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Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Surveillance Outcome Program (AESOP)

Bloodstream Infection Annual Report 2022

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Annual report

Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Surveillance Outcome Program (AESOP)

Bloodstream Infection Annual Report 2022

Geoffrey W Coombs, Denise A Daley, Princy Shoby, Shakeel Mowlaboccus,
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Abstract

From 1 January to 31 December 2022, fifty-five institutions across Australia participated in the Australian Enterococcal Surveillance Outcome Program (AESOP). The aim of AESOP 2022 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 1,535 unique episodes of enterococcal bacteraemia investigated, 92.8% were caused by either *E. faecalis* (52.9%) or *E. faecium* (39.9%). Ampicillin and vancomycin resistance were not detected in *E. faecalis* but were detected in 95.4% and 46.9% of *E. faecium* respectively. One *E. faecalis* isolate, with a daptomycin minimum inhibitory concentration (MIC) of 8.0 mg/L, harboured the F478L GdpD mutation. One *E. faecium* with a daptomycin MIC of 24.0 mg/L harboured the A20D *Cls* mutation; both mutations are known to be associated with daptomycin resistance. Two *E. faecium* isolates, one with a linezolid MIC ≥ 256 mg/L and the other with a linezolid MIC of 16 mg/L, harboured the 23S rRNA G2576T mutation, a mutation associated with linezolid resistance in enterococci.

Overall, 48.8% of *E. faecium* harboured either the *vanA* or the *vanB* gene, of which 28.0% harboured *vanA* and 72.0% harboured *vanB*. The percentage of vancomycin-resistant *E. faecium* bacteraemia isolates in Australia remains substantially higher than that recorded in most European countries. The *E. faecium* isolates consisted of 62 multi-locus sequence types (STs); 85.5% of isolates were classified into eight major STs each containing ten or more isolates. All major STs belonged to clonal complex (CC) 17, a major hospital-adapted polyclonal *E. faecium* cluster. The major STs (ST17, ST78, ST80, ST117, ST555, ST796, ST1421, and ST1424) were each found across most regions of Australia. The predominant ST was ST17, which was identified in all regions. Overall, 53.7% of isolates belonging to the eight major STs harboured the *vanA* or *vanB* gene. AESOP 2022 has shown that enterococcal bacteraemia episodes in Australia are frequently caused by polyclonal ampicillin-resistant high-level gentamicin resistant *vanA*- or *vanB*-positive *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 believed to account for approximately 10% of all bacteraemia cases and is the fourth and fifth leading cause of sepsis in North America and Europe, respectively. In the 1970s, healthcare-associated enterococcal infections were primarily due to *Enterococcus faecalis*, but there has been a steady increasing prevalence of *E. faecium* nosocomial infections.[1–3] 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 further 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 pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) requiring new therapies.[4]

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.[5] In 2011, AGAR commenced the Australian Enterococcal Sepsis Outcome Program,[6,7] now known as the Australian Enterococcal Surveillance Outcome Program (AESOP). The objective of AESOP 2022 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. the molecular epidemiology of *E. faecium*.

Methodology

Participants

Thirty-three laboratories servicing 55 institutions from all Australian states and mainland territories.

Collection period

From 1 January to 31 December 2022, the 33 laboratories collected all enterococcal species isolated from blood cultures. Enterococci of 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 bacteraemia 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, USA) or Vitek-MS (bioMérieux, France)—or by the Vitek2® (bioMérieux). Antimicrobial susceptibility testing was performed using the Vitek2® (bioMérieux) or the BD 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. Clinical and Laboratory Standards Institute (CLSI)[8] and European Committee on Antimicrobial

Susceptibility Testing (EUCAST)[9] MIC breakpoints were utilised for interpretation. Linezolid and daptomycin non-susceptible isolates and vancomycin-susceptible isolates which harboured the *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. For all *E. faecium* received, whole genome sequencing (WGS) was performed by the AMRID Research Laboratory at Murdoch University on the Illumina NextSeq™ 500 platform. The multilocus sequence type (ST) was determined using the PubMLST website; *van* genes were identified using nucleotide sequences from the NCBI database and a BLAST interface.

