Chapter 48
Antibiotic Resistance of Non-Pneumococcal Streptococci and Its Clinical Impact

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1 Characteristics of Non-pneumococcal Streptococci

1.1 Viridans Streptococci

Viridans streptococci (VGS) form a phylogenetically heterogeneous group of species belonging to the genus *Streptococcus* (1). However, they have some common phenotypic properties. They are alfa- or non-haemolytic. They can be differentiated from *S. pneumoniae* by resistance to optochin and the lack of bile solubility (2). They can be differentiated from the *Enterococcus* species by their inability to grow in a medium containing 6.5% sodium chloride (2). Earlier, so-called nutritionally variant streptococci were included in the VGS but based on the molecular data they have now been removed to a new genus *Abiotrophia* (3) and are not included in the discussion below. VGS belong to the normal microbiota of the oral cavities and upper respiratory tracts of humans and animals. They can also be isolated from the female genital tract and all regions of the gastrointestinal tract (2, 3). Several species are included in VGS and are listed elsewhere (2, 3). Clinically the most important species belonging to the VGS are *S. mitis*, *S. sanguis* and *S. oralis*.

1.2 Beta-Hemolytic Streptococci

Beta-hemolytic streptococci can be differentiated from the heterogeneous group of streptococci by the pattern of hemolysis on blood agar plates, antigenic composition, growth characteristics, biochemical reactions and genetic analyses. Beta-hemolytic streptococci commonly produce hemolysins, which cause complete lysis (beta-hemolysis) of red blood cells when cultivated on blood agar plates. Non-hemolytic strains can also be pathogenic. Traditional subdividing into serological groups is based on the detection of group-specific antigenic differences in cell wall carbohydrates using the serologic scheme of classification by Lancefield (4). Serogroups A, B, C, D, F and G are those most commonly found in humans (5).

1.3 Group A Streptococcus (Streptococcus pyogenes)

Group A streptococcus (GAS, *Streptococcus pyogenes*) is an important pathogen confined almost exclusively to human hosts. Transmission occurs from persons with acute infections or from asymptomatic carriers usually through hand contact and respiratory droplets, but food- and waterborne outbreaks have also been documented (6).

GAS is a common cause of bacterial infections especially in children of more than 3 years of age, and also in other age groups. Most commonly the diseases are self-limiting, localized infections of the pharynx and skin (e.g. pharyngitis and impetigo). However, invasion especially from the skin can lead to septicaemia or severe deep-seated tissue infections, such as necrotizing fasciitis and myositis. Other clinical manifestations of GAS include scarlet fever, peritonsillar and retropharyngeal abscesses, otitis media, sinusitis, myositis, lymphangitis, meningitis, suppurative arthritis, endocarditis, osteomyelitis, pneumonia, erysipelas, cellulites, streptococcal toxic shock syndrome, vaginitis, and balanitis (7–10). Primary suppurative infections may also lead to serious nonsuppurative sequelae, acute rheumatic fever and acute glomerulonephritis (11, 12).

Serologic typing of the M (13) and T proteins (14) has traditionally been used in epidemiologic typing of GAS (15). Nowadays, molecular typing methods such as *emm* sequence

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D.L. Mayers (ed.), *Antimicrobial Drug Resistance*,
DOI 10.1007/978-1-60327-595-8_48, © Humana Press, a part of Springer Science+Business Media, LLC 2009

typing, multilocus sequence typing, pulse field gel electrophoresis, inversion gel electrophoresis, restriction length polymorphism analysis of the *mga*-regulon (vir-typing) and random amplified polymorphic DNA analysis, have provided more discriminatory power for studying the clonal relationships between GAS strains.

1.4 Group B Streptococcus (Streptococcus agalactiae)

Group B streptococci (GBS, *Streptococcus agalactiae*) is one of the primary causes of bacteremia and meningitis in neonates and infections in pregnant women (16, 17). It is also an important cause of invasive infections in the elderly and in non-pregnant adults with underlying or chronic diseases. The clinical spectrum of invasive GBS disease in adults includes skin and soft tissue infections, primary bacteremia, urosepsis, pneumonia, osteomyelitis, peritonitis, septic arthritis, meningitis, endocarditis, and intravenous catheter infection. Vaginal colonization of non-pregnant and pregnant women is the principal source of GBS. GBS has been classified into different serotypes on the basis of different chain structures of its capsular polysaccharide.

1.5 Groups C and G Beta-Hemolytic Streptococci

Most of the Lancefield group C streptococci (GCS) produce beta-haemolysis on blood agar although non-hemolytic strains also exist. GCS are mainly animal pathogens. Group C beta-hemolytic streptococci have been isolated from human normal microbiota of nasopharynx, skin and genital tract. Of the four group C streptococci species *S. equisimilis* is the most common human isolate (2). Most of the group G streptococci (GGS) are beta-haemolytic. As GCS, they are also found in human normal microbiota of nasopharynx, skin and genital tract. Both GCS and GGS cause pharyngitis and a variety of severe infections in humans (2).

2 Antimicrobial Resistance in VGS

2.1 Beta-Lactam Resistance

Penicillin and beta-lactam resistance in general, among streptococci is mediated by point mutations in the penicillin-binding proteins (PBPs). PBPs are membrane-bound transpeptidases, active-site serine hydrolases, which catalyse cross-linking of the peptidoglycan subunits during the bacterial cell wall synthesis (18, 19). Beta-lactam antibiotics serve as substrates for PBPs. The active-site serine reacts with the beta-lactam ring and generates a covalently linked enzyme-beta-lactame intermediate. This acyl enzyme intermediate is not able to catalyse cross-linking of the peptidoglycan subunits (18). In streptococci there are low- and high-molecular-weight PBPs (20, 21). Both of these enzymes are important for cell wall synthesis, but only the high-molecular-weight PBPs are important for the bacterial killing activity of the beta-lactam antibiotics (19). In VGS there are two kind of high-molecular-weight PBPs: PBP1 (PBP1a and PBP1b) and PBP2 (PBP2a, PBP2b, PBP2x) (20). Homologous molecules can be found from *S. pneumoniae* and naming conventions for PBPs of the VGS are adapted from *S. pneumoniae* (19–21).

VGS with wild-type PBSs are susceptible to beta-lactam antibiotics (22). In order to become resistant, they have to decrease the affinity of beta-lactams to the high-molecular-weight PBPs. This can be achieved by amino acid substitutions in the transpeptidase domain of the PBPs (19, 22). One point mutation can result in slight increase in the penicillin MIC. Normally more than one mutation is needed for intermediate-level beta-lactam resistance. Highly resistant strains have accumulated several mutations in the PBPs. Based on the data obtained from *S. pneumoniae*; these highly resistant strains may also need mutations other than PBP (19). Accumulation of several mutations in the PBPs may also lead to lethal mutations. Streptococci have overcome this problem by horizontal transfer of functional mutated PBP-coding genes or gene fragments. Transformation and subsequent homologous recombination has produced beta-lactam-resistant VGS with mosaic PBP genes. In these mosaics of PBP genes there are gene regions obtained from resistant strains dispersed through the wild-type PBP genes (23).

