Abstract

Viridans Group Streptococci (VGS) were considered to be commensal organisms of low virulence. Their major disease associations were formerly limited to dental caries and infective endocarditis. Over the last several years, these bacteria have emerged as significant pathogens associated with gingivitis, periodontitis, bacteremia, meningitis, pneumonia and a variety of infections in neonates. Although penicillin remains the drug of choice in the treatment of infections caused by VGS, drug tolerance and clinical therapeutic failures have been reported. Different studies in recent past show that there is an alarming increase in resistance in VGS to various antimicrobial agents. Increase in the incidence of VGS with multiple drug resistance to penicillin and other agents suggest for periodic surveillance of antimicrobial susceptibility among VGS in order to guide appropriate antimicrobial therapy and to develop an appropriate treatment strategy for various infections caused by VGS. The development of appropriate treatment strategy not only helps in effective management but also helps to monitor further spread of resistant pathogens.

**Keywords:** VGS, antimicrobial resistance, treatment strategy, infective endocarditis

Introduction

Viridans Group Streptococci (VGS) are inhabitants of oral cavity. *Streptococcus* species compose 70% of the cultivable oral flora and *Streptococcus salivarus, Streptococcus oralis* and *Streptococcus mitis* are predominant [1]. Viridans streptococci are present in the dental plaque surrounding the teeth. It is generally accepted that the primary etiology for gingivitis and periodontitis is the dental plaque bacteria, bacterial products, and the resulting inflammatory cascade [2]. Gingivitis and periodontitis are among the most common human infections. Gingivitis can develop within days and includes inflammatory changes of the gingiva most commonly induced by accumulation of dental plaque. Periodontitis results from a complex interplay between chronic bacterial infection and the inflammatory host response leading to irreversible destruction of tooth-supporting tissues, with tooth loss as a common end point [3]. Periodontitis may not only affect the oral tissues, but bacteria may translocate into the blood stream via ulcerated inflamed crevice and pocket epithelium and the adjacent gingival microcirculation. This may occur following invasive dental procedures and also during normal daily activities such as chewing and tooth brushing [4-6]. Bacteremia and low-grade systemic inflammation induced by periodontal infections may confer a risk for systemic conditions.
including infective endocarditis and other diseases like cardiovascular diseases, stroke, premature low birth weight delivery and diabetes mellitus [7]. One of the severe infections caused by VGS is Infective Endocarditis (IE) in patients with native and prosthetic valves [8-10]. IE is an infection of the lining of the heart chambers (endocardium), usually the heart valves are involved, and the most common causes of this disease are bacteria and this phenomenon is also known as bacterial endocarditis [11]. IE occurs when bacteria lodge on abnormal heart valves or damaged heart tissue. IE occurs rarely with normal hearts; however people who have preexisting heart defects are at risk of developing endocarditis from an oral induced bacteremia [12].

The most common cause of IE is bacteria and among the wide variety of bacteria, the leading cause of IE is VGS. The most frequently isolated VGS from IE patients is S. sangius (31.9 %), S. oralis (29.8 %) followed by the mutans group Streptococci which is notorious for cariogenecity can also cause IE [13, 14].

IE is a life-threatening disease. It is always fatal if untreated, and it continues to cause substantial morbidity and mortality despite modern antimicrobial and surgical treatment [15]. Antimicrobial chemotherapy is now widely advocated to protect at risk patients, however, frequent use may generate drug-resistant mutant bacteria, which has become a serious problem [16].

Infections Associated With Viridans Streptococci
In the past, the isolation of Viridans streptococci from blood culture or cerebrospinal fluid had often been regarded as contamination. Viridans streptococci are frequently considered to be commensal organisms of low virulence. Their major disease associations were formerly limited to dental caries and infective endocarditis [13, 17]; over the last several years however, these bacteria have emerged as significant pathogens [18-20]. Viridans streptococci are associated with various diseases such as dental caries- a plaque-associated infection [17], a dental abscess- a collection of pus in the pulp or around the root of a tooth, bacteraemia, infective endocarditis, meningitis—most often caused by members of the `mitis' or `salivarius' group [21], pneumonia in both immunocompromised and immunocompetent individuals [22, 23] and a variety of infections in neonates, most commonly associated with obstetric complications such as prolonged rupture of membranes, premature labour or peri-partum fever.

Susceptibility to Antimicrobial Agents
Although, penicillin remains the drug of choice in the treatment of infections caused by VGS, drug tolerance and clinical therapeutic failures have been reported. Resistance to penicillin, ampicillin, cefotaxim, meropenem, erythromycin, azithromycin, levofloxacin, gatifloxacin, chloramphenicol, tetracycline and Trimethoprim-sulfamethoxazole has been reported. The lower rates of non susceptibility to vancomycin and clindamycin have also been documented [24-28]. These earlier studies have shown considerable changes in the pattern of susceptibility of VGS to antimicrobial agents, moreover there is an increase in resistance to all the antimicrobials over a period of time. Macrolides and lincosamides have been frequently used to prevent β-lactam allergies in patients. However, recent studies have shown considerable changes in the susceptibility of VGS to erythromycin and clindamycin, although
different resistance rates to these agents owing to geographical variation and investigators have been reported [24]. β-lactam agents have been the treatment of choice for VGS infections; however, increase in the incidence of VGS with multidrug-resistance to penicillin and other agents, such as cephalosporins, macrolides, lincosamides, tetracycline, quinupristin-dalfopristin, and quinolones, has been reported [29]. Moreover, CLSI has recommended that VGS isolated from normally sterile body sites should be tested for penicillin susceptibility by using a Minimum Inhibitory Concentration (MIC) method and interpretive criteria [30].

