enterococcal bacteraemia were identified. Although nine *Enterococcus* species were identified, 51.4% of isolates (699) were *E. faecalis* and 43.8% (596 isolates) were *E. faecium*. The remaining 66 enterococci were

identified either as *E. casseliflavus* (22 isolates), *E. gallinarum* (21 isolates), *E. avium* (13 isolates), *E. hirae* (3 isolates), *E. raffinosus* (3 isolates), *E. durans* (3 isolates), or *E. thailandicus* (1 isolate).

A significant difference was seen in patient sex ($p < 0.0001$), with 890 patients (65.4%) male (95% CI: 62.8–67.9). The average age of patients was 64 years, ranging from 0 to 102 years, with a median age of 69 years. The majority of episodes, 52.9% (720/1,361), were community-onset (95% CI: 50.2–55.6). However, a significant difference ($p < 0.0001$) in place of onset was seen between *E. faecium* and *E. faecalis*, with only 30.2% (95% CI: 26.5–34.0) of *E. faecium* episodes being community-onset versus 69.7% (95% CI: 66.1–73.1) for *E. faecalis*. All-cause mortality at 30 days, where data were known, was 20.6% (95% CI: 18.2–23.1). There was a significant difference ($p < 0.0001$) in mortality between *E. faecalis* and *E. faecium* episodes (13.7% vs 26.4% respectively), but not between vancomycin-susceptible and vancomycin-non-susceptible *E. faecium* episodes (24.0% vs 30.9% respectively, $p = 0.17$).

E. faecalis phenotypic susceptibility results

Apart from erythromycin, tetracycline, ciprofloxacin and high-level gentamicin, acquired resistance was rare amongst *E. faecalis* (Table 1). One isolate with a vancomycin MIC of 16 mg/L was considered intermediate by CLSI and resistant by EUCAST interpretive criteria. One isolate with an ampicillin MIC of 8 mg/L was considered susceptible by CLSI criteria and intermediate by EUCAST criteria; *van* genes were not detected in this isolate. A total of 43 *E. faecalis* isolates (6.2%) were initially reported as linezolid non-susceptible (CLSI breakpoint > 2 mg/L). However by Etest®, 42 of the 43 isolates had a linezolid MIC of ≤ 2 mg/L and were therefore considered linezolid susceptible. The remaining isolate with an MIC of 4 mg/L, although intermediate by CLSI criteria, was considered susceptible by EUCAST criteria. One isolate was initially reported as daptomycin resistant (≥ 8 mg/L) by CLSI criteria, however this isolate was unavailable for confirmation by Etest®.

E. faecium phenotypic susceptibility results

The majority of *E. faecium* isolates were non-susceptible to multiple antimicrobials including ampicillin, erythromycin, tetracycline, ciprofloxacin, nitrofurantoin and high-level gentamicin (Table 2). Overall, 249 isolates (41.8%) were phenotypically vancomycin non-susceptible (MIC > 4 mg/L). One hundred and seven (18%) and 114 (19.2%) isolates were teicoplanin non-susceptible by CLSI and EUCAST criteria respectively. Nineteen (3.2%) isolates were initially reported as linezolid non-susceptible (CLSI breakpoint > 2 mg/L). However, by Etest®, 15 of the 16 isolates had linezolid MICs of ≤ 2 mg/L and therefore were considered susceptible. One isolate with an MIC of 3.0 mg/L by Etest®, although intermediate by CLSI criteria, was considered susceptible by EUCAST criteria.

Genotypic vancomycin susceptibility results

For 382 (54.7%) of the 699 *E. faecalis* isolates, *vanA/vanB* PCR results were available; *vanA* genes were not detected. One isolate which had a vancomycin MIC of 2 mg/L harboured *vanB* genes. WGS was not performed on the *E. faecalis* isolates.

