

Therapeutic and Preventive Strategy of Antibiotic-resistant Enterococci

Ti Teow Yee MBBS, FRCP (C)

Department of Pharmacology/Medicine
National University of Singapore

In the past decade, the genus Enterococci has become increasingly important both as a major nosocomial pathogen and therapeutic problem because of antibiotic resistance. There are at least 12 species of enterococci but most of the infections in man are caused mainly by *E. faecalis* and a small percentage by *E. Faecium*. In order to appreciate the difficulties in treating enterococcal infections and the importance of preventing the spread of multi-resistant enterococci, and understanding of the antibiotic susceptibility pattern of the organism is essential.

ANTIBIOTIC RESISTANCE

Enterococci have intrinsic resistance to a variety of antibiotics such as the beta-lactams, aminoglycosides, clindamycin and trimethoprim-sulfamethoxazole and in the past decade have rapidly acquired new mechanisms of resistance(1,2,3,4).

Beta-lactams

The intrinsic resistance to the beta lactams is relative and is due to reduced affinity for penicillin-binding proteins. However, the cephalosporins are less active against the enterococci than the penicillins and none are useful clinically. Although the minimal inhibitory concentrations of benzylpenicillin and ampicillin fall within the susceptible range for penicillin treatment, they are much higher than that for streptococci. The effect of the penicillins on the enterococci is only bacteriostatic

In recent years, strains of *E. Faecium* with high level resistance to benzylpenicillin and ampicillin have been reported. This acquired resistance is due to further alteration of PBP 5. In addition, acquired resistance due to beta-lactamase production has been detected, but the clinical significance of this is not known.

Aminoglycosides.

The enterococci are intrinsically resistant to low concentrations of aminoglycosides due to impermeability of the cell wall to these drugs. But a combination of cell wall active agent such as benzylpenicillin ampicillin or vancomycin and an aminoglycoside is bactericidal to the enterococci. Such combination regimens are traditionally used in the management of enterococcal endocarditis where it is essential to have bactericidal effect of the antibiotics. Resistance to high level streptomycin was first discovered in 1959 and to gentamicin in 1979 and today enterococci resistant to high-level aminoglycosides are not uncommon. The combination antibiotic regimen is no longer bactericidal if the enterococci are resistant to high-level aminoglycosides.

Vancomycin

Vancomycin is bacteriostatic to enterococci and has no therapeutic advantage in the management of enterococcal infections compared to the penicillins. The first discovery of vancomycin resistant enterococcal (VRE) was reported in 1988. Since then the incidence of VRE has increased greatly e.g. data from the United States showed that VRE has increased from 0.3% in 1989 to 7.9% in 1993(5). Most of the VRE are *E. faecium* and many of these strains are also resistant to multiple antibiotics including penicillins and aminoglycosides. These multiple antibiotic resistant strains challenge our therapeutic strategy in the management of enterococcal infections.

Other antibiotics

Trimethoprim - sulfamethoxazole is active against enterococci in-vitro testing but this in-vitro susceptibility is not an indication of clinical efficacy as treatment failures have been reported both in animal models and patients. There is also an increase in the strains of enterococci that have acquired resistance to other antibiotics such as chloramphenicol, tetracycline macrolides and the fluoroquinolones.

TREATMENT STRATEGY

From the review of the susceptibility pattern of enterococci, it is obvious that the therapeutic options are limited especially with the emergence of enterococci with increasing resistance to multiple antibiotics. Therefore, the management of enterococcal infections should be guided by detailed laboratory susceptibility testing. Tests for resistance to high level gentamicin and streptomycin of the organism should also be carried out in addition to the routine susceptibility tests to benzylpenicillin, ampicillin and vancomycin.

The choice of antibiotic(s) depends on the results of susceptibility tests and the site of infection (1). The antibiotic of choice for peritonitis, urinary tract wound infections is benzylpenicillin or ampicillin. In these infections monotherapy is usually adequate. Vancomycin is the alternative drug for patients who are allergic to the beta-lactams, or whose infection is caused by high level penicillin resistant *E. faecium*.

