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MULTIPLE ANTIBIOTIC RESISTANCE IN VIRIDANS GROUP STREPTOCOCCI ISOLATED FROM ORAL CAVITY OF APPARENTLY HEALTHY INDIVIDUALS

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ABSTRACT

A total of 525 isolates belonging to 10 different species of Viridans Group Streptococci (VGS) viz., *Streptococcus anginosus* (196), *S. morbillorum* (85), *S. mutans* (76), *S. mitis* (60), *S. uberis* (34), *S. intermedius* (24), *S. sanguis* (20), *S. oralis* (18), *S. salivarius* (07) and *S. acidominimus* (05) were used for determination of antibiotic susceptibility pattern against 24 different antibiotics by standard disc diffusion method. Overall, the highest incidence of resistant strains was noted against Erythromycin (48.4%), followed by Streptomycin (39.0%), Gentamicin (39.0%), Doxycycline (36.6%), Tobramycin (33.1%), Amoxicillin (32.4%), Tetracycline (31.6%), Levofloxacin (31.2%), Chloramphenicol (26.1%), Rifampicin (25.3%), Ciprofloxacin (24.8%), Penicillin (22.5%), Vancomycin (21.7%), Clarithromycin (21.1%), Clindamycin (19.0%), Azithromycin (16.6%), Linezolid (4.0%), Trimethoprim (2.7%), Ceftazidime, Cefazolin, Cefotaxime (2.0%, in each case), Teicoplanin (1.5%), Cephalothin (1.7%) and Imipenem (1.1%). The present study also determined the incidence of multi-drug resistant (MDR) strains among VGS, only 5.5% isolates were found resistant to a single antibiotic, 4.0% isolates were resistant to 2 antibiotics while 41% isolates were resistant to more than 3 antibiotics. The emergence of multi-drug resistance was also noted with respect to species. The highest incidence rate was found among *S. salivarius* (85.7%, 6/7), followed by *S. mutans* (80.3%, 61/76), *S. acidominimus* (80.0%, 4/5), *S. uberis* (79.4%, 27/34), *S. intermedius* (79.2%, 19/24), *S. morbillorum* (70.6%, 60/85), *S. oralis* (61.1%, 11/18), *S. anginosus* (50.0%, 98/196), *S. sangius* (45.0%, 9/20) and *S. mitis* (41.7%, 25/60).

Key words: Viridans group streptococci, multi-drug resistance, Penicillin.

INTRODUCTION

Numerous versatile microorganisms are inhabitant of human oral cavity. The most prominent flora of human and animal oral cavity belongs to *Staphylococci* spp., *Streptococci* spp., *Lactobacilli* spp., *Peptostreptococci* spp., *Veillonella* spp., *Actinomyces* spp., *Haemophilus* spp., *Bacteroides* spp., *Fusobacterium* spp., *Treponema* spp., and *Candida albicans* (Belda-Ferre *et al.*, 2012; Maeda *et al.*, 2011). Among streptococci, the most significant bacteria in the oral cavity are the Viridans Group Streptococci (VGS) comprising mutans group [*Streptococcus mutans* (Serotype c, e, f), *S. sobrinus* (Serotype d, g), *S. rattus* (Serotype b, *S. ratti*), *S. downei* (Serotype h), *S. cricetus* (Serotype a), *S. macacae* (Serotype c) and *S. hyovaginalis*]; sanguinis group [*S. sanguis* (*S. sanguinis*), *S. parasanguis* (*S. parasanguinis*) and *S. gordonii*]; mitis group [*S. mitis*, *S. crista* (*S. cristatus*), *S. oralis* (*S. sanguis II*), *S. infantis* and *S. peroris*]; anginosus group [*S. intermedius*, *S. constellatus* and *S. anginosus*]; salivarius group [*S. salivarius*, *S. thermophilus* and *S. vestibularis*] and three members, S. *uberis*, *S. morbillorum* (*Gemella morbillorum*) and *S. acidominimus* which have not been included in any group of VGS (Gillespie and Hawkey, 2006; Maeda *et al.*, 2011). VGS are reported to cause oral and extra-oral infections. Among prominent oral infections such as dental caries, perioral abscess, gingivitis, recurrent aphthous stomatitis, dentoalveoler infections (Matijevic, *et al.*, 2009), suppurative oral and maxillofacial infections (Bancescu *et al.*, 2012; Volk *et al.*, 1991) and periodontal diseases are caused by VGS (Belda-Ferre *et al.*, 2012; Hardie, 1992). As a result of poor hygiene, presence of some dental diseases or dental manipulations involving gingival margin, these VGS enter the blood stream resulting in transient bacteremia which causes subacute bacterial endocarditits (Infective endocarditis) (Presterl *et al.*, 2005). Other extra-oral infections are sepsis (West *et al.*, 1998), pneumonia (Smith, 2002), myocardial and cerebral infarction, nosocomial bloodstream infections (BSIs), spontaneous bacterial peritonitis (SBP) (McCue, 1983), septicemia (Westling *et al.*, 2004), bacteremia (Ergin, 2010), brain and liver abscess (Fang *et al.*, 2012; Baron *et al.*, 1994), Reiter syndrome (Huang *et al.*, 2000), septic arthritis, acute and chronic urethritis, fatal shock syndrome (Steiner *et al.*, 1993), meningitis (Harrell and Hammes, 2012; Shenep, 2000), cardiovascular diseases (Nakano and Kuramitsu, 1992), acute bronchopulmonary infections (Cade *et al.*,, 1999), septic cavernous sinus thrombosis, pleural empyema (Hocken and Dussed, 1985), empyema thoracis (Jerng *et al.*, 1997), lung abscess, congenital heart disease (Suvarna *et al.*, 2011) and brain stem abscess (Pontine abscess) (Muller-Richter *et al.*, 2007). Among extra-oral diseases caused by VGS, subacute bacterial endocarditis is the most prevalent disease throughout the world (Joel and Ramteke, 2011).

