WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 11, 1812-1819. Review Article ISSN 2277–7105

ANTIBIOTIC RESISTANCE AND PATHOGENICITY OF STREPTOCOCCUS, REVIEW

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Article Received on
20 April 2024,

Revised on 10 May 2024,
Accepted on 30 May 2024

DOI: 10.20959/wjpr202411-32372

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ABSTRACT

Group A *Streptococcus* (GAS; *Streptococcus pyogenes*) is a nearly ubiquitous human pathogen responsible for a significant global disease burden. No vaccine exists, so antibiotics are essential for effective treatment. Despite a lower incidence of antimicrobial resistance than many pathogens, GAS is still a top 10 cause of death due to infections worldwide. According to the World Health Organization, the bacterial resistance to antimicrobial drugs has emerged as one of the major universal problems that requires and needs prime attention by humankind due to the emerging resistant acquired by many of the bacterial species which allows them to evade both antimicrobial drugs and the immune system. *Streptococcus* species (e.g., *Streptococcus pneumonia*, *Streptococcus agalactiae*, and *Streptococcus pyogenes*) are categorized serologically and are grounded on carbohydrates present in the cell wall into different groups, such as Group A to Group V. There are over 85 capsule antigenic types of *S. pneumoniae*, 124 serotypes of *S. pyogenes*, and 9 *S. agalactiae* with capsular polysaccharide serotypes (CPS). Group B *Streptococcus* (GBS) stands out as a major agent of pediatric disease in humans, being responsible for 392,000 invasive disease cases and 91,000 deaths in infants each year across the world. Moreover, GBS, also known as *Streptococcus agalactiae*, is an important agent of infections in animal hosts.

KEYWORDS: Pathogenicity, Antibiotic resistance, Streptococcus.

INTRODUCTION

Streptococcus pyogenes (Group A *Streptococcus*, GAS) is a ubiquitous human pathogen responsible for over half a million deaths per year worldwide. No vaccine exists, and current treatment depends on conventional antibiotics and symptom management. While the b-lactam

penicillin remains the antibiotic of choice for mild to moderate infections, severe or prolonged infections require additional measures for effective clearance. GAS colonizes the nasopharynx, where it can cause disease, disseminate to other sites in the body, and transmit to other humans. GAS is isolated from this site in 12–24% of healthy children and in 37% of those with a sore throat. Pharyngitis, or strep throat, is the most common disease caused by GAS and is estimated to occur more than 600 million times per year. The common symptoms of pharyngitis are a sore throat, fever, enlarged tonsils, and coughing with throat pain, induced by pro-inflammatory exotoxins secreted by GAS. Some individuals are susceptible to recurring pharyngitis. which may be prevented with tonsillectomy, although 33% of children lacking tonsils are still colonized by GAS. The b-lactam penicillin remains the gold standard of antibiotic treatment for many GAS infections. b-lactams target penicillin-binding proteins (PBPs) to block peptidoglycan cross-linking in metabolically active bacteria, leading to bacterial death.

More than 60 Streptococcus species have been recognized so far. Some of these, such as S. pyogenes, S. agalactiae, S. equi, S. canis, and S. iniae, produce hemolytic factors and, when cultivated on solid media S. dysgalactiae subsp. equisimilis may be classified as belonging to the C or G group, while it may also be classified, even though less commonly, as group A or L ; isolates from S. phocae may belong to either the C or G group; isolates from S. infantarius are sporadically considered as group D; isolates from S. anginosus are indifferently classified as group A, C, G, F, or N; isolates from S. constellatus subsp. constellatus belong to either group F or N; sporadic isolates belonging to S. constellatus subsp. pharyngis can be considered as group C; isolates from the S. intermedius species can be considered as group N; and finally, isolates belonging to S. porcinus are classified in either group P, U, or V.

Antibiotic resistance

Streptococcus develops resistance to clindamycin by two primary mechanisms: target site modification or efflux pumps. Methylation of clindamycin target sites on the 23S RNA by ErmA, ErmC, or enzymes are most common. Isolates with this mechanism can either have constitutive or inducible resistance to clindamycin. Inducible resistance can result in treatment failure, as inducible clindamycin resistance is undetectable unless macrolides are also present. Efflux pumps are a common resistance mechanism, such as *msrA* and *mefA* involved in macrolide resistance. Despite the structural similarity of clindamycin and macrolides, these pumps have shown greater efficacy against macrolides. *Staphylococcus*

species may also enzymatically inactivate clindamycin through LinA. Due to the frequency of antibiotic resistance genes being plasmid mediated, there is concern of horizontal gene transfer generating new resistant strains. Clindamycin resistance in the United States is on the rise, from an estimated 0.5% in 2003 to currently as high as 15% in pediatric populations. Isolates from invasive infections are more commonly resistant, increasing from 2% to over 23% in this time.

