Australian Group on Antimicrobial Resistance Australian Enterococcal Sepsis Outcome Programme annual report, 2014

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Abstract

From 1 January to 31 December 2014, 27 institutions around Australia participated in the Australian Enterococcal Sepsis Outcome Programme (AESOP). The aim of AESOP 2014 was to determine the proportion of enterococcal bacteraemia isolates in Australia that were antimicrobial resistant, and to characterise the molecular epidemiology of the *Enterococcus faecium* isolates. Of the 952 unique episodes of bacteraemia investigated, 94.4% were caused by either *E. faecalis* (54.9%) or *E. faecium* (39.9%). Ampicillin resistance was detected in 0.6% of *E. faecalis* and in 89.4% of *E. faecium*. Vancomycin non-susceptibility was reported in 0.2% and 46.1% of *E. faecalis* and *E. faecium* respectively. Overall 51.1% of *E. faecium* harboured *vanA* or *vanB* genes. For the *vanA/B* positive *E. faecium* isolates, 81.5% harboured *vanB* genes and 18.5% *vanA* genes. The percentage of *E. faecium* bacteraemia isolates resistant to vancomycin in Australia is significantly higher than that seen in most European countries. *E. faecium* consisted of 113 pulsed-field gel electrophoresis pulsotypes of which 68.9% of isolates were classified into 14 major pulsotypes containing 5 or more isolates. Multilocus sequence typing grouped the 14 major pulsotypes into clonal cluster 17, a major hospital-adapted polyclonal *E. faecium* cluster. The geographical distribution of the 4 predominant sequence types (ST203, ST796, ST555 and ST17) varied with only ST203 identified across most regions of Australia. Overall 74.7% of isolates belonging to the four predominant STs harboured *vanA* or *vanB* genes. In conclusion, the AESOP 2014 has shown 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. *Commun Dis Intell* 2016;40(2):E236–E243.

Keywords: antimicrobial resistance surveillance, *Enterococcus faecium, Enterococcus faecalis,* vancomycin resistant enterococci, bacteraemia

Introduction

Globally enterococci are thought to account for approximately 10% of all bacteraemias, and in North America and Europe are the 4th and 5th leading causes 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 commenced the Australian Enterococcal Sepsis Outcome Programme (AESOP).[8] The objective of AESOP 2014 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. molecular epidemiology of *E. faecium*.

Methods

Twenty-seven laboratories from all 8 Australian states and territories participated in 2014.

Collection period

From 1 January to 31 December 2014, the 27 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 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 more than 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), API ID32Strep (bioMérieux), Vitek2® (bioMérieux), Phoenix™ (BD), matrix-assisted laser desorption ionization (MALDI) Biotyper (Bruker Daltonics), Vitek-MS (bioMérieux), polymerase chain reaction (PCR), or conventional biochemical tests. Antimicrobial susceptibility testing was performed by using the Vitek2® (bioMérieux, France) or the Phoenix™ (BD, USA) automated microbiology systems according to the manufacturer's instructions. Minimum inhibitory concentration (MIC) data and isolates were referred to the Australian Collaborating Centre for *Enterococcus* and *Staphylococcus* Species (*ACCESS*) Typing and Research. Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were utilised for interpretation.[9,10] Isolates with either a resistant or an intermediate category were classified as non-susceptible. Linezolid and daptomycin non-susceptible isolates and selected vancomycin susceptible isolates were retested by Etest® (bioMérieux, France) using the Mueller-Hinton agar recommended by the manufacturer. *E. faecalis* ATCC® 29212 was used as the control strain. Molecular testing including *vanA/B* PCR, pulsed-field gel electrophoresis (PFGE) and multilocus sequence typing (MLST) was performed as previously described.[11–13]

A chi-square test for comparison of 2 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 2014, 952 unique episodes of enterococcal bacteraemia were identified. Although 10 *Enterococcus* species were identified, 54.9% (523 isolates) were *E. faecalis* and 39.9% (380 isolates) were *E. faecium*. Forty-nine enterococci were identified either as *E. casseliflavus* (19 isolates), *E. gallinarum* (13), *E. avium* (9), *E. hirae* (2) *E. raffinosus* (3), *E. durans* (1), *E. cecorum* (1), *and E. mundtii* (1).