Penicillin resistance among VGS isolated from blood has been extensively studied (Table 1). These results indicate that low-level penicillin resistance is quite a common character in blood isolates (up to 56%). However, highly resistant VGS strains can also be found, and the resistance rates vary between 2 and 24%. There are small differences in the resistance levels in different countries (Table 1). Only few reports are available of the resistance among VGS isolated from human normal microbiota (33, 35). Penicillin resistance of these VGS strains is at the same level as among the strains isolated from blood samples (Table 1).

VGS strains, that have increased MICs for penicillin, have typically decreased susceptibility to all beta-lactams including piperzillin, cephalosporins and carbapenems (24). Of the third-generation cephalosporins, ceftriaxone is the most active against VGS in vitro (24). The NCCLS resistance

Table 1 Beta-lactam resistance of viridans group streptococci

Number of strains	Isolation site	Antibiotic resistance %[a]						Year	Country[d]	References
		Penicillin R	Penicillin I + R	Ceftriaxone R[c]	Ceftriaxone I + R[c]	Cefepime I+R[c]	Cefepime R[c]			
410	Blood	9	33.6					1988–1993	Spain	(24)
65	Blood	3.1	38.5					1989–1993	Denmark	(25)
352	Blood	13.4	56.3	17(R ≥ 2)	18(S ≤ 0.5)			1993–1994	USA	(26)
98	Blood	9.2	39		23(S ≤ 0.5)			1994–1996	USA	(27)
235	Blood		32.3			12.3(≤0.5)		1997–1999	USA	(28)
438	Blood	5.9	33.8			13.9(≤ 0.5)		1997–1999	America	(28)
62	Cancer patients	11.3	33.9	11.3(R ≥ 2)	16.1(S ≤ 0.5)	24.2(≤0.5)	11.3 (≥2)	1998	USA	(29)
68	Blood	7.4	48.5					1997	USA	(219)
89	Blood	22	39	12.7	26.6	41.9	19.4	1986–1996	Spain	(30, 31)
162	Invasive[b]	10						1995–1997	Taiwan	(32)
45	Non-invasive[b]	16						1995–1997	Taiwan	(32)
161	Normal flora	0	16.8					1999–2001	Finland	(33)
108	Blood	5	29					1998–2001	Finland	(34)
200	Pharyngeal	14.5	44						Greece	(35)
77	Blood	23.4	40.3					1986–1996	Spain	(36)
66	Blood	24.3	36.4					1988–1994	Spain	(37)
191	Blood	7	37	4	8			2000	Canada	(38)
211	Blood	9	38	0(R ≥ 2)	0(S ≤ 0.5)			1988–1991	South Africa	(39)
451	Endocarditis	1.3	13					1996–2000	UK	(40)
418	Blood	6	28	6.5(R ≥ 2)	12.4(S ≤ 0.5)			1995–1997	Canada	(41)
57	Blood	2	21					1995–1998	Germany	(42)

[a] Breakpoints (mg/L) used for calculating the percentage of R (resistant), intermediately resistant (I) and susceptible (S) strains: cefepime S ≤ 1 R ≥ 4; ceftriaxone S ≤ 1 R ≥ 4; penicillin S ≤ 0,125 R ≥ 4

[b] *Invasive* = blood, pleural infusion, ascites, abscess aspirate; non-invasive = pus, urine, and in cancer patients = blood or sterile-site

[c] Old breakpoints that were used in studies, are in parenthesis (mg/L).

[d] America = USA, Canada, Latin America

breakpoint for ceftriaxone was 2 mg/L until 2002 when it changed to 4 mg/L (43, 44). Using the old breakpoint for ceftriaxone, penicillin and ceftriaxone resistance levels are similar (Table 1). In different studies, resistance percentages of VGS for ceftriaxone vary between 0 and 27% (Table 1). As expected, cefotaxime is almost as active as ceftriaxone against VGS although there is not as much resistance data available (24, 34). It is of worth to note that a third-generation cephalosporin, ceftazidime, although very active against various Gram-negative bacteria, is not as active as penicillin, cefotaxime or ceftriaxone against VGS (8, 12). As presented in Table 1, most of the blood isolates have a reduced susceptibility to ceftazidime with up to 70% resistance. Resistance levels of the fourth-generation cephalosporin, cefepime, vary between 11 and 42% (Table 1). However, the new NCCLS breakpoint for cefepime is 4 mg/L and if that is used the highest level of resistance is 19% (30). Whatsoever, all this data indicate that penicillin is in vitro as effective as cephalosporins against VGS although ceftriaxone has, in vitro, lower resistance figures than penicillin if the new NCCLS breakpoints are used (43, 44).

Imipemen, a carbapenem antibiotic, is in vitro active against VGS (45). Most of the VGS strains have low imipenem MIC values, i.e. less than 0.5 mg/L (24, 31). However, strains, highly penicillin resistant, can have elevated MICs (1–2 mg/L) (24). Marron et al., have found that 20% of the VGS blood isolates of neutropenic cancer patients can have imipenem MIC of 1 mg/L or more (31). Similarly, Diekema et al. reported that 11% of VGS strains had imipenem MICs equal to or higher than 0.5 mg/L (29). The problem with imipenem is that there are no NCCLS breakpoints for non-pneumococcal streptococci (44). Streptococci are in vitro highly susceptible to another carbapenem compound, meropenem. Only few resistant strains with MICs as high as 2 mg/L have been found (46).

2.2 Resistance to Macrolides, Lincosamides and Ketolides

Macrolides, ketolides, lincosamides and streptogramin B antibiotics, although having different kind of chemical structure, all have similar although not identical antimicrobial activity against VGS. The resistance mechanisms developed by bacteria against these antimicrobials are also similar. All these antibiotics inhibit protein synthesis by binding to bacterial ribosomes. Macrolides can be divided into different groups according to the number of carbon atoms in their lactone ring. 14- and 15-membered ring macrolides, like erythromycin and azithromycin, have similar antibacterial properties. Sixteen-membered ring macrolides, like spiramycin, differ from 14- and 15-membered ring macrolides in their antimicrobial activity against VGS. Also lincosamides (clindamycin) and streptogramins have some differences in their activity against bacteria, when compared to macrolides.

In streptococci, there are two well-characterised macrolide resistance mechanisms: target site modification and active drug efflux. Target site modification is mediated by methylases encoded by the *erm* (erythromycin ribosome methylation) genes or by mutations at the 23S ribosomal RNA or ribosomal proteins L4 and L22. Methylation of adenine 2058 of the peptidyl transferase loop of 23S rRNA causes resistance to macrolides as well as to lincosamides and streptogramin B antibiotics (47). The active efflux mechanism, encoded by the *mef* (macrolide efflux) genes, is more specific and causes resistance only to 14- and 15-membered-ring macrolides (48). Mutations at the macrolide-binding domains of the 23S ribosomal RNA and at the ribosomal proteins L4 and L22 lower the affinity of macrolides to ribosomes (39). Mutations can cause several different kinds of resistance phenotypes. Both *erm* and *mef* genes can be horizontally transferred between different streptococci (49).

