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Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Sepsis Outcome Programme (AESOP) Annual Report 2015

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Annual Report

Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Sepsis Outcome Programme (AESOP) Annual Report 2015

Geoffrey W Coombs, Denise A Daley, Yung Thin Lee, Stanley Pang, Jan M Bell and John D Turnidge for the Australian Group on Antimicrobial Resistance

Abstract

From 1st January to 31st December 2015, 31 Australian institutions participated in the Australian Enterococcal Sepsis Outcome Programme (AESOP). The aim of AESOP 2015 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 1,009 unique episodes of bacteraemia investigated, 95.4% were caused by either *E. faecalis* (55.7%) or *E. faecium* (39.6%). Ampicillin resistance was detected in 0.2% of *E. faecalis* and in 86.0% of *E. faecium*. Vancomycin non-susceptibility was reported in 0.4% and 50.1% of *E. faecalis* and *E. faecium* respectively. Overall 56.2% of *E. faecium* harboured *vanA* or *vanB* genes. For the *vanA/B* positive *E. faecium* isolates, 61.0% harboured *vanB* genes and 36.8% *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 49 multilocus sequence types (STs) of which 85.6% of isolates were classified into 11 major STs containing five or more isolates. All major STs belong to clonal cluster 17, a major hospital-adapted polyclonal *E. faecium* cluster. Four of the five predominant STs (ST796, ST555, ST203, and ST80) were found across most regions of Australia. The second most predominant clone was non-typable by multilocus sequence typing and found only in NSW and the ACT. Overall 73.9% of isolates belonging to the five predominant STs harboured *vanA* or *vanB* genes. In conclusion, the AESOP 2015 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.

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 they are the fourth and fifth leading cause of sepsis respectively.[1,2] Although 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 2015 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*.

Methodology

Participants

Thirty-one laboratories from all eight Australian states and territories.

Collection Period

From 1 January to 31 December 2015, the participating 31 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 >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), 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 Antimicrobial Resistance and Infectious Diseases Laboratory, at Murdoch University. 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 was performed by whole genome sequencing using the MiSeq platform (Illumina, San Diego, USA). Sequencing results were analysed using the Nullarbor pipeline.[17]

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, 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 2015, 1,009 unique episodes of enterococcal bacteraemia were identified. Although nine *Enterococcus* species were identified, 55.7% (562 isolates) were *E. faecalis* and 39.6% (400 isolates) were *E. faecium*. Forty-seven enterococci were identified either as *Enterococcus casseliflavus* (16 isolates), *E. avium* (11), *E. gallinarum* (7), *E. raffinosus* (7), *E. hirae* (4) *E. durans* (1), and *E. gilvus* (1).

A significant difference was seen in patient sex (p<0.0001) with 613 (65.6%) being male (95% CI, 62.6 – 68.5). The average age of patients was 63 years ranging from 0 – 107 years with a median age of 67 years. Of the 1,006 episodes where onset was known, 493 (49.0%) were hospital onset (95% CI, 45.9 – 52.1). However, a significant difference was seen between *E. faecium* and E. *faecalis*, with 72.0% (95% CI, 62.7 – 76.4) of *E. faecium* episodes being hospital onset compared to 34.9% (95% CI, 31.0 – 39.0) for *E. faecalis* (p<0.0001). All-cause mortality at 30 days was 20.1% (95% CI, 14.4 – 26.6). There was no significant difference in mortality between *E. faecalis* and *E. faecium* episodes 15.5% vs 26.2% respectively (95%CI, -2.58 – 23.1), or between vancomycin susceptible and vancomycin non-susceptible *E. faecium* episodes 23.1% vs 29.3% respectively (95%CI, -13.15 – 24.2).

E. faecalis Phenotypic Susceptibility Results

Apart from erythromycin, tetracycline, ciprofloxacin and high-level gentamicin, acquired resistance was rare amongst *E. faecalis* (Table 1). Ampicillin resistance was detected in two isolates and two isolates were vancomycin non-susceptible. Thirty-nine (7.0%) *E. faecalis*, were

Table 1: The number and proportion of *E. faecalis* non-susceptible to ampicillin and the non-β-lactam antimicrobials, Australia, 2015

Antimicrobial	Number of isolates tested	Breakpoint (mg/L)	Non-Susceptible	
			n	%
Ampicillin	561	>8*	1	0.2
		>4†	2	0.4
Vancomycin	561	>4‡	2	0.4
Erythromycin	547	>0.5*	475	86.8
Tetracycline	489	>4*	384	78.5
Ciprofloxacin	521	>1*	90	17.3
Daptomycin	542	>4*	0	0
Teicoplanin	558	>8*	0	0
		>2†	0	0
Linezolid	561	>2*	26	4.6
		>4†	1	0.2
Nitrofurantoin	558	>32*	13	2.3
		>64†	2	0.4
High-Level Gentamicin	554	>128†	151	27.3