The antibiotics are commonly used systematically and locally for the treatment of different type of bacterial diseases including dental associated infections. However, an extensive use and misuse of antibiotics promotes development of multi-drug resistance (MDR) among bacteria which is considered a public health as well as socioeconomic problem. The MDR-strains have elevated the morbidity and mortality rates and also increased the cost of health care services which has turned into a serious worldwide problem (Fang *et al.*, 2012). In view of the emergence of MDR organisms, the current study is targeted to determine the antibiotic susceptibility pattern of VGS isolated from the oral cavity of apparently healthy subjects.

MATERIAL AND METHODS

ISOLATES

The VGS were isolated from oral cavity (gums, teeth and tongue) of 552 apparently healthy subjects of different age groups from both sexes. A total of 525 isolates belonging to 10 different species of VGS viz., *Streptococcus anginosus* (196), *S. morbillorum* (85), *S. mutans* (76), *S. mitis* (60), *S. uberis* (34), *S. intermedius* (24), *S. sanguis* (20), *S. oralis* (18), *S. salivarius* (07) and *S. acidominimus* (05) were used for the determination of antibiotic susceptibility pattern against 24 different antibiotics.

MAINTENANCE OF ISOLATES

All the isolates of VGS were maintained on sodium azide blood agar slants (Andrews, 2005).

ANTIBIOTIC SUSCEPTIBILITY TEST

A total of 24 different antibiotics were used for evaluation of antibiotic susceptibility by disc diffusion method (Table 1). Tryptic Soy Broth (TSB) was used for the preparation and standardization of bacterial inoculum and Tryptic Soy agar (TSA) medium was used for the determination of antibiotic susceptibility pattern. A sterile cotton-wool swab was dipped into the standardized bacterial inoculum and the excess amount of broth was removed by pressing and rotating the swab against the side of the wall of tube. The swab containing bacterial inoculum was spread evenly all over the surface of the TSA medium. Antibiotic discs were firmly placed on the surface of inoculated medium plates by using a sterile forcep. All the inoculated petri plates containing discs were incubated at 35-37°C for 18- 24 hours (Andrews, 2005).

INTERPRETATION OF RESULTS

A standard criterion of interpretation as recommended by the Clinical and Laboratory Standards Institutes (CLSI) was used for all antibiotics (Andrews, 2005). The diameter of inhibitory zone was measured to the nearest millimeter and the susceptibility or resistance was interpreted on the basis of criteria mentioned in the Table 1.

