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Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Sepsis Outcome Programme (AESOP) Annual Report 2018

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Annual report

Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Sepsis Outcome Programme (AESOP) Annual Report 2018

Geoffrey W Coombs, Denise A Daley, Shakeel Mowlaboccus, Yung Thin Lee and Stanley Pang, on behalf of the Australian Group on Antimicrobial Resistance

Abstract

From 1 January to 31 December 2018, thirty-six institutions around Australia participated in the Australian Enterococcal Sepsis Outcome Programme (AESOP). The aim of AESOP 2018 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 1,248 unique episodes of bacteraemia investigated, 93.5% were caused by either *E. faecalis* (54.2%) or *E. faecium* (39.3%). Ampicillin resistance was not detected in *E. faecalis* but was detected in 89.4% of *E. faecium*. Vancomycin non-susceptibility was not detected in *E. faecalis* but was reported in 45.0% of *E. faecium*. Overall 49.3% of *E. faecium* isolates harboured *vanA* or *vanB* genes. Of the *vanA/vanB* positive *E. faecium* isolates, 52.9% harboured *vanA* genes and 46.2% *vanB* genes; 0.8% 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 59 multilocus sequence types (STs) of which 74.4% 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 (ST17, ST1424, ST796, ST80, ST1421, and ST262) were found across most regions of Australia. The most predominant clone was ST17 which was identified in all regions except the Australian Capital Territory and the Northern Territory. Overall, 55.8% of isolates belonging to the six predominant STs harboured *vanA* or *vanB* genes. The AESOP 2018 study has shown that enterococcal bacteraemias in Australia are frequently caused by polyclonal ampicillin-resistant high-level gentamicin-resistant *vanA*- or *vanB*-harbouring *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, enterococci are thought to account for approximately 10% of all bacteraemias, and in North America and Europe are 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, which commenced surveillance of antimicrobial resistance in *Enterococcus* species in 1995.[7] In 2011 AGAR commenced the Australian Enterococcal Sepsis Outcome Programme (AESOP).[8,9] The objective of AESOP 2018 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

3. molecular epidemiology of *E. faecium*

Methodology

Participants

Thirty-six laboratories from all eight Australian states and mainland territories.

Collection period

From 1 January to 31 December 2018, the 36 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, date 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 one of the following methods: API 20S (bioMérieux, France), API ID32Strep (bioMérieux), Vitek2® (bioMérieux), Phoenix™ (Becton Dickinson, USA), matrix-assisted laser desorption ionization (MALDI) Biotyper (Bruker Daltonics, USA), Vitek-MS (bioMérieux), polymerase chain reaction (PCR), or conventional biochemical tests. Antimicrobial susceptibility testing was performed by using the Vitek2 or Phoenix 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. Clinical and Laboratory Standards Institute (CLSI)[10] and European Committee on Antimicrobial Susceptibility Testing (EUCAST)[11] breakpoints were utilised for interpretation. Isolates with either a resistant or an intermediate category were classified as non-susceptible. 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. The control strain used was *E. faecalis* ATCC® 29212. Molecular testing was performed by whole genome sequencing (WGS) using the NextSeq® platform (Illumina, San Diego, USA). Sequencing results were analysed using the Nullarbor pipeline.[12]

A chi-squared 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, Ostend 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 2018, a total of 1,248 unique episodes of enterococcal bacteraemia were identified. Although nine *Enterococcus* species were identified, 54.2% (676 isolates) were *E. faecalis* and 39.3% (491 isolates) were *E. faecium*. Eighty-one enterococci were identified either as *E. gallinarum* (29 isolates), *E. casseliflavus* (21 isolates), *E. avium* (18 isolates), *E. hirae* (6 isolates), *E. raffinosis* (3 isolates) *E. durans* (3 isolates), or *Enterococcus* species (unidentified) (1 isolate).