2.3 Erythromycin Resistance

Erythromycin A has similar *in vitro* activity against VGS strains as other 14- and 15-membered ring macrolides including azithromycin (33). The resistance against erythromycin is quite common among clinical VGS isolates. In the blood isolates, the resistance level is between 27 and 40% (Table 2). The VGS strains isolated from normal microbiota (Table 2) are also often resistant to erythromycin, the resistance levels being at the same level as among the blood isolates (33, 50, 53). The most common erythromycin resistance mechanism is mediated by *mef*(A) genes (33, 53). Roughly 70–80% of the erythromycin resistant VGS strains carry *mef*(A) gene and about 16–20% carry *erm*(B) gene (33, 38, 53). However, the situation may vary. There is one report from France, where *erm*(B) gene was reported to be much more common than *mef*(A) gene among blood isolates of VGS (49).

2.4 Clindamycin Resistance

Resistance against clindamycin is much less frequent among blood and normal microbiota VGS than resistance to erythromycin. Resistance figures vary between 2 and 10%. Resistance levels are similar among both blood and the normal microbiota isolates (Table 2). The reason for lower resistance levels

Table 2 Erythromycin, clindamycin, ketolide and tetracycline resistance of viridans group streptococci

		Antibiotic resistance %[a]									
Number of strains	Isolation site	Erythromycin R	Erythromycin I + R	Clindamycin R	Clindamycin I + R	Telithromycin R	Tetracycline R	Tetracycline I + R	Year	Country	References
200	Ooropharynx	38.5	43.5	7.5	8		23	25.5		Greece	(35)
84	Oral and nasal	17								Japan	(50)
161	Normal flora	22.4		3.7		0	27.3		1999–2001	Finland	(33)
108	Blood	27	27	2		0			1998–2001	Finland	(34)
77	Blood	35.1				0			1986–1996	Spain	(36)
66	Blood	34.8	39.4						1988–1994	Spain	(37)
191	Blood	40	42.4	9.9	9.9	0			2000	Canada	(38)
211	Blood							41	1988–1991	South Africa	(45)
90			30						1988–1995	France	(49)
77	Blood	27	31	6.8					1996–1999	Germany	(51)
418	Blood	28	29.2		4		23.4	26.6	1995–1997	Canada	(41)
57	Blood	32					39		1995–1998	Germany	(42)
107				9					1999–2000	Europe	(52)
352	Blood	38.0	40.9				26.4	34.1	1993–1994	USA	(26)
68	Blood		39.7						1997	USA	(27)
438	Blood		39.7		8.4				1997–1999	America	(28)

[a] Breakpoints (mg/L) used for calculating the percentage of R (resistant), intermediately resistant (I) and susceptible (S) strains: erythromycin $S \leq 0{,}25$, $R \geq 1$; clindamycin $S \leq 0{,}25$, $R \geq 1$; telithromycin $S \leq 1$, $R \geq 4$; tetra $S \leq 2$, $R \geq 8$

is that the efflux mechanism mediated by *mef*(A) resistance gene, does not confer resistance to clindamycin(54).

2.5 Ketolide Resistance

Ketolides, represented here by telithromycin – the first ketolide on the market, are new-generation macrolides, in which a 3-keto group replaces L-cladinose in the lactone ring. Ketolides have shown to be in vitro more active than macrolides against the erythromycin-resistant *S. pneumoniae* and *S. pyogenes* strains (55). NCCLS does not yet offer telithromycin breakpoint values for other streptococci than *S. pneumoniae* (44). If the estimation of telithromycin resistance is done based on the breakpoint values of *S. pneumoniae*, telithromycin-resistant clinical VGS strains do not exist (Table 2). The binding of telithromycin to the bacterial ribosomes is much stronger than the binding of the erythromycin. This is the reason why methylation of the ribosomal RNA does not increase the MIC values as much as it does for erythromycin (56). Neither do the Mef(A) efflux pumps transport telithromycin out of the bacterial cell as well as they pump erythromycin. However, in streptococci, Mef(A) efflux does elevate telithromycin MIC when compared to the strains without *mef*(A) gene (55). In every case, telithromycin seems to be the most active macrolide group antimicrobial on the market at the moment.

2.6 Streptogramin Resistance

Quinupristin–dalfopristin (Synercid^{R}), a combination of streptogramin B and streptogramin A antibiotics, is available for intravenous use. It has rather good in vitro activity against VGS. However, resistance rates between different studies vary a lot (Table 3). In some studies, resistant strains have not been found at all, but in other studies 70% of the strains have showed reduced susceptibility and 28% have been resistant (26, 52). Also VGS strains, which have quinupristin–dalfopristin MIC of 16 mg/L have been described (26). Resistance against quinupristin–dalfopristin combination is linked to the streptogramin A (dalfopristin) resistance, so that in order to be resistant against the antibiotic combination, a strain must be resistant to streptogramin A. Streptogramin B resistance is not necessary. Streptogramin A resistance is mediated by *vga*(A), *vga*(B), *lsa* and various *vat* genes. Thus far, these genes have been found in clinical *Staphylococcus* and *Enterococcus* strains, but the presence of the genes in VGS has not been reported (57). Although not studied in detail (26, 37), it is possible that the resistance is mediated by ribosomal mutation like in *S. aureus* (58).

2.7 Tetracycline and Trimethoprim–Sulfamethoxazole Resistance

Tetracycline resistance among VGS is quite common. 23–39% of the strains are tetracycline resistant (33, 41, 45, 53, 59). Tetracycline resistance rates are similar as are the erythromycin resistance rates. Trimethoprim–sulfamethoxazole is not used for treatment of VGS infections but is commonly used for prophylaxis of neutropenic patients (60). Reduced susceptibility against it is quite common among VGS strains (Table 2).

2.8 Fluoroquinolone Resistance

In streptococci, there are two fluoroquinolone resistance mechanisms: mutations at the quinolone resistance-determining regions (QRDRs) of the topoisomerase IV and DNA gyrase molecules, and an efflux mechanism (61–63). In streptococci, toposisomerase IV molecule has two subunits coded by *par*C and *par*E genes. The DNA gyrase has also two subunits GyrA and GyrB coded by corresponding genes. Topoisomerase IV is the primary target for fluoroquinolones in VGS (61). Mutations at the topoisomerase IV genes confer low-level resistance (MIC 4 mg/L). A combination of topoisomerase IV mutations and fluoroquinolone efflux mechanism is needed for high-level fluoroquinolone resistance (MIC of 16 mg/L or more). Fluoroquinolone resistance determinants can be horizontally transferred between VGS and *S. pneumoniae* strains (61, 64–66).