A significant difference was seen in patient sex ($P < 0.0001$) with 613 (64.4%) being male (95% CI, 61.4–67.5). The average age of patients was 63 years ranging from 0 to 100 years with a median age of 67 years. Of the 952 episodes, 474 (49.8%) were hospital onset (95% CI, 46.5–52.9). However, a significant difference was seen between *E. faecium* and *E. faecalis,* with 71.8% (95% CI, 67.0–76.3) of *E. faecium* episodes being hospital onset compared with 36.5% (95% CI, 32.4–40.8) for *E. faecalis* ($P < 0.0001$). All-cause mortality at 30 days was 18.5% (95% CI, 15.9–21.3). There was a significant difference in mortality between *E. faecalis* and *E. faecium* episodes (13.2% [95% CI, 10.3–16.6] vs 27.6% [95% CI, 22.9–32.7] respectively, $P < 0.0001$) and between vancomycin susceptible and vancomycin non-susceptible *E. faecium* episodes (22.8% [95% CI, 16.9–29.6] vs 32.9% [95% CI, 25.7–40.7] respectively, $P = 0.05$).

Enterococcus faecalis phenotypic susceptibility

Apart from erythromycin, tetracycline, ciprofloxacin and high-level gentamicin, acquired resistance was rare among *E. faecalis* (Table 1). Ampicillin resistance was detected in 3 isolates and only 1 isolate was vancomycin non-susceptible. Thirty-six (6.9%) *E. faecalis,* were initially reported as linezolid non-susceptible (CLSI breakpoint > 2 mg/L). However by Etest®, 22 of the 35 isolates available for MIC testing by Etest® had a linezolid MIC of ≤ 2 mg/L and were therefore considered linezolid susceptible. Thirteen isolates with an MIC of 4 mg/L, although non-susceptible by CLSI guidelines, were considered susceptible by EUCAST guidelines. Eight (1.6%) isolates were initially reported non-susceptible to daptomycin (CLSI and EUCAST breakpoint > 4 mg/L). However by Etest®, 7 of the 8 isolates had an MIC of < 4 mg/L and were therefore considered susceptible. One isolate had an MIC of 8 mg/L, which was considered non-susceptible. All isolates were susceptible to teicoplanin.

Enterococcus faecium phenotypic susceptibility

The majority of *E. faecium* were non-susceptible to multiple antimicrobials (Table 2). Most isolates were non-susceptible to ampicillin, erythromycin, tetracycline, ciprofloxacin, nitrofurantoin and high-level gentamicin. Overall, 175 (46.1%) were phenotypically vancomycin non-susceptible (MIC > 4 mg/L). Thirty-one (8.2%) and 33 (8.8%) isolates were

Table 1: The number and proportion of Enterococcus faecalis non-susceptible to ampicillin and the non-β-lactam antimicrobials, Australia, 2014

Antimicrobial	Tested	Breakpoint (mg/L)	Non-susceptible	
			n	%
Ampicillin	522	>8*	3	0.6
		>4†	3	0.6
Vancomycin	523	>4‡	1	0.2
Erythromycin	509	>0.5*	446	87.4
Tetracycline	501	>4*	363	72.5
Ciprofloxacin	477	>1*	122	25.6
Daptomycin	490	>4*	1	0.2
Teicoplanin	521	>8*	0	0
		>2†	0	0
Linezolid	522	>2*	13	2.5
		>4†	0	0
Nitrofurantoin	521	>32*	11	2.1
		>64†	2	0.4
High level gentamicin	519	>128*	198	38.2

* Clinical and Laboratory Standards Institute (CLSI) non-susceptible breakpoint.
† European Committee on Antimicrobial Susceptibility Testing (EUCAST) non-susceptible breakpoint.
‡ CLSI and EUCAST non-susceptible breakpoint.

