
Antibiotic Resistance of Non-pneumococcal Streptococci and Its Clinical Impact

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1 Introduction

The taxonomy of streptococci has undergone major changes during the last two decades. The present classification is based on both phenotypic and genotypic data. Phylogenetic classification of streptococci is based on 16S rRNA sequences [1], and it forms the backbone of the overall classification system of streptococci. Phenotypic properties are also important, especially for clinical microbiologists. The type of hemolysis on blood agar, reaction with Lancefield grouping antisera, resistance to optochin, and bile solubility remain important for grouping of clinical *Streptococcus* isolates and therefore treatment options [2]. In the following chapter, two phenotypic classification groups, viridans group streptococci (VGS) and beta-hemolytic streptococci, will be discussed.

Antimicrobial resistance is common among VGS and beta-hemolytic streptococci isolates. Beta-lactam resistance is widespread among VGS, and resistance rates to other antimicrobials are continuously increasing. Beta-lactam resistance is uncommon in beta-hemolytic streptococci. Macrolide resistance, however, presents a clinical concern in the outpatient setting. High-level beta-lactam resistance in VGS is a real threat to the treatment of infective endocarditis and empirical treatment of sepsis in neutropenic patients. Treatment of infections, including pharyngitis, caused by macrolide-resistant beta-hemolytic streptococci may also become challenging if resistance rates continue to rise.

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Infections caused by Gram-positive organisms have increased in frequency over time and are almost as common as Gram-negative infections. This has been linked to greater use of invasive procedures and the increasing proportion of hospital-acquired infection. The regular use of broad-spectrum antibiotics in increasingly sick patients has likely resulted in increased bacterial resistance over time [3]. As a result, implementation of antimicrobial stewardship and infection control processes has become progressively more important in protecting patients, health-care providers, and communities.

This chapter summarizes the general characteristics of the streptococci groups, the current antimicrobial resistance trends, resistance mechanisms, and the clinical implication of resistance for viridans and beta-hemolytic streptococci.

2 Characteristics of Non-pneumococcal Streptococci

2.1 Viridans Group Streptococci

Viridans group streptococci form a phylogenetically heterogeneous group of species belonging to the genus *Streptococcus* [1]. However, they have some common phenotypic properties. VGS are a group of catalase-negative, Gram-positive cocci with a chaining morphology upon microscopic examination. They can be grouped as alpha- or nonhemolytic. They can be differentiated from *S. pneumoniae* by their resistance to optochin and lack of bile solubility, though the distinction between the two groups remains difficult due to similar sequence homology [2, 4]. They are leucine aminopeptidase positive, pyrrolidonylaryl amidase negative, and can be differentiated from *Enterococcus* species by their inability to grow in medium containing 6.5% sodium chloride [2]. Nutritionally variant streptococci were once included in VGS but based on molecular data been removed to a new genus *Abiotrophia* [5]. 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, 5]. Although historically VGS are poorly classified, there are many species within the group. The six major groups include *S. mutans*, *S. salivarius*, *S. anginosus*, *S. mitis*, *S. sanguinis*, and *S. bovis* group. The *S. anginosus* group has been the source of much controversy and ambiguity regarding taxonomy and classification. This group of organisms can be alpha-, beta-, or nonhemolytic, and it is the isolates lacking beta-hemolysis that are generally considered to be a part of VGS. Due to the diverse nature of VGS, the rates and patterns of antimicrobial resistance vary greatly. Differences in species identification and patient population contribute to this variability [4].

Streptococcus mitis group organisms are resistant to more antimicrobial agents than the other VGS species [4]. The most clinically relevant species belonging to VGS are *S. mitis*, *S. sanguis*, and *S. oralis*. Lack of alpha-hemolysis does not seem to correlate with clinical outcome or severity of disease and no enzymatic or toxigenic effect has been documented as a by-product of alpha-hemolysis [4].

2.2 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. Traditional subdividing into serological groups is based on the detection of group-specific antigenic differences in cell-wall carbohydrates. The serologic scheme of classification by Lancefield is used [6], and serogroups A, B, C, D, F, and G are those most commonly found in humans [7].

2.2.1 Group A *Streptococcus* (*Streptococcus pyogenes*)

Group A *Streptococcus* (GAS, *Streptococcus pyogenes*) is an important pathogen confined almost exclusively to human hosts [8]. *S. pyogenes* is generally associated with acute pharyngitis or localized skin infections. *S. pyogenes* is highly communicable and can cause disease in healthy people of all ages without type-specific immunity against the serotype responsible for infection [9]. Transmission can occur from those with acute infections or from asymptomatic carriers generally through hand contact or respiratory droplets. Food and waterborne outbreaks have also been documented [8]. Impetigo and pharyngitis are more likely to occur among children living in crowded homes or in suboptimal hygienic conditions. Multiple streptococcal infections may be found in the same family due to the highly contagious nature of the infection [9].

The diseases are commonly self-limiting, localized infections of the pharynx and skin. A ubiquitous organism, *S. pyogenes*, is the most common bacterial cause of acute pharyngitis, accounting for 15–30 % of cases in children and 5–10 % of cases in adults [9]. Invasion from the skin can lead to septicemia 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 [10–13]. Primary suppurative infections may also lead to serious non-suppurative sequelae, acute rheumatic fever, rheumatic heart disease, and acute glomerulonephritis [2, 14, 15].

Group A *Streptococcus* can be distinguished from other groups by susceptibility to bacitracin. A kirby-bauer disc contains 0.04U of bacitracin inhibits the growth of more than 95 % of group A strains, whereas 80–90 % of non-group A strains are resistant to this antibiotic [9]. Serologic typing of the M [16] and T [17] proteins has traditionally been used in epidemiologic typing of GAS [18]. More recently, molecular typing methods such as *emm* sequence 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.

2.2.2 Group B *Streptococcus* (*Streptococcus agalactiae*)

Group B streptococci (GBS, *Streptococcus agalactiae*) are the most common cause of neonatal sepsis. It is one of the primary causes of bacteremia and meningitis in neonates and can cause infections in pregnant women [19, 20]. Vaginal colonization of nonpregnant and pregnant women is the principal source of GBS. However, it also can colonize the gastrointestinal tract and the upper respiratory tract of healthy humans. The portal of entry is not apparent, but possible areas include the skin, genital tract, urinary tract, and respiratory tract [21].

Neonates can acquire the organism vertically in utero or during delivery from the maternal genital tract. Although the transmission rate from mothers colonized with *S. agalactiae* to neonates delivered vaginally is approximately 50 %, with antibiotic prophylaxis, only 1–2 % of colonized neonates develop invasive group B streptococcal disease [21].

GBS may also cause invasive infections in the elderly and in nonpregnant adults with underlying or chronic diseases. The broad 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 [21].

GBS has been classified into different serotypes on the basis of different chain structures of its capsular polysaccharide. Several serotypes are known—Ia, Ib, Ic, II, III, IV, V, VI, VII, and VIII. Isolation of group B streptococci from blood, cerebrospinal fluid (CSF), and/or a site of local supuration is the only method for diagnosing invasive group B streptococcal infection [21].

2.2.3 Groups C and G Beta-Hemolytic Streptococci

Most of the Lancefield group C streptococci (GCS) produce beta-hemolysis on blood agar although nonhemolytic strains also exist [2]. Group C streptococci are mainly animal pathogens; however, beta-hemolytic strains have been isolated from normal human microbiota of the nasopharynx, skin, and genital tract [22]. The majority of group G streptococci (GGS) are beta-hemolytic [2].