RESULTS AND DISCUSSION

In the present study, 525 isolates belonging to 10 different species of VGS viz., *Streptococcus anginosus* (196), *S. morbillorum* (85), *S. mutans* (76), *S. mitis* (60), *S. uberis* (34), *S. intermedius* (24), *S. sanguis* (20), *S. oralis* (18), *S. salivarius* (07) and *S. acidominimus* (05) were used for the determination of antibiotic susceptibility pattern against 24 different antibiotics. The results of antibiotic susceptibility are shown in Fig. 1, Table 2 and 3.

In the present study, overall, 61.1% of different species of VGS were found resistant while only 38.9% were susceptible against all tested antibiotics. Among 525 isolates of VGS, relatively the highest emergence of resistance was noted against Erythromycin (48.4%, 254/525), followed by Streptomycin (39.0%, 205/525), Gentamicin (39.0%, 205/525), Doxycycline (36.6%, 192/525), Tobramycin (33.1%, 174/525), Amoxicillin (32.4%, 170/525), Tetracycline (31.6%, 166/525), Levofloxacin (31.2%, 164/525), Chloramphenicol (26.1%, 137/525), Rifampicin (25.3%, 133/525), Ciprofloxacin (24.8%, 130/525), Penicillin (22.5%, 118/525), Vancomycin (21.7%, 114/525), Clarithromycin (21.1%, 111/525), Clindamycin (19.0%, 100/525), Azithromycin (16.6%, 87/525), Linezolid (4.0%, 21/525), Trimethoprim (2.7%, 14/525), Ceftazidime, Cefazolin, Cefotaxime (2.0%, 10/525), Teicoplanin (1.5%, 08/525), Cephalothin (1.7%, 09/525) and Imipenem (1.1%, 06/525) (Table 2). The results of present study are not supported by earlier findings of Doern *et al.,* (1996) who reported the emergence of high-level resistance towards Cephalosporins, Phenicols, Penicillin, Tetracyclines, beta- lactam and other classes of antibiotics. The reason might be the difference in origin or source of isolation of tested species, variability among species and number of isolates used in the study. Doern *et al.,* (1996) determined antibiotic susceptibility among VGS isolated from different clinical specimens (blood, urine and pus) whereas in the present study VGS were isolated from oral cavity of apparently healthy subjects. In the present study, the distribution of multi-drug resistant strains was also noted (Table 3). Comparatively, out of 525 isolates, only 204 (38.9%) isolates were found susceptible to all antibiotics and 29 (5.5%) isolates were found resistant to single antibiotic, 21 (4.0%) to two, 33 (6.3%) to three, 17 (3.2%) to four, 13 (2.5%) to five, 26 (5.0%) to six, 15 (2.9%) to seven, 10 (2.0%) to eight, 22 (4.2%) to nine, 09 (1.7%) to ten, 11 (2.1%) to eleven and sixteen (in each case), 14 (2.7%) to twelve, 31 (6.0%) to thirteen, 15 (2.9%) to fourteen, 21 (4.0%) to fifteen, 10 (2.0%) to seventeen, 04 (0.8%) to eighteen and nineteen (in each case), 1 (0.2%) to twenty and 2 (0.4%) to twenty one and twenty four antibiotics (Table 3).

Table 1. Interpretation chart of used antibiotics.

S.No,	Name and classes of antibiotics	Abbreviation	Disc Potency (μg)	Diameter of Zone of Inhibition (millimeter)		
				Susceptible	Intermediate	Resistant
	Cephalosporins					
1	Cephalothin	CF	30	≥18	15-17	≤14
2	Cefazolin	CZ	2	≥18	15-17	≤14
3	Cefotaxime	CTX	10	≥23	15-22	≤14
4	Ceftazidime	TAZ	10	≥18	15-17	≤14
	Phenicols					
5	Chloramphenicol	CHL	10	≥18	13-17	≤12
	Lincosamides					
6	Clindamycin	CLI	2	≥21	15-20	≤14
	Pyrimidine analogs					
7	Trimethoprim	TMP	5	≥16	11-15	≤10
	Macrolides					
8	Azithromycin	AZM	15	≥18	14-17	≤13
9	Erythromycin	ERY	5	≥23	14-22	≤13
10	Clarithromycin	CLR	2	≥18	14-17	≤13
	Quinolone					
11	Ciprofloxacin	CIP	1	≥21	16-20	≤15
12	Levofloxacin	LEV	1	≥17	14-16	≤13
	Tetracyclines					
13	Doxycyclines	DOX	30	≥16	13-15	≤12
14	Tetracycline	TET	30	≥19	15-18	≤14
	Aminoglycosides					
15	Gentamicin	GEN	10	≥15	13-14	≤12
16	Streptomycin	STR	10	≥10	7-9	≤12
17	Tobramycin	TOB	10	≥15	13-14	≤12
	Glycopeptides					
18	Teicoplanin	TPN	30	≥14	11-13	≤10
19	Vancomycin	VAN	5	≥17	15-16	≤14
	Pencillins					
20	Pencillin	PEN	10U	≥22	12-21	≤11
21	Amoxicillin	AMX	10	≥15	12-14	≤11
	Other beta lactams					
22	Imipenem	IPM	10	≥16	14-15	≤13
	Miscellaneous					
23	Linezolid	LNZ	10	≥23	19-22	≤20
24	Rifampin	RA	2	≥20	17-19	≤16