The presence of *vanA*/*vanB* genes was determined by polymerase chain reaction (PCR) or WGS on 588 (98.7%) of the 596 *E. faecium* isolates. Overall, 267 of the 588 isolates (45.4%) harboured a *vanA* and/or *vanB* gene. One hundred and 20 of the vancomycin-non-susceptible *E. faecium* isolates harboured *vanA* (Vitek® vancomycin MIC > 4 mg/L). A further 128 *E. faecium* vancomycin non-susceptible isolates harboured *vanB*. One isolate harboured both *vanA* and *vanB* genes. *vanA* or *vanB* genes were detected in eighteen vancomycin-susceptible *E. faecium* isolates. Eleven isolates harboured *vanA*. These isolates had Vitek® vancomycin MICs ≤ 4.0mg/L; 2.0 mg/L [5 isolates], 1.0 mg/L [5 isolates] and ≤ 0.5 mg/L [1 isolate], and teicoplanin 2.0 mg/L (1 isolate] and ≤ 1.0 mg/L [10 isolates]. Seven isolates harboured *vanB* (Vitek® vancomycin MIC 2.0 mg/L [7 isolates]).

E. faecium molecular epidemiology

Of the 596 episodes, 568 *E. faecium* isolates (95.3%) were available for typing by WGS. The 568 isolates were classified into 78 sequence types (STs), including six STs with 10 or more isolates (Table 3). Of the 72 STs with < 10 isolates, 49 had only one isolate. Overall, 432 (75.0%) of the 568 isolates were grouped into the six major STs. Using eBURST, all major STs were grouped into CC 17.

Geographical distribution of the STs varied (Table 3). For the six major STs, ST1424 (133 isolates) was identified in all regions except the Northern Territory and Western Australia; ST17 (102 isolates) was identified in all regions except the Australian Capital Territory; ST796 (74 isolates) in all regions except the Australian Capital Territory and the Northern Territory; ST80 (52 isolates) in all regions except Tasmania; and ST1421 (49 isolates) and ST78 (22 isolates) were each found in all regions except the Northern Territory, South Australia, Tasmania and Western Australia.

In four major STs (118 isolates: ST1424, ST17, ST80 and ST1421), *vanA* was detected; *vanB* was detected in five major STs (103 isolates: ST1424, ST17, ST796, ST80, and ST78) (Table 4). One ST796 isolate harboured both *vanA* and *vanB* genes. Eight minor STs (9 isolates) harboured *vanA* genes and seven minor STs (25 isolates) harboured *vanB* genes.

Discussion

Enterococci are intrinsically resistant to a broad range of antimicrobials including the cephalosporins and sulphonamides. By their ability to acquire additional resistance through the transfer of plasmids and transposons, and to disseminate easily in the hospital environment, enterococci have become difficult to treat and provide major infection control challenges.

As the AGAR programs are similar to those conducted in Europe, comparison of Australian antimicrobial resistance data with other countries is possible.

In the 2018 European Centre for Disease Prevention and Control (ECDC) enterococci surveillance program, the European Union/European Economic Area (EU/EEA) population-weighted mean percentage of *E. faecium* resistant to vancomycin was 17.3% (95% CI: 17–18), which represents a significant increase from 2014 when the percentage was 10.4%. The national percentages ranged from 0.0% in Iceland (95% CI: 0–21), Luxembourg (95% CI: 0–12), and Slovenia (95% CI: 0–3) to 59.1% (95% CI: 43–74) in Cyprus.[13]

In AESOP 2019, 43.8% of enterococcal bacteraemia were due to *E. faecium*, of which 41.8% (95% CI: (37.8-45.9) were phenotypically vancomycin non-susceptible by Vitek2® or Phoenix™. However, 45.4% of *E. faecium* isolates tested (265/588) harboured *vanA*/*vanB* genes, of which 49.1% were *vanA*. Overall, 22.3% (131/588) of *E. faecium* isolates harboured the *vanA* gene. There has been a significant increase in *vanA E. faecium* in Australia over the AGAR surveys 2013 to 2018, from 6% in 2013 to 26.1% in 2018.[14–19] The majority of *E. faecium* isolates were also non-susceptible to multiple antimicrobials, including ampicillin, erythromycin, tetracycline, ciprofloxacin and high-level gentamicin. The AESOP surveys confirm the incidence of vancomycin-resistant *E. faecium* bacteraemia in Australia is a significant problem.