A significant imbalance was seen in patient sex ($p < 0.0001$), with 799 (64.0%) being male (95% CI, 61.3–66.7). The average age of patients was 64 years ranging from 0 to 107 years with a median age of 68 years. The majority of episodes, 53.5% (668/1,248), were community-onset (95% CI, 50.7–56.3). However, a significant difference ($p < 0.0001$) in place of onset was seen between *E. faecium* and *E. faecalis*, with only 30.8% (95% CI, 26.7–35.1) of *E. faecium* episodes being community-onset compared to 68.2% (95% CI, 64.5–71.7) for *E. faecalis*. All-cause mortality at 30 days where data was known was 19.7% (95% CI, 17.3–22.3). There was a significant difference ($p < 0.0001$) in mortality between *E. faecalis* and *E. faecium* episodes, 14.7% vs 27.2% respectively, but not between vancomycin-susceptible and vancomycin non-susceptible *E. faecium* episodes, 24.5% vs 30.1% respectively ($p = 0.2$).

E. faecalis phenotypic susceptibility results

Apart from erythromycin, tetracycline, ciprofloxacin and high-level gentamicin, acquired resistance was rare amongst *E. faecalis* (Table 1). Ampicillin and vancomycin resistance was not detected. Forty-seven (7.0%) *E. faecalis* were initially reported as linezolid non-susceptible (CLSI breakpoint > 2 mg/L). However by Etest®, 43 of the 47 isolates had a linezolid MIC of ≤ 2 mg/L and were therefore considered linezolid susceptible. Two of the remaining four isolates, with MICs of 3 mg/L, although non-susceptible by CLSI guidelines, were considered susceptible by EUCAST guidelines. The remaining two isolates with MICs of 8 mg/L were non-susceptible by both guidelines. Using WGS, both isolates contained the *optrA* gene which is known to confer linezolid resistance.

Seven isolates were initially reported as daptomycin non-susceptible (> 4 mg/L). However by Etest®, five of the isolates had daptomycin MICs of ≤ 4 mg/L and therefore were considered susceptible. The remaining two isolates were confirmed to have a daptomycin MIC of 6 mg/L, however no known single nucleotide mutations were identified using WGS.

E. faecium phenotypic susceptibility results

The majority of *E. faecium* isolates were non-susceptible to multiple antimicrobials (Table 2). Most isolates were non-susceptible to ampicillin, erythromycin, tetracycline, ciprofloxacin, nitrofurantoin and high-level gentamicin. Overall, 221 (45.0%) were phenotypically vancomycin non-susceptible (MIC > 4 mg/L). Ninety-five (19.3%) and 102 (20.8%) isolates were teicoplanin non-susceptible by CLSI and EUCAST guidelines respectively. Sixteen (3.3%) isolates were initially reported as linezolid non-susceptible (CLSI breakpoint > 2 mg/L). However by Etest®, 13 of the 16 isolates had a linezolid MIC of ≤ 2 mg/L and therefore were considered susceptible. Two isolates had MICs of 12 and 64 mg/L and were non-susceptible by both guidelines, however no known single-nucleotide mutations were identified by WGS. One isolate was not available for confirmation.

Genotypic vancomycin susceptibility results

vanA/vanB PCR results were available for 346 of the 676 *E. faecalis* isolates. Neither *vanA* nor *vanB* was detected. WGS was not performed on the *E. faecalis* isolates.

Table 1: The number and proportion of *E. faecalis* isolates non-susceptible to ampicillin and the non-β-lactam antimicrobials, Australia, 2018

Antimicrobial	Tested	Breakpoint (mg/L)	Non-susceptible	
			n	%
Ampicillin	675	8[a]	0	0
		> 4[b]	0	0
Vancomycin	675	> 4[c]	0	0
Erythromycin	560	> 0.5[a]	499	89.1
Tetracycline/ doxycycline	504	> 4[a]	377	74.8
Ciprofloxacin	548	> 1[a]	71	13.0
		> 4[b]	54	9.9
Daptomycin	674	> 4[a]	2	0.3
Teicoplanin	676	> 8[a]	0	0
		> 2[b]	2	0.3
Linezolid	675	> 2[a]	5	0.7
		> 4[b]	2	0.3
Nitrofurantoin	668	> 32[a]	10	1.5
		> 64[b]	3	0.4
High-level gentamicin	602	> 128[b]	135	22.4

a CLSI non-susceptible breakpoint

b EUCAST non-susceptible breakpoint

c CLSI and EUCAST non-susceptible breakpoint

Table 2: The number and proportion of *E. faecium* isolates non-susceptible to ampicillin and the non-β-lactam antimicrobials, Australia, 2018

