JKIMSU, Vol. 5, No. 4, October-December 2016 **ISSN 2231-4261**

REVIEW ARTICLE

Susceptibility, Resistance and Treatment Strategy for Infections Caused by Viridans Group Streptococci - A Review

Shree V. Dhotre[1], Vilas L. Jahagirdar[2], Milind S. Davane[3], Basavraj S. Nagoba[3]

[1]Department of Microbiology, M. M. Patel Public Charitable Trust's, Ashwini Medical College & Hospital, Kumbhari, Solapur- 413006 (Maharashtra) India, [2]Department of Microbiology, Government Medical College, Miraj-416410 (Maharashtra) India, [3]Department of Microbiology, Maharashtra Institute of Medical Sciences & Research, Latur- 413736 (Maharashtra) India

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 micro-circulation. 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].

Table 1: Common Antibiotic Therapies in the Treatment of Periodontitis

Antimicrobial Agent	Dosage in Adult
Metronidazole	500 mg/tid/8 days
Clindamycin	300 mg/tid/8 days
Doxycycline or minocycline	100-200 mg/qd/21 days
Ciprofloxacin	500 mg/bid/8 days
Azithromycin	500 mg/qd/4-7 days
Metronidazole+amoxicillin	250 mg each/tid/8 days
Metronidazole+ciprofloxacin	500 mg each/bid/8 days

Adapted from Academy report: Research, Science and Therapy Committee and approved by the Board of Trustees of the American Academy of Periodontology [49].

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 reticulo-endothelial 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 VG*S*. 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 2: Antibiotic Prophylactic Regimens for Bacteremia Inducing Dental Procedures

Situation	Agent	Regimen—Single Dose 30-60 Minutes before Procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin OR cefazolin or ceftriaxone	2 g IM Or IV* 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin via oral route	Cephalexin**† OR Clindamycin OR Azithromycin or clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin via oral route, and unable to take oral medication	Cefazolin or ceftriaxone† OR Clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

**Im—intramuscular; IV—intravenous, ** or other first or second generation oral cephalosporin in equivalent adult or pediatric dosage, † Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema or urticaria with penicillins or ampicillin. Adapted from Wilson et al. Prevention of infective endocarditis: guidelines from the American Heart Association [53].*

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 beta-lactam 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

1. Lucas VS, Beighton D, Roberts GJ. Composition of oral streptococcal flora in healthy children. *J Dent* 2000; 28(1):45-50.
2. Albandar JM. Tinoco EM. Global epidemiology of periodontal diseases in children and young persons. *Periodontol 2000* 2002; 29:153-176.
3. Noack B, Genco RJ, Trevisan M, Grossi S, Zambon JJ, De Nardin E. Periodontal infections contribute to elevated systemic C-reactive protein level. *J Periodontol* 2001; 72(9):1221-27.
4. Lockhart PB, Brennan MT, Thornhill M, Michalowicz BS, Noll J, Bahrani-Mougeot FK, Sasser HC. Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. *J Am Dent Assoc* 2009; 140(10): 1238-44.
5. Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. *Circulation* 2008; 117(24):3118-25.
6. Lucas VS, Gafan G DS, Roberts GJ. Prevalence, intensity and nature of bacteraemia after toothbrushing. *J Dent* 2008; 36(7):481-87.
7. Seymour GJ, Ford PJ, Cullinan MP, Leishman S, Yamazaki K. Relationship between periodontal infections and systemic disease. *Clin Microbiol Infect* 2007; 13(Suppl 4): 3–10.
8. Bouvet A. Invasive infections by *Streptococcus Viridans* (oral Streptococci) excluding Pneumococci. *Presse Med* 1997; 26(37):1768-73.
9. Westling KP, Ljungman A, Thalme and Julander. Streptococcus Viridans septicemia: a comparison study in patients admitted to the departments of infectious diseases and hematology in a university hospital. *Scand J Infect Dis* 2002; 34(4): 316-9.
10. Wilson WR, Karchmer AW, Dajani AS, Taubert KA, Bayer A, Kaye D, *et al*. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci and HACEK micro-organisms. American Heart Association *JAMA* 1995; 274(21):1706-13.
11. Dajani AS, Taubert KA, Wilson W, Bogler AF, Bayer AF, Ferrierip *et al*. Prevention of bacterial endocarditis. recommendations by the American Heart Association. *JAMA* 1997; 128(8): 1142-51.
12. Boon NA and Fox KAA. Diseases of Cardiovascular System P. In C.R.W. Edwards, I.A.D. Bouchier, C. Haslet, and E.R. Chilvers (ed.) Davidson's Principle and Practice of Medicine. 17th ed. Curchill Livingstone New York N.Y. 1995: 191-312.
13. Douglas CWI, Heath J, Hampton, KK, Preston, FE. Identity of viridans streptococci isolated from cases of infective endocarditis. *J Med Microbiol* 1993; 39(3):179-82.
14. Drangsholt MT. A new causal Model of dental diseases associated with endocarditis. *Ann Periodontol* 1998; 3(1):184-96.
15. Moreillon P. Endocarditis and Endocarditis in infectious disease. Armstrong D., Cohen J. eds Harcourt publisher London, 1999.
16. Ito HO. Infective endocarditis and dental procedures: evidence, pathogenesis, and prevention. *J Med Invest*. 2006; 53(3-4):189-98.
17. Bagg J, MacFarlane TW, Poxton IR, Miller CH, Smith AJ. Dental Caries. In Essentials of microbiology for dental students. Oxford University Press, Oxford. 1999: 248-58.