More recently, group C streptococci and group G streptococci of human origin are thought to comprise a single subspecies, *Streptococcus dysgalactiae* subsp. *equisimilis*. It can be found in normal flora of the upper airways and are often asymptomatic colonizers of other areas. It may also be implicated in skin and soft tissue infections, pharyngitis, bacteremia, endocarditis, septic arthritis, osteomyelitis, puerperal infections, and meningitis [22].

3 Antimicrobial Resistance in VGS

For the purpose of this chapter, we will use data from contemporary large-scale surveillance studies to show recent resistance trends for relevant antibiotics. As both the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) breakpoints will be presented, epidemiology and resistance rates will primarily be described as defined by CLSI criteria.

3.1 Beta-Lactam Activity

Among streptococci, beta-lactam resistance is mediated by point mutations in penicillin-binding proteins (PBPs). PBPs are membrane-bound transpeptidases. They are active-site serine hydrolases, which catalyze cross-linking of the peptidoglycan subunits during bacterial cell-wall synthesis [23, 24]. Beta-lactams serve as substrates for PBPs. The active-site serine reacts with the beta-lactam ring and generates a covalently linked enzyme-beta-lactam intermediate. This acyl enzyme intermediate is not able to catalyze cross-linking of the peptidoglycan subunits [23]. In streptococci there are low and high molecular weight PBPs [25, 26]. Both of these enzymes are important for the cell-wall synthesis,

but only the high molecular weight PBPs are important for the bacterial killing activity of the beta-lactam antibiotics [24]. In VGS there are two kinds of high molecular weight PBPs, PBP1 (PBP1a and PBP1b), and PBP2 (PBP2a, PBP2b, PBP2x) [25]. Homologous molecules can be found in *S. pneumoniae* and naming conventions for PBPs of VGS are adapted from *S. pneumoniae* [24–26].

VGS with wild-type PBPs are susceptible to beta-lactam antibiotics [27]. Resistance results when the high molecular weight PBPs have decreased affinity for beta-lactams. Decreased affinity can be achieved by amino acid substitutions in the transpeptidase domain of the PBPs [24, 27]. A single point mutation can result in an increase in the penicillin minimum inhibitory concentration (MIC) value. Normally more than one mutation is needed for intermediate level beta-lactam resistance. Highly resistant strains have accumulated several mutations in the PBPs, altering the PBPs significantly so the beta-lactams can no longer bind to the PBP. Accumulation of several mutations in the PBPs may also result in lethal mutations if cell-wall integrity is compromised. Based on the data obtained in *S. pneumoniae*, these highly resistant strains may also have mutations beyond those found in PBPs [24]. 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 mosaic PBP genes, there are gene regions obtained from resistant strains dispersed through the wild-type PBP genes [28].

Penicillin resistance among VGS isolated from blood has been extensively studied. Farrell et al. at JMI laboratories performed a large-scale surveillance study to examine the susceptibility profiles of various antibiotics against 60,084 clinical isolates from 33 European region medical centers. Over 1200 viridans group streptococci isolates were collected between 2005 and 2010 and were tested for susceptibility to a range of antibiotics. The penicillin MIC₅₀ and MIC₉₀ was 0.06 and 1 mg/L, respectively. Per CLSI breakpoints, 77.5 % VGS were susceptible, 17 % intermediate, and 5.5 % resistant [29] (Table 50.1). The 2012 LEADER surveillance study evaluated 7429 isolates, including 526 VGS, from 60 US sites. The penicillin MIC₅₀ was ≤0.06 mg/L and the MIC₉₀ was 0.5 mg/L, similar to the European susceptibility pattern [30].

Overall, in VGS cephalosporins have similar susceptibility rates, MIC₅₀ and MIC₉₀. The cefepime MIC₅₀ and MIC₉₀ were ≤0.12 mg/L and 1 mg/L, respectively, with 92.1 % of isolates susceptible. Between 3 % and 5 % of isolates showed intermediate susceptibility or were considered resistant. Ceftriaxone MIC₅₀ was ≤0.25 mg/L with an identical MIC₉₀ and similar percent resistance [29] (Table 50.1). US surveillance data were similar with MIC₅₀ and MIC₉₀ values of 0.25 mg/L and 0.5 mg/L with only 1.2 % resistance rates [30].

Table 50.1 Antimicrobial activities of ceftobiprole and comparator agents when tested against bacterial isolates from European medical centers (2005–2010)

Organism (no. of isolates tested) and antimicrobial agent	MIC			% of isolates susceptible/intermediate/resistant	
	MIC ₅₀	MIC ₉₀	Range	CLSI	EUCAST
<i>B-Hemolytic streptococci</i> (2, 981)					
Ceftobiprole	≤0.06	≤0.06	≤0.06–0.25	–/–/–	–/–/–
Penicillin	≤0.03	0.06	≤0.03–0.12	100.0/–/–	100.0/0.0/0.0
Cefepime	≤0.12	≤0.12	≤0.12–2	99.9/–/–	100.0/0.0/0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25–4	99.9/–/–	100.0/0.0/0.0
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	91.9/0.5/7.6	92.4/0.0/7.6
Erythromycin	≤0.25	>2	≤0.25 to >2	82.0/1.0/17.0	82.0/1.0/17.0
Daptomycin	≤0.06	0.25	≤0.06–0.5	100.0/–/–	100.0/0.0/0.0
Levofloxacin	≤0.5	1	≤0.5 to >4	99.6/0.0/0.4	95.6/4.0/0.4
Linezolid	1	1	0.25–2	100.0/–/–	100.0/0.0/0.0
Tetracycline	4	>8	≤2 to >8	49.5/2.6/47.9	49.3/0.2/50.5
Tigecycline	≤0.03	0.06	≤0.03–0.5	>99.9/–/–	>99.9/0.1/0.0
Trimethoprim/sufamethoxazole	≤0.5	≤0.5	≤0.5 to >2	–/–/–	99.0/0.4/0.6
Vancomycin	0.25	0.5	≤0.12–1	100.0/–/–	100.0/0.0/0.0
<i>Viridans group streptococci</i> (1, 264)					
Ceftobiprole	≤0.06	0.25	≤0.06 to >8	–/–/–	–/–/–
Penicillin	0.06	1	≤0.03 to >4	77.5/17.0/5.5	84.3/10.2/5.5
Cefepime	≤0.12	1	≤0.12 to >16	92.1/3.4/4.5	88.1/0.0/11.9
Ceftriaxone	≤0.25	1	≤0.25 to >8	92.2/3.2/4.6	88.8/0.0/11.2
Daptomycin	0.25	0.5	≤0.06–2	99.8/–/–	–/–/–
Clindamycin	≤0.25	>2	≤0.25 to >2	88.0/0.3/11.7	88.3/0.0/11.7
Erythromycin	≤0.25	>2	≤0.25 to >2	61.6/2.2/36.2	–/–/–
Levofloxacin	1	2	≤0.5 to >4	96.8/1.1/2.1	–/–/–
Linezolid	1	1	≤0.12 to 2	100.0/–/–	–/–/–
Tetracycline	≤2	>8	≤2 to >8	62.2/2.2/35.6	–/–/–
Tigecycline	≤0.03	0.06	≤0.03–0.5	99.9/–/–	–/–/–
Vancomycin	0.5	1	≤0.12–1	100.0/–/–	100.0/0.0/0.0

Ceftobiprole medocaril is described as a fifth-generation cephalosporin with a wide spectrum of antibiotic activity. Per European surveillance data, the ceftobiprole MIC₅₀ and MIC₉₀ are ≤0.06 mg/L and 0.25 mg/L, respectively, for VGS [29] (Table 50.1). Ceftaroline fosamil is a broad-spectrum parenteral cephalosporin which treats certain skin infections and community-acquired bacterial pneumonia (CABP). A recent report from the SENTRY antimicrobial surveillance program tested ceftaroline against 1273 streptococci isolates between 2008 and 2011. Ceftaroline showed activity against all VGS species with the highest MIC, 1 mg/L, observed in *S. oralis*, *S. mitis*, and *S. parasanguinis* [31].