Confidence intervals for proportions, Fisher's exact test for categorical variables, and chi-square test for trend were calculated, if appropriate, 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 2022, there were 1,535 unique episodes of enterococcal bacteraemia identified. Although thirteen *Enterococcus* species were identified, *E. faecalis* and *E. faecium* predominated: 812 isolates (52.9%) were *E. faecalis* and 613 isolates (39.9%) were *E. faecium*. One hundred and ten enterococci were identified either as *E. lactis* (previously identified as *E. faecium,* 29 isolates), *E. casseliflavus* (21 isolates*), E. gallinarum* (17 isolates), *E. avium* (16 isolates), *E. raffinosus* (13 isolates), *E. hirae* (5 isolates), *E. durans* (4 isolates), *E. gilvus* (2 isolates), *E. dispar* (1 isolate), *E. cecorum* (1 isolate) or *Enterococcus* sp. [not speciated] (1 isolate).

A significant difference was observed in patient sex ($p < 0.0001$), with 1,034 (67.4%) being male (95% confidence interval [95% CI]: 65.0–69.7). The average age of patients was 64 years, ranging from 0 to 101 years, with a median age of 69 years. Overall, isolates were evenly divided by place of onset: 767/1,535 (50.0%) were community-onset and 768/1,535 were hospital-onset (95% CI: 47.5–52.5). However, a significant difference ($p < 0.01$) was observed between

Table 1: The number and proportion of *E. faecalis* isolates non-susceptible to ampicillin, penicillin and the non-β-lactam antimicrobials, AGAR, 2022

		CLSI[a]		EUCAST[b]	
Antimicrobial	*E. faecalis* **isolates (n)**	**Intermediate % (*n*)**	**Resistant % (*n*)**	**Susceptible, increased exposure % (*n*)**	**Resistant % (*n*)**
Ampicillin	807	–[c]	0.0 (0)	0.0 (0)	0.0 (0)
Benzylpenicillin	664	–[c]	0.9 (6)	–[d]	–[d]
Daptomycin	745	38.9 (290)	0.1 (1)	–[d]	–[d]
Linezolid	804	0.4 (3)	0.0 (0)	–[c]	0.0 (0)
Teicoplanin	807	0.0 (0)	0.0 (0)	–[c]	0.0 (0)
Vancomycin	807	0.0 (0)	0.0 (0)	–[c]	0.0 (0)

a CLSI: Clinical and Laboratory Standards Institute

b EUCAST: European Committee on Antimicrobial Susceptibility Testing.

c No guidelines for indicated species.

d No category defined.

E. faecium and *E. faecalis* in place of onset, with only 25.6% (95% CI: 22.2–29.3) of *E. faecium* episodes being community-onset compared to 67.0% (95% CI: 63.7–70.2) for *E. faecalis*. All-cause mortality at 30 days, where outcome was known, was 21.2% (95% CI: 19.0–23.5). There was a significant difference in mortality between *E. faecalis* and *E. faecium* episodes (17.2% vs 26.9% respectively, $p < 0.01$). There was also a significant difference in mortality between vancomycin-susceptible and vancomycin non-susceptible *E. faecium* episodes (19.7% vs 34.4% respectively, $p < 0.01$).

Enterococcus faecalis phenotypic susceptibility

Apart from erythromycin, high-level gentamicin and tetracycline, acquired resistance was rare amongst *E. faecalis* isolates (Table 1). Twenty-one *E. faecalis* isolates (2.6%) were initially reported as linezolid non-susceptible (CLSI breakpoint > 2 mg/L). Four isolates were unavailable for linezolid susceptibility test confirmation. By Etest®, 14 of the 17 referred isolates had a linezolid MIC ≤ 2 mg/L and were therefore considered linezolid susceptible. One isolate with a linezolid MIC of 3.0 mg/L and two isolates with linezolid MICs of 4 mg/L, although intermediate by CLSI criteria, were considered susceptible by EUCAST criteria.

Four isolates were initially reported as daptomycin resistant (≥ 8 mg/L) by CLSI criteria. One isolate was unavailable for confirmation. By Etest®, two of the three referred isolates had a daptomycin MIC < 8 mg/L. The remaining isolate, with a MIC of 8.0 mg/L, harboured the F478L GdpD mutation, a mutation known to be associated with daptomycin resistance.