The antibiotic resistance pattern was also compared at the species level (Table 2). *S. mutans* is the only species of the mutans group which was isolated in the present study. *S. mutans* is associated with the tooth surface and appears to be the major causative agent of dental caries or tooth decay (Belda-Ferre *et al.,* 2012). It has also been isolated from oral cavity of newborns acquired through maternal transmission (Zhan *et al.,* 2012). They form a very important category in the members of oral VGS due to their ability to synthesize soluble and insoluble extracellular polysaccharides from dietary sucrose (Oh *et al.,* 2011). Glucan producing ability of VGS has considerable importance in the pathogencity (cariogencity) and in the formation of dental plaque in the human oral cavity (Ito *et al.,* 2011). The most significant incidence of resistance was observed against Erythromycin, followed by Gentamicin, Doxycycline and Levofloxacin. It was noted as 80.3% (61/76), 77.6% (59/76), 71.1% (54/76) and

61.8% (47/76), respectively (Table 2). Besides cariogenic role of *S. mutans*, it is also involved in other important extra oral diseases. Among extra-oral diseases, subacute bacterial endocarditis is the most prevalent disease throughout the world. *S. mutans* enters into blood stream due to dental procedure or poor hygiene and result in bacteremia which could progress to sub acute bacterial endocarditis. *S. mutans* is also involved, often in combination with anaerobic or other bacterial strains, in brain and liver abscesses, aspiration pneumonia, acute and chronic urethritis and other suppurative infections (Volk *et al*., 1991). Among these diseases, the most common type of disease caused by *S. mutans* is dental caries and periodontal disorders. Both are related to dental plaque. Dental caries is an infectious disease. It is widespread, multifactorial and expensive to treat (Belda-Ferre *et al*., 2012). It is predominant cause of tooth loss in children and young adults (Joel and Ramteke, 2011).

Table 2A. Antibiotic resistant pattern of different species of viridans group streptococci