3.2 Macrolide, Lincosamide, and Ketolide Activity

Macrolides, ketolides, lincosamides, and streptogramin B antibiotics, although having different chemical structures, have similar, although not identical, antimicrobial activity

against VGS since the resistance mechanisms developed by bacteria against these antimicrobials is similar. 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. Fourteen- and 15-membered ring macrolides such as erythromycin and azithromycin have similar antibiotic properties. Sixteen-membered ring macrolides including spiramycin differ from 14- and 15-membered ring macrolides in their antimicrobial activity against VGS. Lincosamides such as clindamycin and streptogramins also have some differences in their activity against bacteria when compared to macrolides.

In streptococci, there are two well-characterized macrolide resistance mechanisms. These are 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 [32]. 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 [33]. 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 [34]. Mutations can cause several different kinds of resistance phenotypes. Both *erm* and *mef* genes can be horizontally transferred between different streptococci [35].

3.2.1 Erythromycin

Erythromycin A has similar in vitro activity against VGS strains as other 14- and 15-membered ring macrolides including azithromycin [36]. Erythromycin resistance is quite common among clinical VGS isolates. In Europe, the MIC₅₀ and MIC₉₀ for erythromycin for VGS is ≤0.25 mg/L and >2 mg/L. Resistance levels continue to remain high with 36.2 % of isolates resistant to erythromycin [29] (Table 50.1). In the United States, macrolide MIC values and resistance rates continue to rise. Approximately 50 % of VGS isolates in the LEADER study were resistant to erythromycin with MIC₅₀ and MIC₉₀ values of 0.5 mg/L and 16 mg/L, respectively [30]. The most common erythromycin resistance mechanism is mediated by *mef*(A) genes azithromycin [36, 37]. Roughly 70–80 % of the erythromycin-resistant VGS strains are carrying *mef*(A) gene and about 16–20 % are carrying *erm*(B) gene [36–38]. However, the situation may vary. There is one report from France, where *erm*(B) was reported to be much more common than *mef*(A) among blood isolates of VGS [35]. The continuous surveillance of invasive VGS isolates is warranted and can guide better treatment options especially in patients with underlying diseases [39].

3.2.2 Clindamycin

Resistance to clindamycin is much less frequent among blood and normal microbiota VGS than resistance to erythromycin [40]. MIC₅₀ and MIC₉₀ values were similar to erythromycin (≤0.25 mg/L and >2 mg/L, respectively), with up to 12 % of VGS isolates resistant to clindamycin in both Europe and the United States [29, 30] (Table 50.1). Resistance levels are similar among both blood and the normal microbiota isolates. The reason for lower resistance levels is that the efflux mechanism mediated by *mef*(A) resistance gene does not confer resistance to clindamycin [40]. An autopsy report of a patient with a *S. mitis* strain found that the pattern of resistance in this isolate resembled an induced macrolide, lincosamide, and streptogramin B resistance (MLSB) phenotype as a result of short-term use of clindamycin. This mechanism induces resistance to both clindamycin and minocycline [41].

3.2.3 Ketolide

The binding of telithromycin to the bacterial ribosomes is much stronger than the binding of erythromycin. This is the reason why methylation of the ribosomal RNA does not increase the MIC values as much for telithromycin compared to erythromycin [42]. Mef(A) efflux pumps transport telithromycin out of the bacterial cell as well as they pump erythromycin. However, in streptococci, Mef(A) efflux does increase telithromycin MIC values when compared to the strains without *mef*(A) gene [43].

3.2.4 Streptogramin

Quinupristin-dalfopristin, a combination of streptogramin B and streptogramin A, is available for intravenous use. It has good in vitro activity against VGS. However, resistance rates vary considerably between studies. In some studies, resistant strains have not been isolated, whereas other studies show reduced susceptibility in as much as 70 % of strains and resistance in 28 % [44, 45]. VGS strains with quinupristin-dalfopristin MIC values of 16 mg/L have also been described [44]. Resistance to quinupristin-dalfopristin is linked to the streptogramin A (dalfopristin) resistance. Therefore in order to be resistant to the antibiotic combination, a strain must be resistant to streptogramin A. 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 [46]. Although not studied in detail [44, 47], it is possible that the resistance is mediated by ribosomal mutation as in *S. aureus* [48].

3.3 Tetracyclines and Trimethoprim-Sulfamethoxazole Activity

Tetracycline resistance in VGS is quite common. In the European surveillance study, the VGS MIC₅₀ was ≤2 mg/L and MIC₉₀ was >8 mg/L. Up to 36 % of VGS strains are tetracycline resistant [29] (Table 50.1). Tigecycline activity is much higher with 99.9 % of isolates susceptible and an MIC₅₀ and MIC₉₀ of ≤0.03 mg/L and 0.06 mg/L, respectively [29] (Table 50.1). Trimethoprim-sulfamethoxazole is not used for treatment of VGS infections but has been commonly used for prophylaxis in neutropenic patients [49]. Decreased susceptibility for trimethoprim-sulfamethoxazole is quite common among VGS strains.

3.4 Fluoroquinolone Activity

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 [50–52]. In streptococci, the topoisomerase IV molecule has two subunits coded by *parC* and *parE* genes. DNA gyrase has two subunits, GyrA and GyrB, coded by corresponding genes. Topoisomerase IV is the primary target for fluoroquinolones in VGS [50]. Mutations at the topoisomerase IV genes confer low-level resistance (MIC 4 mg/L). A combination of topoisomerase IV mutations and the fluoroquinolone efflux mechanism is needed for high-level fluoroquinolone resistance (MIC \geq 16 mg/L). Fluoroquinolone resistance determinants can be horizontally transferred between VGS and *S. pneumoniae* strains [50, 53–55]. Levofloxacin was the only fluoroquinolone evaluated in the European and US surveillance studies. Data demonstrated high susceptibility rates with a MIC₅₀ of 1 mg/L and MIC₉₀ of 2 mg/L. Approximately 2% of VGS isolates were determined to be resistant in Europe and 6% in the United States [29, 30] (Table 50.1).

3.5 Glycopeptide Activity

3.5.1 Vancomycin

Vancomycin, a glycopeptide antibiotic, has retained its activity against VGS. Not a single vancomycin-resistant VGS has been reported thus far [36, 56–62]. The vancomycin MIC₅₀ was 0.5 mg/L and MIC₉₀ was 1 mg/mL in both Europe and the United States [29, 30] (Table 50.1).