Enterococcus faecium phenotypic susceptibility

The majority of *E. faecium* were non-susceptible to multiple antimicrobials including ampicillin, erythromycin, high-level gentamicin and tetracycline (Table 2). Overall, 285 *E. faecium* isolates (46.9%) were phenotypically vancomycin non-susceptible (MIC > 4 mg/L). Sixty-three (9.4%) and 80 (13.2%) isolates were teicoplanin non-susceptible by CLSI and EUCAST criteria, respectively. Fifteen isolates (2.5%) were initially reported as linezolid non-susceptible (CLSI breakpoint > 2 mg/L). Two isolates were unavailable for confirmation. By Etest®, nine of the thirteen referred isolates had a linezolid

Table 2: The number and proportion of *E. faecium* isolates non-susceptible to ampicillin, penicillin and the non-β-lactam antimicrobials, AGAR, 2022

		CLSI[a]		EUCAST[b]	
Antimicrobial	***E. faecium* isolates (n)**	**Intermediate % (*n*)**	**Resistant % (*n*)**	**Susceptible, increased exposure % (*n*)**	**Resistant % (*n*)**
Ampicillin	606	–[c]	95.4 (578)	0.5 (3)	95.4 (578)
Benzylpenicillin	480	–[c]	94.2 (452)	–[d]	–[d]
Daptomycin	58	98.3 (57)[e]	1.7 (1)	–[d]	–[d]
Linezolid	607	0.3 (2)	0.3 (2)	–[c]	0.3 (2)
Teicoplanin	605	1.5 (9)	8.9 (54)	–[c]	13.2 (80)
Vancomycin	608	1.0 (6)	45.9 (279)	–[c]	46.9 (285)

a CLSI: Clinical and Laboratory Standards Institute

b EUCAST: European Committee on Antimicrobial Susceptibility Testing.

c No guidelines for indicated species.

d No category defined.

e Susceptible dose-dependent (SDD) category for CLSI. (*E. faecium* are usually SDD to daptomycin.)

MIC ≤ 2 mg/L and were therefore considered linezolid susceptible. One isolate with a MIC of 3.0 mg/L and one isolate with a MIC of 4 mg/L by Etest®, although intermediate by CLSI criteria, were considered susceptible by EUCAST criteria. The two remaining isolates, one with a linezolid MIC ≥ 256 mg/L and the other with a linezolid MIC of 16 mg/L, harboured the 23S rRNA G2576T mutation which is associated with linezolid resistance in enterococci. Two isolates were initially reported as daptomycin resistant ≥ 8 mg/L. One isolate was unavailable for confirmation. The other isolate, with an MIC of 24 mg/L, was confirmed as daptomycin resistant. This isolate harboured the A20D *Cls* mutation, a mutation known to be associated with daptomycin resistance.

Genotypic vancomycin susceptibility

For 384 (47.3%) of the 812 *E. faecalis* isolates, *vanA*/*vanB* polymerase chain reaction (PCR) results were available. No *vanA*/*vanB* genes were detected in *E. faecalis*.

The presence of *vanA* or *vanB* genes was determined by PCR and/or WGS on 592 (96.6%) of the 613 *E. faecium* isolates. Overall, 289 of the 592 isolates (48.8%) harboured a *vanA* or *vanB* gene. Of the vancomycin non-susceptible *E. faecium* isolates (Vitek2® vancomycin MIC > 4 mg/L), 79 harboured *vanA* and 199 harboured *vanB*. The *vanA* or *vanB* gene was detected in nine vancomycin-susceptible *E. faecium* isolates. One isolate with a vancomycin MIC of 2.0 mg/L and teicoplanin MIC of 1.0 mg/L harboured *vanA*. The eight *vanB*-positive vancomycin-susceptible isolates had vancomycin MICs ranging from ≤ 0.5 mg/L to 4.0 mg/L.

E. faecium molecular epidemiology

Of the 613 episodes, 560 *E. faecium* isolates (91.4%) were available for typing by WGS. The 560 isolates were classified into 62 STs, including eight STs with ten or more isolates (Table 3). Of the 54 STs with fewer than ten isolates each, 40 STs were each represented by only one isolate. Overall, 479 (85.5%) of the 560 isolates were grouped into the eight major STs. Using eBURST, all major STs were grouped into CC17.