Antimicrobial	Tested	Breakpoint (mg/L)	Non-susceptible	
			n	%
Ampicillin	491	> 8[a]	439	89.4
		> 4[b]	440	89.6
Vancomycin	481	> 4[c]	221	45.0
Erythromycin	437	> 0.5[a]	410	93.8
Tetracycline/ doxycycline	408	> 4[a]	256	62.7
Ciprofloxacin	390	> 1[a]	355	91.0
		> 4[b]	339	86.9
Teicoplanin	491	> 8[a]	95	19.3
		> 2[b]	102	20.8
Linezolid	481	> 2[a]	4	0.8
		> 4[b]	2	0.4
Nitrofurantoin	453	> 32[a]	392	86.5
		> 64[b]	190	41.9
High-level gentamicin	418	> 128[b]	179	42.8

a CLSI non-susceptible breakpoint

b EUCAST non-susceptible breakpoint

c CLSI and EUCAST non-susceptible breakpoint

The presence of *vanA*/*vanB* genes was determined by PCR or WGS on 483 of the 491 *E. faecium* isolates. Overall, 238 (49.3%) of the 483 isolates harboured a *vanA* and/or *vanB* gene. A total of 116 of the vancomycin non-susceptible *E. faecium* isolates harboured *vanA* (Vitek® vancomycin MIC > 4 mg/L). A further 102 *E. faecium* vancomycin non-susceptible isolates harboured *vanB*. Two isolates harboured both *vanA* and *vanB* genes. Eighteen vancomycin-susceptible *E. faecium* isolates harboured *vanA* or *vanB* genes. Ten of these isolates harboured *vanA* (Vitek® vancomycin MIC ≤ 0.5 mg/L [8 isolates], MIC = 1 mg/L [1 isolate], MIC = 2 mg/L [1 isolate], teicoplanin ≤ 1 mg/L [10 isolates]). Eight isolates harboured *vanB* (Vitek® vancomycin MIC ≤ 0.5 mg/L [7 isolates] and 4 mg/L [1 isolate]).

E. faecium molecular epidemiology

Of the 491 episodes, 465 *E. faecium* isolates were available for typing by WGS. The 465 isolates were classified into 59 sequence types (STs) including six STs with 10 or more isolates (Table 3). Of the 53 STs with < 10 isolates, 33 had only one isolate. Overall 346 (74.4%) of the 465 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, ST17 (88 isolates) was identified in all regions except the Australian Capital Territory and the Northern Territory; ST1424 (73 isolates) in all regions except the Northern Territory and Western Australia; ST796 (64 isolates) in all regions except the Australian Capital Territory and Queensland; ST80 (55 isolates) in all regions except Tasmania; ST1421 (55 isolates) in all regions except the Northern Territory, South Australia and Western Australia and ST262 (11 isolates) in all regions except New South Wales, the Northern Territory, South Australia and Western Australia.