Organisms	**Number of Isolates**	**Percentage of isolates resistant to**											
		AZM	**AMX**	**DOX**	**LEV**	**CLR**	**ERY**	**TMP**	**STR**	**LNZ**	**VAN**	**TOB**	**GEN**
S. anginosus	196	6.6 (13)	28.1 (55)	37.2 (73)	38.8 (76)	44.9 (88)	41.3 (81)	2.0 (04)	50.0 (98)	1.0 (02)	27.6 (54)	43.9 (86)	36.2 (71)
S. intermedius	24	4.2 (01)	29.2 (07)	20.9 (05)	37.5 (09)	0	4.2 (01)	0	45.8 (11)	16.7 (04)	66.7 (16)	29.2 (07)	79.2 (19)
S. sanguis	20	15.0 (03)	25.0 (05)	45.0 (09)	30.0 (06)	0	15.0 (03)	0	35.0 (07)	10.0 (02)	40.0 (08)	15.0 (03)	25.0 (05)
S. oralis	18	11.1 (02)	38.9 (07)	38.9 (07)	0	0	61.1 (11)	0	22.2 (04)	5.6 (01)	5.6 (01)	22.2 (04)	38..9 (07)
S. mutans	76	26.3 (20)	35.5 (27)	71.1 (54)	61.8 (47)	13.2 (10)	80.3 (61)	9.2 (07)	39.5 (30)	11.8 (09)	17.1 (13)	11.8 (09)	77.6 (59)
S. mitis	60	16.7 (10)	31.7 (19)	36.7 (22)	21.7 (13)	10.0 (06)	20.0 (12)	3.3 (02)	25.0 (15)	5.0 (03)	11.7 (07)	20.0 (12)	30.0 (18)
S. acidominimus	05	20.0 (01)	40.0 (02)	20.0 (01)	20.0 (01)	0	80.0 (04)	0	40.0 (02)	0	20.0 (01)	40.0 (02)	40.0 (02)
S. morbillorum	85	27.1 (23)	45.9 (39)	0	5.9 (05)	4.7 (04)	70.6 (60)	1.2 (01)	30.6 (26)	0	8.2 (07)	52.9 (45)	9.4 (08)
S. salivarius	07	57.1 (04)	42.9 (03)	85.7 (06)	28.6 (02)	0	85.7 (06)	0	28.6 (02)	0	28.6 (02)	14.3 (01)	100 (07)
S. uberis	34	29.4 (10)	17.7 (06)	44.1 (15)	14.7 (05)	8.8 (03)	44.1 (15)	0	29.4 (10)	0	14.7 (05)	14.7 (05)	26.5 (09)
Total	525	16.5 (87)	32.3 (170)	37.0 (192)	31.2 (164)	21.1 (111)	48.3 (254)	2.7 (14)	39.0 (205)	4.0 (21)	21.7 (114)	33.1 (174)	39.0 (205)

Figures in parenthesis are number of isolates

Table 2B. Antibiotic resistant pattern of different species of viridans group streptococci

Isolates	**Total Number of Isolates**	**Percentage of isolates resistant to**											
		RA	**IPM**	**CHL**	**TAZ**	**TPN**	**CZ**	**CTX**	**PEN**	**TET**	**CLI**	**CF**	**CIP**
S. anginosus	196	33.7 (66)	1.5 (03)	25.5 (50)	2.0 (02)	4.1 (08)	2.1 (04)	1.0 (02)	12.8 (25)	33.2 (65)	11.2 (22)	3.6 (07)	26.0 (51)
S. intermedius	24	33.3 (08)	0	12.5 (03)	8.3 (02)	0	0	0	25.0 (06)	45.8 (11)	29.2 (07)	0	33.3 (08)
S. sanguis	20	30.0 (06)	0	5.0 (01)	0	0	0	0	45.0 (09)	35.0 (07)	45.0 (09)	0	10.0 (02)
S. oralis	18	16.7 (03)	0	5.6 (01)	5.6 (01)	0	5.6 (01)	0	38.9 (07)	22.2 (04)	0	0	5.6 (01)
S. mutans	76	14.5 (11)	4.0 (03)	52.6 (40)	0	0	2.6 (02)	10.5 (08)	31.6 (24)	19.7 (15)	11.8 (09)	0	11.8 (09)
S. mitis	60	5.0 (03)	0	11.7 (07)	0	0	1.7 (01)	0	13.3 (08)	30.0 (18)	41.7 (25)	3.3	33.3 (20)
S. acidominimus	05	20.0 (01)	0	20.0 (01)	0	0	0	0	60.0 (03)	60.0 (03)	0	0	20.0 (01)
S. morbillorum	85	16.5 (14)	0	31.8 (27)	2.4 (02)	0	0	0	5.9 (05)	30.6 (26)	10.5 (09)	0	34.1 (29)
S. salivarius	07	71.4 (05)	0	42.9 (03)	0	0	0	0	57.1 (04)	71.4 (05)	71.4 (05)	0	57.1 (04)
S. uberis	34	47.1 (16)	0	11.8 (04)	8.8 (03)	0	5.9 (02)	0	79.4 (27)	35.3 (12)	41.2 (14)	0	14.7 (05)
Total	525	25.3 (133)	1.1 (06)	26.0 (137)	2.0 (10)	2.0 (08)	2.0 (10)	2.0 (10)	22.4 (118)	31.6 (166)	19.0 (100)	1.7 (09)	25.0 (130)

