Australian Government
Department of Health

COMMUNICABLE DISEASES INTELLIGENCE

2019 Volume 43

https://doi.org/10.33321/cdi.2019.43.42

Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Sepsis Outcome Programme (AESOP) Annual Report 2017

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Communicable Diseases Intelligence
ISSN: 2209-6051 Online

This journal is indexed by Index Medicus and Medline.

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http://www.health.gov.au/cdna

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Communicable Diseases Intelligence is produced by:
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Australian Government
Department of Health
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Annual report

Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Sepsis Outcome Programme (AESOP) Annual Report 2017

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

Abstract

From 1 January to 31 December 2017, 36 institutions around Australia participated in the Australian Enterococcal Sepsis Outcome Programme (AESOP). The aim of AESOP 2017 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 1,137 unique episodes of bacteraemia investigated, 95.2% were caused by either *E. faecalis* (52.9%) or *E. faecium* (42.3%). Ampicillin resistance was not detected in *E. faecalis* but in 89.6% of *E. faecium*. Vancomycin non-susceptibility was reported in 0.3% and 47.0% of *E. faecalis* and *E. faecium* respectively. Overall 50.9% of *E. faecium* harboured *vanA* or *vanB* genes. For the *vanA/B* positive *E. faecium* isolates, 49.6% harboured *vanB* genes and 49.2% *vanA* genes; 1.2% harboured *vanA* and *vanB* 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 76 multilocus sequence types (STs) of which 77% of isolates were classified into nine major STs containing ten or more isolates. All major STs belong to clonal cluster (CC) 17, a major hospital-adapted polyclonal *E. faecium* cluster. Seven of the nine predominant STs (ST80, ST1421, ST17, ST296, ST555, ST203 and ST18) were found across most regions of Australia. The most predominant clone was ST17 which was identified in all regions except the Australian Capital Territory, the Northern Territory and Tasmania. Overall 60.7% of isolates belonging to the nine predominant STs harboured *vanA* or *vanB* genes. The AESOP 2017 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 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 17 (CC17) 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).[8,9] The objective of AESOP 2017 was to determine the proportion of *E. faecalis* and *E. faecium* bacteraemia isolates demonstrating antimicrobial resistance with particular emphasis on:

- Assessing susceptibility to ampicillin
- Assessing susceptibility to glycopeptides
- 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 2017, 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 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), Vitek-MS (bioMérieux), polymerase chain reaction (PCR), or conventional biochemical tests. Antimicrobial susceptibility testing was performed by using the Vitek2® or the 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) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were utilised for interpretation.[10,11] 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. *E. faecalis* ATCC® 29212 was used as the control strain. Molecular testing was performed by whole genome sequencing (WGS) using the MiSeq® 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 2017, a total of 1,137 unique episodes of enterococcal bacteraemia were identified. Although nine *Enterococcus* species were identified, 52.9% (602 isolates) were *E. faecalis* and 42.3% (481 isolates) were *E. faecium*. Fifty-four enterococci were identified either as *E. casseliflavus* (19 isolates), *E. gallinarum* (14 isolates), *E. avium* (9 isolates), *E. durans* (4 isolates), *E. raffinosis* (4 isolates) *E. hirae* (2 isolates), *E. saccharolyticus* (1 isolate) or *Enterococcus* species (unidentified) (1 isolate).

A significant difference was seen in patient sex (p<0.001) with 731 (64.3%) being male (95% CI, 61.3–67.1). The average age of patients was 63 years ranging from 0–99 years with a median age of 67 years. The majority of episodes, 53.9% (613/1,137), were community-onset (95% CI, 51.0–56.8). However, a significant difference (p<0.001) in place of onset was seen between *E. faecium* and E. *faecalis*, with only 29.9% (95% CI, 25.8–34.2) of *E. faecium* episodes being community-onset compared to 71.1% (95% CI, 67.3–74.7) for *E. faecalis*. All-cause mortality at 30 days where data was known was 20.0% (95% CI, 17.5–22.7). There was a significant difference (p<0.001) in mortality between *E. faecalis* and *E. faecium* episodes, 14.1% vs 27.3% respectively, but not between vancomycin-susceptible and vancomycin non-susceptible *E. faecium* episodes, 25.9% vs 27.7% respectively (p=0.7).