3.5.2 Oritavancin and Dalbavancin

Newer glycopeptides include oritavancin and dalbavancin. Oritavancin, a bactericidal lipoglycopeptide, was assessed in the SENTRY surveillance program in order to expand current limited in vitro data. Oritavancin has activity against many Gram-positive pathogens including streptococci with oritavancin MIC₅₀ and MIC₉₀ results of \leq 0.008 mg/L and 0.06 mg/L, respectively, for the VGS studied [63]. The SENTRY program also evaluated in vitro activity of dalbavancin. VGS isolates were tested using CLSI reference broth microdilutions and interpretations. The MIC₅₀ and MIC₉₀ ranges were \leq 0.03–0.25 mg/L and 0.06–0.12 mg/L, respectively [64]. Overall, all currently existing glycopeptides are potent against the VGS.

3.6 Aminoglycoside Activity

In general, the activity of the aminoglycosides against VGS is limited [65]. Aminoglycosides including gentamicin, amikacin, streptogramin, and netilmicin have been used in combination with penicillin or a cephalosporin for the treatment of infective endocarditis [66] and sepsis in neutropenic patients

[67]. High-level gentamicin resistance in VGS is rare. This is true with VGS isolates of blood origin [59–61] and normal microbiota [68]. MIC values are typically between 0.25 and 96 mg/L [59, 60, 69] and the MIC₉₀ values are between 0.5 and 32 mg/L [59, 68]. Few high-level aminoglycoside-resistant *S. mitis* strains have been detected. In these strains gentamicin MIC values have been as high as 1000 mg/L [69].

3.7 Oxazolidinone Activity

3.7.1 Linezolid

Linezolid belongs to the oxazolidinone group of antibiotics [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 well studied. However, ongoing surveillance programs that monitor the in vitro activity of linezolid against comparator agents with Gram-positive coverage do exist. The LEADER surveillance study demonstrates MIC values of linezolid against VGS to be predominantly 1 mg/L and 100% susceptible in the United States [72]. International data through the ZAAPS program revealed similar findings [73].

3.7.2 Tedizolid

Tedizolid is the active moiety of the prodrug tedizolid phosphate. It is a novel oxazolidinone whose in vitro activity has been studied against viridans group streptococci. Fifteen VGS isolates from a phase 2 trial were obtained and tested in patients with complicated skin and skin structure infections. Susceptibility testing from phase 2 data resulted in a MIC₅₀ and MIC₉₀ of 0.25 mg/L [74].

3.8 Daptomycin Activity

Daptomycin is a bactericidal lipopeptide with activity against streptococci. It is used successfully to treat endocarditis caused by vancomycin-resistant enterococci and methicillin-resistant staphylococci. It is the only agent indicated for *S. aureus* bacteremia and endocarditis. Large surveillance studies have demonstrated daptomycin MIC₅₀ of 0.25 mg/L and MIC₉₀ of 0.5 mg/L [29] (Table 50.1). VGS has historically been considered uniformly susceptible to daptomycin; however, the development of high-level daptomycin resistance (HLDR; MIC $>$ 256 mg/L) after exposure to daptomycin has recently been reported among these isolates. In vitro studies were performed and 114 VGS strains were tested from patients diagnosed with infective endocarditis. Daptomycin susceptibilities of the baseline clinical isolates by Etest ranged between 0.03 and 1.5 mg/L for *S. mitis*, 0.023–0.12 mg/L for

S. bovis, 0.12–0.5 mg/L for *S. anginosus*, 0.25–0.5 mg/L for *S. mutans*, and 0.016–0.047 mg/L for *S. salivarius*. HLDR was only observed after 24 h of exposure to daptomycin in 27 % of *S. mitis* isolates, 47 % of *S. oralis* isolates, and 13 % of *S. sanguis* isolates [75]. No clinical isolates have been identified or reported to date.

4 Antimicrobial Resistance in Beta-Hemolytic Streptococci

4.1 Resistance to Macrolides

4.1.1 Incidence of Macrolide Resistance in GAS, GBS, GCS, and GGS

In 1959 Lowbury and Hurst reported the first isolate of erythromycin-resistant GAS from burns of four patients in the United Kingdom [76]. 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 [76–81]. In the 1970s a large 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 (MIC values >100 mg/L) to macrolides and lincomycin and were often resistant to tetracycline and chloramphenicol as well. Strains were exclusively of the T12 serotype. From 1985 to 1987, an increase from 1 % to 17.6 % in the frequency of erythromycin-resistant GAS was seen in Australia's Fremantle area [83]. These strains represented different serotypes and exhibited overall low-level resistance to erythromycin (MIC range 2–8 mg/L). Resistance to clindamycin and tetracycline was rare. Sporadic isolates and family outbreaks with 22 % erythromycin-resistant GAS, predominantly of T4M4 serotype, was reported between 1988 and 1989 from Dundee area in the United Kingdom [84].

Resistance to erythromycin continues to be reported in GBS since 1962. The first description was from the United States [85], and in the same country macrolide resistance in GBS increased from 1.2 % among isolates collected from 1980 to 1993 to 18 % in 1997 and 1987. Increasing resistance has been reported from other countries as well. In Spain, the frequency of macrolide resistance in GBS increased from 2.5–5.6 % in 1993–1996 to 14.5–18 % in 1998–2001 [86] and in Taiwan from 19 % in 1994 to 46 % in 1997 [87]. Since the end of the 1990s, frequencies of 15–21 % have been reported in France [88–90], 13–18 % in Canada [91, 92], 40 % in Korea [93], and 22 % in Turkey [94].

Macrolide resistance among group C and G streptococci varies between different countries. Resistance is uncommon in Finland with 1 % and 3.6 % of group C streptococci found to be resistant to clindamycin and erythromycin, respec-

tively. The most common resistance mechanism to macrolides has been via the *mef(A)* gene [95]. Similar to group C streptococci resistance rates, 3.5 % and 0.3 % of the group G streptococci have been resistant to erythromycin and clindamycin, respectively. Most of these strains have had *erm(TR)* resistance gene and one with the *erm(B)* resistance gene [95]. Higher numbers of erythromycin resistance among group C and G streptococci have been reported from Turkey. Ergen et al. reported that 1.4 % and 16.2 % of GCS and GGS, respectively, were resistant to erythromycin [28]. Erythromycin resistance among GCS and GGS in Taiwan is even more common. Resistance has been seen in 41.7 % of GCS isolates and 53.3 % of GGS isolates reported [96].

Macrolide resistance continues to rise in both European and North American countries. A total of 2981 beta-hemolytic streptococci isolates were collected from Europe, Turkey, and Israel and 950 isolates from the United States. Current cumulative surveillance data, accounting for all beta-hemolytic streptococci groups, show 7.6 % resistance to clindamycin and 17 % resistance to erythromycin in European countries. This rate is increased in the United States, with 19.4 % and 38 % resistance to clindamycin and erythromycin, respectively [29, 30] (Table 50.1).

4.1.2 Mechanisms of Macrolide Resistance in Beta-Hemolytic Streptococci

The macrolide resistance mechanism by ribosomal methylation encoded by *erm* genes was first identified in 1956 in *Staphylococcus aureus* [97]. This resistance mechanism affects macrolides, lincosamides, and streptogramin B (MLSb) antibiotics. The inducible and constitutive forms of MLSb resistance have been found in beta-hemolytic streptococci since the early 1970s [98–100]. The *erm(B)* methylase gene was the only *erm* gene class found in streptococci [101–103] until 1998, when the sequence of *erm(TR)* in *S. pyogenes* was published [104]. 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 [105]. The inducible or constitutive production of the methylase is dependent on the sequence of the regulatory region situated upstream from the structural methylase gene. Resistance is associated to structural changes in the regulatory sequence. Exposing *S. pyogenes* harboring the inducible *erm* gene to clindamycin results in highly resistant mutants of *S. pyogenes* [106].