Figures in parenthesis are number of isolates

TABLE 3 EMERGENCE OF MULTI-DRUG RESISTANCE AMONG VIRIDANS GROUP STREPTOCOCCI

Organisms	Percentage of isolates resistant to different number of antibiotics																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
S. anginosus	5.1	1.0	2.6	2.6	1.5	1.0	2.6	5.0	5.1	0.5	1.5	0.5	12.8	1.5	4.6	2.6	0.5	0.5	0	0.5	0.5	0	0	1.0
(196)	(10)	(02)	(05)	(05)	(03)	(02)	(05)	(01)	(10)	(01)	(03)	(01)	(25)	(03)	(09)	(05)	(01)	(01)		(01)	(01)			(02)
S. intermedius	12.5	8.3	33.3	4.2	0	4.2	0	12.5	4.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(24)	(03)	(02)	(08)	(01)		(01)		(03)	(01)															
S. sanguis	10.0	0	5.0	5.0	0	5.0	0	5.0	5.0	0	5.0	5.0	0	0	0	0	0	0	0	0	0	0	0	0
20)	(02)		(01)	(01)		(01)		(01)	(01)		(01)	(01)												
S. oralis	11.1	5.6	5.6	0	0	5.6	5.6	0	0	0	0	0	5.6	0	0	11.1	0	5.6	5.6	0	0	0	0	0
(18)	(02)	(01)	(01)			(01)	(01)						(01)			(02)		(01)	(01)					
S. mutans	5.3	3.9	1.3	2.6	7.9	17.1	1.3	2.6	5.3	6.6	1.3	2.6	0	5.3	4.6	1.3	1.3	0	1.3	0	1.3	0	0	0
(76)	(04)	(03)	(01)	(02)	(06)	(13)	(01)	(02)	(04)	(05)	(01)	(02)		(04)	(09)	(01)	(01)		(01)		(01)			
S. mitis	0	10.0	3.3	3.3	1.7	6.7	1.7	1.7	0	3.3	1.7	0	1.7	0	1.7	0	1.7	0	3.3	0	0	0	0	0
(60)		(06)	(02)	(02)	(01)	(04)	(01)	(01)		(02)	(01)		(01)		(01)		(01)		(02)					
S. acidominimus	20.0	0	20.0	0	0	0	20.0	0	0	0	0	0	0	20.0	0	0	0	0	0	0	0	0	0	0
(05)	(01)		(01)				(01)							(01)										
S. morbillorum	7.1	2.4	7.1	3.5	1.2	2.4	4.7	1.2	4.7	1.2	4.7	10.6	2.4	4.7	1.2	3.5	8.2	0	0	0	0	0	0	0
(85)	(06)	(02)	(06)	(03)	(01)	(02)	(04)	(01)	(04)	(01)	(04)	(09)	(02)	(04)	(01)	(03)	(07)							
S. salivarius	14.3	0	14.3	0	0	14.3	0	0	14.3	0	14.3	0	0	14.3	14.3	0	0	0	0	0	0	0	0	0
(07)	(01)		(01)			(01)			(01)		(01)			(01)	(01)									
S. uberis	0	14.7	20.6	8.8	5.9	2.9	5.9	2.9	2.9	0	0	2.9	5.9	5.9	0	0	0	0	0	0	0	0	0	0
(34)		(05)	(07)	(03)	(02)	(01)	(02)	(01)	(01)			(01)	(02)	(02)										
Total	5.5	4.0	6.3	3.2	2.5	5.0	2.9	2.0	4.2	1.7	2.1	2.7	6.0	2.9	4.0	2.1	2.0	0.8	0.8	0.2	0.4	0	0	0.4
(525)	(29)	(21)	(33)	(17)	(13)	(26)	(15)	(10)	(22)	(09)	(11)	(14)	(31)	(15)	(21)	(11)	(10)	(04)	(04)	(01)	(02)			(02)

Figures in parenthesis are number of isolates

Another important group of VGS is anginosus group which includes *S. constellatus*, *S. anginosus* and *S. intermedius* (Gillespie and Hawkey, 2006). In the present study, among isolates of *S. anginosus* the most significant incidence of resistant strains was noted against Streptomycin (50.0%, 98/196), followed by Clarithromycin (44.9%, 88/196) and Tobramycin (43.9%, 86/196) (Table 2). *S. anginosus* is significantly associated with purulent infections, brain and liver abscesses in human as compared to other species of VGS (Bancescu *et al*., 2012; Jerng *et al*., 1997). Furthermore, they are also responsible to cause subacute bacterial endocarditis, hepatobiliary, dental and brain infections (Asmah *et al.*, 2009; Murray *et al.*, 2007). Additionally, they can play an important role during transformation of different resistance traits to more pathogenic bacteria like *S. pyogenes* and *S. pneumoniae* and may participate as reservoir of antimicrobial resistance genes (Uh *et al*., 2007).

