

The implications of enterococci for the intensive care unit

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Enterococci are gram-positive bacteria that occur singly, in pairs or short chains, and are physiological commensals of the gastrointestinal and the female genital tracts of humans, several mammals and birds. The name "enterococcus" is derived from the French word "*Enterocoque*", first used by Thiercelin in an article published in 1899,¹ to emphasise the intestinal origin of this new gram-positive diplococcus. In the same year, MacCallum and Hastings reported a case of endocarditis caused by an organism they named *Micrococcus zymogenes*, which we now know as a haemolytic enterococcus.² In 1906, Andrewes and Horder isolated an organism which they named *Streptococcus faecalis*, as it was "so characteristic of the human intestine that the term '*Streptococcus faecalis*' may justly be applied to it".³ In the mid-1980s, biochemical and DNA hybridisation data indicated that enterococci were not related to streptococci, and a new genus *Enterococcus* was proposed, with the species designations *faecalis*, *faecium*, *durans*, *avium*, *casseliflavus*, *malodoratus*, *gallinarum*, *hirae*, *mundtii*, *raffinosis*, *solitarius* and *pseudoavium*.

Epidemiology

Enterococcus spp. are the third most common pathogen isolated from bloodstream infections and the most common pathogen in surgical-site infections reported from intensive care units.⁴ They are also the second most common nosocomial pathogen in the United States, responsible for three to four cases of nosocomial bloodstream infection per 10 000 hospital discharges.⁵ Since vancomycin-resistant enterococci (VRE) were isolated in Europe in 1987,⁶ they have emerged as one of the most feared nosocomial pathogens. The incidence of VRE colonisation among US hospital patients increased 26-fold, from 0.4% in 1989 to 13.6% in 1993,⁷ 12.8% in 1995 and 25.9% in 2000.⁸ The SENTRY program, a global network of hospitals tracking antimicrobial susceptibility of pathogens, reported substantial increases in the proportion of VRE (vancomycin minimum inhibitory concentration [MIC] \geq 8 mg/mL) among enterococci causing bloodstream infections.⁹ These increases have been most dramatic in Latin and North America.

VRE is a less important nosocomial pathogen in Europe, its prevalence being always lower than in the US. However, SENTRY data may underestimate the prevalence of VRE in Europe, as shown in the Pan-European Antimicrobial Resistance Using Local Surveillance (PEARLS) study.¹⁰ This multina-

ABSTRACT

Objective: To review the evidence of pathogenicity and virulence of *Enterococcus* spp. in the intensive care unit.

Data sources: MEDLINE search for studies and articles on *Enterococcus* spp.

Results: *Enterococcus* spp. are normal commensal organisms in the alimentary tract and are traditionally considered to have relatively low virulence. However, they can cause a variety of life-threatening infections, especially in immunocompromised patients and nosocomial settings. The role of enterococci as primary pathogens in polymicrobial intra-abdominal infections remains controversial. There is enough evidence to suggest that complicated, community-acquired intra-abdominal infections involving mixed flora can be treated with surgery and non-enterococcal antibiotic cover. Recent studies have shown that enterococcal peritonitis is associated with increased mortality.

Conclusions: Although the prevalence of enterococcal infections may be low in Australian ICUs, these infections are associated with a higher prevalence of treatment failure and mortality. We therefore suggest the use of enterococcal antibiotic coverage in: immunocompromised patients with a high risk of bacteraemia (eg, liver transplant patients); patients with peritonitis and valvular heart disease or prosthetic intravascular material; patients with severe sepsis of abdominal origin who have previously received broad-spectrum antibiotics; and patients with persistent intra-abdominal collection without clinical improvement.

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tional study of 38 centres in Europe and North Africa, conducted from February 2001 to December 2002, found that 9% of enterococcal infections of the bloodstream, urinary tract and wounds were caused by vancomycin-resistant *Enterococcus faecium*. Rates ranged from 1% in France to 59% in Portugal. However, the data from France may be an underestimate, with a recent study in a large Paris hospital showing that *Enterococcus faecalis* was the cause of all enterococcal infections at that hospital, and that 8% of *E. faecalis* isolates were resistant to vancomycin (MIC \geq 4 mg/mL).¹¹

The appearance of VRE as a nosocomial pathogen may be related to a large community reservoir of VRE in healthy

people and farm animals, possibly associated with the use of avoparcin in animal husbandry. Avoparcin is a glycopeptide antibiotic which has been used since the 1970s as a growth promoter in animals. It is known to confer cross resistance to vancomycin, and its use has been associated with high numbers of VRE in animal faeces and meat samples.¹² Subsequent transmission to humans via the food chain results in colonisation of the healthy community with VRE.

