



ENTEROCOCCAL NEONATAL SEPTICEMIA

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ABSTRACT

Enterococci are among the leading cause of several human infections including bacteraemia, septicaemia, endocarditis, Urinary tract infections ,wound infections, neonatal sepsis and meningitis. Enterococci are frequently associated with the late onset septicemia in premature neonates. Most human clinical isolates are due to either *E.faecalis* (74-90%) or *E.faecium* (5-16%). Risk factors for development of bacteremia include immunosuppression, diabetes, malignancy, deep seated infections, prior instrumentation, long term hospitalization and use of broad spectrum antibiotics. In addition, to natural resistance, enterococci have developed plasmid and transposon mediated resistance The problem of multidrug resistant enterococci continues to create new therapeutic problems and dilemmas in neonatal septicemia.

Key words: Septicemia, Enterococcus, VRE



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INTRODUCTION

Enterococci are facultative anaerobes that are part of the normal intestinal flora in humans. Although considered as bacteria of low virulence, they have now emerged as important nosocomial and community acquired pathogens. They are anticipated to precipitate management problems in the near future as isolates with novel mechanism of acquired resistance to antimicrobials are more frequently seen. They have greater capacity for transmitting these resistance to other species and even other genera. Enterococci are among the leading cause of several human infections including bacteraemia, septicaemia, endocarditis, Urinary tract infections, wound infections, neonatal sepsis and meningitis. The incidence of enterococcal bacteremia has increased in pediatric population and it is a frequent cause of late onset septicemia in premature neonates.¹

Neonatal septicemia

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteraemia in the first month of life. It can be classified as:-

i) Early onset sepsis(EOS) : It presents within first 72 hrs of life. The source of infection is usually the maternal genital tract. Various risk factors with EOS are – low birth weight (<2500gm) or prematurity, febrile illness in the mother with evidence of bacterial infection before delivery, foul smelling or meconium stained liquor, rupture of membrane >24hrs, single unclean or more than three sterile vaginal examination during labor, prolonged labor and perinatal asphyxia.

ii) Late onset sepsis(LOS) : It usually presents after 72hrs of age. It can be nosocomial or community acquired. Various risk factors for LOS are – Low birth weight, prematurity, ICU admission, mechanical ventilation, invasive procedures, parenteral fluids, poor hygiene, poor cord care, and breast feeding.²

Risk factors for development of enterococcal bacteremia in neonates include:-

- Immunosuppression or debilitation because of prematurity
- Diabetes
- Malignancy
- Deep seated infections (e.g secondarily infected decubitus ulcers)
- Prior gastrointestinal, genitor-urinary or respiratory tract instrumentation
- Long term hospitalization
- Presence of vascular or urinary catheters
- Use of broad spectrum antibiotics having little or no anti-enterococcal activity (e.g cephalosporins)³

The organisms generally enter into the bloodstream through the urinary tract, intra-abdominal or pelvic sepsis, wounds or intravenous access devices.

Enterococci account for as many as 10% cases of neonatal bacteremia and septicemia.[4] Enterococci may cause early onset(within 7 days of birth) and/or late onset(> 7 days) neonatal sepsis. Most cases of enterococcal bacteremia in neonates are nosocomial.⁴ Enterococci are among the first bacteria to colonize the neonatal gastrointestinal tract either through oral ingestion of breast milk or from the vaginal and gastrointestinal flora of the mother during the birth passage. It is reported that colonization with multidrug resistant enterococci has increased in preterm newborns during the winter/spring months. It is because of prepartal use of antibiotics with no known activity against enterococci.⁵

Neonatal enterococcal sepsis has an acute early onset presentation characterized by fever and respiratory distress accompanied by bacteremia and meningitis. Premature neonates are at greater risk of developing serious nosocomial enterococcal infections particularly if peripheral access devices or feeding tubes are in place.⁶