E. faecalis Phenotypic Susceptibility Results

Apart from erythromycin, tetracycline, ciprofloxacin and high-level gentamicin, acquired resistance was rare amongst *E. faecalis* (Table 1). Two isolates were vancomycin non-susceptible. Ampicillin resistance was not detected. Sixteen (2.7%) *E. faecalis* were initially reported as linezolid non-susceptible (CLSI breakpoint >2 mg/L). However by Etest® eight of the 16 isolates had a linezolid MIC of ≤2 mg/L and were therefore considered linezolid susceptible. The remaining eight isolates with MICs of 3 mg/L and 4 mg/L, although non-susceptible by CLSI guidelines, were considered susceptible by EUCAST guidelines. Two isolates were reported as daptomycin non-susceptible (>4 mg/L). One isolate was confirmed to have a daptomycin MIC of 8.0 mg/L by Etest®, however no known single nucleotide mutations were identified by WGS. The second isolate was unavailable for confirmation.

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 226 (47.0%) were phenotypically vancomycin non-susceptible (MIC >4 mg/L). One hundred and ten (22.9%) and 120 (24.9%) isolates were teicoplanin non-susceptible by CLSI and EUCAST guidelines respectively. Fourteen (2.9%) isolates were initially reported as linezolid non-susceptible (CLSI breakpoint >2 mg/L). However by Etest® nine of the 14 isolates had a linezolid MICs of ≤2 mg/L and therefore were considered susceptible. Of the remaining five isolates, three had MICs of 3 mg/L which is considered susceptible by EUCAST guidelines but non-susceptible by CLSI guidelines, and two isolates were unavailable for confirmation.

Genotypic Vancomycin Susceptibility Results

vanA/vanB PCR results were available for 328 of the 602 *E. faecalis* isolates. Two of the 328 isolates harboured a *vanB* gene. Both isolates had a vancomycin MIC of 8.0 mg/L.

The presence of *vanA*/*B* genes was determined by PCR or whole genome sequencing on 479 of the 481 *E. faecium* isolates. Overall 244 (50.9%) of the 479 isolates harboured a *vanA* and/or *vanB* gene. One hundred and thirteen of the vancomycin non-susceptible *E. faecium* isolates harboured *vanA* (Vitek® vancomycin MIC >4 mg/L). A further 110 *E. faecium* vancomycin non-susceptible isolates harboured *vanB*. Three isolates harboured *vanA* and *vanB* genes.

Table 1: The number and proportion of *E. faecalis* non-susceptible to ampicillin and the non-β-lactam antimicrobials, Australia, 2017

Antimicrobial	Tested	Breakpoint (mg/L)	Non-Susceptible	
			n	%
Ampicillin	602	>8[a]	0	0
		>4[b]	1	0.2
Vancomycin	601	>4[c]	2	0.3
Erythromycin	572	>0.5[a]	508	88.8
Tetracycline/Doxycycline	565	>4[a]	419	74.2
Ciprofloxacin	546	>1[a]	88	16.1
		>4[b]	67	12.3
Daptomycin	580	>4[a]	2	0.3
Teicoplanin	601	>8[a]	0	0
		>2[b]	0	0
Linezolid	601	>2[a]	8	1.3
		>4[b]	0	0
Nitrofurantoin	595	>32[a]	3	0.5
		>64[b]	1	0.2
High Level Gentamicin	591	>128[b]	123	20.8

a CLSI non-susceptible breakpoint

b EUCAST non-susceptible breakpoint

c CLSI and EUCAST non-susceptible breakpoint

Eighteen vancomycin-susceptible E. faecium isolates were found to harbour vanA or vanB genes. Seven isolates harboured *vanA* (Vitek® vancomycin MIC ≤ 0.5 mg/L [4 isolates], MIC = 1 mg/L [2 isolates], MIC = 2.0 mg/L [1 isolate], teicoplanin ≤1mg/L [7 isolates]). Eleven isolates harboured *vanB* (Vitek® vancomycin MIC = 1.5 mg/L).

E. faecium Molecular Epidemiology

Of the 481 episodes, 461 *E. faecium* isolates were available for typing by WGS. The 461 isolates were classified into 64 sequence types (STs) including nine STs with 10 or more isolates (Table 3). Of the 55 STs with <10 isolates, 47 had only one isolate. Overall 369 (80%) of the 461 isolates were grouped into the nine major STs. Using eBURST, all nine major STs were grouped into CC17.