The presence of such a large reservoir of VRE in the community is a risk for VRE transmission into hospitals, predominantly of the VRE strains themselves, but perhaps also rarely via horizontal spread of the genetic elements. Transfer of resistance determinants from enterococci to other more virulent gram-positive bacteria, such as staphylococci, has been observed *in vitro*. The isolation of a fully vancomycin-resistant *Staphylococcus aureus* strain in a patient previously colonised with VRE is alarming, and suggests the possibility of in-vivo exchange of resistance traits.¹³

In Australia, the first case of VRE infection occurred in Melbourne in 1994 in a liver transplant recipient.¹⁴ Since then, reports of cases have increased exponentially, and several outbreaks, mainly of VRE colonisation, have been noted, although many more may have gone unreported. Australia has not yet felt the impact of VRE to anywhere near the extent experienced in North America. In Australia, the strain which tends to predominate is an *E. faecium* strain with a VanB phenotype (see *Vancomycin* section), which has more treatment options than other phenotypes, although some cities have had significant outbreaks of the VanA type. Recently published data from the Australian Group for Antimicrobial Resistance (AGAR) showed an increase in *E. faecium* as a proportion of all enterococcal isolates, from 5% in 1995 to 10% in 1999.¹⁵ VRE strains also steadily increased, from none in 1995 to 0.3% of all enterococcal isolates in 1999. Ampicillin resistance in *E. faecium* increased, from 57% in 1995 to 77% in 1999. Beta-lactamase production remained uncommon, with only one β -lactamase-producing *E. faecalis* isolate detected. During 1999, 18 institutions collected all enterococci isolated from blood cultures. Over 370 strains were isolated, of which 74% were *E. faecalis*, and 20% were *E. faecium*. Vancomycin resistance was detected in 8% of all *E. faecium* isolates.¹⁵ In another 12-month prospective study of bloodstream infections, from Royal Darwin Hospital in 2000, only seven (3%) of 257 blood culture isolates were enterococci, and none were VRE.¹⁶

Implications of vancomycin-sensitive enterococcal infection in the ICU

Generally, enterococci are considered to have relatively low virulence. However, they can cause a variety of clinical

syndromes, including urinary tract infections, endocarditis, bacteraemia, meningitis, and intra-abdominal infections. Enterococcal endocarditis is a particular problem, largely because of the difficulty of eradicating the infection. Although endocarditis is mostly caused by *E. faecalis*, other species can also be responsible, the common risk factors being underlying heart disease, genitourinary instrumentation and biliary portals.¹⁷

The mechanisms which transform commensals into life-threatening pathogens are not well understood. Normally, enterococci colonising the intestinal tract are held in check by host defence mechanisms. A weakened host immunity may disturb the balance of this system and allow translocation of organisms from the intestinal lumen into the bloodstream, eventually resulting in systemic spread. More importantly, perineal colonisation seeds other sites, including intravenous, urinary or biliary catheters, foreign bodies, the urinary tract, surgical wounds and the oropharynx.

While the clinical impact of enterococci in cases of bacteraemia and superinfection has been well established in selected patient populations, the role of enterococci as primary pathogens in polymicrobial intra-abdominal infections remains controversial. Enterococci may lack the capacity to induce late abscess formation in animal models of monomicrobial, intra-abdominal enterococcal infections. They may express bacterial synergy and proinflammatory activity only in the presence of more virulent bacteria, by inhibiting phagocytosis and intracellular killing of those primary pathogens.¹⁸

Evidence suggests that complicated, community-acquired intra-abdominal infections involving mixed flora can be treated with surgery and antibiotics that lack consistent anti-enterococcal activity (eg, cephalosporins and fluoroquinolones). In a review of six clinical trials examining the use of antibiotics which lacked in-vitro activity against enterococci in the treatment of intra-abdominal infections, 20%–30% of cultures grew enterococci, but there were no cases of treatment failure.¹⁹ However, two recent studies showed that enterococcal peritonitis is associated with increased mortality.^{20,21} Multiple regression analysis showed the independent postoperative risk factors for enterococcal infection to be tertiary peritonitis, APACHE II score over 12, age over 50 years, a non-colonic focus, and inappropriate initial enterococcal coverage.

Although recently published guidelines from the Infectious Diseases Society of America (IDSA) strongly advocate against empirical therapy directed at enterococci,²² there is some evidence to suggest the use of enterococcal coverage for intra-abdominal infections in the following cases:²³

- immunocompromised patients with high risk of bacteraemia;

- patients with peritonitis and valvular heart disease or prosthetic intravascular material, which places them at high risk of endocarditis;
- patients with severe sepsis of abdominal origin who have previously received cephalosporins and other broad-spectrum antibiotics selecting for *Enterococcus* spp; and
- patients with a persistent intra-abdominal collection who show no clinical improvement.

Antibiotic resistance of enterococci

The focus on enterococci is a result not only of their increasing role in nosocomial infections, but also of their resistance to various antimicrobial agents. Enterococci are naturally resistant to semisynthetic penicillinase-resistant penicillins, cephalosporins, low levels of aminoglycosides and low levels of clindamycin. They may also acquire resistance to penicillin, chloramphenicol, erythromycin, tetracycline, high levels of clindamycin, high levels of aminoglycosides, fluoroquinolones and vancomycin.