Table 3: The number and proportion of major *Enterococcus faecium* sequence types, AGAR, 2022, by jurisdiction

	Percentage, % (*n*)[a]								
MLST[b]	ACT	NSW	NT	Qld	SA	Tas.	Vic.	WA	Australia
ST17	6.3 (1)	8.3 (15)	7.7 (1)	52.2 (24)	17.5 (7)	40.9 (9)	14.9 (26)	52.2 (36)	21.3 (119)
ST78	37.5 (6)	21.1 (38)	23.1 (3)	2.2 (1)	20.0 (8)	18.2 (4)	25.3 (44)	8.7 (6)	19.6 (110)
ST1424	12.5 (2)	30.6 (55)	0.0 (0)	6.5 (3)	2.5 (1)	18.2 (4)	9.2 (16)	0.0 (0)	14.5 (81)
ST796	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	7.5 (3)	9.1 (2)	25.3 (44)	0.0 (0)	8.9 (50)
ST80	31.3 (5)	5.6 (10)	7.7 (1)	21.7 (10)	2.5 (1)	4.5 (1)	5.7 (10)	10.1 (7)	8.0 (45)
ST1421	6.3 (1)	18.3 (33)	0.0 (0)	6.5 (3)	0.0 (0)	0.0 (0)	4.0 (7)	0.0 (0)	7.9 (44)
ST555	0.0 (0)	0.6 (1)	23.1 (3)	0.0 (0)	32.5 (13)	0.0 (0)	1.1 (2)	1.4 (1)	3.6 (20)
ST117	0.0 (0)	1.1 (2)	0.0 (0)	0.0 (0)	2.5 (1)	0.0 (0)	0.0 (0)	10.1 (7)	1.8 (10)
Other types (n = 54)	6.3 (1)	13.9 (25)	38.5 (5)	10.9 (5)	15.0 (6)	9.1 (2)	14.4 (25)	17.4 (12)	14.5 (81)
Total	**16**	**180**	**13**	**46**	**40**	**22**	**174**	**69**	**560**

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

b MLST: multi-locus sequence type.

Geographical distribution of the STs varied (Table 3). Amongst the eight major STs, ST17 (119 isolates), ST78 (110 isolates) and ST80 (45 isolates) were identified in all regions; ST1424 (81 isolates) was identified in all regions except Western Australia and the Northern Territory; ST796 (50 isolates) was identified in all regions except the Australian Capital Territory, the Northern Territory, Queensland and Western Australia; ST1421 (44 isolates) was identified only in New South Wales, Victoria, Queensland and the Australian Capital Territory; ST555 (20 isolates) was identified in all regions except Queensland, Tasmania and the Australian Capital Territory; and ST117 (10 isolates) was identified only in New South Wales, South Australia and Western Australia.

The *vanA* gene was detected in five major STs (72 isolates from ST17, ST1424, ST80, ST1421 and ST117) (Table 4).The *vanB* gene was detected in seven of the eight major STs (185 isolates from ST17, ST78, ST1424, ST796, ST80, ST555, and ST117). One minor ST (ST18) harboured one *vanA*-positive isolate and six minor STs (ST612, ST203, ST2217, ST2430, ST341, and ST2439) harboured at least one *vanB*-positive isolate.

Discussion

Enterococci are intrinsically resistant to a broad range of antimicrobials including the cephalosporins and sulfonamides. Because of 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.

In AESOP 2022, a total of 39.9% of enterococcal bacteraemia were due to *E. faecium*, of which 46.9% (95% CI: 42.9–51.0) were phenotypically vancomycin non-susceptible by Vitek2® or BD Phoenix™. However, 48.8% of *E. faecium* isolates tested (289/592) harboured a *vanA/vanB* gene, of which 28.0% were *vanA*-positive. Overall, 81 *E. faecium* isolates (13.7%) harboured the *vanA* gene. Over the last five years, there has been a significant decreasing trend in *vanA*-positive *E. faecium* in Australia (χ^2 for linear trend = 36.41, $p < 0.01$).[10–14] This was primarily due to a decrease in the number of ST1424 isolates. The majority of *E. faecium* isolates were non-susceptible to multiple antimicrobials including ampicillin, erythromycin, high-level gentamicin and tetracycline.