The phenotypic expression of macrolide resistance in streptococci has been commonly studied by MIC determinations and induction tests including the double-disc test (erythromycin and clindamycin disks placed in vicinity on inoculated agar). Analysis of the Finnish GAS strains isolated in 1990 revealed a new erythromycin resistance phenotype with low- or moderate-level resistance (MIC range 1–32 mg/L) to 14- and 15-membered macrolides only

(M-phenotype). Thirty-four percent of the studied isolates represented the new M-phenotype [80]. 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* [33, 107]. Isolates with this mechanism have been found among beta-hemolytic streptococci in different parts of the world. Countries where strains of GAS carrying *mef(A)* have been observed now account for the majority of macrolide-resistant isolates. These countries include Spain [108, 109], Germany [110], Greece [111], Finland [112], Taiwan [113], the United States [114], Chile [115], and Argentina [116]. Predominance of GAS strains carrying *erm(A)* have been reported from Russia, Slovakia, the Czech Republic, and Croatia [117, 118]. GBS isolates with MLS resistance caused by *erm(B)* and *ermA* predominate in most reports in Canada and other parts of the Western Hemisphere [92, 119], France [88, 89, 120], Spain [86, 121], and Taiwan [87]. In both GBS and GCS, the highest proportion of isolates carrying *mef(A)* have been reported from Taiwan (37%) and Finland (95%) [95, 96].

In addition to familiar macrolide resistance determinants including *erm(B)*, *erm(A)*, and *mef(A)*, a more rare mechanism has also been shown to cause resistance to macrolides. This mechanism involves mutations in the *S. pyogenes* ribosomal protein L4 and in positions 2611 and 2058 of the 23S rRNA encoding gene. Mutations in positions 2611 and 2058 of the 23S rRNA gene cause resistance to clindamycin and streptogramin B (quinupristin). Additionally, a mutation at position 2058 confers resistance to telithromycin [122–124].

The presence of a putative novel efflux system associated with *erm(TR)* in *S. pyogenes* has also been found [125]. Another gene, *mreA*, which was originally described as a macrolide efflux gene in *S. agalactiae* [107], encodes riboflavin kinase and is also found in erythromycin-susceptible GBS strains [126]. Strains with two different macrolide resistance mechanisms (*mef* and *erm*) within a single bacterial cell may coexist among GAS and more commonly among GBS [88, 94, 108, 126–129]. The phenotype of these strains is usually determined by the *erm* gene.

Resistance gene *erm(B)* has been shown to be either plasmid or chromosome associated in streptococci [105]. In earlier studies conjugative plasmids with erythromycin resistance determinants were found from group A, B, C, and G streptococci and were shown to transfer by conjugation between streptococcal species [130]. Transfer was also seen by transduction among VGS [131, 132]. However, most antibiotic resistance genes in streptococci are currently thought to be chromosomal in origin. Beta-hemolytic streptococci belonging to groups A, B, C, and G have been shown to transfer their chromosomal macrolide resistance determinants by conjugation [126, 133–135]. A composite chromosomal conjugative element, Tn3701, encoding resistance to erythromycin and tetracycline has been described in GAS [136].

Within this element the resistance genes are carried by a Tn916-like transposon. The presence of Tn916-Tn1545-like conjugative transposons carrying *erm(B)* and *tet(M)* has been verified, and an association of chromosomal *erm(A)* with *tet(O)* has been noted among GAS [137, 138]. An unusual chimeric genetic element containing DNA identical to Tn1207.1, 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 [139]. 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, particularly *erm(B)*. This suggests 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 [138]. Macrolide resistance mechanisms differ among streptococcal Lancefield groups and geographical area. New gene sequences demonstrating resistance continue to evolve.

4.1.3 Epidemiology of Macrolide-Resistant Beta-Hemolytic Streptococci

A large variety of clones of GAS are drug resistant [113, 138, 140, 141]. 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 [140]. Same clones have been found among susceptible isolates as well, but in general the heterogeneity of GAS clones seems to be lower among resistant than susceptible isolates [138, 140, 141]. Single clones of GAS with a macrolide-resistant determinant may become predominant or cause outbreaks both regionally and nationwide [128, 142–144]. For example, in 1994, 82% of erythromycin-resistant GAS isolates collected in Finland expressed the M-phenotype. Although multiple clones were found among these isolates, increased regional resistance rates were clearly associated to T4M4 serotype with *mef(A)* [112, 134]. In the United States, isolates carrying *mef(A)* of an emm6 (M6 serotype) clone caused an epidemic among schoolchildren in 2001. In April–May of 2002, this serotype was not found in the same region when the resistance rate was high. Thirty-five percent of isolates were resistant to erythromycin, with an emm75 (M75 serotype) clone predominating [114, 143]. 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 considerable diversity of these genetic elements both among clonally unrelated and within clonally identical strains [138]. The increase of resistance includes a complex genetic interaction within circulating streptococcal population and may be between streptococci and other species [145]. Macrolide consumption, differing immunities, and other host factors of populations may also contribute to this interplay and spread of resistance determinants and resistant clones [146–148].

4.1.4 Resistance to Clindamycin

Clindamycin resistance is almost exclusively related to MLS resistance found in beta-hemolytic streptococci. It is thus mediated by *erm* genes. In some studies, among GBS, the frequency of clindamycin resistance exceeds that of macrolide resistance suggesting another mechanism of clindamycin resistance may exist [86, 93, 149]. In one isolate of GBS from Canada, the *linB* gene encoding a lincosamide-inactivating nucleotidyltransferase was found [92]. This gene has previously been identified in *Enterococcus faecium*.

Both constitutive and inducible clindamycin resistances have increased in recent years, especially in group A and B streptococci [150]. Inducible clindamycin resistance in beta-hemolytic streptococci remains an under-recognized phenomenon of unknown clinical significance. Lewis et al. evaluated inducible clindamycin resistance through an animal model and retrospective patient chart review. In the animal model, inducible resistance impaired killing of beta-hemolytic streptococci and bacterial load by 48 h were similar to the control isolated that were constitutively clindamycin resistant. Eight of these cases resulted in both microbiological and clinical failure [151]. Thus, inducible and constitutive resistance should be detected during routine antimicrobial susceptibility testing.

European surveillance data demonstrated a clindamycin MIC₅₀ and MIC₉₀ of ≤ 0.25 mg/L with 91.9 % susceptible isolates, 0.5 % intermediate, and 7.6 % resistant [29] (Table 50.1). US data suggests a similar MIC₅₀ of ≤ 0.25 mg/L and a MIC₉₀ of > 2 mg/L. Eighty percent of the 960 beta-hemolytic streptococci isolates were susceptible. Susceptibility rates in other commonly used macrolides tend to be lower [30].

4.1.5 Resistance to Erythromycin

Increased levels of erythromycin resistance in GAS have been reported in Europe. The mechanisms of erythromycin resistance in *S. pyogenes* include target site modification and active drug efflux. Target site modification is mediated by an erythromycin resistance methylase, encoded by an *erm* gene,

which reduces binding of macrolide, lincosamide, and streptogramin B (MLS_B) antibiotics to the target site in the 50S ribosomal subunit. Resistance in other beta-hemolytic streptococci groups can also be seen with recent surveillance data suggesting MIC₅₀ and MIC₉₀ values of ≤ 0.25 mg/L and > 2 mg/L, respectively [29] (Table 50.1). MIC values in the US deviate from those found in other countries. Recent data report MIC₅₀ values of ≤ 0.12 mg/L and MIC₉₀ of > 16 mg/L. Resistance is high with 60 % of isolates susceptible to erythromycin [30].