Enterococci

Previously enterococci were classified as Group D streptococci, which have now been

reclassified as a separate genus called Enterococcus. They are gram-positive, catalase-negative, facultative anaerobes that grow as diplococci arranged at angles and in short chains. The enterococci possess several distinctive features that distinguish them from streptococci. They can grow in the presence of 40% bile, 6.5% sodium chloride, at pH 9.6, at 45°C and in 0.1% methylene blue milk and can grow on MacConkey agar producing tiny deep pink colonies. They are usually non-hemolytic though some strains may show alpha or beta hemolysis.⁷

The genus Enterococcus includes 17 species. Most human clinical isolates are due to either *E.faecalis* (74-90%) or *E.faecium* (5-16%). Occasionally human infections can be due to *E.raffinosis*, *E.casseliflavus*, *E.durans*, *E.avium* and *E.gallinarum*.^{4,8}

Virulence factors

The virulence factors that contribute to the pathogenesis of Enterococci are not completely understood. A number of studies have identified different virulence factors, most important among them being hemolysin, gelatinase, enterococcal surface protein, aggregation substance, serine protease, capsule, cell wall polysaccharide, superoxide and biofilm formation. The pathogenicity islands (PAI) of enterococcus was identified in the genome of Multidrug resistant strain of *E.faecalis* (MMH594) which had caused a nosocomial infection outbreak in 1980's.^{9,10}

- Some strains of *E.faecalis* and *E.faecium* produce a cytolysin that acts as a hemolysin against human, rabbit, equine and bovine erythrocytes and intoxic for certain eukaryotic cell types.¹¹
- Aggregation substance is a surface bound plasmid encoded protein that promotes clumping of the organisms and facilitates the exchange of plasmids.^{4,11}
- Gelatinase is an extracellular zinc endopeptidase which has been found to be produced by large percentage of *E.faecalis* isolates from hospitalized patients.^{3,4}
- *E.faecium* may have a carbohydrate moiety that makes it resistant to phagocytosis.⁴

- *E.faecalis* strains also produce pheromones which are small peptides that are secreted by the organisms and that promote the conjugative transfer of plasmid DNA between strains.¹²
- Some *E.faecalis* strains also produce a plasmid encoded bacteriocin which has lytic activity for a wide spectrum activity of Gram positive and Gram negative bacteria.¹³
- Some *E.faecalis* strains also produce hyaluronidase.¹⁴

Mortality

In preterm infants and immunocompromised patients, infections with enterococci can be life threatening. Urinary catheters, central lines, mechanical ventilation, previous surgeries, prior stay in an ICU and the presence of severe underlying disease has been associated with mortality. Neonatal infections are associated with a 6.0% mortality rate in EOS, 8% in LOS which rises to 17.0% in late onset infections associated with necrotising enterocolitis.¹⁵

A study from Saudi Arabia [16] in neonates and adults had mentioned the crude mortality rate among patients with enterococcal bacteremia to be similar to the rate among patients with bacteremia caused by other gram positive cocci (crude mortality, 14-24%) and in-hospital mortality rate as 28%. The crude mortality rate was not related to age and the prognosis was not different for patients treated with monotherapy or combined therapy.¹⁶ Where as, in another study crude mortality rates with drug therapy, appropriate monotherapy and either no therapy or inappropriate therapy were 7%, 20% and 6.25% respectively.¹⁷

Das et al. from UK reported 7.5% overall mortality rate in children with enterococcal bacteremia.¹⁸

Antimicrobial resistance

Enterococci have a remarkable ability to survive in an environment of heavy antibiotics. Antimicrobial resistance in Enterococci is of two types:

- Intrinsic or inherent resistance (low level) is chromosomally mediated and non-transferable.

- Acquired resistance (high level) is mediated by plasmids, transposons, chromosomal exchange or mutations and it is transferable.

Enterococci are inherently resistant to various drugs including cephalosporins, semi-synthetic penicillinase resistant penicillins, clinically achievable concentrations of clindamycin and aminoglycosides.