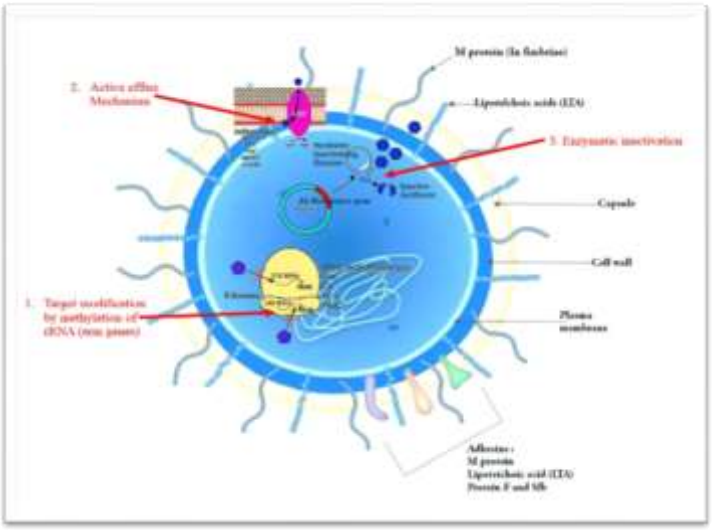

Figure 1: Ability of Streptococcus for antibiotics resistance.

Resistance is primarily found in PBP mutations. One proposal is that PBPs with low affinity for b-lactams are poorly tolerated by GAS. Consistent with this, GAS engineered to express low-affinity PBPs had growth defects, poor growth rates, and morphological abnormalities. Additional work showed that decreases in the M protein production could lead to resistance, at the cost of being avirulent. Taken together, this suggests that PBPs are essential to GAS biology, and changes that would support resistance are either fatal or so detrimental that survival in a clinical setting is quite difficult. This has been partially backed up by recent work showing that three or fewer amino acid changes to PBP have occurred in 99% or more of the clinically relevant GAS strains.

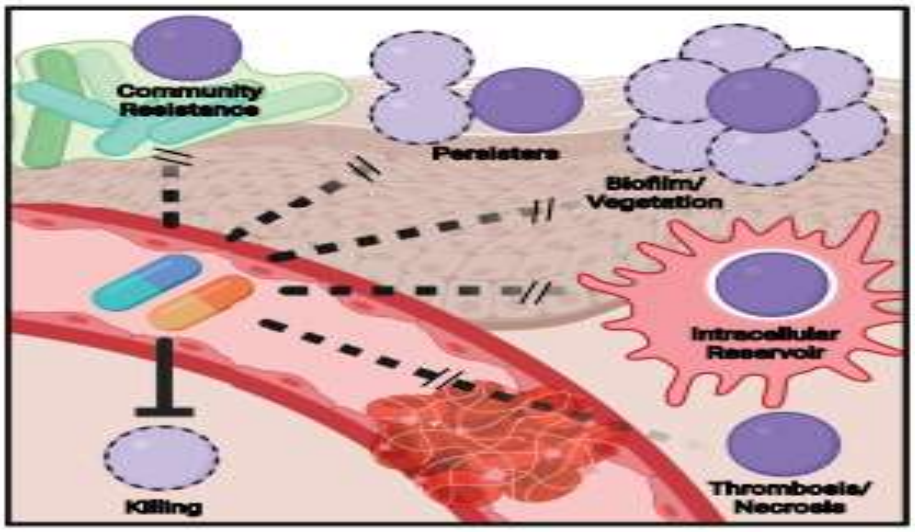

Figure 2: Role of defense mechanisms in bacteria to control action against antibiotic effect.

Mechanisms related with macrolides

Resistance to macrolides in the genus *Streptococcus* is due to three different mechanisms: ribosomal post- and pre-transcriptional modifications, active expulsion of the antibiotic by efflux pumps and target protection. These resistance mechanisms usually confer resistance to other antibiotic groups which have their target site in the 50S ribosomal unit, such as lincosamides or streptogramins. This fact is the basis of phenotypic classification of macrolide and lincosamide resistance. Resistance due to ribosomal mutations in the 23S rRNA or L4 and L22 proteins is very rare in streptococci, conferring different resistance phenotypes depending on the mutations found. For instance, mutations in 23S rRNA, or near the macrolide binding residue A2058, result in different levels of macrolide resistance, depending on the copies of the rRNA operons mutated, which means that high-level resistance requires mutation of most of these operons. Regarding riboproteins, substitutions in the L4 protein (*rplD*) such as K63E, deletions in L4, such as Del65WR66 or deletions of the 82ME84 in the L22 (*rplV*) are the most frequently found associated with macrolide resistance. These bacteria have different levels of resistance tetracycline in different period as shown in table-1.

Table 1: Tetracycline resistance genes.