4.1.6 Resistance to Telithromycin

Resistance to telithromycin is currently uncommonly (< 6 %) rare [152]. Few resistant strains have been isolated to date. This is due to either a constitutively expressed *erm(B)* gene or an adenine to guanine mutation at position 2058 [43, 124].

4.2 Resistance to Tetracycline

Resistance to tetracycline is common among beta-hemolytic streptococci, especially among macrolide-resistant strains. Resistance is caused by tetracycline resistance 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 [137]. In GBS, it is found both among macrolide-susceptible and macrolide-resistant organisms with all different macrolide resistance determinants [127]. *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)* [137]. Surveillance data shows a tetracycline MIC₅₀ of 4 mg/L and MIC₉₀ of > 8 mg/L. Of 2981 beta-hemolytic streptococci isolates tested, approximately 50 % were susceptible and 50 % resistant [29] (Table 50.1).

5 Clinical Significance of Resistance

5.1 Infections Caused by VGS

VGS are a part of the normal flora and can be found in the oropharyngeal, urogenital, and gastrointestinal microbiota. They are generally considered to have a low pathogenic potential and, however, can cause disease in immunocompromised patients as well as patients with cardiac abnormalities. As antibiotic resistance continues to rise, VGS infections are associated with significant morbidity and mortality [4]. Though other infections have been noted, this review will focus on the two predominate clinical presentations of VGS infections: infective endocarditis (IE) and neutropenic fever. It will also highlight rising challenges associated with resistance in treatment of cystic fibrosis.

5.1.1 Infective Endocarditis

Infective endocarditis most frequently presents acutely, and complete history and physical examination should be performed for source identification. The diagnosis is based off a combination of factors and may be straight forward with culture-positive endocarditis. Viridans streptococci are a common causative agent. Among 2781 patients with infective endocarditis, VGS was the underlying pathogen in 17% of patients [153]. Several different VGS species have been reported to cause infective endocarditis, a life-threatening condition [154]. Of the VGS, *S. bovis*, *S. sanguis*, *S. mitis*, *S. oralis*, and *S. gordonii* remain some of the most common species isolated from blood or infected valves in both adults and children [66, 155, 156]. Infective endocarditis caused by *S. mitis* is a relatively common event and is empirically treated with penicillin or macrolides in immunologically stable patients. The etiology of infective endocarditis varies according to the age of the patient and the clinical nature of the disease [154, 155, 157, 158].

In adults, the epidemiology of IE caused by VGS is changing. From 1987 to 2009, the mean age of patients with native-valve endocarditis increased from 38 ± 22 years to 60 ± 16 years ($P < 0.001$). The proportion of IE cases without predisposed heart disease has progressively increased from 25% to 67% ($P < 0.001$) [159]. Other risk factors include dental infection as well as injection drug use, although VGS does not play a significant role in IE among intravenous drug users [155]. Although less virulent than other microorganisms, VGS continues to be the predominant cause of community-acquired IE. VGS and *Streptococcus bovis* account for 40–60% of native-valve endocarditis in the community. In children, VGS was noted as the most common cause of IE, accountable for 32–43% of cases [4].

Historically VGS were susceptible to many commonly administered antimicrobials including beta-lactams, macrolides, tetracycline, and aminoglycosides. As noted in the section above, there has been an increase in resistance including multiple-drug-resistant strains of *S. mitis* among patients with bacteremia. As with other pathogens, drug resistance in VGS is most clinically prevalent in patients with immunocompromised conditions. This is likely a result of exposure to hospital settings where resistant organisms are present or patients have increased exposure to multiple courses of antibiotics.

For treatment and prophylaxis, penicillin is an important antibiotic in treating VGS infections though resistance continues to present a clinical concern. A recent survey of children with Gram-positive cocci isolated in North America showed that of 182 VGS, 28.6% were nonsusceptible to penicillin, 4.9% of which were fully resistant [4].

Treatment recommendations depend on susceptibility patterns. The treatment recommendation per The American Heart Association (AHA) guidelines for adults with native-valve infective endocarditis caused by highly penicillin-susceptible

(MIC ≤ 0.12 mg/L) VGS is intravenous penicillin G. Among the elderly, penicillin or ceftriaxone for 4 weeks is preferred. Uncomplicated episodes can also use gentamicin in combination with penicillin or ceftriaxone for 2 weeks. Patients with penicillin allergies can usually be treated with ceftriaxone; however, if patients experience immediate hypersensitivity, vancomycin for 4 weeks may be considered. Susceptibility testing of pathogens as well as repeat cultures is recommended [153].

Intermediate susceptibility is defined as MIC > 0.12 mg/L and ≤ 0.5 mg/L. AHA guidelines recommend the same treatment as penicillin-susceptible *Streptococcus* with the addition of gentamicin in the first 2 weeks of the 4-week course. This combination has been demonstrated to be synergistic against VGS [160]; however, higher doses of penicillin and longer treatment times (4–6 weeks) are recommended [66, 160, 161]. As before, vancomycin should be considered for penicillin-allergic patients. Bacterial eradication rates greater than 98% can be anticipated in patients who complete appropriate therapy [162]. Fully resistant strains have MICs > 0.5 mg/L and recommended treatment is intravenous gentamicin for 4–6 weeks plus intravenous penicillin (4–6 weeks), ampicillin (4–6 weeks), or vancomycin (6 weeks) [153].

In recent years, beta-lactam and macrolide resistance rates among clinically isolated VGS have increased. Antimicrobial susceptibility testing for beta-lactams and macrolides suggest that mutated PBP genes in combination with the acquisition of certain macrolide resistance genes may underlie a broader resistance phenotype [41]. This is a challenge because there is limited clinical data to support alternative regimens to optimize endocarditis treatment for penicillin-resistant VGS. However, options are available and antidotal data is presented below.

The majority of VGS strains tested are susceptible to vancomycin [66, 160]. There are reports where vancomycin alone and vancomycin used in combination with ceftriaxone and gentamicin have been successfully used for treatment of endocarditis caused by resistant VGS [163, 164]. Treatment of penicillin-resistant VGS can present a more challenging clinical picture. One case showed that vancomycin treatment alone or in combination with cefotaxime and gentamicin did not completely eradicate a highly penicillin-resistant *S. mitis* strain in a human immunodeficiency virus positive man with endocarditis [165]. Vancomycin and gentamicin in combination also failed to cure endocarditis caused by highly penicillin-resistant *S. sanguis* in a 65-year-old woman with multiple medical problems. [166]. Though case reports tend to be biased toward negative outcomes, these data do demonstrate the need for new therapeutic options.

Additional antibiotics with demonstrated in vitro activity against VGS isolates include levofloxacin, moxifloxacin, quinupristin/dalfopristin, linezolid, and daptomycin. Though rare, in vitro resistance has been documented for these

antimicrobials as well. As with other antibiotics, culture and susceptibility should guide treatment. Limited clinical outcome data exists for some of the other, newer antimicrobials though typical resistance mechanisms will play a role in these antibiotics as potential treatment options. Linezolid-resistant strains are uncommon and it has been used successfully to treat endocarditis caused by vancomycin-resistant enterococci and methicillin-resistant staphylococci [71, 167]. However, oxazolinones are bacteriostatic antibiotics, and as a result their usage for treatment of infective endocarditis may be compromised [70]. Currently there is no information supporting the efficacy of linezolid in the treatment of endocarditis caused by VGS [38].