Geographical distribution of the STs varied (Table 3). For the nine major STs, ST17 (72 isolates) was identified in all regions except the Australian Capital Territory, the Northern Territory and Tasmania; ST1421 (70 isolates) was identified in all regions except the Northern Territory and Western Australia; ST796 (63 isolates) in all regions except the Australian Capital Territory, the Northern Territory and Western Australia; ST1424 (62 isolates) in all regions except the Northern Territory, South Australia, Tasmania and Western Australia; ST80 (42 isolates) found in all regions except the Northern Territory; ST555 (21 isolates) found in all regions

Table 2: The number and proportion of *E. faecium* non-susceptible to ampicillin and the non-β-lactam antimicrobials, Australia, 2017

Antimicrobial	Tested	Breakpoint (mg/L)	Non-Susceptible	
			n	%
Ampicillin	481	>8[a]	431	89.6
		>4[b]	432	89.8
Vancomycin	481	>4[c]	226	47.0
Erythromycin	466	>0.5[a]	437	93.8
Tetracycline/Doxycycline	461	>4[a]	285	61.8
Ciprofloxacin	444	>1[a]	410	92.3
		>4[b]	390	87.8
Teicoplanin	481	>8[a]	110	22.9
		>2[b]	120	24.9
Linezolid	481	>2[a]	5	1.0
		>4[b]	0	0
Nitrofurantoin	471	>32[a]	367	77.9
		>64[b]	250	53.1
High Level Gentamicin	473	>128[a]	228	48.2

a CLSI non-susceptible breakpoint

b EUCAST non-susceptible breakpoint

c CLSI and EUCAST non-susceptible breakpoint

except the Australian Capital Territory, New South Wales and Queensland; ST203 (14 isolates) found in all regions except the Australian Capital Territory, the Northern Territory and Western Australia; ST18 (14 isolates) found in all regions except the Northern Territory, South Australia and Tasmania; and ST78 (11 isolates) identified only in New South Wales and Queensland.

ST1421 was the second most predominant ST in AESOP 2017 and was first described in AESOP 2015. In AESOP 2016 there were three single locus variants (slvs) of ST1421, classified as ST1422, ST1423 and ST1424. A fourth slv, named M-type 5, was identified in AESOP 2017. In all five STs the MLST *pstS* housekeeping gene was absent.

vanA was detected in five major STs (104 isolates, ST1421, ST17, ST1424, ST80 and ST203). *vanB* was detected in eight major STs (111 isolates, ST17, ST796, ST1424, ST80, ST555, ST203, ST18 and ST78) (Table 4). One ST796 isolate harboured *vanA* and *vanB* genes. Seven minor STs (eight isolates) harboured *vanB* genes, four minor STs (one isolate) harboured *vanA* genes and one minor ST (one isolate) harboured *vanA* and *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

Commun Dis Intell (2018) 2019;43(https://doi.org/10.33321/cdi.2019.43.42) Epub 16/09/2019

Table 3: The number and proportion of major *Enterococcus faecium* sequence types, Australia, 2017, by region

ST	ACT		NSW		NT		Qld		SA		Tas		Vic		WA		Aus	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ST17			6	3.8			20	45.5	1	3.8			13	10.0	32	52.5	72	15.6
ST1421	9	42.9	41	25.9			1	2.3	2	7.7	1	5.9	16	12.3			70	15.2
ST796			4	2.5	1	25.0	1	2.3	1	3.8	4	23.5	52	40.0			63	13.7
ST1424	3	14.3	57	36.1			1	2.3					1	0.8			62	13.4
ST80	4	19.0	7	4.4			4	9.1	1	3.8	1	5.9	19	14.6	6	9.8	42	9.1
ST555					2	50.0	1	2.3	8	30.8	1	5.9	5	3.8	4	6.6	21	4.6
ST18	4	19.0	1	0.6			3	6.8					4	3.1	2	3.3	14	3.0
ST203			4	2.5			3	6.8	1	3.8	2	11.8	4	3.1			14	3.0
ST78			8	5.1			3	6.8									11	2.4
Other	1	4.8	30	19.0	1	25.0	7	15.9	12	27.9	8	47.1	16	12.3	17	15.9	92	20.0
Total	21	100	158	100	4	100	44	100	26	100	17	100	130	100	61	100	461	100

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

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.[13]

In the 2017 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 14.9% (95% CI, 14–16), which represents a significant increase from 2014 when the percentage was 10.4%. The national percentages ranged from 0.0% in Iceland (95% CI, 0–20), Luxembourg (95% CI, 0–10), Malta (95%CI, 0–25) and Sweden (95% CI, 0–1) to 43.9% (95% CI, 28–60) in Cyprus.[13]

In AESOP 2017, approximately 42.3% of enterococcal bacteraemia were due to *E. faecium*, of which 47.0% (95% CI, 42.5–51.6) were phenotypically vancomycin non-susceptible by Vitek2® or Phoenix™. However 50.9% of *E. faecium* isolates tested (244/479) harboured *vanA/vanB* genes, of which 49.6% were *vanB*. Overall 25.1% (120/479) of *E. faecium* isolates harboured a *vanA* gene. There has been a significant increase in *vanA E. faecium* in Australia over the last four AGAR surveys from 6% (8/310) in AESOP 2013,[14] 9.5% (35/370) in 2014,[15] 20.7% (82/397) in 2015[16] and 21.6% (88/408) in 2016.[17] 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, 2013, 2014, 2015 and 2016, 37.0%, 48.6%, 51.1%, 49.3% and 50.9% of *E. faecium* respectively harboured *vanA/vanB*, confirming the incidence of vancomycin-resistant *E. faecium* bacteraemia in Australia is a significant problem.