Enterococci can transfer resistance genes to other bacteria, including staphylococci and streptococci. Experimental transfer of vancomycin resistance from enterococci to *S. aureus*, *Listeria monocytogenes* and *Streptococcus pyogenes* has been reported.^{24,25}

Beta-lactams

The characteristic feature of enterococci is resistance to β -lactams, particularly by overproduction or structural alteration of penicillin-binding protein (PBP 5).²⁶ In-vitro testing of *E. faecalis* shows that penicillin MICs average 2–8 $\mu\text{g}/\text{mL}$, which is at least 10–100 times greater than those for most streptococci.²⁷ *E. faecium* is even more resistant; typical penicillin MICs are often 16–32 $\mu\text{g}/\text{mL}$ or higher.²⁸ MICs of ampicillin and the ureidopenicillins for *E. faecalis* are usually 1–4 $\mu\text{g}/\text{mL}$. Resistance to the semisynthetic penicillinase-resistant penicillins is more pronounced, with MICs in the range 8–50 $\mu\text{g}/\text{mL}$ for nafcillin and usually > 50 $\mu\text{g}/\text{mL}$ for methicillin.²⁷ MICs of carbenicillin and ticarcillin are often 64 $\mu\text{g}/\text{mL}$, comparable to those for *Pseudomonas aeruginosa*.²⁹ In addition to the high MICs, enterococci are typically “tolerant” to all β -lactams — that is, they are not killed by concentrations many times higher than the MIC. The minimum bacteriocidal concentration (MBC) of ampicillin and other penicillins in broth macrodilution systems is typically > 100 $\mu\text{g}/\text{mL}$.³⁰

Beta-lactamase production by enterococci is rare,³¹ but some enterococci may exhibit this phenotype through acquisition of the β -lactamase determinant from *S. aureus*. More recently, a novel mechanism of β -lactam resistance that circumvents the DD-transpeptidation reaction in the final stage of peptidoglycan synthesis was reported in *E. faecium*.³²

None of the cephalosporins routinely inhibit enterococci sufficiently to warrant clinical use. MICs of cephalothin range from 6.3 to > 100 $\mu\text{g}/\text{mL}$, but MICs of cefoxitin and moxalactam are higher.³³ Although the in-vitro activity of cephalosporins against enterococci is poor when tested by conventional methods, MICs may be lower in the presence of serum and lysed blood.³⁴

Aminoglycosides

Another inherent property of enterococci is low-level resistance to aminoglycosides, apparently due to an inability of these drugs to cross the cell membrane. High-level resistance also occurs commonly through the production of a spectrum of aminoglycoside-modifying enzymes, notably aminoglycoside acetyltransferases, phosphotransferases and nucleotidyltransferase.³⁵ The actual level of resistance varies between the different aminoglycosides. For *E. faecalis*, the average MIC of streptomycin or kanamycin is around 250 $\mu\text{g}/\text{mL}$, whereas MICs for gentamicin and tobramycin are 8–64 $\mu\text{g}/\text{mL}$.^{36,37} However, in the presence of cell wall synthesis inhibitors such as penicillin or vancomycin, uptake of the aminoglycoside is markedly increased, resulting in enhanced killing — the well-known synergistic effect of cell wall synthesis inhibitors plus aminoglycosides.³⁷

Clindamycin

Resistance to clindamycin and lincomycin is another characteristic feature of enterococci. The MICs for most strains vary from 12.5 to 100 $\mu\text{g}/\text{mL}$.³⁸

Vancomycin

Six phenotypes of vancomycin resistance have been described in enterococci: VanA, VanB, VanC, VanD, VanE and VanG. Of the six, VanA and VanB are more clinically relevant. Both result from the acquisition of new genetic determinants of resistance carried on transposon Tn 1546. The origin of these genes remains unknown, but a potential source could be organisms that produce glycopeptides.³⁹ In the presence of vancomycin, a sensory kinase interacts with a response regulator, activating transcription of the genes necessary for vancomycin resistance. The transcribed genes are translated into enzymes, some of which make cell-wall precursors ending in the sequence D-alanyl-D-lactate (D-Ala-D-Lac), to which vancomycin binds with very low affinity. Other enzymes prevent synthesis of, or modify, endogenous cell-wall precursors ending in D-alanyl-D-alanine (D-Ala-D-Ala), to which vancomycin binds with high affinity.^{40,41} Enterococci with VanA resistance possess high-level resistance to vancomycin (MIC > 128 mg/mL) and teicoplanin (MIC > 16 mg/mL). Enterococci with VanB resistance possess a broad range of resistance to vancomycin (MIC, 4–1024 mg/mL) and are susceptible to teicoplanin (MIC < 0.5 mg/mL).⁴²

In contrast, VanC resistance is a constitutive, non-transmissible, chromosome-based endogenous species-specific component of *E. gallinarum* (VanC-1) and *E. casseliflavus*/*E. flavescens* (VanC-2/VanC-3), respectively.⁴³ This type of resistance is typically of lower magnitude than that mediated by VanA or VanB. VanD, VanE and VanG resistance have been reported only sporadically, and nothing is known about their mode of resistance.