*CLSI non-susceptible breakpoint

†EUCAST non-susceptible breakpoint

‡CLSI and EUCAST non-susceptible breakpoint

Table 2: The number and proportion of *E. faecium* non-susceptible to ampicillin and the non-β-lactam antimicrobials, Australia, 2015

Antimicrobial	Number tested	Breakpoint (mg/L)	Non-Susceptible	
			n	%
Ampicillin	398	>8*	343	86.2
		>4†	345	86.3
Vancomycin	400	>4‡	200	50.0
Erythromycin	391	>0.5*	374	95.7
Tetracycline	342	>4*	199	58.2
Ciprofloxacin	372	>1*	342	91.9
Teicoplanin	399	>8*	70	17.5
		>2†	71	17.8
Linezolid	399	>2*	6	1.5
		>4†	0	0
Nitrofurantoin	398	>32*	306	76.9
		>64†	150	37.7
High-Level Gentamicin	385	>128*	230	59.7

*CLSI non-susceptible breakpoint

†EUCAST non-susceptible breakpoint

‡CLSI and EUCAST non-susceptible breakpoint

initially reported as linezolid non-susceptible (CLSI breakpoint >2 mg/L). However by Etest® 12 of the 39 isolates available for MIC testing by Etest® had a linezolid MIC of ≤2 mg/L and were therefore considered linezolid susceptible. Twenty five isolates with an MIC of 4 mg/L although non-susceptible by CLSI guidelines were considered susceptible by EUCAST guidelines. One isolate had an MIC of 6 mg/L and was non-susceptible and one isolate was not received for confirmation. All isolates were susceptible to daptomycin and teicoplanin.

E. faecium Phenotypic Susceptibility Results

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 200 (50%) were phenotypically vancomycin non-susceptible (MIC >4 mg/L). Seventy (17.5%) and 71 (17.8%) isolates were teicoplanin non-susceptible by CLSI and EUCAST guidelines respectively. This is an increase from 2014, where 31 (8.2%) and 33 (8.8%) isolates were teicoplanin non-susceptible by CLSI and EUCAST guidelines respectively. Thirteen (3.3%) isolates were initially reported as linezolid non-susceptible (CLSI breakpoint >2 mg/L). However, by Etest® seven of the nine isolates had a linezolid MIC of ≤2 mg/L. Six isolates had MICs of 4mg/L which was considered susceptible by EUCAST guidelines but non-susceptible by CLSI guidelines.

Genotypic Vancomycin Susceptibility Results

vanA/vanB PCR was performed on 420 of the 562 *E. faecalis* isolates. Overall, two (0.4%) of the 420 isolates harboured a *vanA* or *vanB* gene.

Table 3: The number and proportion of major *E. faecium* sequence types, Australia, 2015, by region

Sequence Types	ACT		NSW		NT		Qld		SA		Tas		Vic		WA		Aus	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
17			7	6.4			1	3.2					2	1.7	9	17.3	19	4.9
18			2	1.8					1	2.3			1	0.9	1	1.9	5	1.3
78			12	10.9			9	29							1	1.9	22	5.6
80	6	27.3	15	13.6	1	12.5	3	9.7	1	2.3			14	12	6	11.5	46	11.8
117	1	4.5	5	4.5			2	6.5					2	1.7			10	2.6
192													9	7.7			9	2.3
203	4	18.2	6	5.5			7	22.6	7	16.3	2	28.6	10	8.5	3	5.8	39	10
262									11	25.6			1	0.9			12	3.1
555			1	0.9	6	75			17	39.5	1	14.3	3	2.6	21	40.4	49	12.6
796			2	1.8			3	9.7	1	2.3	1	14.3	63	53.8			70	17.9
Non-typable *	9	40.9	44	40													53	13.6
Other	2	9.1	16	14.5	1		6	19.4	5	11.6	3	42.9	12	10.3	11	21.2	56	14.4
Total	22	100	110	100	8		31	100	43	100	7	100	117	100	52	100	390	100

*The non-typable group were a single clone missing the *pstS* gene
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

The two vancomycin non-susceptible *E. faecalis* isolates (Vitek® vancomycin MIC ≥32 mg/Land 8mg/L) harboured the *vanB* gene.

The presence of *vanA*/*B* genes was determined by PCR or whole genome sequencing on 397 of the 400 *E. faecium* isolates. Overall, 223 (56.2%) of the 397 isolates harboured a *vanA* and/or *vanB* gene. Seventy-four of the vancomycin non-susceptible *E. faecium* isolates harboured *vanA* (Vitek® vancomycin MIC = >16mg/). A further 121 *E. faecium* vancomycin non-susceptible isolates harboured *vanB* (Vitek® vancomycin MIC = 8 mg/L [two isolates] and >16 mg/L [119 isolates]). Five isolates harboured both *vanA* and v*anB* genes (Vitek® vancomycin MIC >16 mg/L).

vanA or *vanB* genes were detected in 23 vancomycin susceptible *E. faecium* isolates. Eight isolates harboured *vanA* (Vitek® vancomycin MIC ≤ 0.5mg/L [three isolates], MIC = 1 mg/L [five isolates], teicoplanin ≤1mg/L [8 isolates]). Fifteen isolates harboured *vanB* (Vitek® vancomycin MIC ≤ 0.5mg/L [seven isolates], MIC = 1 mg/L [eight isolates].