Clinical microbiology laboratories, especially in developing countries, where macrolide and β-lactam antibiotics are frequently overprescribed, have to perform periodic surveillance of antimicrobial susceptibility among VGS. Periodic susceptibility testing for VGS is required in order to guide appropriate antimicrobial therapy and to monitor further spread of resistant pathogens. Rapid reporting of the results of an Antimicrobial Susceptibility Test (AST) has been shown to improve patient outcomes and reduce hospital costs [31, 32].

Mechanism of Antimicrobial Resistance in VGS

Reduced susceptibility of viridans streptococci to penicillin was first described in 1949. However, around that time little clinical significance was attached to this or other early reports. Resistance to penicillin amongst viridans streptococci, particularly of the mitis group, is now common in many hospitalized patients, with resistance rates exceeding 50% in some reports [33]. Resistance has also been reported in viridans streptococci colonizing healthy individuals [34]. Resistance to penicillin in these organisms is due to the development of altered forms of penicillin binding proteins which have reduced affinity for the antibiotic. These high-molecular weight proteins are encoded by ‘mosaic’ genes that are produced by genetic recombination events between different strains or species of oral streptococci [35]. Several streptococcal species, including S. oralis, S. mitis, S. sanguis and S. pneumoniae are naturally transformable, and can easily transfer antibiotic resistance markers into closely related species [36].

Resistance to penicillin in viridans streptococci is also associated with resistance or decreased susceptibility to other β-lactam antibiotics, including cephalosporins [29, 37, 38]. The prevalence of resistance of viridans streptococci to erythromycin and other macrolide antibiotics has also increased [39]. Resistance to macrolides in viridans streptococci is associated with the presence of an rRNA methylase gene, ermB, which confers resistance to macrolides, lincosamides and streptogramin B antibiotics [40]. A different mechanism, conferring resistance to macrolides but not to lincosamides and streptogramin B, has more recently been described [41]. The gene responsible, mef, codes for a membrane bound efflux protein. Resistance to tetracycline in viridans streptococci is encoded by the tetM gene which is often found linked with ermB [42]. Resistance to chloramphenicol and kanamycin is encoded by the cat and apha genes respectively. Several studies have described resistance to two or more different classes of antibiotic amongst Viridans streptococci [43].

Susceptibility of viridans streptococci to the glycopeptide antibiotics, vancomycin and teicoplanin has remained high [33, 38]. However, the potential for nephrotoxicity associated with the use of vancomycin, results in this agent commonly
being reserved until microbial documentation of infection is available. During the early years, there existed some concern that the observed increase in resistance of viridans streptococci to β-lactam antibiotics such as penicillin, cefaclor and ceftazidime might escalate and possibly spread to include the more modern β-lactam agents such as ceftriaxone and the carbapenems. Information is required on the susceptibility of viridans streptococci to the more modern β-lactam antibiotics, such as the carbapenems and the fourth generation cephalosporins and to the newer agents, quinupristin/dalfopristin and linezolid.

**Antimicrobial Treatment of VGS Infections**

Viridans streptococci are generally penicillin sensitive, some strains may be resistant. It is therefore essential to determine antimicrobial susceptibility so that appropriate antimicrobial in adequate bactericidal concentration can be employed for treatment purpose.

### i. Treatment of Periodontitis

During the past 2 decades, dentists and microbiologists have embraced periodontal antibiotic therapy, as evidence for bacterial specificity in periodontitis has accumulated and strengthened. Actively progressing periodontitis is virtually always associated with specific bacterial infections and often requires the adjunctive use of systemic antibiotic therapy [44]. Early approaches to systemic antibiotics in periodontal treatment included mainly single drug therapies with tetracyclines, penicillins, metronidazole or clindamycin. Recently, the gingival crevice fluid concentration of systemically administered tetracyclines was reported to be less than that of plasma concentration and vary widely among individuals (between 0 and 8 µg/ml), with approximately 50% of samples not achieving a level of 1 µg/ml, possibly explaining much of the variability in clinical response to systemic tetracyclines observed in practice [45]. Since periodontitis lesions often harbor a mixture of pathogenic bacteria, drug combination therapies have gained increasing importance [46].

Relatively few studies have been performed regarding which antibiotics should be selected for aggressive periodontitis patients in whom the subgingival micobiota have been characterized through microbiological testing. In addition, the optimal dose of antibiotics remains unclear [47] since most current antibiotic regimens are empirically developed rather than through systematic research [48]. Table 1 lists frequently prescribed antibiotic regimens for treatment of periodontitis.