Seven of the 135 *vanB E. faecium* isolates (6.6%) and eleven (8.3%) of the 131 *vanA E. faecium* isolates had a vancomycin MIC at or below the CLSI and the EUCAST susceptible breakpoint (≤ 4 mg/L), and therefore would not have been identified using routine phenotypic antimicrobial susceptibility methods.

By WGS, *E. faecium* was shown to be very polyclonal, consistent with the known plasticity of the enterococcal genome. The six major *E. faecium* STs form part of CC 17, a global hospital-derived lineage that has successfully adapted to hospital environments. The CC 17 lineage is characteristically ampicillin and quinolone resistant, and subsequent acquisition

Table 1: The number and proportion of *E. faecalis* non-susceptible to ampicillin and the non-β-lactam antimicrobials, Australia, 2019

Antimicrobial	Tested	Breakpoint Guideline	Breakpoint (mg/L)[a]			Susceptible	Intermediate	Resistant
			S	I	R	N (%)	N (%)	N (%)
Ampicillin	698	CLSI	≤ 8		≥ 16	698 (100)		0 (0)
		EUCAST	≤ 4	8	> 8	697 (99.9)	1 (0.1)	0 (0)
Vancomycin	698	CLSI	≤ 4	8–16	≥ 32	697 (99.9)	1 (0.1)	0 (0)
		EUCAST	≤ 4		> 4	697 (99.9)		1 (0.1)
Erythromycin	549	CLSI	≤ 0.5	1–4	≥ 8	45 (8.2)	276 (50.3)	228 (41.5)
Tetracycline/doxycycline	425	CLSI	≤ 4	8	≥ 16	141 (33.2)		284 (66.8)
Ciprofloxacin	429	CLSI	≤ 1	2	≥ 4	379 (88.3)	14 (3.3)	36 (8.4)
Daptomycin	679	CLSI	≤ 2	4	≥ 8	579 (77.6)	151 (22.2)	1 (0.1)
Teicoplanin	698	CLSI	≤ 8	16	≥ 32	698 (100)	0 (0)	0 (0)
		EUCAST	≤ 2		> 2	696 (99.7)		2 (0.3)
Linezolid	698	CLSI	≤ 2	4	≥ 8	694 (99.4)	4 (0.6)	0 (0)
		EUCAST	≤ 4		> 4	698 (100)	0 (0)	0 (0)
Nitrofurantoin	693	CLSI	≤ 32	64	≥ 128	683 (98.6)	9 (1.3)	1 (0.1)
High-level gentamicin	510	EUCAST	< 128		≥ 128	423 (82.9)		87 (17.1)

a S: susceptible; I: intermediate; R: resistant

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Table 2: The proportion of *E. faecium* non-susceptible to ampicillin and the non-β-lactam antimicrobials, Australia, 2019

Antimicrobial	Tested	Breakpoint Guideline	Breakpoint (mg/L)[a]			Susceptible	Intermediate	Resistant
			S	I	R	%	%	%
Ampicillin	595	CLSI	≤ 8		≥ 16	8.9		91.1
		EUCAST	≤ 4	8	> 8	8.7	0.2	91.1
Vancomycin	596	CLSI	≤ 4	8–16	≥ 32	58.2	0.7	41.1
		EUCAST	≤ 4		> 4	58.4		41.6
Erythromycin	500	CLSI	≤ 0.5	1–4	≥ 8	5.4	10.2	84.4
Tetracycline/doxycycline	442	CLSI	≤ 4	8	≥ 16	36.9	0.0	63.1
Ciprofloxacin	386	CLSI	≤ 1	2	≥ 4	7.5	3.1	89.4
Daptomycin	96	CLSI		4[b]	≥ 8		99.0	1.0
Teicoplanin	594	CLSI	≤ 8	16	≥ 32	82.0	1.3	16.7
		EUCAST	≤ 2		> 2	81.5		19.2
Linezolid	594	CLSI	≤ 2	4	≥ 8	99.6	0.2	0.2
		EUCAST	≤ 4		> 4	99.8		0.2
Nitrofurantoin	513	CLSI	≤ 32	64	≥ 128	16.4	25.3	58.3
High-level gentamicin	427	EUCAST	< 128		≥ 128	54.6		45.4

a S: susceptible; I: intermediate; R: resistant
b Susceptible dose dependant

Table 3: The number and proportion of major *Enterococcus faecium* sequence types, Australia, 2019, by region[a]