Combination therapy of a cell wall active agent and an aminoglycoside is indicated for enterococcal endocarditis and meningitis where bactericidal effect is essential. Benzylpenicillin or ampicillin is usually combined with gentamicin or streptomycin (1,6).

If the organism exhibit high level penicillin resistance, then vancomycin is used as an alternative in the combination therapy. However, if the organism is also resistant to vancomycin, susceptibility test to teicoplanin should be done. If the resistance due to vancomycin is of Van A phenotype then the organism may be susceptible to teicoplanin in vitro. But the efficacy of teicoplanin treatment in such a situation is not well proven (1,6).

Penicillin/ampicillin or vancomycin in combination with an aminoglycoside is not bactericidal if the organism is resistant to both gentamicin and streptomycin. high

dose ampicillin for prolonged period is recommended but the efficacy of this therapy is not known (1). In patients with endocarditis surgery may be indicated if the infection cannot be controlled

If the infection is due to VRE which also exhibit high level penicillin and aminoglycoside resistance, then there is no proven effective antibiotic therapy. Treatment is empirical.

PREVENTIVE STRATEGY

There is no effective treatment for some strains of multi-drug resistant enterococci. Therefore, it is important to limit the spread of such organisms within an institution or from one institution to another. In addition, the possibility of transfer of multi-drug resistance determinants from enterococci to other gram positive cocci such staphylococci is of great concern. Transfer of vancomycin resistance from enterococci to staphylococci has been done in the laboratory. It is only a matter of time that multi-drug resistance determinants spread from enterococci to other gram positive cocci in the environment.

The basic principles in the prevention of the spread of multi drug resistant enterococci is the same as for any other types of antibiotic resistant organisms. However, one must bear in mind that enterococci are part of the normal flora of the gut and very often infection is from the patient's own flora. It is important to prevent the patients from being colonised by multi-drug resistant strains. Another factor that should be taken into consideration is that enterococci are hardy organisms and can survive heat and desiccation., It is not difficult to isolate these organisms from inanimate objects in the hospital environment. Every hospital should have a strategy to prevent the spread of multi-resistant enterococci. The Hospital Infection Control Practices Advisory Committee(CDC) had published their recommendations for preventing the spread of vancomycin resistance(7).

Some of the important preventive measures listed below will be discussed :

1. Laboratory Surveillance

The microbiology laboratory should be vigilant in the identification multi-drug resistant enterococci, especially VRE. Once a strain has been identified the Infection control team must be alerted and preventive measures to reduce the spread should be instituted.

2. If multi-drug resistant strains are detected then strict barrier nursing should be practised by :

- (i) Isolating patients who are infected or colonised into single rooms or cohorting them in a ward
- (ii) Glove and gown - when attending to patient.
- (iii) Equipments such as thermometers, blood pressure sets, stethoscopes and etc should be dedicated for use in the isolation room only.

3. Handwashing

A simple cost effective method : should be practised by all staff both before and after contact with all patients.

REFERENCES

- 1 Moellering, Jr. R.C. Enterococcus species, Sheptococcus bovis and Leuconostoc species. In: Mandell GL, Bennett JE, Dolin R. eds, Principles and Practice of Infectious Diseases 4th Ed. 1995, 1826 - 25.
- 2 Health CH, TK, Blackmore, D L Gordon. Emerging resistance in Enterococcus Spp. MJA 1996, Vol 164:116 - 120.
- 3 Rice LB, D.M Shlaes. Vancomycin resistance in the Enterococcus. Pediatric Clinics of North America 1995, 42:601-618.
- 4 Spera Jr RV, B F Faber. Multi drug-Resistant Enterococcus faecium. Drugs 1994,48(5) 678-688.
- 5 Francioli, P. Antibiotic treatment of Streptococcal and enterococcal endocarditis : An overview. European Heart Journal 1995, 15(SB) 75-79
- 6 CDC - Recommendation for prevention and spread of vancomycin resistance. MMWR 1995, Vol. 44 No. RR-1.