New fluoroquinolones levofloxacin and moxcifloxacin are active against Gram-positive bacteria. Levofloxacin is active against both VGS strains of normal microbiota (33) and blood isolates (38, 41). Only few levofloxacin resistant strains have been found thus far (33, 38, 41). NCCLS does not have interpretive standards for moxifloxacin yet, and therefore resistance rates cannot be determined. However, the activity of the moxifloxacin is somewhat better than that of levofloxacin. MIC_{90} values for moxifloxacin and levofloxacin are 0.25 mg/L and 0.5 mg/L, respectively (38). In addition, all VGS strains studied for their in vitro susceptibility for moxcifloxacin so far have had MIC of equal or less than 2 mg/L (33, 38) (Table 3). Ciprofloxacin is less active than levofloxacin or moxifloxacin. About 8% of the VGS blood isolates are resistant to ciprofloxacin (38).

2.9 Activity of Glycopeptides and Aminoclycosides

Vancomycin, a glycopeptide antibiotic, has retained its activity against VGS. Not a single vancomycin-resistant VGS has been reported thus far (25, 27, 31–33, 40, 51, 59). MICs

Table 3 Fluoroquinolone, quinupristin–dalfopristin and trimethoprim–sulfamethoxazole resistance of viridans group streptococci

		Antibiotic resistance %[a]										
Number of strains	Isolation site	Levofloxacin R	Levofloxacin I + R	Moxifloxacin R	Moxifloxacin I + R	QD R	QD (I + R)	Trim/sulfa (R)	Trim/sulfa (I + R)	Year	Country	References
200	Oropharynx					0	33.8				Greece	(35)
84	Oral and nasal										Japan	(50)
161	Normal flora	1.9	3.1	1.9		13	38.5			1999–2001	Finland	(33)
108	Blood	0	16							1998–2001	Finland	(34)
77	Blood									1986–1996	Spain	(36)
66	Blood					12				1988–1994	Spain	(37)
191	Blood	4.2	2.1	0	2.1			11.0	45.0	2000	Canada	(38)
211	Blood									1988–1991	South Africa	(45)
90										1988–1995	France	(49)
77	Blood						4.1			1996–1999	Germany	(51)
418	Blood	1.3	5.1					13.9	33.7	1995–1997	Canada	(41)
57	Blood					0				1995–1998	Germany	(42)
107						0	5.7			1999–2000	Europe	(52)
352	Blood					27.6	70.1	16.5	33.2	1993–1994	USA	(26)
68	Blood		2.9				14.7			1997	USA	(27)
438	Blood						2.7		20.1	1997–1999	America	(28)

[a] Breakpoints (mg/L) used for calculating the percentage of R (resistant), intermediately resistant (I) and susceptible (S) strains: levofloxacin S ≤ 2, R ≥8; linezolid S ≤ 2; moxifloxacin S ≤ 1, R ≥ 4; quinupristin–dalfopristin (QD) S ≤ 1, R ≥ 4; trimethoprim–sulfamethoxazole (trim/sulfa) S ≤ 0,5/9,5, R ≥ 4/76

for vancomycin are typically between 0.125 and 1 mg/L (27, 30–32, 51) and MIC_{90} values between 0.5 and 1 mg/L (27, 51). Teicoplanin, another glycopeptide antibiotic, is also active against VGS, although there are no NCCLS breakpoints available for this antibiotic (44). MIC_{90} values for teicoplanin are 0.25 mg/L or less (25, 32, 40, 51).

In general, the activity of the aminoglycosides against VGS is limited (67). Aminoglycosides like gentamycin, amikacin, streptogramin and netilmicin, are used in combination with penicillin or a cephalosporin for the treatment infective endocarditis (68) and sepsis in neutropenic patients (69). High-level gentamicin resistance (MIC of 500 mg/L or more) to VGS is very rare. This is true with VGS isolates of blood origin (25, 32, 40) as well as with VGS strains from the normal microbiota (35). MIC values are typically between 0.25 and 96 mg/L (25, 32, 45) and the MIC_{90} values between 0.5 and 32 mg/L (32, 35). However, few high-level aminoglycosides-resistant *S. mitis* strains have been detected. In these strains gentamicin MICs have been as high as 1,000 mg/L (45).

2.10 Activity of Linezolid

Linezolid is an antibacterial agent belonging to the new oxazolidinone group of antibacterials. Oxazolidinones are not related to any other antibacterials in use (70). Linezolid has been used in the treatment of vancomycin-resistant *Enterococcus faecium* infections, hospital-acquired pneumonia and complicated skin infections (71). The activity of linezolid against VGS strains has not been studied well. However, in those few studies the in vitro activity of linezolid has been good. Only one VGS strain of the 298 strains studied have had linezolid MIC of 4 mg/L (38, 52).

3 Antimicrobial Resistance in Beta-Hemolytic Streptococci

3.1 Resistance to Macrolides

3.1.1 Incidence of Macrolide Resistance in GAS

In 1959 Lowburry and Hurst (72) reported the first isolate of erythromycin-resistant GAS from burns of four patients in the United Kingdom. During the following years in Europe, mainly sporadic cases and small epidemics of erythromycin-resistant GAS were reported from the United Kingdom, Sweden, Italy and Spain (72–77). Also in the United States and Canada low proportions, 5% or less, were reported (78–80) except in a study with 22% of erythromycin-resistant GAS in Florida in 1980 (81). In the 1970s the largest outbreak of erythromycin-resistant GAS occurred in Japan, where the proportion of resistant strains increased from 12% in 1971 to 82% in 1977 (82). These strains were characterized as highly resistant (MICs > 100 mg/L) to macrolides and lincomycin and they were often resistant also to tetracycline and chloramphenicol and were exclusively of T12 serotype. In 1985–1987, an increase from 1 to 17.6% in the frequency of erythromycin-resistant GAS was seen in Australia Fremantle area (83). These strains represented different serotypes and exhibited low-level resistance to erythromycin (MICs (2–8 mg/L) and resistance to clindamycin and tetracycline was rare. In 1988–1989 sporadic isolates and family outbreaks with 22% of erythromycin-resistant GAS was reported from the Dundee area in the United Kingdom with predominance of T4M4 serotype (84). Thereafter, in 1990 a nationwide increase of erythromycin-resistant GAS of multiclonal origin was reported from Finland, where the frequencies reached 24%, 20% and 31% among blood culture, pharyngeal and pus isolates, respectively (75). Since the beginning of 1990s increased frequencies has been reported from several countries. Today macrolide resistance in GAS is a worldwide problem. Increased figures include the following frequencies of macrolide-resistant GAS: In Europe, frequencies of 20–29% in 1996–2001 have been reported from Spain (85–87), 15–42% in 1996–2001 in Greece (88–93), 8–14% in Germany in 1996–2001 (94–97), 43–51% in 1997 in Italy (98, 99), 6–10% in 1996–1999 in France (100, 101) and 16–25% in Croatia, Czech Republic and Slovakia (102). An average frequency of 11% of macrolide-resistant GAS in 2000–2001 was recorded in isolates from different parts of Russia; the frequency (25%) was highest among Siberian isolates (103). In Asian countries the frequency of erythromycin-resistant GAS was 53–71% between 1985 and 1998 in Taiwan (104, 105), 41% in 1998 in Korea (106) and 31% in 1998–2000 in Hong Kong (107). In North America, an increase of erythromycin-resistant GAS occurred from 2.1% in 1997 to 14% in 2001 in Toronto, Canada, with a predominace of a M4 serotype clone (108), and from 0% in 1998 to 38–48% in 2000–2001 among school children in Pittsburgh, PA, the United States, where the increase was caused by one single clone of emm6 (M6 serotype) (109). In South America, frequencies of 7% of erythromycin-resistant GAS have been reported from Chile in 1994–1998 (110) and 8% in Argentina (111).