S. intermedius, a member of anginosus group, was found resistant against Clarithromycin, Trimethoprim, Imipenem, Teicoplanin, Cefazolin, Cefotaxime and Cephalothin. The highest emergence of resistance rate was found against Gentamicin (79.2%, 19/24), followed by Vancomycin (66.7%, 16/24), Streptomycin and Tetracycline (45.8%, 11/24, in each case) (Table 2). *S. intermedius* is a commensal organism and has been reported to be involved in periodontitis and fatal purulent infections such as liver and brain abscesses (Ito *et al.*, 2011). It has also been reported to cause osteomyelitis and has been associated with adult septic cavernous sinus thrombosis (Chang *et al.*, 2003; Calza *et al*., 2000). Another member of anginosus group, *S. contellatus* resembles *S. intermedius* and has been isolated from abdominal, respiratory, gastrointestinal and pelvic sites (Flynn *et al*., 1995). It has also been found in the gingival crevices around the margin of teeth (Peterson *et al*., 2002). Bielecki *et al*., (2000) reported involvement of *S. contellatus* with spontaneous bacterial peritonitis in an HIV patient.

Another group of VGS, sanguinus group consists of *S. sanguis* (*S. sanguinus*), *S. parasanguinus* and *S. gordonii*. *S. sanguis* is a part of dental plaque as a primary colonizer and is associated with the formation of dental plaque (Volk *et al*., 1991). It has been isolated from buccal mucosa (Frandsen *et al*., 1991). It is also associated with periodontal disease, bacterial endocarditis and plays most prominent role in the dental caries. It plays antagonistic role in dental caries (Caufield *et al.*, 2000). *S. parasanguinus*, another member of sanguinus group was previously reported in mitis group. *S. parasanguinus* is not sufficiently discussed in literature. *S. gordonni* is also included in sanguis group. It has been isolated from oropharyngeal mucosa and dental plaque. Like other species of VGS, it has also been reported to be involved in native valve infective endocarditis (Ruoff, 2002). In the present study, only *S. sanguis* was isolated from oral cavity of apparently healthy subjects. None of the isolates of *S. sangius* were inhibited by Clarithromycin, Trimethoprim, Imipenem, Ceftazidime, Teicoplanin, Cefazolin, Cefotaxime and Cephalothin while the highest resistance level was noted against Doxycyclines, Penicillin, Clindamycin (45.0%, 09/20, in each case) and Vancomycin (40.0%, 08/20) (Table 2). Mitis group streptococci, a group of VGS, are part of oropharyngeal microflora of human. This group comprises *S. mitis* (previously known as *S. mitior*), *S. oralis* (previously known as *S. sanguis II*), *S. infantis*, *S. cristatus* and *S. peroris* (Facklam, 2002). They are normal inhabitant of the buccal mucosa and oral cavity but oral cavity is not a preferred site especially for *S. mitis* (Gillespie and Hawkey, 2006). They are responsible to cause bacterial endocarditis (Do *et al*., 2011), nosocomial blood stream infections (Lyytikainen *et al.*, 2004) and bacteremia in immunocompromised and neutropenic cancer patients (Alcaide *et al.*, 1995). Besides, they can cause serious clinical manifestations including pneumonia (Smith *et al.*, 2004), suppurative oral and maxillofacial infections, toxic shock syndrome (Tunkel *et al.*, 2002), encephalopathy and adult respiratory distress syndrome, which cause appreciable and significant mortality (Alcaide *et al.*, 1995). *S. oralis* has the ability to synthesize an enzyme, exo-glycosidase (Sialidase) that helps in multiplication and divisions of *S. oralis* during disease process (Byers *et al.*, 2000). *S. oralis* has also been reported for endocarditis (Ruoff, 2002). Among *S. mitis* isolates, the highest incidence of resistance was found against Clindamycin (41.7%, 25/60) while the highest emergence of resistant isolates of *S. oralis* was noted against Erythromycin. It was noted as 61.1%, (11/18) (Table 2). Notably, none of isolates of *S. oralis* were found resistant to Levofloxacin, Clarithromycin, Trimethoprim, Imipenem, Teicoplanin, Cefotaxime, Clindamycin and Cephalothin (Table 2).