Table 2: The number and proportion of Enterococcus faecium non-susceptible to ampicillin and the non-β-lactam antimicrobials, Australia, 2014

Antimicrobial	Tested	Breakpoint (mg/L)	Non-susceptible	
			n	%
Ampicillin	379	>8*	339	89.5
		>4†	343	90.5
Vancomycin	380	>4‡	175	46.1
Erythromycin	371	>0.5*	351	94.6
Tetracycline	369	>4*	194	52.6
Ciprofloxacin	351	>1*	321	91.5
Teicoplanin	377	>8*	31	8.2
		>2†	33	8.8
Linezolid	378	>2*	2	0.5
		>4†	1	0.3
Nitrofurantoin	377	>32*	289	76.5
		>64†	137	36.2
High level gentamicin	377	>128*	233	61.5

* Clinical and Laboratory Standards Institute (CLSI) non-susceptible breakpoint.
† European Committee on Antimicrobial Susceptibility Testing (EUCAST) non-susceptible breakpoint.
‡ CLSI and EUCAST non-susceptible breakpoint.

teicoplanin non-susceptible by CLSI and EUCAST guidelines respectively. Nine (2.4%) isolates were initially reported as linezolid non-susceptible (CLSI breakpoint > 2 mg/L). However by Etest®, 7 of the 9 isolates had a linezolid MIC of ≤ 2 mg/L. One isolate had an MIC of 4 mg/L, which was considered susceptible by EUCAST guidelines but non-susceptible by CLSI guidelines. One isolate had an MIC of 8 mg/L, which was considered non-susceptible by CLSI and EUCAST guidelines.

Genotypic vancomycin susceptibility

VanA/vanB PCR was performed on 512 of the 523 *E. faecalis* isolates. Overall, 7 (1.4%) of the 512 isolates harboured a *vanA* or *vanB* gene. The vancomycin non-susceptible *E. faecalis* isolate (Vitek® vancomycin MIC ≥ 32 mg/L) harboured a *vanB* gene. One phenotypically vancomycin/teicoplanin susceptible isolate (Vitek® vancomycin MIC = 1 mg/L, teicoplanin MIC = ≤ 0.5 mg/L) harboured *vanA*. A further 5 phenotypically vancomycin susceptible *E. faecalis* isolates (Vitek® vancomycin MIC = 1) harboured *vanB* genes.

VanA/B PCR was performed on 370 of the 380 *E. faecium* isolates, including 171 of the 175 vancomycin non-susceptible isolates and 199 of the 205 vancomycin susceptible isolates. Overall, 189 (51.1%) of the 370 isolates harboured a *vanA* or *vanB* gene.

Thirty-one of the vancomycin non-susceptible *E. faecium* isolates harboured *vanA* (Vitek® vancomycin MIC = 8 mg/L [1 isolate] and > 16 mg/L [30 isolates]). A further 140 *E. faecium* vancomycin non-susceptible isolates harboured *vanB* (Vitek® vancomycin MIC = 8 mg/L [2 isolates] and > 16 mg/L [135 isolates]).

VanA or *vanB* genes were detected in 18 vancomycin susceptible *E. faecium* isolates. Four isolates harboured *vanA* (Vitek® vancomycin MIC ≤ 0.5 mg/L [2 isolates], MIC = 1 mg/L [1 isolate] and MIC = 2 mg/L [1 isolate], teicoplanin ≤ 1 mg/L [4 isolates]). Fourteen isolates harboured *vanB* (Vitek® vancomycin MIC ≤ 0.5 mg/L [7 isolates], MIC = 1 mg/L [6 isolates] and MIC = 2 mg/L [1 isolate]).

Of the 154 *vanB E. faecium* isolates, 3 were teicoplanin resistant (MIC > 32 mg/L).

Enterococcus faecium molecular epidemiology

Of the 380 episodes, 369 *E. faecium* isolates were available for typing. By PFGE, 367 isolates were classified into 113 pulsotypes, including 14 major pulsotypes with 5 or more isolates (Table 3). Two isolates were not typable by PFGE. Of the 99 pulsotypes with less than 5 isolates, 90 had only 1 isolate. Overall 253 (68.9%) of the 367 isolates were grouped into the 14 major pulsotypes from which 9 multilocus sequence types (STs) were identified. Using eBURST, the 9 STs were grouped into CC 17.