The *vanA* gene was detected in four major STs (114 isolates, ST1424, ST1421, ST80 and ST262); *vanB* was detected in five major STs (77 isolates, ST796, ST17, ST80, ST262 and ST1424) (Table 4). One ST796 and one ST1421 isolate harboured both *vanA* and *vanB* genes. Five minor STs (six isolates) harboured *vanA* genes and seven minor STs (thirty 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 substantial 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 2018, 39.3% of enterococcal bacteraemia were due to *E. faecium*, of which 45.0% (95% CI, 42.2–47.8) were phenotypically vancomycin non-susceptible by Vitek2® or Phoenix™. However 49.3% of *E. faecium* isolates tested (238/483) harboured *vanA/vanB* genes, of which 53.8% were *vanA*. Overall, 26.1% (126/483) of *E. faecium* isolates harboured the *vanA* gene. There has been a substantial increase in *vanA E. faecium* in Australia over the AGAR surveys 2013 to 2018 from 6.2% to 26.1% in 2018.[14–18] The majority of *E. faecium* isolates were also non-susceptible to multiple antimicrobials including ampicillin, erythromycin, tetracycline, ciprofloxacin and high-level gentamicin. The

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Table 3: The number and proportion of major *Enterococcus faecium* sequence types, Australia, 2018, by region

ST	ACT		NSW		NT		Qld		SA		Tas		Vic		WA		Aus	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ST17	–	–	10	7.2%	–	–	31	58.5%	8	21.1%	3	13.0%	12	9.8%	24	46.2%	88	18.9%
ST1424	9	36.0%	53	38.1%	–	–	3	5.7%	1	2.6%	5	21.7%	2	1.6%	–	–	73	15.7%
ST796	–	–	2	1.4%	1	8.3%	–	–	3	7.9%	8	34.8%	49	39.8%	1	1.9%	64	13.8%
ST80	4	16.0%	12	8.6%	2	16.7%	3	5.7%	5	13.2%	–	–	9	7.3%	20	38.5%	54	11.8%
ST1421	8	32.0%	30	21.6%	–	–	1	1.9%	–	–	1	4.3%	15	12.2%	–	–	55	11.8%
ST262	1	4.0%	–	–	–	–	–	–	8	21.1%	–	–	1	0.8%	1	1.9%	11	2.4%
Other	3	12.0%	32	23.0%	9	75.0%	15	28.3%	13	34.2%	6	26.1%	35	28.5%	6	11.5%	119	25.6%
Total	25	100.0%	139	100.0%	12	100.0%	53	100.0%	38	100.0%	23	100.0%	123	100.0%	52	100.0%	465	100.0%

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, 2018

ST	n	vanA		vanB		*vanA* and *vanB*		Not detected	
		n	%	n	%	n	%	n	%
ST17	88	–	–	7	8.0%	–	–	81	92.0%
ST1424	73	53	72.6%	2	2.7%	–	–	18	24.7%
ST796	64	–	–	62	96.9%	1	1.6%	1	1.6%
ST80	55	12	21.8%	3	5.5%	–	–	40	72.7%
ST1421	55	45	81.8%	–	–	1	1.8%	9	16.4%
ST262	11	4	36.4%	3	27.3%	–	–	4	36.4%
Other	119	6	5.0%	30	25.2%	–	–	83	69.7%
Total	465	120	25.8%	107	23.0%	2	0.4%	236	50.8%

AESOP surveys confirm that the incidence of vancomycin-resistant *E. faecium* bacteraemia in Australia is a substantial problem.

Eight (7.3%) of the 110 *vanB E. faecium* and ten (7.9%) of the 126 *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 of *vanA*- or *vanB*-containing transposons by horizontal transfer in CC 17 clones has resulted in VRE with pandemic potential.

In AESOP 2018, six *E. faecium* STs predominated: ST17 (of which 8.0% of isolates harboured *vanB* genes); ST1424 (72.6% *vanA*, 2.7% *vanB)*; ST796 (0% *vanA,* 96.9% *vanB,*1.6% *vanA* and *vanB*); ST1421 (81.8% *vanA,* 0% *vanB,* 1.8% *vanA* and *vanB*), ST80 (21.8% *vanA,* 5.5% *vanB*), and ST262 (36.4% *vanA,* 27.3% *vanB*).

Conclusions

The AESOP 2018 study has shown that, although 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 notably higher than that seen in almost all European countries. While the *vanB* operon was the predominant genotype in Australia, in 2018 52.8% of *E. faecium* harboured the *vanA* gene. In addition to being a substantial 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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