Animal host	Country	Year	Bacterial species	No. of isolates	Tetracycline genes: Efflux *tet*(K)	Efflux *tet*(L)	Ribosomal protection *tet*(M)	Ribosomal protection *tet*(O)	Ribosomal protection *tet*(S)	No. of TetR isolates[b]	Percentage of resistance (%)
Cattle	USA	1990	*S. agalactiae*	39	0	0	NT[a]	7	NT	10	25.6
			S. dysgalactiae	21	1	1	NT	1	NT	9	42.9
			S. uberis	11	1		NT	1	NT	2	18.2
Cattle	France	1984–2008	*S. agalactiae*	76	NT	NT	16	13	1	30	39.5
			S. dysgalactiae	32	NT	NT	5	4	4	32	100.0
			S. uberis	101	NT	NT	23	36	3	62	61.4
Cattle	Portugal	2002–2003	*S. agalactiae*	60	34	NT	13	20	0	34	56.7
			S. dysgalactiae	18	0	NT	6	6	0	18	100.0
			S. uberis	30	0	NT	2	9	8	18	60.0
Ovine	Italy	2004–2014	*S. uberis*	51	9	NT	12	12	NT	18	35.3
Pig	USA	1986	*S. suis*	21	0	0	5	NT	NT	14	66.7
Pig	Denmark	1989–2002	*S. suis*	103	NT	0	11	6	0	25	24.3
Pig	Italy	2003–2007	*S. suis*	57	0	0	2	38	0	51	89.5
Pig	China	2005–2012	*S. suis*	62	NT	NT	53	42	NT	57	91.9
				34	NT	NT	24	9	NT	28	82.4
Pig	China	2008–2010	*S. suis*	106	NT	2	16	86	1	105	99.1
Dog/cat	France	2010	*S. canis*	112	NT	1	31	16	5	36	32.1
Dog/cat	Japan	2015	*S. canis*	68	0	0	13	10	NT	16	23.5
Dog/cat/horse/human[c]	Portugal	2000–2010	*S. canis*	85	NT	1	11	8	1	23	27.0

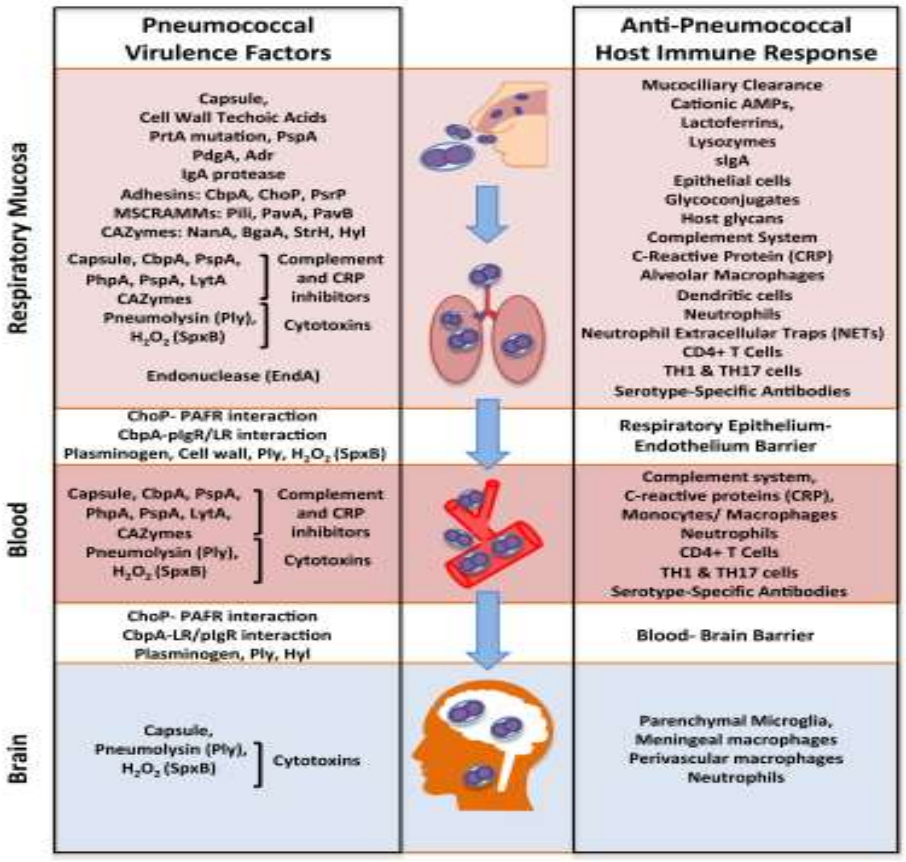

Figure 3: Virulence factors of bacteria and response in human body.

CONCLUSION

Resistance to antimicrobial agents among numerous microbes (Pathogens) has increased at an alarming rate around the world, posing a serious threat to human health. Because of the emergence of new resistant mechanisms and a decline in the efficacy of infectious disease therapy, microbial responses to routine treatment fail have resulted in longer sickness, higher healthcare costs, and a significant risk of mortality. The development of drug-resistant species and the MDR strains of *Streptococcus* species require uninterrupted national and international monitoring of susceptibility, to develop the best line of treatment. Antimicrobial drug resistance among *Streptococcus* species arising from earlier sensitive inhabitants resulted in parallel gene transfer or point mutations in chromosomes due to the unnecessary use of antibiotics.

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