Geographical distribution of the 9 STs varied (Table 3). For the 4 most prominent STs, ST203 (69 isolates) was identified across most of Australia, ST796 (65 isolates) primarily in Victoria, ST555 (45 isolates) primarily in South Australia and Western Australia and ST17 (34 isolates) primarily in New South Wales. For the remaining 5 STs, ST117 (16 isolates) was found in New South Wales, Queensland and the Australian Capital Territory, ST 761 (7 isolates) in New South Wales and Queensland, ST192 (6 isolates) in Victoria and Tasmania, ST80 (7 isolates) in New South Wales and Western Australia and ST341 (5 isolates) in New South Wales and the Australian Capital Territory.

VanA was detected in two major pulsotypes (29 isolates, Efm18 and Efm85), and *vanB* in 8 major pulsotypes (137 isolates, Efm1, Efm2, Efm3, Efm18, Efm74, Efm75, Efm76, Efm77) (Table 4). Efm18 (ST17) harboured *vanA* and *vanB* genes. Twelve minor pulsotypes (14 isolates) also harboured *vanB* genes. In addition, *vanA* genes were detected in 6 minor pulsotypes (6 isolates).

Discussion

Enterococci are intrinsically resistant to a broad range of antimicrobials including the cephalosporins and sulphonamides. Due to 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[14] comparison of Australia antimicrobial resistance data with other countries is possible.

In the 2013 European Centre for Disease Prevention and Control and Prevention (ECDC) Enterococci surveillance program the European Union/European Economic Area (EU/EEA) population-weighted mean percentage of *E. faecium* resistant to vancomycin was 8.9% (95% CI, 7–12), ranging from 0.0% (95% CI, 0–9) in Estonia, Lithuania, Malta and Sweden to 42.7% (95% CI, 38–48) in Ireland. Cyprus (23.3%), United Kingdom (23.3%), Portugal (22.0%) and Greece (21.2%) were the only other EU/EEA countries to report above 20%.[15]

Table 3: The number and proportion of major Enterococcus faecium (Efm) pulsed-field gel electrophoresis pulsotypes, Australia, 2014, by region

		ACT		NSW		NT		Qld		SA		Tas.		Vic.		WA		Aus.	
Type	ST	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Efm1	ST203	0		6	4.5	0		0		0		0		2	2.1	2	4.0	10	2.6
Efm2		1	9.1	3	2.2	0		14	37.8	16	34.8	0		2	2.1	0		36	9.5
Efm75		2	18.2	5	3.7	0		1	2.7	0		0		1	1.1	0		9	2.4
Efm76		1	9.1	13	9.7	0		0		0		0		0		0		14	3.7
Efm74	ST796	0		0		0		0		2	4.3	1	14.3	62	66.0	0		65	17.1
Efm4	ST555	0		0		0		0		6	13.0	0		1	1.1	21	42.0	28	7.4
Efm77		0		0		0		1	2.7	9	19.6	0		0		7	14.0	17	4.5
Efm5	ST17	0		4	3.0	0		3	8.1	0		0		1	1.1	0		8	2.1
Efm18		0		26	19.4	0		0		0		0		0		0		26	6.8
Efm80	ST117	4	36.4	11	8.2	0		1	2.7	0		0		0		0		16	4.2
Efm78	ST761	0		6	4.5	0		1	2.7	0		0		0		0		7	1.8
Efm24	ST192	0		0		0		0		0		2	28.6	4	4.3	0		6	1.6
Efm85	ST80	0		5	3.7	0		0		0		0		0		1	2.0	6	1.6
Efm3	ST341	1	9.1	4	3.0	0		0		0		0		0		0		5	1.3
Other		2	18.2	43	32.1	1	100	15	40.5	12	26.1	2	28.6	20	21.3	19	38.0	114	30.0
NT		0		0		0		1	2.7	0		1	14.3	0		0		2	0.5
ND		0		7	5.2	0		0		1	2.2	1	14.3	1	1.1	0		11	2.9
Total		11	100	134	100	1	100	37	100	46	100	7	100	94	100	50	100	380	100

NT Non-typeable.

ND Not done.