Linezolid

In 2001, seven clinical isolates of linezolid-resistant vancomycin-resistant *E. faecium* were reported from the Mayo Clinic. All isolates had a G-to-T mutation at position 2576 (*Escherichia coli* numbering) of 23S ribosomal DNA. The strain was selected in a liver transplant recipient and then transmitted nosocomially to six other patients, despite strict isolation of the index case, the use of private rooms, and universal gloving of health care workers before entering patients' rooms.⁴⁴

VRE colonisation and infection

Enterococci are normal inhabitants of the human gut, and VRE colonisation has been identified in hospital patients from the groin, axilla, oropharynx, and gastric and endotracheal aspirates. Colonisation at these sites is persistent, and direct contamination of the environment (such as bed rails and sheets) is frequent.⁴⁵ Widespread VRE colonisation may occur with a comparatively small number of documented infections. This is of concern as VRE-colonised patients serve as a silent reservoir for colonisation of other patients.

VRE colonisation

The risk of VRE colonisation depends first on being exposed to VRE, and second on being a susceptible host. VRE is transmitted by direct contact, the most likely vectors for transmission being the hands of health care workers and contaminated equipment. VRE is capable of prolonged survival (at least 1 week) on fabric seat cushions, and can be transferred from this site to the hands of staff.⁴⁶ VRE has been isolated from virtually everything in the health care environment, including monitoring devices, furniture (eg, telephones, air cushions, headboards, tables, chairs and bed rails), toilet seats, doors, floors, linen and other medical equipment.⁴⁷

Colonisation pressure (defined as the number of colonised patients present each day) also influences the likelihood of acquisition of VRE. In an intensive care unit where colonisation was endemic, colonisation pressure was the most important variable for acquisition of VRE. Other

relevant variables, such as enteral feeding and the use of third-generation cephalosporins, hardly influenced the spread of VRE and were important only when colonisation pressure was less than 50%.⁴⁸

Selective antibiotic pressure is another important variable in VRE colonisation. For example, oral administration of glycopeptides strongly selected for intestinal carriage of VRE in healthy patients in Belgium.⁴⁹ The emergence of VRE in US hospitals has been linked to higher rates of vancomycin use in these hospitals compared with European hospitals.⁵⁰ Although VRE emerged after a dramatic increase in global vancomycin use in the 1980s, increasing data suggest that other antibiotics can also have important selective effects, especially antimicrobial agents with anti-anaerobic activity (eg, second- and third-generation cephalosporins, clindamycin, amoxicillin-clavulanate, piperacillin-tazobactam, meropenem and metronidazole). Antimicrobial agents lacking anti-anaerobic activity did not appear to have an effect (dicloxacillin, levofloxacin, ciprofloxacin, cephalexin and trimethoprim-sulfamethoxazole).⁵¹ In a meta-analysis, Carmeli and colleagues found that the reported association between vancomycin use and colonisation was confounded by variables such as length of stay and publication bias. Controlling for length of stay, they found that vancomycin use was no longer significantly associated with the risk for VRE.⁵²

VRE infection

Portals of entry for VRE include the urinary tract, intra-abdominal (including the biliary tree) or pelvic sources, wounds (eg, surgical wounds and decubitus ulcers) and intravascular catheters. Skin colonisation with VRE increases the risk not only of blood culture contamination, but also of catheter-related infections. Isolation of VRE from the urine alone may not represent true infection but rather asymptomatic bacteriuria, limiting its clinical significance. Urinary tract infections caused by VRE are mostly nosocomial and include cystitis, pyelonephritis, prostatitis and perinephric abscess. In liver transplant recipients, the peritoneal space and biliary tract are the most common source of VRE bacteraemia. Precipitating cofactors include biliary leaks, stenosis or obstruction, viscus perforation, and stenosis or thrombosis of the hepatic artery.⁵³ Infections of the pleural space, meningitis and endocarditis have been reported rarely.⁵⁴

Risk factors for VRE bacteraemia include haemodialysis, corticosteroid therapy, antineoplastic agents or total parenteral nutrition, surgery, severity of illness, antimicrobial agents, indwelling bladder catheters, neutropenia and mucositis.^{55,56}

Implications of VRE infection in the ICU

What impact does vancomycin resistance have on the clinical effect of enterococcal infection? Vancomycin resistance has been shown to be an independent predictor of death in enterococcal bacteraemia. In a large prospective study of enterococcal bacteraemia, vancomycin resistance was a significant independent risk factor for 14-day mortality (odds ratio [OR], 2.10; 95% CI, 1.14–3.88; $P=0.02$). Bacteriological failure, defined as enterococcal bacteraemia recurring 5 to 60 days after the initial episode, was also more common in VRE-infected patients (75% versus 25%, $P<0.001$).⁵⁷