3.1.2 Incidence of Macrolide Resistance in GBS

Resistance to erythromycin has been reported in GBS since 1962. The first description was from the United States (112) and in the same country an increase in the rate of macrolide resistance in GBS from 1.2% among isolates collected in 1980–1993 to 18% in 1997–1998 was reported (113). Increasing frequencies have been reported also from other

countries. In Spain, the frequency of macrolide resistance in GBS increased from 2.5 to 5.6% in 1993–1996 to 14.5–18% in 1998–2001 (114) and in Taiwan from 19% in 1994 to 46% in 1997 (115). Since the end of the 1990s frequencies of 15–21% have been reported in France (116–118), 13–18% in Canada (119, 120), 40% in Korea (121) and 22% in Turkey (122).

3.1.3 Incidence of Macrolide Resistance in GCG and GGS

Macrolide resistance among group C and G streptococci varies a lot among different countries. In Finland resistance has not been very common. 3.6% and 1.0% of the GCS have been resistant to erythromycin and clindamycin, respectively. The most common macrolide resistance mechanism has been *mef*(A) (123). Similarly 3.5% and 0.3% of the GGS have been resistant to erythromycin and clindamycin, respectively. Most of these strains have had *erm*(TR) resistance gene and only one have had *erm*(B) (123). A bit higher numbers of erythromycin resistance among GCS and GGS have been reported from Turkey. Ergen et al. (23) reported that 1.4% and 16.2% of GCS and GGS were resistant to erytromycin respectively. In Taiwan, erythromycin resistance among GCS and GGS has been more common, 41.7% and 53.3% of the GCS and GGS isolates being erythromycin resistant (124).

3.1.4 Mechanisms of Macrolide Resistance in Beta-Hemolytic Streptococci

The macrolide resistance mechanism by ribosomal methylation encoded my *erm* genes, which was first identified in 1956 in *Staphylococcus aureus* (125), affects macrolides, linconamides and streptogramin B (MLSb) antibiotics. The inducible and constitutive forms of MLSb resistance has been found in beta-hemolytic streptococci since the early 1970s (126–128). The *erm*(B) methylase gene was the only *erm* gene class found in streptococci (129–131) until 1998, when the sequence of *erm*(TR) in *S. pyogenes* was published (132). Its nucleotide sequence is 82.5% identical to staphylococcal *erm*(A) and 58% identical to *erm*(B) and therefore *erm*(TR) belongs to *erm*(A) methylase gene class (133). The inducible or constitutive production of the methylase is dependent on the sequence of the regulatory region situated upstream from the structural methylase gene. It has been shown that in clindamycin, highly resistant mutants of *S. pyogenes* harbouring inducible *erm*(TR) and originally susceptible to clindamycin could be selected by 0.12–1 mg/L concentrations of clindamycin. Resistance was associated to structural changes in the regulatory sequence (134). The phenotypic expression of macrolide resistance in streptococci has been commonly studied by MIC determinations and induction tests including the double-disk test (erythromycin and clindamycin disks placed in vicinity on inoculated agar). Analysis of the Finnish GAS strains isolated in 1990 indicated a new erythromycin resistance phenotype with low- or moderate-level resistance (MICs 1–32 mg/L) to 14- and 15-membered macrolides only (M-phenotype). Thirty-four percent of the studied isolates represented the new phenotype (76). Subsequently, the active efflux mechanism causing this phenotype and the encoding *mef*(A) and *mef*(E) (macrolide efflux) genes were characterized in *S. pyogenes* and *S. pneumoniae* (48, 135, 136) and isolates with this mechanism have been found among beta-haemolytic streptococci in different parts of the world. Countries, where strains of GAS carrying *mef*(A) have been observed to account nowadays for the majority of macrolide-resistant isolates, include Spain (86, 137), Germany (97) and Greece (93), Finland (138), Taiwan (105), the United States (139), Chile (110) and Argentina (111). Predomination of GAS strains carrying *erm*(A) have been reported from Russia, Slovakia, Czech Republic and Croatia (103, 140). In GBS isolates with MLS resistance caused by *erm*(B) and *erm*A predominate in most reports in Canada and other parts of the Western Hemisphere (120, 141), France (116, 117, 142), Spain (114, 143, 144) and Taiwan (115). So far, GBS and GCS with the highest proportion of isolates carrying *mef*(A), 37% and 95%, have been reported from Taiwan and Finland, respectively (145, 146).

In addition to macrolide resistance determinants of *erm*(B), *erm*(A) and *mef*(A), all of which have been found from beta-haemolytic streptococci all over the world, a more rare mechanism, i.e. mutations in the *S. pyogenes* ribosomal protein L4 and in positions 2611 and 2058 of 23S rRNA encoding genes have been recently shown to cause resistance to macrolides. Mutations in positions 2611 and 2058 of the 23S rRNA gene cause resistance to clindamycin and streptogramin B (quinupristin), and also mutation at 2058 to telithromycin (147–149). The presence of a putative novel efflux system associated with *erm*(TR) in *S. pyogenes* has also recently been found (150). Another gene, *mre*A, which was originally described as a macrolide efflux gene in *S. agalactiae* (151), is encoding riboflavin kinase and is found also in erythromycin-susceptible GBS strains (152). Strains with two different macrolide resistance mechanisms (*mef* and *erm*) within a single bacterial cell also exist among GAS and more commonly among GBS (86, 100, 116, 122, 143, 152, 153). The phenotype of these strains is usually that determined by the *erm* gene.