Of the 136 *vanB E. faecium* isolates, three were teicoplanin resistant (MIC >32 mg/L).

E. faecium Molecular Epidemiology

Of the 400 episodes, 390 *E. faecium* isolates were available for typing by whole genome sequencing. The 390 isolates were classified into 49 sequence types (STs) including 11 STs with five or more isolates (Table 3). Based on six of the seven MLST housekeeping genes, 53 *pstS*-negative isolates were considered the same clone. Of the 38 STs with <5 isolates, 25 had only one isolate. Overall, 334 (85.6%) of the 390 isolates were grouped into the 11 major STs. Using eBURST, the eleven STs were grouped into CC 17.

Geographical distribution of the STs varied (Table 3). For the five most prominent STs, ST796 (70 isolates) was identified primarily in Victoria; the non-typable clone (53 isolates) primarily in New South Wales; ST555 (49 isolates) across most of Australia except Queensland and the Australian Capital Territory; ST80 (46 isolates) found in all mainland regions; and ST203 (39 isolates) found in all regions except the Northern Territory. For the remaining six STs, ST78 (22 isolates) was found in New South Wales, Queensland and Western Australia, ST17 (19 isolates) in New South Wales, Queensland, Victoria and Western Australia, ST262 (12 isolates) predominantly in South Australia, ST117 (10 isolates) in New South Wales, the Australian Capital Territory, Queensland and Victoria, ST192 (9 isolates) found exclusively in Victoria and ST18 (5 isolates) in New South Wales, South Australia, Victoria and Western Australia.

vanA was detected in five major STs (79 isolates, the non-typable clone, ST80, ST203, ST78 and ST117). *vanB* was detected in six major STs (135 isolates, ST796, ST555, ST203, ST78, ST17 and ST117) (Table 4). ST78, ST117 and ST203 harboured *vanA* and *vanB* genes. Four minor STs (5 isolates) also 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 programmes are similar to those conducted in Europe[18] comparison of Australia antimicrobial resistance data with other countries is possible.

In the 2015 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 8.3% (95% CI, 8 – 9), ranging from 0.0% (95% CI, 0 – 17) in Estonia, Luxembourg, Iceland, Norway and Sweden to 45.8% (95% CI, 41 – 51) in Ireland.[19]

Table 4: The number and proportion of major *Enterococcus faecium* sequence types harbouring vanA/B genes, Australia, 2015

Sequence Types	n	*vanA*		*vanB*		*vanA and vanB*		Not Detected	
		n	%	n	%	n	%	n	%
17	19			2	1.5			17	9.9
18	5							5	2.9
78	22	1	1.3	15	11.1	3	60	3	1.8
80	46	23	29.1					23	13.5
117	10	1	1.3	2	1.5			7	4.1
192	9							9	5.3
203	39	8	10.1	18	13.3	1	20	12	7
262	12							12	7
555	49			24	17.8			25	14.6
796	70			69	51.1	1	20		
Non-typable*	53	46	58.2					7	4.1
Other	56			5	3.7			51	29.8
Total	390	79	100	135	100	5	100	171	100

*The non-typable group were a single clone missing the *pstS* gene

In AESOP 2015, approximately 40% of enterococcal bacteraemia were due to *E. faecium* of which 50% (95% CI, 45.0 – 55.0) were phenotypically vancomycin non-susceptible by Vitek2® or Phoenix™. However, 56.2% of *E. faecium* isolates tested (223/397) harboured *vanA/vanB* genes, of which 61% were *vanB*. Overall, 20.7% 82/397 of *E. faecium* isolates harboured a *vanA* gene. There has been a significant increase over the last two surveys from 9.5% (35/370) in 2014 and 6% (8/310) in AESOP 2013.[14 15] 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[16], 2013[14] and 2014[15], 37.0%, 48.6% and 51.1% of *E. faecium* harboured *vanA/vanB* respectively confirming the incidence of vancomycin resistant *E. faecium* bacteraemia in Australia is increasing.

Fifteen (11%) of the 136 *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.

By whole genome sequencing, *E. faecium* was shown to be very polyclonal, consistent with the known plasticity of the enterococcal genome. The 11 major *E. faecium* STs 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 VRE with pandemic potential. In AESOP 2015, five *E. faecium* STs predominated: ST796 (of which 98.6% of isolates harboured *vanB* genes, one isolate had both *vanA* and *vanB* genes); the non-typable clone (100% harboured *vanA*); ST555 (100% harboured *vanB*); ST80 (100% harboured *vanA*) and ST 203 (46.2% harboured vanB, 20.5% harboured *vanA* and one isolate had both *vanA* and *vanB* genes).

Conclusions

The AESOP 2015 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 2015 has significantly increased when compared to AESOP 2013 and 2014. 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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