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Editors

TANIA SIH
ALBERTO CHINSKI
ROLAND EAVEY
RICARDO GODINHO

Coordinator
TANIA SIH

Group A Streptococcus pyogenes Antibiotic Resistance in Brazil

Rosângela S. L. de Almeida Torres

In the pre-antibiotic era, streptococcal diseases were feared, frequent, and highly lethal. In 1908, the 177 cases of scarlet fever/100,000 inhabitants reported represented a percentage of 12% of fatal cases. High rates of incidence of the disease were found both in classrooms as well as at home. The introduction of penicillin in antimicrobial therapeutics was a remarkable event that changed the epidemiological profile of infections, drastically reducing not only the number of cases but also their mortality rates. Although the use of antimicrobial therapeutics in the treatment of bacterial infections was viewed with great enthusiasm, the appearance of several microorganisms resistant to penicillin during the first decade of the introduction of this drug led the pharmaceutical industry seek more potent new drugs, with a broader spectrum of action. Today, we are aware that microorganisms exist that do not respond to any known antimicrobials.

In contrast to this gloomy scenario, *Streptococcus pyogenes* or group A *Streptococcus pyogenes* (GAS) continues to be particularly susceptible to ß-lactam antibiotics. Epidemiological surveys carried out in the states of Paraná, São Paulo, Rio de Janeiro and in the Federal District of Brazil, as well as in several other regions in the world, prove the absolute susceptibility of GAS to penicillin, which remains the first choice therapeutic drug for the treatment of infections caused by that microorganism.

We have checked the susceptibility of GAS to several antimicrobial classes that were routinely used in clinical practice throughout 17 years. Out of a total of 1,112 samples analyzed, 626 (56%) isolates were recovered from pharyngeal carriers; 357 (32%) belonged to patients with pharyngitis, and 129 (12%) to patients suffering from other infections. Penicillin maintained constant levels of the Minimum Inhibitory Concentration (MIC), which ranged from 0.015 – 0.03 μg/mL.

As can be seen from **Table 1** the diverse formulations, doses and routes of administration of penicillin reached higher or similar blood levels to the MIC presented by GAS.

Based on its high incidence and the diversity of the infections caused by GAS, the outcome showed it was one of the major human pathogens. Its natural reservoir is the respiratory tract as well as the skin, where it can either linger without causing any diseases or it may progress into pharyngitis/tonsillitis or impetigo/pyoderma, followed or not by scarlet fever. Moreover, it may trigger autoimmune diseases such as rheumatic fever (RF) and acute glomerulonephritis (AGN). From those primary sites (oropharynx and skin), the bacterium may access sterile tissues causing invasive illnesses such as pneumonia, bacteremia,

meningitis, cellulites, necrotizing fasciitis (NF), and streptococcal toxic shock syndrome (STSS)- some of which are severe life-threatening diseases. Interactions between the pathogen and the host contribute to the development and severity of the invasive infections. Such interactions vary according to the GAS (M-type) strain, its virulence, antimicrobial susceptibility, and individual characteristics in the modulation of an inflammatory immune response in the host.

Table 1. Concentrations of Penicillin in Serum (U/mL[3])

	U/mL[3]
Penicillin G Potassium *(*continuous infusion/24h 20,000,000 U endovenous)	27
Penicillin G Procaine (600,000 U IM injection)	Maximum = 5 Minimum = 0,16
Penicillin G Benzathine (1,200,000 U IM injection)	Maximum = 0,12 24 hours = 0,03 After 14 days = 0,02

Strep throat is common in our environment and affects mainly school age children (15 to 30% of cases), the target population for the more than 200 existing M-types of GAS. Various types of GAS are classified in M-types, according to differences in fimbriae, which are appendages found in the bacterial cell surface composed by protein M. Although each M-type induces a distinct immune response, an infection by a specific M-type provides immunity to it but the child remains susceptible to the other types. This is why there are fewer cases in adults, once those who have already suffered a number of challenges with diverse strains become immune to them. Infections in adults occur in about 5 to 10% of cases.

Macrolides (erythromycin, azithromycin) are important antimicrobials for the treatment of streptococcal infections in cases presenting failure to the treatment with or allergic reactions to penicillin. However, unlike what happens with penicillin, GAS has developed resistance to macrolides, lincosamides and streptogramin B (MLS_B phenotype) through multiple mechanisms, among which are ribosomal modifications (acquisition of *erm*A, *erm*B genes) and the active efflux of the drug (*mef*A gene). Susceptibility of GAS to macrolides has varied significantly in different regions of the world, and is especially linked to the abusive use of these drugs in therapy. Very high rates of resistance have been reported in Japan (80%), Taiwan (63%), and in Korea (20.2%), as well as in several European countries such as Italy, France, Greece and Spain which have rates of 56.3%, 22.4%, 24%, and 21.3%, respectively.

Differentiated rates of resistance to macrolides have been found in the Americas. Canada reported a 2.1% rate (2003) that rose to 14.4% in subsequent years. An average 6.8% resistance to erythromycin was found in several medical centers that were examined in the U.S. (2005). Argentina, located in the same geographical region showed rates ranging from 0.5 to 14.1% (2004).

