EDUCATIONAL COMMENTARY – VANCOMYCIN-RESISTANT ENTEROCOCCUS

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Learning Outcomes

Upon completion of this exercise, the participant will be able to:

- Discuss the epidemiology of vancomycin-resistant Enterococcus species.
- Explain the mechanisms of antibiotic resistance found in Enterococcus species.
- Discuss the role of polymerase chain reaction tests in identifying vancomycin-resistant Enterococcus.

Members of the genus Enterococcus are normal flora in humans and animals, and they may either colonize or infect an individual. A person who harbors a potential pathogen but shows no signs of disease is colonized, whereas a person who has disease caused by the organism is infected. Infections caused by Enterococcus are usually nosocomial. They occur when these bacteria enter normally sterile sites through direct transmission from a colonized person or by contaminated equipment. Commonly infected sites include the urinary tract, blood, wounds, endocardium, abdomen, and pelvis. Eye infections sometimes occur, but central nervous system and respiratory tract infections are rare. Patients most likely to develop infections are those receiving therapies to suppress the immune system, such as organ transplant recipient and hematology patients.

Enterococcus faecalis and Enterococcus faecium, which normally inhabit the gastrointestinal and female genitourinary tracts, cause most human infections. Enterococcus faecalis is most often isolated, but the incidence of E. faecium is increasing. This development is thought to be related to the rise of vancomycin resistance in these bacteria.

Emergence of Vancomycin Resistance

The first case of vancomycin-resistant Enterococcus (VRE) in the United States appeared in 1989. The incidence of VRE has since increased rapidly, and VRE now comprise nearly 30% of enterococci isolated from patients in intensive care units (ICU).\(^1\)\(^2\) Also, a study by Warren and colleagues showed that 9.5% of ICU patients who were colonized or infected with VRE were also colonized or infected with methicillin-resistant Staphylococcus aureus (MRSA).\(^3\) This is particularly worrisome because VRE can transfer genes that cause vancomycin resistance to MRSA,\(^2\) making these infections extremely difficult to eradicate.

Although most enterococcal infections are caused by E. faecalis, most vancomycin-resistant enterococci are E. faecium. According to data from the Surveillance Network Database-USA, the percentage of vancomycin-resistant E. faecium strains increased from 26.2% in 1995 to 48.8% in 1997,\(^4\) and more recent reports indicate that the percentage of vancomycin-resistant E. faecium strains is now nearly...
EDUCATIONAL COMMENTARY – VANCOMYCIN-RESISTANT ENTEROCOCCUS (cont.)

70%. In contrast, the proportion of vancomycin-resistant *E. faecalis* strains has remained low at 1.9% and 1.4% in 1995 and 1997, respectively.4

**Antibiotic Treatments and Mechanisms of Resistance**

All enterococci are inherently at least somewhat resistant to most commonly prescribed antibiotics. Ampicillin or penicillin is usually effective in uncomplicated infections, but because these antibiotics only inhibit growth rather than kill the bacteria, they cannot be used alone to treat serious infections. Likewise, aminoglycosides cannot be used alone because enterococci are resistant to low levels of these drugs. Instead, serious infections caused by susceptible *Enterococcus* strains are treated with a combination of ampicillin or penicillin (or vancomycin for patients who are allergic to penicillin) and an aminoglycoside such as gentamicin or streptomycin. This combination produces a synergistic effect that kills the bacteria.

In enterococci, resistance to penicillin and ampicillin can be caused by altered penicillin-binding proteins or by production of the enzyme β-lactamase. Resistance caused by altered penicillin-binding proteins, which is common in *E. faecium* but not *E. faecalis*, can be detected by routine disk diffusion or dilution tests. Resistance caused by production of β-lactamase can only be detected by a rapid β-lactamase test.

Low-level resistance to aminoglycosides is caused by poor antibiotic uptake by the bacterial cells. High-level aminoglycoside resistance, on the other hand, is caused by enzymes that inactivate the antibiotics. Both disk diffusion and dilution susceptibility tests can detect high-level aminoglycoside resistance, but high concentrations of the drugs must be used.

Resistance to vancomycin (a glycopeptide) occurs when an *Enterococcus* strain possesses a gene sequence that alters peptidoglycan cell-wall precursors, thereby preventing binding by vancomycin. Currently, there are 6 known glycopeptide-resistant phenotypes: VanA, VanB, VanC, VanD, VanE, and VanG. Of these, the VanA and VanB genotypes, which possess the *vanA* and *vanB* gene sequences, are most important. Resistance to vancomycin can be detected by conventional broth dilution and disk diffusion methods or by brain-heart infusion agar permeated with 6 µg/mL vancomycin. In addition, polymerase chain reaction (PCR) tests can detect the *vanA* and *vanB* genes.

Several new antibiotics have been introduced in recent years to treat VRE, including quinupristin-dalfopristin in 1999, linezolid in 2000, daptomycin in 2003, and tigecycline in 2005. However, all of these drugs have drawbacks. Quinupristin-dalfopristin is effective against *E. faecium* but not *E. faecalis*, and it has adverse effects that limit its use. Linezolid is active against both *E. faecium* and *E. faecalis*, but resistance to this drug has begun to emerge. Clinical trials have shown that daptomycin is often ineffective in treating pneumonia, and resistance to this drug also has begun to emerge. Finally, little data exists regarding the effectiveness of daptomycin and tigecycline in treating VRE infections.
EDUCATIONAL COMMENTARY – VANCOMYCIN-RESISTANT ENTEROCOCCUS (cont.)

Current Research
Because infection with VRE often results from transmission of the bacteria from a colonized person, researchers are interested in identifying factors that promote colonization. One area of research has been the relationship between antibiotic use and VRE colonization. Results of studies exploring this issue suggest that, although the relationship between antibiotic use and colonization is complex, colonization appears to be related to anti-anaerobic and anti-enterococcal activity and biliary excretion of the drug.¹

In addition to identifying factors that promote colonization, researchers are also working to devise faster methods to detect VRE colonization. Conventional laboratory methods take up to 5 days to identify patients who are VRE positive and up to 3 days to identify patients who are VRE negative. To shorten this time, researchers have used 24- to 36-hour broth cultures and PCR tests that detect the vanA and vanB gene sequences. Recently, Drews and colleagues described a 24-hour screening protocol that uses VRE enrichment culture and a PCR assay to identify vancomycin-resistant E. faecium.⁷

In contrast to colonization, infection by VRE must still be detected by conventional culture for 4 reasons. First, PCR methods may fail to detect the vanA or vanB genes if only a few bacteria are present. Second, PCR methods may give false-positive results because other bacteria can carry the van genes. Third, conventional culture methods allow susceptibility testing, which is essential when Enterococcus is implicated in infection. Finally, culture is needed for DNA analysis of strains isolated in outbreaks.

Conclusion
Due to the unique characteristics of Enterococcus, special procedures must be followed to guarantee reliable antimicrobial susceptibility test results. Also, because antibiotic resistance patterns change rapidly and new antibiotics are being introduced to treat enterococcal infections, laboratories should review their antibiotic susceptibility testing protocols every year to ensure that they incorporate the most up-to-date information. These recommendations appear in the standards and supplemental tables published by the Clinical and Laboratory Standards Institute (CLSI). Revised supplemental tables are published in January of each year, so for best practice, laboratories should obtain these as early as possible. The standards and supplemental tables can be purchased directly from CLSI (www.clsi.org). Alternatively, many state health departments make these publications available to laboratories.

References

EDUCATIONAL COMMENTARY – VANCOMYCIN-RESISTANT ENTEROCOCCUS (cont.)


*Suggested Reading*