ST	ACT		NSW		NT		Qld		SA		Tas		Vic		WA		Aus	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ST1424	3	15.8	80	41.5			3	5.0	2	4.8	16	64.0	29	17.9			133	23.4
ST17			16	8.3	1	7.7	33	55.0	14	33.3	1	4.0	11	6.8	26	48.1	102	18.0
ST796			4	2.1			1	1.7	2	4.8	4	16.0	62	38.3	1	1.9	74	13.0
ST80	5	26.3	17	8.8	1	7.7	3	5.0	5	11.9			9	5.6	12	22.2	52	9.2
ST1421	4	21.1	37	19.2			2	3.3					6	3.7			49	8.6
ST78	1	5.3	8	4.1			4	6.7					9	5.6			22	3.9
Other	6	31.6	31	16.1	11	84.6	14	23.3	19	45.2	4	16.0	36	22.2	15	27.8	136	23.9
Total	**19**	**100**	**193**	**100**	**13**	**100**	**60**	**100**	**42**	**100**	**25**	**100**	**162**	**100**	**54**	**100**	**568**	**100**

a ACT = Australian Capital Territory; NSW = New South Wales; NT = Northern Territory; Qld = Queensland; SA = South Australia; Tas = Tasmania; Vic = Victoria; WA = Western Australia; Aus = Australia

Table 4: The number and proportion of major *Enterococcus faecium* sequence types harbouring *vanA/vanB* genes, Australia, 2019

ST	n	*vanA*		*vanB*		*vanA* and *vanB*		Not detected	
		n	%[a]	n	%[a]	n	%[a]	n	%[a]
ST1424	133	72	56.7	2	1.6			59	18.9
ST17	102	3	2.4	4	3.1			95	30.4
ST796	74			71	55.5	1	100	2	0.6
ST80	52	6	4.7	5	3.9			41	13.1
ST1421	49	37	29.1					12	3.8
ST78	22			21	16.4			1	0.3
Other	136	9	7.1	25	19.5			102	32.7
Total	**568**	**127**	**100**	**128**	**100**	**1**	**100**	**312**	**100**

a Percentage of isolates having the identified sequence type among isolates of major *E. faecium* sequence types harbouring the identified gene(s).

of *vanA*- or *vanB*-containing transposons by horizontal transfer in CC 17 clones has resulted in VRE with pandemic potential.

In AESOP 2019, six *E. faecium* STs predominated: ST1424 (of which 54.1% of isolates harboured *vanA* genes and 1.5% *vanB* genes); ST17 (2.9% *vanA*, 3.9% *vanB)*; ST796 (0% *vanA*, 95.9% *vanB,* 1.4% *vanA* and *vanB)*; ST80 (11.5% *vanA,* 9.6% *vanB*); ST1421 (75.5% *vanA,* 0% *vanB*); and ST78 (0% *vanA*, 95.5% *vanB*).

Conclusions

The AESOP 2019 study has shown that, although still predominately caused by *E. faecalis,* enterococcal bacteraemia in Australia is frequently caused by ampicillin-resistant, high-level gentamicin-resistant vancomycin-resistant *E. faecium*. Furthermore, the percentage of *E. faecium* bacteraemia isolates resistant to vancomycin in Australia is significantly higher than that seen in almost all European countries. While the *vanB* operon was the predominant genotype in Australia, in 2019 49.1% of *E. faecium* harboured the *vanA* gene. In addition to being a significant cause of healthcare-associated sepsis, the emergence of multiple multi-resistant hospital-adapted *E. faecium* strains has become a major infection control issue in Australian hospitals. Ongoing studies on the enterococcal genome will contribute to our understanding of the rapid and ongoing evolution of enterococci in the hospital environment and will assist in preventing their nosocomial transmission.

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