The periodontopathic microbiota includes a variety of microorganisms with differing antimicrobial susceptibility and clinical disease features can only rarely incriminate the offending bacteria, and because inappropriate antibiotic therapy may adversely affect human microbial ecology and give rise to resistance development among serious pathogens, microbiological analysis and antimicrobial susceptibility testing should ideally form the basis for selecting the optimal antimicrobial therapy [46]. Microbiological analysis is particularly advisable in periodontal lesions that are recalcitrant to conventional periodontal therapy and may harbor a great variety of periodontal pathogens [44].
ii. Treatment of Bacteremia
Bacteremia is induced by a wide variety of clinical procedures and manipulations, particularly those involving heavily colonized mucous membranes or infected sites. It has been known for a long time that invasive procedures of oral tissues result in the translocation and release of microorganisms from the oral cavity into the bloodstream. Generally the microorganisms are eliminated by the reticuloendothelial system within a few minutes [50]. However, bacteremia may lead to seeding of organisms in different target organs resulting in subclinical, acute or chronic infections.

A potential hazard to patients with abnormal heart valves or other cardiac abnormalities is infective endocarditis. Infective endocarditis is a well-known complication of oral induced bacteremia and has been a matter of great concern for dentists, cardiologists and microbiologists. The literature and guidelines on the prevention and management of bacteremia of oral origin have been under constant review, particularly with regard to prophylactic antibiotics and dental procedures, with differing opinions expressed [51-53].

The current practice of giving patients, antibiotics prior to a dental procedure, is no longer recommended except for patients with the highest risk of adverse outcomes resulting from IE. The dental procedures which include, manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa in the above mentioned high risk patients are only recommended for antibiotic prophylaxis (Table 2) [53].

iii. Treatment of Infective Endocarditis
Since the introduction of penicillin, the cure rate of VGS has exceeded 95%. Reasons for failure include bacterial tolerance (when MBC is 32 times higher than MIC), inadequate antimicrobial level in the vegetation (most likely due to inadequate dosing or poor drug penetration), and heart failure [37]. In addition to the maintenance of pump function, the major objective is the eradication of the infecting VGS. The American Heart Association's guidelines for the treatment of native valve infection by penicillin susceptible VGS (MIC <0.1 µg/mL) including S. bovis consists of four-week therapy with a single beta-lactam agent or two-week therapy with a combination of a beta-lactam agent plus aminoglycoside.

<table>
<thead>
<tr>
<th>Table 1: Common Antibiotic Therapies in the Treatment of Periodontitis</th>
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<tr>
<td><strong>Antimicrobial Agent</strong></td>
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<tr>
<td>Metronidazole</td>
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<tr>
<td>Clindamycin</td>
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<tr>
<td>Doxycycline or minocycline</td>
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<tr>
<td>Ciprofloxacin</td>
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<tr>
<td>Azithromycin</td>
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<tr>
<td>Metronidazole+amoxicillin</td>
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<td>Metronidazole+ciprofloxacin</td>
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Adapted from Academy report: Research, Science and Therapy Committee and approved by the Board of Trustees of the American Academy of Periodontology [49].
Francioli et al. have recently reported successful treatment of VGS endocarditis using a 2-week course of ceftriaxone 2g plus netilmicin at dose of 4 mg/kg [54]. Although the guidelines recommended four-week single beta-lactam agent for the elderly, it is generally preferred to treat with combination therapy except in patients with impaired renal function or in the presence of high level aminoglycoside resistance (MIC >500 µg/mL). The overall bacteriologic failure rate is extremely low [55]. In patients who have been ill for longer than 3 months before therapy, relapse rate is higher and a longer duration of therapy is recommended [56].

Successful oral penicillin plus intramuscular aminoglycoside therapy for penicillin susceptible VGS has been reported [57]. This form of therapy should only be tried in a setting where blood levels can be monitored, and patient compliance can be assured. For patients who have allergy to beta-lactam agents, vancomycin may be used. In younger patients, vancomycin clearance may be faster, therefore it may be prudent to know the vancomycin half-life and adjust the dosing interval [53]. For patients with native valve endocarditis due to strains with MIC between 0.1 and 0.5µg/mL, American Heart Association, recommends
combining 4 weeks treatment with penicillin plus 2 weeks of aminoglycoside therapy. If high level resistance to aminoglycoside is present or synergism with aminoglycoside cannot be demonstrated, vancomycin should be used [53]. Based on the study by Alcaide et al., another option is to check for the susceptibility to cefotaxime, ceftriaxone, and imipenem. If the MIC is low, any of these agents may be considered [37]. If the MIC is high, vancomycin should be used. However, no official recommendation is available for the treatment of these highly betalactam resistant organisms. Experimental studies using vancomycin plus gentamicin have shown that this combination is effective against strains that are penicillin resistant [58]. Patients infected with anginosus group streptococci are at a higher risk for complications, therefore a higher dose of penicillin is recommended [59].

References


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