In a study comparing vancomycin-resistant versus vancomycin-sensitive enterococcal infections, greater proportions of clinical failure (60% versus 40%, $P<0.001$) and all-cause mortality (52% versus 27%, $P<0.001$) were seen in patients with VRE bacteraemia.⁵⁸ In a similar study, vancomycin resistance was found to be an independent predictor of crude mortality (OR, 4.0; 95% CI, 1.2–13.3), infection-related mortality rate (OR, 5.2; 95% CI, 1.4–20.0), clinical failure at 1 week after onset of enterococcal bacteraemia (OR, 4.6; 95% CI, 1.2–17.3) and overall clinical failure (OR, 4.3; 95% CI, 1.3–14.5).⁵⁹ In a retrospective study analysing the clinical features and outcome of 53 patients with *E. faecium* bacteraemia, patients infected with VRE had longer hospitalisations than those with vancomycin-sensitive enterococci (VSE) (34.8 versus 16.7 days, $P=0.004$). Despite similar severity-of-illness scores, survival was lower in patients with VRE than in those with VSE bacteraemia (24% versus 59%, $P=0.009$). In 62% of these patients with VRE sepsis, death was related to the bacteraemia ($P=0.01$).⁶⁰

However, other studies have not confirmed the association between vancomycin resistance and mortality. In a study comparing outcomes for patients infected with vancomycin-resistant versus vancomycin-susceptible *E. faecium*, vancomycin resistance was not associated with mortality (OR, 1.74; 95% CI, 0.5–6.12).⁶¹

The increased proportion of comorbid conditions observed among patients with enterococcal infections has led investigators to question the contribution of the infection itself to the morbidity and mortality seen among such patients. It has been suggested that VRE may in fact be only a marker of the severity of disease.⁶² In a study of VRE infection in liver transplant patients, Newell and colleagues reported a relatively long interval between the diagnosis of VRE infection and death (80 ± 64 days), and a high incidence of co-infection among these cases. The authors suggested that these findings support the argument that VRE is a marker of disease severity.⁶³ It is debatable whether VRE causes life-threatening diseases more often than VSE. High mortality rates seen in VRE infections could arise from the fact that these patients often have a more complicated

medical course and are therefore at higher risk of dying. VRE colonisation and infection may merely reflect this complicated medical course and prolonged hospitalisation.

Infection control strategies

The Hospital Infection Control Practices Advisory Committee (HICPAC) of the US Centers for Disease Control and Prevention formulated guidelines for the prevention of VRE infections, focusing on limiting vancomycin use, performing surveillance cultures, and improving infection control measures.⁶⁴ Although these guidelines could not reverse the increase in prevalence of VRE, perhaps because of incomplete adherence, their assiduous use successfully controlled the spread of VRE in a region with overall low rates of prevalence (with a decrease from 2.2% to 0.5%).⁶⁵

Epidemiological surveillance studies have shown that the natural history of uncontrolled VRE spread progresses from sporadic introductions of patients colonised with VRE, to small outbreaks caused by single clones of VRE, to a final state of polyclonal endemicity. Hayden proposed that infection control measures should consider the estimated risks of VRE infection for the specific patient population, and the stage of evolution of VRE epidemiology in the hospital or ward where the control program will be implemented.⁶⁶ More aggressive measures should be considered in wards where patients are highly vulnerable to enterococcal infections, such as oncology and transplant units.

Once VRE colonisation has become endemic, it is extremely difficult to effectively control the spread of infection, and institutions should aim to prevent the development of endemicity in wards where vulnerable patients are treated. Therefore, the VRE problem and response reflect a broader need to improve hospital hygiene and responsible antibiotic use.

Conclusions

The prevalence of enterococcal infections, although increasing worldwide, remains low in Australia, which has not yet felt the impact of VRE to anywhere near the extent experienced in America and Europe. Moreover, the VRE strain which seems to predominate in Australia is VanB *E. faecium*, which has many more treatment options than other strains. However, we must keep in mind that the level of vancomycin use in Australia is relatively high and varies significantly between regions because of the differing prevalence of methicillin-resistant *S. aureus*. Also, Australia is a high-level user of avoparcin as a growth promoter in animal husbandry. The combination of these two factors may create a potential for rapid development and spread of VRE in the community and health care sector.

What is the importance of enterococci in the ICU? Although enterococci can cause a variety of clinical syndromes, including urinary tract infections, endocarditis, bacteraemia, meningitis and intra-abdominal infections, the clinical impact is unknown. The pathogenic role of enterococcal infection in peritonitis remains controversial. However, animal studies have shown that enterococci may limit phagocytosis and intracellular killing of other pathogens, and therefore prolong the peritoneal inflammatory response.⁶⁷ Although the IDSA guidelines do not suggest routine enterococcal cover for community-acquired intra-abdominal infections, there is evidence to justify the use of empirical anti-enterococcal antibiotics in postoperative nosocomial peritonitis in a subset of patients:

- those who have been previously treated with antibiotics that select for *Enterococcus* spp.;
- patients with valvular heart disease or intravascular prosthetic material;
- patients who are immunocompromised; and
- patients who have a persistent intra-abdominal collection and show no clinical improvement.