One case report of an immunocompromised patient with infective endocarditis revealed multidrug-resistant (MDR) VGS as the causative pathogen. Recurrent cycles of therapy to treat bacterial infections throughout the patients' lifecycle could have resulted in the penicillin, cephalosporin, carbapenem, macrolide, and fluoroquinolone-resistant *S. mitis*. Due to multiple complications, the patient died from pulmonary thromboembolism [41]. Another case report of a levofloxacin-resistant *S. mitis* manifested into endogenous endophthalmitis in the setting of mitral valve endocarditis as the presumed source of infection. The patient fully recovered after 6 weeks of intravenous ceftriaxone therapy based on the 2005 treatment guidelines of the AHA for patients with native-valve endocarditis caused by viridans streptococcal isolates with a penicillin MIC of 0.12–0.5 mg/L [168].

Increasing numbers of penicillin-resistant VGS strains among normal microbiota may also challenge prophylactic treatment of infective endocarditis. Amoxicillin or ampicillin is the current recommendation for endocarditis prophylaxis [66]. The prophylactic use of these antibiotics may select for penicillin-resistant VGS strains among normal microbiota, and these strains may be able to cause infective endocarditis [165]. Clindamycin is recommended for prophylaxis for patients allergic to penicillin [66]; however, it should be noted that use of macrolides can also select for clindamycin-resistant strains among streptococci in the normal flora. Telithromycin is very active against VGS strains in the normal microbiota. Despite resistance patterns, penicillin continues to serve as a widely used classical antimicrobial agent in the treatment of infective endocarditis. In patients with infective endocarditis, among other diseases, continuous surveillance of VGS isolates is warranted and can help guide appropriate treatment.

5.1.2 Neutropenic Fever

Neutropenic fever is defined as an absolute neutrophil count of less than 1500 cells/ μ L with a single oral temperature of $>38.3^{\circ}\text{C}$ (101°F) or a temperature of $>38.0^{\circ}\text{C}$ (100.4°F) sustained for >1 h [169]. There have been changes in the etiology of bacteremia in febrile neutropenic patients, and

infections are an important cause of morbidity and mortality among this population. Gram-negative pathogens was historically the primary cause; however, up to 70 % of bacteremia cases in neutropenic patients are now associated with Gram-positive bacteria [170–173]. Bacteremia is identified in 10–27 % of febrile neutropenic patients with hematologic malignancies, and 18–29 % of the bacteremia is caused by viridans streptococci. Possible reasons for this shift are use of prophylactic antibiotics, increased use of intravenous catheters, and aggressive chemotherapies resulting in prolonged neutropenia and mucositis [171, 172, 174, 175]. VGS are an important cause of bacteremia among neutropenic patients. One study assessed 528 episodes of bloodstream infections, 15 % of which were associated with neutropenia. Thirty-five percent of the blood stream infections were caused by Gram-positive pathogens, with VGS being the most frequent causative pathogen at 22 % [176]. The proportion of VGS as a cause of bacteremia ranges between 3 % and 30 % [56, 172, 173, 177–179]. *S. mitis* followed by *S. oralis* or *S. sanguis* are the most commonly isolated species [173, 179–182]. Bacteremia caused by VGS strains often originate from the oral mucosa [183, 184]. 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 [174, 182]. VGS infections can be rather asymptomatic, fever being the most common symptom [174, 181, 185–187]. Eighteen to 39 % of the patients with VGS infections develop serious complications, including septic shock, acute respiratory distress syndrome (ARDS), or both. Viridans streptococci are currently one of the most common pathogens in both adults and children, and bacteremia caused by this bacteria can result in death in up to 20 % of patients [188].

Multiple guidelines exist to combat neutropenic fever. Guidelines continue to be revised based on continued clinical evidence, experience, and advances in drug development. The Infectious Diseases Society of America's (IDSA) most recent update in recommendations in treatment of patients with fever and neutropenia discuss risk assessment. Once fever is detected, risk and severity infection should be assessed in order to help guide type, venue, and duration of empirical treatment. Updated European guidelines review the importance of appropriate initial antibiotic therapy in febrile neutropenia to minimize the collateral damage associated with antibiotic overuse and the further selection of drug-resistant pathogens. The guidelines suggest that infection control procedures and new antibiotic regimens based on local epidemiology, risk factors, escalation and de-escalation approaches, duration of empiric therapy, nonconventional therapies against MDR, and other bacterial management issues are vital to optimize antibiotic choice. For the purposes of this chapter, we will focus on IDSA-based recommendations.

Low-risk patients are defined as those having neutropenia for less than 7 days and no or few comorbid conditions. Oral empiric therapy is warranted in this population. In both low- and high-risk patients, empiric therapy should appropriately cover both Gram-positive and Gram-negative bacteria with special attention to VGS and *Pseudomonas aeruginosa* strains because infection may progress rapidly. Ciprofloxacin plus amoxicillin-clavulanate in combination is the treatment of choice, and antibiotic prophylactic treatment is not recommended in low-risk patients [189].

Per IDSA guidance, risk is affected by duration of neutropenia. High-risk is defined as neutropenia for greater than 7 days in duration with an absolute neutrophil count of ≤ 100 cells/mm [3] and/or significant comorbid conditions. For these patients, hospitalization and intravenous empirical treatment may be necessary. Preferred agents include an antipseudomonal beta-lactam, carbapenem, or piperacillin-tazobactam, although initiation of monotherapy with an antipseudomonal beta-lactam agent, such as cefepime, meropenem, imipenem-cilastatin, or piperacillin-tazobactam, may be used. Ceftazidime monotherapy has also been shown to be effective and continues to be used at some cancer centers. However, many experts avoid ceftazidime monotherapy because of rising resistance rates among Gram-negative bacteria and its limited activity against Gram-positive bacteria, such as streptococci, compared with newer alternatives [169]. Glycopeptides should be avoided first-line because of limited Gram-negative coverage, and empirical addition of vancomycin did not give extra benefit when compared to piperacillin-tazobactam therapy [190]. Regardless, the addition of this agent could benefit those with suspected catheter-related infection, skin or soft tissue infection, pneumonia, or hemodynamic instability [169].

For patients with methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), extended-spectrum β -lactamase (ESBL)-producing gram-negative bacteria, and carbapenemase-producing organisms, including *Klebsiella pneumoniae* carbapenemase (KPC), other agents may be added for adequate coverage. Fluoroquinolone prophylaxis should be considered for high-risk patients [191]. In multiple institutions, the use of quinolone prophylaxis in high-risk neutropenic patients is considered standard of care but the rapid development of resistance on therapy is a concern. Garnica et al. analyzed outcomes associated with quinolone prophylaxis and observed fewer episodes of febrile neutropenia and bacteremia, shorter duration of antibiotic therapy and hospitalization, as well as increased use of carbapenems and higher rates of quinolone resistance [192]. Although IDSA, among other treatment guidelines, recommend beta-lactam therapy as drug of choice, it is uncertain whether these practice guidelines can be applied to both adults and children due to potential differences in complication frequencies and antibiotic susceptibilities.