Salivarius group streptococci, another group of VGS, are normal inhabitant of most areas of oral cavity such as tongue, mucosal surfaces and saliva (Cawson, 1991). They are early colonizer in oral cavity of human after birth. *S. salivarius*, a member of salivarius group is rarely responsible to cause any infection in human except dental caries. They are most important members of VGS because of their ability to synthesize an extracellular polysaccharide by using dietary sucrose which is considered the most potent virulence factor (Tamura *et al.*, 2009). It has also been reported from patients of bacterial endocarditis. In case of *S. salivarius*, Gentamicin was the most useful antibiotic as all isolates of *S. salivarius* were susceptible to it. The most prominent incidence of resistant strains was noted against Doxcycline (85.7%, 6/7), Erythromycin (85.7%, 6/7), Rifampicin (71.4%, 3/7), Tetracycline (71.4%, 3/7) and Clarithromycin (71.4%, 3/7) (Table 2).

As compared to other species of VGS, *S. uberis* and *S. morbillorum* have not been studied sufficiently. *S. morbillorum* (Currently known as *Gemella morbillorum*) exhibited 70.6% (60/85) incidence of resistance against

Erythromycin. It has been isolated from oral cavity, vaginal secretions and gastrointestinal tract of human (Condoluci *et al.*, 1995; Egido *et al*., 1995). It is associated with endovascular infections, endocarditis (Ubeda Ruiz *et al.*, 2000) and acute invasive infections such as meningitis, septicemia and septic arthritis (Garavelli, 1990). Recently, involvement of *S. morbillorum* in pleural empyema (Marcos Sanchez *et al.*, 2000), lung abscess and empyema thoracis has been reported (Condoluci *et al.*, 1995). Moreover, it is also associated with retropharyngeal abscess (Pradeep *et al.*, 1997) and pericarditis (Condoluci *et al.*, 1995).

As far as *S. uberis* concerns, it is famous as environmental serological heterogeneous Gram positive streptococci and associated with dairy industries as formidable pathogenic bacteria (Khan *et al.*, 2003). According to Slot (1958) and Schurman *et al.* (1937) *S. uberis* resembled with *Enterococcus* however, recently Lammler (1991), Hahn (1981) and Schleifer (1987) revealed that *S. uberis* is closely similar to genus *Streptococcus* (Khan *et al.*, 2003). It has been isolated from animals such as goats, sheep, pigs, horses, dogs, foxes and buffaloes but occasionally found in human. Mastitis, pyrexia and mammary quarter infections are caused by *S. uberis* (Hillerton and Berry, 2003). The most effective antibiotic against the isolates of *S. uberis* was Penicillin. The incidence of resistant isolates against Penicillin was found as 79.4% (27/34) (Table 2).

Another member of VGS, *S. acidominimus* is normal inhabitant of vaginal tract and skin of calves and also present in raw milk. It is rarely associated with human infections (Baker and Carlson, 2008) however recent literature has documented its isolation from abscess, wound and genital tract of humans (Baker and Carlson, 2008). It is associated with endocarditis, pneumonia (Baker and Carlson, 2008), meningitis, pericarditis (Finkelstein *et al.*, 2003), brain abscess, upper genital tract infections (Cone *et al.*, 2007) and massive ascites (Zhang and Qian, 2004). Besides, it has also been reported to cause bovine fibrinopurulent metritis (Zhang and Qian, 2004). The highest incidence of resistant isolates of *S. acidominimus* was observed against Erythromycin (80.0%, 4/5), followed by Penicillin and Tetracycline (60.0%, 03/5, in each case) (Table 2).

CONCLUSION

There is a need to evaluate the antibiotic susceptibility pattern of VGS periodically against most widely used antibiotics to detect emerging resistance pattern. This will help the clinicians to select the most effective antibiotic against VGS associated infections, reduce the cost of treatment and minimize complications due to infections with antibiotic resistant strains.

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