Table 4: The number and proportion of major *Enterococcus faecium* sequence types harbouring *vanA/vanB* genes, AGAR, 2022

	Percentage[a] (n)				
MLST[b]	*vanA*	*vanB*	*vanA* and *vanB*	*vanA* or *vanB* not detected	Total, n
ST17	0.8 (1)	2.5 (3)	0.0 (0)	96.6 (115)	119
ST78	0.0 (0)	100.0 (110)	0.0 (0)	0.0 (0)	110
ST1424	34.6 (28)	1.2 (1)	0.0 (0)	64.2 (52)	81
ST796	0.0 (0)	100.0 (50)	0.0 (0)	0.0 (0)	50
ST80	6.7 (3)	4.4 (2)	0.0 (0)	88.9 (40)	45
ST1421	81.8 (36)	0.0 (0)	0.0 (0)	18.2 (8)	44
ST555	0.0 (0)	90.0 (18)	0.0 (0)	10.0 (2)	20
ST117	40.0 (4)	10.0 (1)	0.0 (0)	50.0 (5)	10
Other types (n = 54)	1.2 (1)	11.1 (9)	0.0 (0)	87.7 (71)	81
Total	**13.0 (73)**	**34.6 (194)**	**0.0 (0)**	**52.3 (293)**	**560**

a Percentage of total with *van* genes.

b MLST: multi-locus sequence type.

As the AGAR programs are similar to those conducted in Europe, comparison of Australian antimicrobial resistance data with other countries is possible. In the 2021 European Antimicrobial Resistance Surveillance Network (EARS-Net) program, the national percentages of vancomycin-resistant *E. faecium* ranged from 0.0% in Luxembourg to 66.4% in Lithuania.[15,16]

The AESOP 2022 survey confirms the incidence of vancomycin resistant *E. faecium* bacteraemia in Australia continues to be a significant problem.

Where vancomycin results were available, eight (3.9%) of the 207 *vanB*-positive *E. faecium* and one (1.3%) of the 80 *vanA*-positive *E. faecium* isolates had a vancomycin MIC at or below the CLSI and 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 polyclonal, consistent with the known plasticity of the enterococcal genome. The eight major *E. faecium* STs identified form 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 multi-resistant enterococci with pandemic potential.

In AESOP 2022, eight *E. faecium* STs predominated: ST17 (of which 0.8% of isolates harboured *vanA*, 2.5% *vanB* genes); ST78 (100% *vanB)*; ST1424 (34.6% *vanA,* 1.2% *vanB)*; ST796 (100% *vanB*), ST80 (6.7% *vanA,* 4.4% *vanB*); ST1421 (81.8% *vanA,* 0% *vanB*), ST555 (0% *vanA,* 90% *vanB*), and ST117 (40.0% *vanA*, 10.0% *vanB*).

Conclusions

The AESOP 2022 study has shown that, although predominately caused by *E. faecalis,* enterococcal bacteraemia in Australia is frequently caused by ampicillin-resistant, high-level gentamicin-resistant and vancomycin-resistant *E. faecium*. Furthermore, the percentage of *E. faecium* bacteraemia isolates resistant to vancomycin in Australia (46.9%) remains significantly higher than that seen in most European countries. 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.

Of particular concern, one *E. faecalis* with a daptomycin MIC of 8.0 mg/L harboured the F478L GdpD mutation and one *E. faecium* with a daptomycin MIC of 24.0 mg/L harboured the A20D *Cls* mutation, mutations both known to be associated with daptomycin resistance. Two *E. faecium*, one with a linezolid MIC ≥ 256 mg/L and the other with a linezolid MIC of 16 mg/L, harboured the 23S rRNA G2576T mutation which is associated with linezolid resistance in enterococci. Linezolid and daptomycin are considered 'last-line' antimicrobials used in the treatment of enterococcal bacteraemia; resistance to these drugs is a public health concern.

Ongoing studies on the enterococcal genome will contribute to our understanding of the rapid and continuing evolution of enterococci in the hospital environment and will assist in preventing their nosocomial transmission.

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