18. Koneman EW, Allen SD, Janda WM, *et al*. The gram-positive cocci: Part II. Streptococci, enterococci, and the "streptococcus-like" bacteria. In Color Atlas and Textbook of Diagnostic Microbiology, 5th ed. Philadelphia, JB Lippincott, 1997.
19. Johnson C, Tunkel AR. *Viridans streptococci*, Groups C and G *streptococci*, and *Gemella morbillorum*. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 6th ed. 2005; 2434-51.
20. Enting RH, de Gans J, Blankevoort JP, Spanjaard L. Meningitis due to viridans streptococci in adults. *J Neurol* 1997; 244(7):435-38.
21. Cabellos C, Viladrich PF, Corredoira J, Verdaguer R, Ariza J, Gudiol F. Streptococcal meningitis in adult patients: current epidemiology and clinical spectrum. *Clin Infect Dis* 1999; 28(5):1104-08.
22. Pratter MR, Irwin RS. Viridans streptococcal pulmonary parenchymal infections. *JAMA* 1980; 243(24): 2515-17.
23. Marrie TJ. Bacteraemic community-acquired pneumonia due to viridans group streptococci. *Clin Invest Med* 1993; 16(1): 38-44.
24. Kim SJ, Uh Y, Jang IH, Lee KS, Park SD, Yoon KJ. Evaluation of the MicroScan MICroSTREP Plus Antimicrobial Panel for Testing ß-Hemolytic Streptococci and Viridans Group Streptococci. *Korean J Lab Med* 2011; 31(3):185-90.
25. Azavedo JCSDE, Trpeski L, Matsumura S. In vitro activities of fluoroquinolones against Antibiotic-resistant blood culture isolates of viridans group streptococci from across Canada. *Antimicrob Agents Chemother* 1999; 43(9):2299–301.
26. Prabhu RM, Piper KE, Baddour LM, Steckelberg JM, Wilson WR, Patel R. Antimicrobial susceptibility patterns among viridans group streptococcal isolates from infective endocarditis patients from 1971 to 1986 and 1994 to 2002. *Antimicrob Agents Chemother* 2004; 48(11):4463–5.
27. Han XY, Kamana M, Rolston KVI. Viridans Streptococci isolated by culture from blood of cancer patients: clinical and microbiologic analysis of 50 cases. *J Clin Microbiol* 2006; 44(1):160–5.
28. Percin D, Bozdoğan B, Ayangil D, Sümerkan B, Appelbaum PC. Molecular epidemiology and antibacterial susceptibility of streptococci isolated from healthy children attending day care units. *Balkan Med J* 2011; 28:414–9.
29. Doern GV, Ferraro MJ, Brueggemann AB, Ruoff KL. Emergence of high rates of antimicrobial resistance among viridans group streptococci in the United States. *Antimicrob Agents Chemother* 1996; 40(4): 891-4.
30. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; Twenty-third informational supplement. *CLSI document M100-S23* 2013; 32(3): 180-120.
31. Barenfanger J, Short MA, Groesch AA. Improved antimicrobial interventions have benefits. *J Clin Microbiol* 2001; 39(8):2823-8.
32. Kerremans JJ *et al*. Rapid identification and antimicrobial susceptibility testing reduce antibiotic use and accelerate pathogen-directed antibiotic use. *J Antimicrob Chemother* 2008; 61(2): 428-35.
33. Tuohy M, Washington JA. Antimicrobial susceptibility of Viridans streptococci. *Diagn Microbiol Infect Dis* 1997; 29(4): 277-80.
34. Guiot HFL, Corel JA, Vossen JMJJ. Prevalence of penicillin resistant viridans streptococci in healthy children and in patients with malignant haematological disorders. *Eur J Clin Microbiol Infect Dis* 1994; 13(8): 645-50.
35. Chalkley L, Schuster C, Potgieter E, Hakenbeck R. Relatedness between Streptococcus pneumoniae and viridans streptococci: transfer of penicillin resistance determinants and immunological similarities of penicillin binding proteins. *FEMS Microbiol Lett* 1991; 69(1): 35-42.
36. Potgieter E, Chalkley LJ. Relatedness among penicillin-binding protein 2b genes of Streptococcus mitis, Streptococcus oralis and Streptococcus pneumoniae. *Microbiol Drug Resist* 1995; 1(1):35-42.
37. Alcaide F, Linares J, Pallares R, *et al*. In vitro activities of 22 beta-lactam antibiotics against penicillin resistance and penicillin-susceptible viridans group stretptococci isolated from blood. *Antimicrob Agents Chemother* 1995; 39(10): 2243-47.
38. McWhinney PHM, Patel S, Whiley RA, Hardie JM, Gillespie SH, Kibbler CC. Activities of potential therapeutic and prophylactic antibiotics against blood culture isolates of viridans group streptococci from neutropenic patients receiving ciprofloxacin. *Antimicrob Agents Chemother* 1993; 37(11): 2493-95.
39. Maskell JP, Sefton AM, Cannall H, Kerawala C, Seymour A, Sun ZM, Williams JD. Predominance of resistant oral streptococci in saliva and the effect of a single course of josamycin or erythromycin. *J Antimicrob Chemother* 1990; 26(4): 539-48.
40. Clermont D, Horaud T. Identification of chromosomal antibiotic resistance genes in Streptococcus anginosus ("S. milleri"). *Antimicrob Agents Chemother* 1990; 34(9):1685-90.