Nevertheless, in view of the doubts about the benefit of empirical anti-enterococcal cover for abdominal infections, we plan to compare data on enterococcal infections from two ICUs — one that empirically provides enterococcal cover, and one that does not. These data will be derived from a cycling study conducted in 2004–2005 to compare cefepime and piperacillin–tazobactam in the ICUs of Westmead Hospital, Sydney, and Royal Brisbane and Women's Hospital, Brisbane.

Enterococci have clearly emerged from being a physiological commensal of the gastrointestinal and female genital tract to an important drug-resistant nosocomial pathogen which, on its own, may increase the risk of death. In the setting of increasing vancomycin resistance, the ideal therapeutic regimen remains to be determined, with emphasis on prudent use of antibiotics and strict reinforcement of infection control practices.

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References

- 1 Thiercelin ME. [Sur un diplocoque saprophyte de l'intestin susceptible de devenir pathogene.] [French]. *C R Soc Biol* 1899; 5: 269-71.
- 2 Sherman JM. The streptococci. *Bacteriol Rev* 1937; 1: 3-97.
- 3 Andrewes FW, Horder TJ. A study of streptococci pathogenic for man. *Lancet* 1906; ii: 708-13.
- 4 Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in combined medical-surgical intensive care units in the United States. *Infect Control Hosp Epidemiol* 2000; 21: 510-5.
- 5 Banerjee SN, Emori TJ, Culver DH, et al. National Nosocomial Infection Surveillance System. Secular trends in nosocomial primary bloodstream infections in the United States, 1980-1989. *Am J Med* 1991; 91(3B): 86S-9S.
- 6 Uttley AH, Collins CH, Naidoo J, George RC. Vancomycin-resistant enterococci. *Lancet* 1988; 1: 57-8.
- 7 Centers for Disease Control and Prevention (CDC). Nosocomial enterococci resistant to vancomycin – United States, 1989-1993. *MMWR Morb Mortal Wkly Rep* 1993; 42: 597-9.
- 8 National Nosocomial Infection Surveillance (NNIS) System Report, data summary from January 1992-April 2000, issued June 2000. *Am J Infect Control* 2000; 28: 429-48.
- 9 Biedenbach DJ, Moet GJ, Jones RN. Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997–2002). *Diagn Microbiol Infect Dis* 2004; 50: 59-69.
- 10 Bouchillon SK, Johnson BM, Hoban DJ, et al. Determining incidence of extended spectrum beta-lactamase producing *Enterobacteriaceae*, vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* in 38 centres from 17 countries: the PEARLS study 2001–2002. *Int J Antimicrob Agents* 2004; 24: 119-24.
- 11 Garnier F, Ducancelle A, Boisset S, et al. High incidence of vancomycin resistance in *Enterococcus faecalis* strains in a French hospital. *Int J Antimicrob Agents* 2004; 23: 529-30.
- 12 Wegener HC. Historical yearly usage of glycopeptides for animals and humans: the American-European paradox revisited. *Antimicrob Agents Chemother* 1998; 42: 3049.
- 13 Chang S, Sievert DM, Hageman JC, et al. Infection with vancomycin-resistant *Staphylococcus aureus* containing the vanA resistance gene. *N Engl J Med* 2003; 348: 1342-7.
- 14 Kamarulzaman A, Tosolini FA, Boquest JE, et al. Vancomycin-resistant *Enterococcus faecium* infection in a liver transplant recipient. *Aust N Z J Med* 1995; 25: 560.
- 15 Nimmo GR, Bell JM, Collignon PJ; Australian Group for Antimicrobial Resistance. Fifteen years of surveillance by the Australian Group for Antimicrobial Resistance (AGAR). *Commun Dis Intell* 2003; 27 Suppl: S47-54.
- 16 Douglas MW, Lum G, Roy J, et al. Epidemiology of community-acquired and nosocomial bloodstream infections in tropical Australia: a 12-month prospective study. *Trop Med Int Health* 2004; 9: 795-804.
- 17 Murray BE. The life and times of enterococcus. *Clin Microbiol Rev* 1990; 3: 46-65.
- 18 Montravers P, Mohler J, Saint Julien L, Carbon C. Evidence of the proinflammatory role of *Enterococcus faecalis* in polymicrobial peritonitis in rats. *Infect Immun* 1997; 65: 144-9.
- 19 Gorbach SL. Intraabdominal infections. *Clin Infect Dis* 1993; 17: 961-5.
- 20 Sotto A, Lefrant JY, Fabbro-Peray P, et al. Evaluation of antimicrobial therapy management of 120 consecutive patients with secondary peritonitis. *J Antimicrob Chemother* 2002; 50: 569-76.
- 21 Sitges-Serra A, Lopez MJ, Girvent M, et al. Postoperative enterococcal infection after treatment of complicated intra-abdominal sepsis. *Br J Surg* 2002; 89: 361-7.
- 22 Solomkin JS, Mazuski JE, Baron EJ, et al. Guidelines for the selection of anti-infective agents for complicated intraabdominal infections. *Clin Infect Dis* 2003; 37: 997-1005.