While *mef*(A) and constitutively expressed *erm*(B) and *erm*(A) determinants provide constant and predictable phenotypes in beta-haemolytic streptococci, the phenotypes of inducible expressed *erm*(B) and especially *erm*(A) may vary. Isolates with *mef*(A) have low- or moderate-level resistance

to 14- and 15-membered macrolides and isolates with either of the *erm* genes with constitutive expression have commonly high-level resistance to 14-, 15- and 16-membered macrolides, lincosamides and streptogramin B antibiotics. Inducible strains, especially those with *erm*(A) are often susceptible to 16-membered macrolides and clindamycin, but become highly resistant (MICs > 128 mg/L) to clindamycin and moderately or highly resistant to 16-membered macrolides after induction with subinhibitory concentrations of erythromycin. Also low-level resistance to ketolides can be induced (76, 153). Beta-haemolytic streptococci with inducible *erm*(B) are more commonly associated to high-level resistance to MLSb-antibiotics than isolates with inducible *erm*(A) gene(122, 153). In epidemiological studies the distribution of the resistance mechanisms, the expression of *erm*(A) has more often been inducible and that of *erm*(B) has more often been constitutive in GAS, but among GBS constitutive *erm*(A) and inducible *erm*(B) are also rather common (122, 144), e.g. in Turkey, isolates with inducible *erm*(B) accounted for majority of macrolide resistance in GBS (122).

erm(B) has been shown to be either plasmid or chromosome borne in streptococci (133). In earlier studies conjugative plasmids with the erythromycin resistance determinants were found from group A, B, C and G streptococci and they were shown to transfer by conjugation between streptococcal species (154) and among GAS also by transduction (155, 156). However, most antibiotic resistance genes are nowadays thought to be chromosomal in streptococci, and beta-haemolytic streptococci belonging to groups A, B, C and G have been shown to transfer their chromosomal macrolide resistance determinants by conjugation (152, 157–159). A composite chromosomal conjugative element Tn3701, encoding resistance to erythromycin and tetracycline has been described in GAS (160). Within this element the resistance genes are carried by a Tn*916*-like transposon. The presence of Tn916-Tn1545-like conjugative transposons carrying *erm*(B) and *tet*(M) has been verified later in GAS in other studies (161, 162) and an association of chromosomal *erm*(A) with *tet*(O) has been noted in some strains of GAS (161). An unusual chimeric genetic element containing DNA identical to *Tn*1207.1, a transposable element carrying *mef*(A) in macrolide-resistant *S. pneumoniae*, has also been found in different GAS strains. The mechanism of horizontal transfer in these strains was suggested to be transduction (163). Furthermore, analysis of the genetic environments of the *mef*(A) and *erm*(B) genes by Southern blot experiments have indicated a remarkable heterogeneity of genetic elements carrying these genes, especially *erm*(B), suggesting that different mobile elements can be recruited into the chromosomes of the circulating GAS population and that genetic rearrangement may also occur after a strain has acquired the resistance determinant (162).

3.1.5 Epidemiology of Macrolide-Resistant Beta-Haemolytic Streptococci

A large variety of clones of GAS are mediating macrolide resistance (105, 162, 164, 165). Increased resistance rates may be caused by clonal spread of resistant strains and by horizontal transfer of resistance determinants among the circulating microbial population. Macrolide-resistant GAS of the same clone have been found from different countries and even different continents (164) and the same clones have been found among susceptible isolates, but in general the heterogeneity of GAS clones seems to be lower among resistant than susceptible isolates (162, 164, 165). Single clones of GAS with a macrolide-resistant determinant may become regionally or nationally widely predominant or cause outbreaks (100, 108, 109, 166). For example, in Finland, 82% of isolates of erythromycin-resistant GAS collected all over the country in 1994 expressed the M-phenotype; although multiple clones were found among these isolates, increased regional resistance rates were clearly associated to a clone of T4M4 serotype with *mef*(A) (138, 158). In Taiwan, 33% of the erythromycin-resistant GAS collected in 1992–1995 and 1997–1998 carried constitutive *erm*(B) and were of one clonal origin. Sixty-four percent carried *mef*(A) of which only 23% were of one clonal origin and 16 other clones were found among the rest of these isolates (105). In Russia, 87% of erythromycin-resistant GAS collected in 2000–2001 carried inducible *erm*(TR) and 86% of these were of one clonal origin (103). In the United States, Pittsburgh, isolates carrying *mef*(A) of an emm6 (M6 serotype) clone that caused an epidemic among school children in 2001 were not at all found in the region within a two-month period in April–May in 2002, when the resistance rate was again at a high level (35% of isolates were resistant to erythromycin); this time an emm75 (M75 serotype) clone predominated (109, 139). In Italy, Cresti et al. found that a steady increase of erythromycin-resistant GAS from 9% in 1992 to 53% in 1997 in an area in central Italy was caused by an increase of the proportion of strains carrying inducible and constitutive *erm*(B) and *erm*(TR) determinants. These strains were of multiclonal origin. Correlation of the erythromycin-resistant GAS clones to the heterogeneity of genetic elements carrying the *erm*(B) indicated identical genetic environments of *erm*(B) in clonally unrelated strains, but on the other hand also indicated considerable diversity of these genetic elements both among clonally unrelated and within clonally identical strains (162). The increase of resistance, therefore, includes a complex genetic interaction within circulating streptococcal population and maybe between streptococci and other species (167). Macrolide consumption and different immunity status and other host factors of populations are also possible factors that contribute to this interplay and spread of resistance determinants and resistant clones (168–170).

3.2 Resistance to Clindamycin

Clindamycin resistance is almost exquisitely related to MLS resistance in beta-haemolytic streptococci and is thus mediated by *erm* genes. However, in some studies among GBS the frequency of clindamycin resistance exceeds that of macrolide resistance suggesting another mechanism of clindamycin resistance (114, 121, 171). In one isolate of GBS from Canada, the *linB* gene encoding a lincosamide-inactivating nucleotidyltransferase, was found (120). This gene has previously been identified in *Enterococcus faecium*.

3.3 Resistance to Telithromycin

Resistance to telitromycin is so far rare. Only a few strains, with such high MIC values for telithromycin that they can be considered as resistant, have been isolated. These isolates have constitutively expressed *erm*(B) gene or they have adenine-to-guanine mutation at the position 2058 (55, 149).

3.4 Resistance to Tetracycline

Resistance to tetracycline is common among beta-haemolytic streptococci, especially among macrolide resistant strains. As much as 80% of the beta-haemolytic streptococci in Korea, have been reported to be resistant to tetracycline (121). However, only 16.1% and 0.5% of GAS isolated in Germany and Canada respectively, are shown to be resistant to tetracycline (97, 172). Resistance is caused by tetracycline resistance to ribosomal protection proteins encoded by *tet*(M) or *tet*(O). The *tet*(M) gene is the most widely distributed and is found in GAS often in linkage with *erm*(B) on mobile elements (161), but in GBS it is found both among macrolide-susceptible and macrolide-resistant organisms with all different macrolide resistance determinants (143). *Tet*(O) has been found in GAS carrying chromosomal *erm*(A) or *mef*(A) and it can transfer with or without *erm*(A) and with *mef*(A) (161).

4 Clinical Significance of Resistance

4.1 Infections Caused by VGS

4.1.1 Infective Endocarditis

Infective endocarditis, despite proper treatment, is a life-threatening condition (173). The etiology of infective endocarditis varies according to the age of patients and the clinical nature of the disease (173–176). VGS cause about 28% of all cases (173, 176). The proportion of VGS among native valve endocarditis varies between 11 and 43% (174, 177), and VGS are the most common cause of late prosthetic-valve endocarditis (174, 175, 177). Several different VGS species have been reported to cause endocarditis, *S. sanguis* (68, 174), *S. mitis*, *S. oralis* and *S. gordonii* (177) being the most common species isolated from blood or infected valves. Among intravenous drug abusers, the VGS do not have as important a role as they have in general (174). In the point of view of the treatment and prophylaxis, penicillin resistance is a cause of concern.