Table 4: The number and proportion of major Enterococcus faecium (Efm) pulsed-field gel electrophoresis pulsotypes harbouring *vanA* or *vanB* genes, Australia, 2014

			vanA		vanB		Not detected	
Pulsotypes	ST	n	n	%	n	%	n	%
Efm1	ST203	10	0	0.0	3	30.0	7	70.0
Efm2		36	0	0.0	34	94.4	2	5.6
Efm75		9	0	0.0	3	33.3	6	66.7
Efm76		14	0	0.0	13	92.9	1	7.1
Efm74	ST796	65	0	0.0	65	100.0	0	0.0
Efm4	ST555	28	0	0.0	0	0.0	28	100.0
Efm77		17	0	0.0	16	94.1	1	5.9
Efm5	ST17	8	0	0.0	0	0.0	8	100.0
Efm18		26	24	92.3	1	3.8	1	3.8
Efm80	ST117	16	0	0.0	0	0.0	16	100.0
Efm78	ST761	7	0	0.0	0	0.0	7	100.0
Efm24	ST192	6	0	0.0	0	0.0	6	100.0
Efm85	ST80	6	5	83.3	0	0.0	1	16.7
Efm3	ST341	5	0	0.0	5	100.0	0	0.0
Total		253	29	11.5	140	53.3	84	33.2

In AESOP 2014 approximately 40% of enterococcal bacteraemia were due to *E. faecium,* of which 46.1% (95% CI, 41.0–51.2) were phenotypically vancomycin non-susceptible by Vitek2® or Phoenix™. However, 51.1% of *E. faecium* isolates tested (189/370) harboured *vanA/vanB* genes, of which 81.5% were *vanB*. Overall, 9.5% (35/370) of *E. faecium* isolates harboured a *vanA* gene, which is a significant increase from the 2.6% (8/310) of isolates reported in AESOP 2013 ($P = 0.0005$).[16] The majority of *E. faecium* isolates were also non-susceptible to multiple antimicrobials, including ampicillin, erythromycin, tetracycline, ciprofloxacin and high level gentamicin. In AESOP 2011[17] and 2013,16 37.0% and 48.6% of *E. faecium* harboured *vanA/vanB* respectively confirming the incidence of vancomycin resistant *E. faecium* bacteraemia in Australia is increasing.

Fourteen (9.1%) of the 154 *vanB E. faecium* isolates had a vancomycin MIC at or below the CLSI and the EUCAST susceptible breakpoint (≤ 4 mg/L) and would not have been identified using routine phenotypic antimicrobial susceptibility methods. Furthermore, 6 *vanA/B E. faecalis* were also phenotypically vancomycin susceptible (MIC 1 mg/L).

By PFGE, *E. faecium* was shown to be very polyclonal, consistent with the known plasticity of the enterococcal genome. The 14 major *E. faecium* pulsotypes formed part of CC17, a global hospital-derived lineage that has successfully adapted to hospital environments. CC17 is characteristically ampicillin and quinolone resistant and subsequent acquisition of *vanA*– or *vanB*-containing transposons by horizontal transfer in CC17 clones has resulted in vancomycin resistant enterococci with pandemic potential. In AESOP 2014, 4 *E. faecium* STs predominated: ST203 (of which 77% of isolates harboured *vanB* genes); ST796 (100% harboured *vanB*); ST555 (37% harboured *vanB*); and ST17 (71% harboured *vanA* and 3% harboured *vanB*). Two minor PFGE pulsotypes identified in AESOP 2013 have become major pulsotypes in AESOP 2014: Efm80–ST117 (16 isolates) found in New South Wales (11 isolates), the Australian Capital Territory (4 isolates) and Queensland (1 isolate) and Efm85–ST80 (6 isolates), in New South Wales (5 isolates) and Western Australia (1 isolate). The majority of Efm85–ST80 isolates harboured *vanA* genes.

Conclusions

The AESOP 2014 study has shown that although predominately caused by *E. faecalis,* enterococcal bacteraemia in Australia is frequently caused by ampicillin-resistant high-level gentamicin-resistant *vanB 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. Although the *vanB* operon continues to be the predominant genotype, the number of *vanA E. faecium* identified in AESOP 2014 has significantly increased when compared with AESOP 2013. 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. Further studies on the enterococcal genome will contribute to our understanding of the rapid and ongoing evolution of enterococci in the hospital environment and assist in preventing their nosocomial transmission.

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