Eleven (9.1%) of the 121 *vanB E. faecium* and seven (5.8%) of the 120 *vanA 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 very polyclonal, consistent with the known plasticity of the enterococcal genome. The nine major *E. faecium* STs 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 VRE with pandemic potential.

In AESOP 2017, nine *E. faecium* STs predominated: ST1421 (of which 84.3% of isolates harboured *vanA* genes); ST17 (13.8% *vanB*, 1.5% *vanA)*; ST796 (93.5% *vanB,* 1.6% *vanA* and *vanB*); ST 1424 (54.8% *vanA,* 1.6% *vanB*); ST80 (21.4% *vanA,* 23.8% *vanB*); ST555 (73.7% *vanB*); ST203 (35.7% *vanB*, 7.1% *vanA*); ST18 (33.3% *vanB*) and ST78 (100% *vanB*).

Conclusions

The AESOP 2017 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 significantly higher than that seen in almost all European countries. Although the *vanB* operon continues to be a predominant genotype, the number of *vanA E. faecium* isolates identified in AESOP 2017 has significantly increased when compared to AESOP 2013–2016. 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

Table 4: The number and proportion of major *Enterococcus faecium* sequence types harbouring *vanA/B* genes, Australia, 2017

ST	n	*vanA*		*vanB*		*vanA* and *vanB*		Not Detected	
		n	%	n	%	n	%	n	%
ST17	72	1	1.4	9	12.5			62	86.1
ST1421	70	59	84.3					11	15.7
ST796	63			59	93.7	1	1.6	3	4.8
ST1424	62	34	54.8	1	1.6			27	43.5
ST80	42	9	21.4	10	23.8			23	54.8
ST555	21			16	76.2			5	23.8
ST18	14			4	28.6			10	71.4
ST203	14	1	7.1	5	35.7			8	57.1
ST78	11			11	100				
Other	92	8	8.7	4	4.3	1	1.1	79	85.9
Total	461	112	24.3	119	25.8	2	0.4	228	49.5

evolution of enterococci in the hospital environment and assist in preventing their nosocomial transmission.

Acknowledgments

This study was funded by a grant from the Australian Commission on Safety and Quality in Healthcare.

Members of the AGAR in 2017 were:

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Peter Collignon and Susan Bradbury,
The Canberra Hospital

New South Wales

Thomas Gottlieb and Graham Robertson,
Concord Hospital

James Branley and Donna Barbaro,
Nepean Hospital

Peter Huntington, Royal North Shore Hospital

Sebastiaan van Hal and Alicia Beukers,
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Jon Iredell and Andrew Ginn,
Westmead Hospital

Rod Givney and Ian Winney,
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Peter Newton and Melissa Hoddle,
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Clare Nourse, Lady Cilento Children's Hospital

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Kelly Papanaoum and Xiao Ming Chen, SA Pathology (Flinders Medical Centre)

Morgyn Warner and Kija Smith, SA Pathology (Royal Adelaide Hospital and Women's and Children's Hospital)

Tasmania

Louise Cooley and David Jones, Royal Hobart Hospital

Pankaja Kalukottege and Kathy Wilcox, Launceston General Hospital

Victoria

Denis Spelman and Rose Bernhard, The Alfred Hospital

Paul Johnson and Frances Hurren, Austin Health

Tony Korman and Despina Kotsanas, Monash Medical Centre and Monash Children's Hospital

Andrew Daley and Gena Gonis, Royal Women's and Children's Hospital

Mary Jo Waters and Lisa Brenton, St Vincent's Hospital

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David McGechie and Denise Daley, PathWest Laboratory Medicine – WA Fiona Stanley Hospital

Ronan Murray and Jacinta Bowman, PathWest Laboratory Medicine – WA Sir Charles Gairdner Hospital

Michael Leung and Jacinta Bowman, PathWest Laboratory Medicine – Northwest WA

Owen Robinson and Geoffrey Coombs, PathWest Laboratory Medicine – WA Royal Perth Hospital

Sudha Pottumarthy-Boddu and Fay Kappler, Australian Clinical Laboratories, St John of God Hospital, Murdoch

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