REVIEWS

- 23 Harbarth S, Uckay I. Are there patients with peritonitis who require empiric therapy for enterococcus? *Eur J Clin Microbiol Infect Dis* 2004; 23: 73-7.
- 24 Leclercq R, Derlot E, Weber M, et al. Transferable vancomycin and teicoplanin resistance in *Enterococcus faecium*. *Antimicrob Agents Chemother* 1989; 33: 10-5.
- 25 Noble WC, Virani Z, Cree RG. Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTC 12201 to *Staphylococcus aureus*. *FEMS Microbiol Lett* 1992; 93: 195-8.
- 26 Ligozzi M, Pittaluga F, Fontana R. Modification of penicillin-binding protein 5 associated with high-level ampicillin resistance in *Enterococcus faecium*. *Antimicrob Agents Chemother* 1996; 40: 354-7.
- 27 Tofte RW, Solliday J, Crossley KB. Susceptibilities of enterococci to twelve antibiotics. *Antimicrob Agents Chemother* 1984; 25: 532-3.
- 28 Moellering RC Jr, Korzeniowski OM, Sande MA, Wennersten CB. Species-specific resistance to antimicrobial synergism in *Streptococcus faecium* and *Streptococcus faecalis*. *J Infect Dis* 1979; 140: 203-8.
- 29 Fass RJ. In vitro activities of beta-lactam and aminoglycoside antibiotics. A comparative study of 20 parenterally administered drugs. *Arch Intern Med* 1980; 140: 766-7.
- 30 Krogstad DJ, Parquette AR. Defective killing of enterococci: a common property of antimicrobial agents acting on the cell wall. *Antimicrob Agents Chemother* 1980; 17: 965-8.
- 31 Smith MC, Murray BE. Comparison of enterococcal and staphylococcal beta-lactamase-encoding fragments. *Antimicrob Agents Chemother* 1992; 36: 273-6.
- 32 Mainardi JL, Legrand R, Arthur M, et al. Novel mechanism of beta-lactam resistance due to bypass of DD-transpeptidation in *Enterococcus faecium*. *J Biol Chem* 2000; 275: 16490-6.
- 33 Weinstein AJ, Moellering RC Jr. Studies of cephalothin: aminoglycoside synergism against enterococci. *Antimicrob Agents Chemother* 1975; 7: 522-9.
- 34 Sahn DF, Baker CN, Jones RN, Thornsberrry C. Influence of growth medium on the in vitro activities of second- and third-generation cephalosporins against *Streptococcus faecalis*. *J Clin Microbiol* 1984; 20: 561-7.
- 35 Chow JW. Aminoglycoside resistance in enterococci. *Clin Infect Dis* 2000; 31: 586-9.
- 36 Mederski-Samoraj BD, Murray BE. High-level resistance to gentamicin in clinical isolates of enterococci. *J Infect Dis* 1983; 147: 751-7.
- 37 Moellering RC Jr, Weinberg AN. Studies on antibiotic synergism against enterococci. I Effect of various antibiotics on the uptake of ¹⁴C-labeled streptomycin by enterococci. *J Clin Invest* 1971; 50: 2580-4.
- 38 Karchmer AW, Moellering RC Jr, Watson BK. Susceptibility of various serogroups of streptococci to clindamycin and lincomycin. *Antimicrob Agents Chemother* 1975; 7: 164-7.
- 39 Leclercq R. Heterospecific transfer and expression of enterococcal resistance to glycopeptides. In: Brun-Buisson C, Eliopoulos G, Leclercq R, editors. Bacterial resistance to glycopeptides. Paris: Medecine-Sciences Flammarion, 1998; 39-46.
- 40 Evers S, Quintiliani R Jr, Courvalin P. Genetics of glycopeptide resistance in enterococci. *Microb Drug Resist* 1996; 2: 219-23.
- 41 Arthur M, Depardieu F, Cabanie L, et al. Requirement of the VanY and VanX D, D-peptidases for glycopeptide resistance in enterococci. *Mol Microbiol* 1998; 30: 819-30.
- 42 Murray BE. Vancomycin-resistant enterococci. *Am J Med* 1997; 102: 284-93.
- 43 Cetinkaya Y, Falk P, Mayhall CG. Vancomycin resistant enterococci. *Clin Microbiol Rev* 2000; 13: 686-707.
- 44 Herrero IA, Issa NC, Patel R. Nosocomial spread of linezolid-resistant, vancomycin-resistant *Enterococcus faecium*. *N Engl J Med* 2002; 346: 867-9.
- 45 Bonten M, Hayden MK, Nathan C, et al. Epidemiology of colonisation of patients and environment with vancomycin-resistant enterococci. *Lancet* 1996; 348: 1615-9.
- 46 Noskin GA, Bednarz P, Suriano T, et al. Persistent contamination of fabric-covered furniture by vancomycin-resistant enterococci: implications for upholstery selection in hospitals. *Am J Infect Control* 2000; 28: 311-3.