41. Luna VA, Coates P, Eady EA, Cove JH, Nguyen TTH, Roberts MC. A variety of Gram-positive bacteria carry mobile mef genes. *J Antimicrob Chemother* 1999; 44(1):19-25.
42. Poutanen SM, De Azavedo J, Willey BM, Low DE, MacDonald KS. Molecular characterization of multidrug resistance in Streptococcus mitis. *Antimicrob Agents Chemother* 1999; 43:1505-7.
43. Pfaller MA, Jones RN. In vitro evaluation of contemporary beta-lactam drugs tested against viridans group and beta-haemolytic streptococci. *Diagn Microbiol Infec Dis* 1997; 27(4):151-54.
44. Slots J. Selection of antimicrobial agents in periodontal therapy. *J Periodont Res* 2002; 37(5):389-398.
45. Sakellari D, Goodson JM, Kolokotronis A, Konstantinidis A. Concentration of 3 tetracyclines in plasma, gingival crevice fluid and saliva. *J Clin Periodontol* 2000; 27(1):53-60.
46. Slots J, Ting M. Systemic antibiotics in the treatment of periodontal disease. *Periodontol 2000* 2002; 28:106–176.
47. Pallasch TJ. Pharmacokinetic principles of antimicrobial therapy. *Periodontol 2000* 1996; 10:5-11.
48. Ellen RP, McCulloch CAG. Evidence versus empiricism: Rational use of systemic antimicrobials for treatment of periodontitis. *Periodontol 2000* 1996; 10:29-44.
49. Research, Science and Therapy Committee: Academy Report. Systemic Antibiotics in Periodontics. *J Peridontol* 2004; 75:1553–65.
50. Heimdahl A. et al. Detection and quantitation by lysis-filtration of bacteremia after different oral surgical procedures. *J Clin Microbiol* 1990; 28(10):2205-9.
51. Gould FK, Elliott TS, Foweraker J, Fulford M, Perry JD, Roberts GJ, Sandoe JA, Watkin RW, *et al*. Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob. Chemother* 2006; 57(6):1035–1042.
52. Richey RD, Wray and Stokes T. Prophylaxis against infective endocarditis: summary of NICE guidance. *BMJ* 2008; 336(7647):770-1.
53. Wilson W *et al*. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; 116(15):1736–54.
54. Francioli P, Ruch W, Stamboulian D, and the International Infective Endocarditis Study Group. Treatment of streptococcal endocarditis with a single daily dose of ceftriaxone and netilmicin for 14 days: a prospective multicenter study. *Clin Infect Dis* 1995; 21(6):1406-1410.
55. Scheld WM, Sande MA. Endocarditis and intravascular infections. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. New York: Churchill Livingstone, 1995:740-783.
56. Phair JP, Tan JS. Therapy for streptococcus viridans endocarditis. In: Kaplan EL, Taranta AV, eds. Infective Endocarditis. Dallas: American Heart Association, 1977:55-57.
57. Tan JS, Terhune CA, Kaplan S, Hamburger M. Successful two-week treatment schedule for penicillin susceptible streptococcus viridans endocarditis. *Lancet* 1971; 2(7738):1340-1343.
58. Martinez F, Martin-Luengo F, Garcia A, Valdes M. Treatment with various antibiotics of experimental endocarditis caused by penicillin-resistant *Streptococcus sanguis*. *European Heart J* 1995; 16(5):687-91.
59. Baddour LM *et al*. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation* 2005; 111(23):394- 434.

[*]***Author for Correspondence:*** *Dr. B. S. Nagoba, Assistant Dean (Research & Development), Maharashtra Institute of Medical Sciences & Research, Latur-413 531, Maharashtra, India*
Email: dr_bsnagoba@yahoo.com, bsnagoba@gmail.com Cell: 9423075786