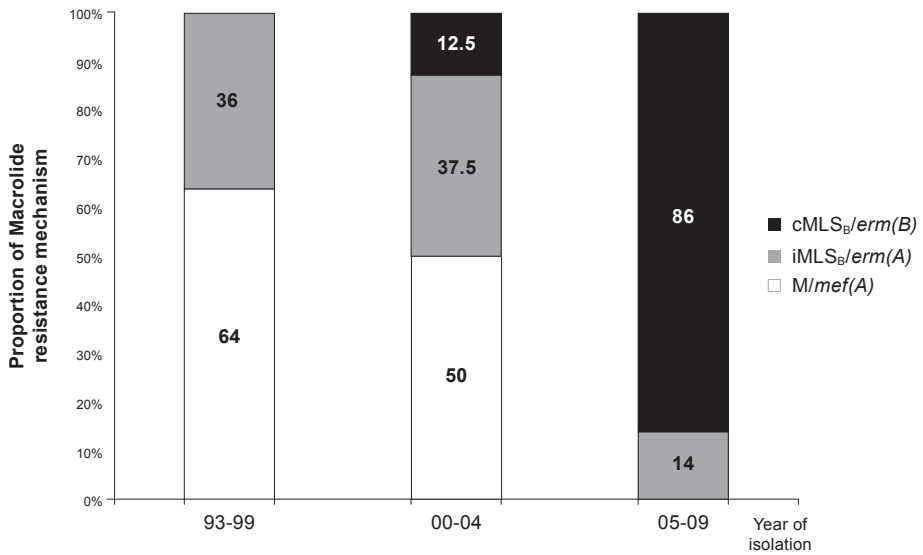
Few studies have been carried out in Brazil. In Rio de Janeiro (2003), 357 isolates of GAS were analyzed and only 1.6% was resistant to erythromycin. In the same year, 145 samples from São Paulo, Brasilia and Florianopolis were analyzed in a study (*PROTEKT Surveillance Study)* that reported 6.2% resistance.

Another study carried out in Brasilia (2010), did not identify any resistance among the 130 isolates of GAS analyzed.

Out of the 1,112 isolates of GAS analyzed in our study, 739 had been isolated before the year 2000 and presented a 2.9% resistance to erythromycin. After 2000, 373 samples were analyzed, and the rate of resistance was 4.0% (p=0.001). The rate of resistance to erythromycin is low in Brazil when comparing it with the results obtained in other countries, however, a rising trend was noted mainly during the last year of our study (2009), when a 15.6% resistance to erythromycin was found among 32 samples analyzed.

In 2004, we observed the emergence of a clone of GAS M-type 22, resistant both to erythromycin and clindamycin (cMLS$_B$/*erm*B), which had not yet been described in Brazil. The same phenotype of resistance was found again in subsequent years (2005 – 2009), that also included other M-types (11, 28, 73, 76) (**Figure 1**).

Figure 1. Macrolide Resistance Mechanisms - From 1993 to 2009



1993–2009: 739 isolates (*mef*(A) [N = 9], *erm*(A) [N = 5]); 00–04: 194 isolates (*mef(*A) [N =4], *erm*(A) [N = 3] and *erm*(B) [N=1]); 05-09: 179 isolates *erm*(A) [N = 1], *erm*(B) [N=6]).

M-types 11 and 28 were responsible for the high rates of double resistance to erythromycin and clindamycin reported in European countries such as France (2004), Belgium (2005), and Spain (2010), and showed great potential for dissemination. Surprisingly, resistance to erythromycin was significantly associated with pharyngitis ($p < 0.001$). In comparison to other clinical manifestations, the pharyngitis group was associated with a relative risk of acquiring an erythromycin-resistant GAS of 4.7 (95% CI: 2.1%–10.1%).

Not withstanding the above, some treatment failures have been reported despite the total susceptibility of GAS to penicillin. One of the possible explanations for this is that s**ome GAS strains have the ability to internalize in epithelial cells**. Penicillin does not penetrate in eukaryotic cells thus, internalization provides the microorganism a survival niche. Strains that contain adhesion-invasion genes are responsible for failure to eradicate GAS after treatment with penicillin, and contribute to keeping carrier status and recurrence of streptococcal infection.

On the other hand, macrolides produce levels of activity in eukaryotic and prokaryotic cells. Thus they are becoming the drugs of choice for treating and eradicating infections caused by those microorganisms.

Some countries have observed with concern a statistically significant association between the presence of genes that promote internalization of GAS in epithelial cells and resistance to macrolides. Therefore, **macrolides should be used rationally. Indiscriminate use of such drugs results in the selection of resistant strains of GAS that easily disseminate among the population**.

In addition to the growing increase of resistance to erythromycin and clindamycin reported over the last few decades in many countries, the emergence of highly virulent clones bearing the return of severe streptococcal diseases in several parts of the world has also been detected. In 2011, Paraná State registered an increase in the number of severe cases caused by GAS (complicated pharyngitis, scarlet fever, pneumonia, meningitis, NF, and STSS), some of them followed by death.

Brazil is going through a phase of profound changes with regard to the use of antimicrobials. In October 25, 2010, ANVISA (Brazilian National Agency for Sanitary Vigilance) issued a Resolution (RDC # 44) **prohibiting the sale of antimicrobials without a prescription**. This was an extremely important step taken to reduce the indiscriminate use of antibiotics by the population. The first step has been taken. On the other hand, if microorganisms develop even more skills to survive and multiply themselves within human tissue, we humans must, on the other, be ready to recognize their assail and administer the appropriate treatment. **The rational use of antimicrobials may reduce the danger of repeating the scenarios of the past when, due to the lack of effective drugs, streptococcal infections used to develop into severe conditions**.

Recommended readings

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