- 47 Livornese LL Jr, Dias S, Samel C, et al. Hospital-acquired infection with vancomycin-resistant *Enterococcus faecium* transmitted by electronic thermometers. *Ann Intern Med* 1992; 117: 112-6.
- 48 Bonten MJM, Slaughter S, Ambergen AW, et al. The role of "colonization pressure" in the spread of vancomycin-resistant enterococci. An important infection control variable. *Arch Intern Med* 1998; 158: 1127-32.
- 49 Van der Auwera P, Pensart N, Korten V, et al. Influence of oral glycopeptides on the fecal flora of human volunteers: selection of highly glycopeptide-resistant enterococci. *J Infect Dis* 1996; 173: 1129-36.
- 50 Kirst HA, Thompson DG, Nicas TI. Historical yearly usage of vancomycin. *Antimicrob Agents Chemother* 1998; 42: 1303-4.
- 51 Donskey CJ, Chowdhry TK, Hecker MT, et al. Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. *N Engl J Med* 2000; 343: 1925-32.
- 52 Carmeli Y, Samore MH, Huskins C. The association between antecedent vancomycin treatment and hospital-acquired vancomycin-resistant enterococci. A meta-analysis. *Arch Intern Med* 1999; 159: 2461-8.
- 53 Patel R. Clinical impact of vancomycin-resistant enterococci. *J Antimicrob Chemother* 2003; 51 Suppl 3: iii13-21.
- 54 Koc Y, Snyderman DR, Schenkein DS, Miller KB. Vancomycin-resistant enterococcal infections in bone marrow transplant recipients. *Bone Marrow Transplantation* 1998; 22: 207-9.
- 55 Bhavnani SM, Drake JA, Forrest A, et al. A nationwide, multicenter, case-control study comparing risk factors, treatment, and outcome for vancomycin-resistant and -susceptible enterococcal bacteremia. *Diagn Microbiol Infect Dis* 2000; 36: 145-58.
- 56 Lautenbach E, Bilker WB, Brennan PJ. Enterococcal bacteremia: risk factors for vancomycin resistance and predictors of mortality. *Infect Control Hosp Epidemiol* 1999; 20: 318-23.
- 57 Vergis EN, Hayden MK, Chow JW, et al. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia — a prospective multicenter study. *Ann Intern Med* 2001; 135: 484-92.
- 58 Bhavnani SM, Drake JA, Forrest A, et al. A nationwide, multicenter, case-control study comparing risk factors, treatment, and outcome for vancomycin-resistant and -susceptible enterococcal bacteremia. *Diagn Microbiol Infect Dis* 2000; 36: 145-58.
- 59 Lodise TP, McKinnon PS, Tam VH, Rybak MJ. Clinical outcomes for patients with bacteremia caused by vancomycin-resistant enterococcus in a level 1 trauma center. *Clin Infect Dis* 2002; 34: 922-9.
- 60 Stosor V, Peterson LR, Postelnick M, Noskin GA. *Enterococcus faecium* bacteremia: does vancomycin resistance make a difference? *Arch Intern Med* 1998; 158: 522-7.
- 61 Garbutt JM, Ventrapragada M, Littenberg B, Mundy LM. Association between resistance to vancomycin and death in cases of *Enterococcus faecium* bacteremia. *Clin Infect Dis* 2000; 30: 466-72.
- 62 Bryan CS, Reynolds KL, Brown JJ. Mortality associated with enterococcal bacteremia. *Surg Gynecol Obstet* 1985; 160: 557-61.
- 63 Newell KA, Millis JM, Arnow PM, et al. Incidence and outcome of infection by vancomycin-resistant enterococcus following orthotopic liver transplantation. *Transplantation* 1998; 65: 439-42.
- 64 Hospital Infection Control Practices Advisory Committee. Recommendations for preventing the spread of vancomycin resistance. *Infect Control Hosp Epidemiol* 1995; 16: 105-13.
- 65 Ostrowsky BE, Trick WE, Sohn AH, et al. Control of vancomycin resistant enterococcus in health care facilities in a region. *N Engl J Med* 2001; 344: 1427-33.
- 66 Hayden MK. Insights into the epidemiology and control of infection with vancomycin-resistant enterococci. *Clin Infect Dis* 2000; 31: 1058-65
- 67 Montravers P, Mohler J, Saint Julien L, Carbon C. Evidence of the proinflammatory role of *Enterococcus faecalis* in polymicrobial peritonitis in rats. *Infect Immun* 1997; 65: 144-9. □