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SPECIAL ARTICLE

Susceptibility to β-lactams in β-hemolytic streptococci

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Abstract Group A (GAS), B (GBS), c (GCS) and G (GGS) β-hemolytic streptococci are important human pathogens. They cause infections of different severity and frequency. Nowadays, after 70 years of use, penicillin is still universally active against GAS, GCS and GGS. However, therapeutic failures have been recorded in 2–28% of pharyngitis cases (median: 12%) attributable to different causes. By contrast, some GBS with reduced susceptibility to penicillin have been described, especially in Japan. In this group of bacteria, it is important to highlight that confirmation by reference methods is mandatory when decreased susceptibility to penicillin is suspected as well as checked for the detection of the mechanisms involved.

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PALABRAS CLAVE
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Streptococcus dysgalactiae subsp. *equisimilis*;
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Penicilina;
Sensibilidad

Sensibilidad a los β-lactámicos en estreptococos β-hemolíticos

Resumen Los estreptococos β-hemolíticos de los grupos A (GAS), B (GBS), C (GCS) y G (GGS) son importantes patógenos humanos. Ellos producen infecciones de diversa gravedad y frecuencia. Aún después de más de 70 años de uso, la penicilina sigue siendo activa *in vitro* frente al 100% de los GAS, GCS y GGS. No obstante se han producido fallas terapéuticas entre el 2-28% de los casos de faringitis (media: 12%), atribuibles a diversas causas. En cambio se han descrito aislados de GBS con sensibilidad reducida a la penicilina, especialmente en Japón. Es importante que toda sospecha de sensibilidad disminuida a la penicilina en este grupo de bacterias sea confirmada por los métodos de referencia y comprobada mediante la detección de los mecanismos involucrados.

Introduction

Group A (*Streptococcus pyogenes*), and large colony group C and G (*Streptococcus dysgalactiae* subsp. *equisimilis*) streptococci share the profile of being transient colonizers of human skin and mucous and produce several infections such as pharyngitis, scarlet fever, acute otitis media, impetigo, erysipelas, cellulitis, necrotizing fasciitis, septic arthritis, pneumonia, bacteremia and toxic shock syndrome, among the most frequent ones. Their impact is not only quantitative (more than 600 million infections annually) but it is also qualitative, regarding the severity of necrotizing fasciitis, myositis, puerperal sepsis, and the toxic shock syndrome. Additionally, group A streptococci (GAS) have been investigated for their significant role in the development of post-streptococcal infection sequelae, including acute rheumatic fever, acute glomerulonephritis, and reactive arthritis. Group A streptococcal infections have also been associated with Tourette's syndrome, tics, and movement and attention deficit disorders[5].

Streptococcus agalactiae or group B streptococci (GBS) colonize the genital and gastrointestinal tract of women and men and vertical transmission from a colonized mother to her newborn during labor can result in life threatening infections. Because of the latter, GBS is the leading cause of neonatal sepsis and meningitis. In addition, it has been recognized as an important pathogen in non-pregnant individuals, especially elderly people and those suffering from underlying medical disorders[29].

Treatment of different streptococcal infections is mainly based on the use of penicillin V administered orally, intramuscular benzathine penicillin, parenteral penicillin G, amoxicillin or cephalosporins (cephalexin, cefotaxime, ceftriaxone). In allergic patients or special clinical presentations, the first options are macrolides (erythromycin, azithromycin, clarithromycin) and/or lincosamides (lincomycin, clindamycin). Clindamycin is the recommended antibiotic to treat severe infections of skin and soft tissues (necrotizing fasciitis, toxic shock syndrome).

Depending on the susceptibility tests, the patient may be treated with tetracyclines (tetracycline, minocycline, doxycycline), vancomycin or fluoroquinolones (levofloxacin, moxifloxacin). Aminoglycosides were added to β-lactam antibiotics to treat rare cases of endocarditis due to groups C or G streptococci.

The aim of the present review is to describe the mechanisms and the prevalence of β-lactam resistance in β-hemolytic streptococci of groups A, B, C and G.

Resistance to β-lactam antibiotics in groups A, C and G streptococci

To date, no group A, C or G streptococci with diminished susceptibility to penicillin or third generation cephalosporins have been detected[31]. Values of minimal inhibitory concentration (MIC), MIC_{90}, published in different studies showed a median of 0.016 μg/ml and a range of 0.0025–0.032 μg/ml. Some authors described ranges of MICs showing some values higher than the CLSI breakpoint for penicillin (0.125 μg/ml) for group C and G streptococci; however, these results were not confirmed by reference centers.

In Japan, 61.4% of intermediate susceptibility (MIC = 0.25 μg/ml) and 2.3% of resistance to penicillin (one isolate with a MIC = 2 μg/ml) was reported in patients with an initial episode of pharyngitis due to *S. pyogenes*; however, these results were also not confirmed[23].

With regard to group A streptococci, one hundred and thirty-three strains were collected in the Rockefeller University (New York, USA) during 80 years and neither of them showed changes in penicillin susceptibility. The MIC_{90} for the oldest strains (0.032 μg/ml) was the same of those collected in the last year of the study[17].

The question of why GAS remains susceptible to penicillin, can only be answered with speculations[8]:

a. β-Lactamase may not be expressed or may be toxic to GAS.
b. Low affinity PBPs are neither expressed nor render organisms nonviable.
c. GAS produce at least four different DNases that could limit the opportunity for acquisition of exogenous DNA via transformation.
d. Circumstances favorable for the development of resistance have not yet occurred.

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