Han et al. compared clinical characteristics and antibiotic susceptibility patterns in patients with bacteremia caused by VGS in febrile neutropenic adults and children. Among the 202 episodes of viridans streptococcal bacteremia in adults and children, there were 20.8 % of cases with severe complications including 6.9 % identified deaths. Approximately 13 % of these episodes were attributable to bacteremia caused by VGS. Susceptibility testing results demonstrated that 80 % of the 199 isolates were susceptible to cefepime, and there was no association with patient age and pathogen susceptibility. This data suggests that it may not be necessary to adjust treatment guidelines between adults and children. In pediatric cancer patients, VGS strains are predominantly *S. mitis* and *S. oralis*. *S. mitis* is the most frequent VGS species causing bacteremia and is also most likely to be penicillin resistant [188].

Antimicrobial resistance in streptococci is rising. Studies have shown penicillin resistance is greater than 50 % and imipenem resistance is up to 25 % of *Streptococcus* from bone marrow transplant recipients [171]. As a result, some institutions may include vancomycin in the initial empiric treatment of febrile neutropenia. Studies have shown increased mortality in patients with viridans streptococcal bacteremia when vancomycin was not included in the initial empiric regimen [173]. More recently, Shelburne et al. developed a clinical prediction model for beta-lactam resistance in VGS causing bloodstream infection. The study validates use of Gram-positive spectrum antibiotics, including vancomycin, for empiric therapy of febrile neutropenia. Several assumptions were made including the definition of penicillin non-susceptibility, an MIC value ≥ 2 mg/L, increased risk of shock syndrome, and mortality. It was also assumed that vancomycin administered at onset of fever in neutropenic patients with VGS bacteremia will improve outcomes. Beta-lactam use in the prior 30 days, beta-lactam prophylaxis, and inpatient status at onset of febrile neutropenia correlated with a predicted MIC value ≥ 2 mg/L and non-susceptibility. It was determined in this one study that glycopeptides can be safely deferred until documentation of a resistant Gram-positive bacterial infection is made, despite IDSA guidelines stricter criteria [193].

5.1.3 Cystic Fibrosis

Cystic fibrosis (CF) is an inherited condition which affects the cells that produce mucous, sweat, and digestive secretions. Secretions become thick and plug passageways in the lungs and sinuses. Bacteria can adhere to this thick mucus and result in sinusitis, bronchitis, and pneumonia. Although CF has no cure, antibiotics are a staple in the treatment and prevention of lung infections. Evidence suggests *S. anginosus*, among other VGS organisms, may be important pathogens in this population. Recent studies have compared resistance patterns in CF and non-CF patient populations and have shown that both penicillin- and erythromycin-resistant VGS isolates in fibrotic

patients have reached 38.4 % and 87.9 %, respectively. Among CF isolates, resistance rates are increasing as patients are living longer and continuously face antibiotic exposure. Moreover, as the physiology of the lung is affected in these patients, so is drug penetration into their lungs. This may result in suboptimal drug concentrations at the site of infection, leading to increased selection of resistance [194].

5.2 Infections Caused by Beta-Hemolytic Streptococci

Beta-hemolytic streptococci are causative of a wide-range of diseases, both invasive and noninvasive. Some of these include streptococcal pharyngitis, neonatal sepsis, endocarditis, meningitis, and urinary tract infections. For the purpose of this review, we will focus on two clinically relevant presentations: pharyngitis and neonatal sepsis.

5.2.1 Pharyngitis

Severity of pharyngitis may vary but is traditionally defined by discomfort and pain in the throat, making it difficult to swallow. It is caused by swelling in the pharynx and may be bacterial in nature. Five to 15 % of pharyngitis cases are caused by GAS [195]. Penicillin is the drug of choice for treatment of streptococcal infections and macrolides are considered as alternative treatment for patients allergic to penicillin. Susceptibility testing should be used to confirm treatment choice and repeated cultures should be monitored for resistance development while on therapy.

Treatment eradication rates are associated with pathogen susceptibility. Specifically, studies have demonstrated the eradication rate is only 38–60 % when macrolides are used to treat macrolide-resistant strains in comparison to an eradication rate of 80–92 % when these agents are used against macrolide-susceptible organisms. [196–198]. 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 [198]. Again, emphasizing the importance of culture and susceptibility results in treatment selection. A recent study has also shown *erm* and *emm* 90 to be important resistance genes in invasive GAS [199]. Few resistant strains exist and the knowledge of resistance and resistance mechanisms is important. For example, use of clindamycin against an erythromycin-resistant isolate requires knowledge of the result of both the susceptibility testing and the determination of the macrolide resistance phenotype for a given isolate, because clindamycin should not be used to treat isolates with the MLSb-phenotype [106].

There has been debate of the remarkable stability of penicillin susceptibility in GAS and other beta-hemolytic streptococci and whether these high susceptibility rates will remain stable. Resistance to penicillin occurs in related spe-

cies, such as *S. pneumoniae*, VGS, and enterococci at high rates. Reasons for the continued high susceptibility rates to penicillin in GAS include the inefficient mechanisms for genetic transfer in GAS, barriers to DNA uptake and replication, and the findings that altered PBPs expressed by penicillin-resistant laboratory mutants of GAS have defective cell-wall biosynthesis thus decreasing the viability of the penicillin-resistant organism [200, 201].

Beta-hemolytic streptococci, especially GAS and GBS, may cause serious infections and alternatives to macrolides are scarce. Limiting use of these agents should be encouraged [202, 203]. 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, and reduction of use of these agents has been shown to lead in reduction of macrolide resistance [146–148, 202–204]. Macrolide-resistant GAS strains remain susceptible to telithromycin and therefore could be a better treatment option.

5.2.2 Neonatal Sepsis

GBS is the leading cause of neonatal infections and intrapartum antibiotic prophylaxis. Per guidelines, all pregnant women in the United States are screened and are prophylactically treated. For those at risk, intrapartum penicillin therapy is recommended, with ampicillin, clindamycin, erythromycin, and vancomycin as acceptable alternative treatments, with penicillin G being the drug of choice [205]. Previously considered a genitourinary pathogen, it has emerged as a non-nosocomial opportunistic pathogen causing serious clinical complications including bloodstream infection, endocarditis, and CNS infections. Sunkara et al. evaluated the epidemiology of GBS in nonpregnant adults. It was found that GBS is associated with younger age, higher incidence of beta-lactam allergy, and independently linked to immunosuppression. GBS are susceptible to commonly used antimicrobials including penicillins and cephalosporins and therefore are not associated with a delay in initiation of appropriate antimicrobial therapy. Resistance rates in second-line treatment options, including macrolides and clindamycin, continue to rise and should be closely monitored [206].

6 Conclusion

In this review, we discussed key global resistance data, including incidence and mechanisms of resistance. Beta-lactam resistance is primarily mediated by point mutations in penicillin-binding proteins (PBPs) and presents clinical challenges due to its role in treatment of infective endocarditis and neutropenic fever. Common macrolide resistance genes include *erm* and *mef*. Resistance with this class of antibiotics may be responsible for a variety of infections including phar-

yngeitis and neonatal sepsis. Both resistance genes and mechanisms continue to evolve, and new sequences have been discovered in recent years. Antibiotic overuse, inappropriate antibiotic use, and delayed antibiotic administration are contributing factors to the rise in antibiotic resistance. Clinical studies and drug development continue to provide guidance and new treatment options; however, use of local antibiograms, implementation of infection control procedures, and antimicrobial stewardship are critical in treating patients with invasive streptococcal infections including VGS and beta-hemolytic streptococci.

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