The treatment recommendation for infective endocarditis caused by penicillin-susceptible (MIC ≤0.1 mg/L) streptococci is intravenous penicillin G for 4 weeks combined with intravenous gentamicin for 2 weeks (68, 178, 179). Instead of penicillin, ceftriaxone also can be used in combination with gentamicin (68, 178). Streptococcal strains with reduced susceptibility to penicillin (MIC > 0.1 mg/L) can be treated with penicillin G in combination with gentamicin. However, higher dose of penicillin and longer treatment times (4–6 weeks) are recommended (68, 178, 179). Low-level penicillin resistance among VGS isolated either from blood samples or normal microbiota is quite common. From 17 up to 56% show penicillin MIC of 0.125 mg/L or higher (Table 1). Although, there is not much data available in the literature, this low-level penicillin resistance seem not to be a significant clinical problem. Penicillin and aminoglycoside, most often penicillin and gentamicin, combination has synergistic activity against VGS (178). In the literature there are a few documented cases where patients with endocarditis caused by intermediately penicillin-resistant streptococcus were treated successfully with penicillin-gentamicin or in one case a penicillin-streptomycin combination (180). Also penicillin therapy alone followed by cephalotin and vancomycin therapies has been successfully used for treatment of endocarditis caused by low-level penicillin resistant streptococci (180).

High-level penicillin resistance (MIC of 4 mg/L of more) rates among VGS vary between 2 and 24% (Table 1). Among VGS from endocarditis patients, high-level penicillin resistance is rare. Only a few strains with MICs higher than or equal to 4 mg/L, have been reported (40, 179–183). Decreased susceptibility among VGS strains from normal microbiota is common. In the future, penicillin non-susceptible streptococci will more often cause endocarditis infections, and it is also likely that high-level penicillin resistance will increase. This is a challenge because optimal treatment regimens have not yet been determined in endocarditis caused by highly penicillin-resistant VGS. Thus far, all VGS strains tested have been susceptible to vancomycin (68, 178). There are reports where vancomycin alone (182) and vancomycin, ceftriaxone and gentamicin in combination (183) has been successfully used for treatment of endocarditis caused by highly resistant streptococci. However,

some reports show that treatment of endocarditis caused by highly penicillin-resistant streptococci can be difficult. In one study, neither vancomycin treatment alone, nor a cefotaxime-gentamicin combination, was enough to completely cure endocarditis caused by a highly penicillin-resistant *S. mitis* strain in a human immunodeficiency virus positive individual (181). Also the vancomycin-gentamicin combination failed to cure endocarditis caused by highly penicillin-resistant *S. sanguis* in a 65-year-old woman with multiple medical problems (180). This indicates that other antibiotic regimens may be needed. Possible new candidates are levofloxacin, moxifloxacin, quinupristin/dalfopristin and linezolid. Resistance against these antibiotics is rare. However, the usage of these agents may select resistant strains especially among streptococci in the normal microbiota. For example, point mutations causing resistance to quinupristin/dalfopristin combination have already been described in other bacterial species (58). The same is true with fluoroquinolones, where point mutations are able to cause low-level resistance among streptococci (38, 61, 64). Linezolid-resistant strains are very rare, although one strain with linezolid resistance (MIC 4 mg/L) has been reported (38). Oxazolinones are bacteriostatic antibiotics and in that sense their usage for treatment of infective endocarditis may be compromised (70). However, linezolid has been successfully used for treatments of endocarditis caused by vancomycin-resistant enterococci and methicillin-resistant staphylococci (71, 184). At the moment there is no information of the efficacy of linezolid in the treatment of endocarditis caused by VGS.

Increasing numbers of penicillin-resistant VGS strains among normal microbiota may also challenge the prevention therapies of infective endocarditis. Amoxicillin or ampicillin is recommended for endocarditis prophylaxis (68). The prophylactic use of these antibiotics may select penicillin-resistant VGS strains among normal microbiota and these strains may be able to cause infective endocarditis (181). Clindamycin, which is recommended for prophylaxis for patients allergic to penicillin (68), might be, from the point of view of resistance, a better choice at the moment (Table 2). However, use of macrolides can also select clindamycin-resistant strains among normal microbiota streptococci, because Erm(B) methylase is able to cause both macrolide and clindamycin resistance. So, it is possible that in the future the clindamycin resistance rates are also higher than now. Telithromycin is very active against VGS strains of normal microbiota. *erm*(B) and *mef*(A) resistance genes do not mediate telithromycin resistance among VGS (33), although the presence of *mef*(A) gene in streptococci is increasing the MIC values (55). So, just from the resistance point of view, prophylactic use of telithromycin might be a better choice than the use of clindamycin.

4.1.2 Septic Infections Due to VGS in Neutropenic Patients

Infections are an important cause of morbidity and mortality among neutropenic patients, although the mortality caused by infections has significantly decreased during recent years (185, 186). There have been changes in the aetiology of bacteremia in febrile neutropenic patients. Earlier, Gram-negative bacteria were the most common cause. Nowadays, up to 70% of the bacteremia in neutropenic patients is caused by Gram-positive bacteria (185–188). Possible reasons for this shift in the aetiology are the use of antibiotic prophylaxis, increased use of intravenous catheters and aggressive chemotherapies with prolonged neutropenia and mucositis (186, 187, 189, 190). VGS are an important cause of bacteremia among neutropenic patients. Depending on the study the proportion of VGS as a cause of bacteremia ranges between 3 and 30% (31, 187, 188, 191–193). *S. mitis* followed by *S. oralis* or *S. sanguis* are the most commonly isolated species (24, 188, 193–195). Bacteremias caused by VGS strains originate from the oral mucosa (42, 196). Predisposing factors for VGS infections are severe and prolonged neutropenia, prophylactic antibiotic treatments with quinolones or trimethoprim–sulfamethoxazole, mucositis and treatment of chemotherapy-induced gastritis with antacids or histamine type 2 antagonists (189, 195). VGS infections can be associated with a high morbidity and mortality. Range of overall mortality of VGS bacteremia is between 6 and 18%, but this does not differ from the mortality rate of bacteremia caused by other bacteria (185, 194, 197). VGS infections can be rather asymptomatic, fever being the most common symptom (189, 194, 197–199). 4 to 26% of the patients with VGS infections develop serious complications, like septic shock, acute respiratory distress syndrome (ARDS) or both (31, 189, 194, 197, 198). Mortality among patients that develop ARDS is high, up to 60–100% (31, 189, 194).