In addition, to natural resistance, Enterococci have developed plasmid and transposon mediated resistance to penicillins by beta-lactamases, tetracyclines, macrolides, chloramphenicol and vancomycin.¹⁹

Resistance to beta-lactams

The mechanisms involved in this resistance are over production of a low affinity penicillin binding protein and a further decrease in the affinity of one of these enzymes for penicillin. Most of *E.faecalis* isolates can be inhibited by MIC of 1-8 mcg/ml concentration of penicillin achievable in plasma whereas *E.faecium* is inhibited at MIC of 16-64 mcg/ml.

Penicillin or ampicillin resistance due to beta-lactamase production is not reliably detected with routine disc diffusion or dilution methods but is detected using a direct, nitrocefin-based β -lactamase test. A positive β -lactamase test predicts resistance to penicillin as well as amino- and ureido-penicillins.^{20,21}

High level aminoglycoside resistance (HLAR)

HLAR is most often due to aminoglycoside modifying enzymes. HLR to streptomycin may be ribosomal. HLR to kanamycin is due to production of 3'phosphotransferase, APH(3') – III. HLR to gentamicin results from bifunctional protein [AAC(6')-I/APH(2'')-I], encoded by a single gene with two active sites, one with 6'acetyltransferase activity and the other 2'' with phosphotransferase activity.

Screening for HLAR can be carried out by agar screening, high content disks and broth dilution methods.^{21,22}

Vancomycin resistance

The resistance of enterococci to glycopeptides such as vancomycin and teicoplanin were first discovered in late 1980's. The three major phenotypes of vancomycin resistance have been described in enterococci.

- Van A is characterized by HLR to vancomycin(MIC>64mcg/ml) and teicoplanin(MIC>32 mcg/ml). This phenotype is mediated by a transposon that carries seven genes and is usually seen in *E.faecium*.
- Van B phenotype has variable levels of resistance to vancomycin (MIC 4-1000mcg/ml) but not to teicoplanin. It is mediated by transposons (Tn 1547). This phenotype is usually seen in *E.faecium* but can also be seen in *E.faecalis*.
- Van C phenotype is limited to certain species of enterococci. This phenotype demonstrates low level vancomycin resistance(MIC 8-32mcg/ml) and is susceptible to teicoplanin.²¹

Vancomycin resistant enterococci(VRE) have emerged as the major nosocomial pathogen. Increasing outburst of VRE colonization is attributed to frequent exposure to antimicrobial agents, mainly cephalosporins, metronidazole and vancomycin, decreased immunity, hepatic and renal insufficiency, proximity to other patients with VRE, prior surgery, invasive procedures and prolonged hospital stay. Once colonized by VRE, a person has 5-10 fold increased risk of developing severe infection.²³ VRE bacteraemia is associated with extensive co morbid pathology, prolonged hospitalization, heavy exposure to antimicrobial agents and high crude mortality rates.²⁴

Treatment

In neonatal sepsis due to enterococcus a combination of ampicillin and gentamicin may be used for initial therapy. If there is resistance to first line of therapy, vancomycin should be used. In cases of VRE, linezolid is

the drug of choice but few studies have reported daptomycin(a semisynthetic cyclic lipopeptide) to be as effective as linezolid . The dosing, efficacy and adverse effects of daptomycin need to be evaluated in pediatric patients.^{25,26}

Adjunct therapy like exchange transfusion, intravenous immunoglobulin and granulocyte macrophage colony stimulating factor (GM-CSF) may have some role in the treatment but these are still in experimental stage.²

Probiotic fortified diet may have a role in reducing bacterial colonization.²⁷

CONCLUSION

The problem of multidrug resistant enterococci continues to create new

therapeutic problems and dilemmas in neonatal septicemia. With the ability to transfer some of its plasmids to streptococci and staphylococci and the implications of a possible spread of penicillin and vancomycin resistance to these and other Gram positive species are also of concern. Primarily the use of those antimicrobial agents that select for their isolations must be limited. There should be surveillance for colonization, identification of colonized and infected patients, isolation of colonized patients, minimizing the use of intravenous and urinary catheters and removal when no longer needed, education of hospital staff about scrupulous hand washing, the use of gowns and gloves by health care workers and environmental decontamination with effective disinfectants.

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