Adequate empirical antimicrobial therapy of neutropenic patients with fever is essential, because infection may progress rapidly. The empirical therapy should cover both Gram-positive and Gram-negative bacteria (200–202). Especially important is that empirical treatment cover VGS and *Pseudomonas aeruginosa* strains (201). Recommendation for empirical therapy depend on the risk of the of neutropenic patients to develop serious complication during the febrile episode (200). Empiric antibacterial treatment for low-risk neutropenic patients relies on ciprofloxacin or levofloxacin with or without amoxicillin-clavulanate (200–202). In addition, fluoroquinolones with clindamycin has been suggested (200). Monotherapy with new fluoroquinolones, which show better activity against Gram-positive bacteria is not yet suggested for empirical treatment of low-risk neutropenic patients (200). Empirical antibacterial treatment of

high-risk neutropenic patient relies on broad-spectrum parenteral antibiotics. Third- (ceftazidime) or fourth- (cefepime) generation cephalosporin alone or together with an aminoglycoside, or carbapenem either alone or in combination with aminoglycoside are the first choice of drugs (201, 202). Also, piperacillin-tazobactam either alone or in combination with aminoglycoside is recommended (185). Glycopeptides should be avoided in order to reduce the development of glycopeptide-resistant bacterial strains (185). It has also shown that empirical addition of vancomycin to the therapy would not give any benefit, when compared to piperacillin-tazobactam therapy (203).

Antimicrobial resistance of streptococci isolated from neutropenic patients have been widely studied. These studies indicate that low-level penicillin resistance is common. 21 to 39% of the VGS strains isolated from neutropenic patients present reduced susceptibility against penicillin (28, 30, 36, 42, 51). However, as much as 57% of the VGS strains have been reported to be non-susceptible to penicillin (204). Highly resistant VGS strains (MIC≥4 mg/L) can also be found, the resistance rates varying typically between 2 and 24% (30, 36, 42, 51). Penicillin and especially highly penicillin resistant VGS strains are often resistant to cephalosporins and also express reduced susceptibility to imipenem (30). In these cases ceftazidime is not active (29, 30). Despite the high rates of penicillin resistance among VGS strains, penicillin resistance has not been associated with the development of severe complications, like ARDS (30, 31, 189) or the overall mortality (30). However, there are few reports, which indicate that increasing rates of penicillin resistance might cause problems in the empirical treatment of neutropenic patients with VGS bacteremia. For example, Marron et al. (30) reported a breakthrough bacteraemia of ceftazidime-resistant VGS strains among patients receiving ceftazidime treatment. Similarly, Elting et al. (188) reported that neutropenic patients with VGS infections who did not receive vancomycin in the initial empiric therapy, died more often than-patients who received initial vancomycin therapy. Also in the same study it was shown that patients with penicillin-susceptible VGS infections responded to the initial therapy better than patients with penicillin-resistant VGS, although the final outcome was not affected by penicillin resistance (188).

Carbapenems are active against VGS in vitro (46) and are recommended for empirical treatment of neutropenic patients (200–202). However, VGS strains with elevated (1–2 mg/L) MICs for carbapenems have been isolated from neutropenic patients (24, 29, 30). Whether resistance among VGS strains will in the future compromise the use of carbapenems for monotherapy of neutropenic patients will be seen.

Glycopeptides, linezolid and quinupristin/dalfopristin are not used alone for empirical treatment of febrile neutropenic patients because of their low activity against Gram-negative bacteria. However, glycopeptides are in vitro very effective against VGS and are widely used as a combination with other antibacterials (203). Linezolid has been shown to be as effective as teicoplanin for treatment of Gram-positive infections (205, 206). The same is true with quinupristin/dalfopristin (207). However, there is lack of data as to how well these new drugs are suited for treatment of streptococcal infections. At the moment they are not recommended for empirical therapy of febrile neutropenic patients (200).

The combined use of both fluoroquinolones and penicillin as prophylaxis for bacterial infections in neutropenic patients has reduced bacteremic, especially streptococcal, episodes (199, 208, 209). However, this kind of prophylaxis does not reduce the overall morbidity or mortality. Penicillin resistance among VGS strains may affect the efficiency of penicillin prophylaxis. Whether this will affect the morbidity or mortality of neutropenic patients will be seen.

4.2 Beta-Hemolytic Streptococci

The importance of identifying antimicrobial resistance in beta-hemolytic streptococci is dependent upon whether these antimicrobials are used for treatment and whether the in vitro resistance leads to clinical treatment failure. Penicillin is the drug of choice for treatment of streptococcal infections and macrolides are considered as an alternative treatment for penicillin-allergic patients. In the treatment of pharyngitis caused by GAS, it has been shown that the eradication rate is lower (38–60%) when 14- and 15-membered macrolides are used against macrolide-resistant strains in comparison to the eradication rate (80–92%) when these agents are used against macrolide-susceptible organisms (99, 210, 211). The use of a macrolides for the treatment of macrolide-resistant GAS pharyngitis is also associated with a significantly lower clinical cure rate compared to that achieved with amoxicillin, amoxicillin-clavulanate or cefaclor (211). In addition, it has been shown that regardless of the macrolide resistance mechanism and of epidemiological origin, the erythromycin-resistant isolates harbour the *prt*F1 gene, more often, encoding a protein that enhances the ability to enter respiratory cells, than erythromycin-susceptible organisms (212). Macrolide-resistant GAS strains are so far mostly susceptible to telithromycin, which is a better choice than macrolides. However, few resistant strains exist and the knowledge of resistance and resistance mechanisms is important. The same is true with clindamycin. Use of clindamycin against an erythromycin-resistant isolate requires knowledge of the result of both the susceptibity testing and the determination of the macrolide resistance phenotype for a given isolate, because

clindamycin should not be used against isolates with the MLSb-phenotype (134). Since we lack many alternatives for macrolides, and beta-hemolytic streptococci, especially GAS and GBS, may cause serious infections and non-suppurative sequelae, limiting the use of macrolides should be encouraged (213, 214). The selective pressure caused by the amount of macrolides used in the community has been shown to correlate to the level of macrolide resistance in GAS in the community (168–170, 215) and reduction of use of these agents has been shown to lead to reduction of macrolide resistance (213, 214).

Because GBS is the leading cause of neonatal infections, intrapartum antibiotic prophylaxis is recommended for colonized women with increased risk factors, such as low gestational age. For those at risk, intrapartum penicillin therapy is recommended, with ampicilin, clindamycin, erythromycin and vancomycin as acceptable alternative treatments (CDC), with penicillin G being the drug of choice (216).

There has been debate of the remarkable state of susceptibility to penicillin in GAS and other beta-hemolytic streptococci and of the probability of this state to continue. Resistance to penicillin occurs in related species, such as *S. pneumoniae*, VGS and enterococci. Among the reasons for the continuing susceptibility to penicillin in GAS, the following have been suggested: the pathogens inefficient mechanisms for genetic transfer or barriers to DNA uptake and replication and the findings that low-affinity PBPs expressed by penicillin-resistant laboratory mutants of GAS have a potentially defective performance in the cell-wall biosynthesis, thus decreasing the viability of the penicillin-resistant organism (28, 217).

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