BETALACTAM FAILURE IN TREATMENT OF TWO GROUP G STREPTOCOCCUS DYSGALACTIAE SUBSP. EQUISIMILIS PHARYNGITIS CASES

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CASE REPORTS

1. A 35-year old female patient had an acute exudative tonsillopharyngitis, with sore throat, enlarged tonsils, enlarged tender anterior cervical lymph nodes, elevated temperature (38.5°C) and elevated antistreptolysin O titers.

Group G beta-hemolytic *S. dysgalactiae* subsp. *equisimilis* was isolated from the throat (>100 colonies). MIC values were: amoxicillin 0.03 mg/L, clarithromycin 0.12 mg/L, levofloxacin 0.25 mg/L, moxifloxacin 0.25 mg/L, doxycycline 0.5 mg/l, clindamycin 0.25 mg/L.

No non-hemolytic streptococcal colonies were detected.

A concurrent diagnosis of infectious mononucleosis was excluded.

The patient was treated with 10 days of amoxicilline (1000 mg every 12 h) and had prompt relief of symptoms within few days of starting antibiotic therapy.

About 2 weeks later he had persistently elevated antistreptolysin O titers and the same organism was isolated from throat cultures (11-50 colonies). The patient was treated with 10 days of amoxicilline-clavulanic acid (1000 mg every 12 h).

15 days later, antistreptolysin O titers were persistently elevated and the same isolate of *S. dysgalactiae* subsp. *equisimilis* was cultured from the throat (11-50 colonies).

The patient was treated with 10 days of clarithromycin (500 mg every 12 h). Throat swabs performed after 15, 30 and 45 days were negative for beta-haemolytic and non-haemolytic streptococci and antistreptolysin O titers were no more elevated.
2. A 31-year old male patient, had an acute exudative tonsillopharyngitis, with enlarged tonsils, enlarged tender anterior cervical lymph nodes and increased antistreptolysin O titers. Temperature was not elevated (37°C).

Throat culture was positive for group G beta-hemolytic *Streptococcus dysgalactiae* subsp. *equisimilis* (>100 colonies). MIC values were: amoxicillin 0.03 mg/L, clarithromycin 0.12 mg/L, levofloxacin 0.5 mg/L, moxifloxacin 0.25 mg/L, doxycycline 1 mg/L, clindamycin 0.5 mg/L.

No non-hemolytic streptococcal colonies were observed.

A concurrent diagnosis of infectious mononucleosis was excluded.

She was treated with 10 days of amoxicillin (1000 mg every 12 h), which led to a rapid disappearance of symptoms, within few days of starting therapy.

About 10 days later she had persistently elevated antistreptolysin O titers and the same organism was detected in throat cultures (11-40 colonies). The patient was treated with 10 days of amoxicillin-clavulanic acid (1000 mg every 12 h).

15 days later, antistreptolysin O titers were persistently elevated and the same isolate of *S. dysgalactiae* subsp. *equisimilis* was cultured from the throat (11-45 colonies). She was treated with 10 days of clarithromycin (500 mg every 12 h). Throat cultures performed after 15, 30 and 45 days were negative for beta-haemolytic and non-haemolytic streptococci. Antistreptolysin O titers were no more elevated.

Throat swabs from the two patients were carefully rubbed over the posterior pharynx and in both tonsillar fossae and plated on Columbia agar base (Biolife, Italia) (4).

Each swab was inoculated onto three plates: the first plate was incubated at 37°C in aerobic atmosphere; the second plate was incubated at 37°C in anaerobic atmosphere; the third plate was incubated at 37°C in an atmosphere of CO₂ 5%. All plates were examined after 24 and 48 h.
Beta-hemolytic streptococcal colonies were observed on all media tested under the three different atmospheric conditions and subcultured to Blood-sheep agar (Biolife, Italia), at 37°C, in aerobic atmosphere.

Their Lancefield group G was established serologically by latex agglutination (Streptococcal grouping kit, Oxoid) with group A, B, C, D, F and G antisera.

The beta-hemolytic group G isolate was identified as \textit{S. dysgalactiae} subsp. \textit{equisimilis} by the Vitek 2 automatic system for biochemical identification of bacteria and yeasts (Biomérieux).

Non-hemolytic streptococci were not detected.

No \textit{Streptococcus salivarius} colonies were detected. This was important because the growth of beta-hemolytic streptococcal colonies is inhibited in the vicinity of bacteriocin-producing \textit{S. salivarius} colonies, especially when beta-hemolytic colonies are present in small numbers as in the carrier state (13).

MICs values were determined by the National Committee for Clinical Laboratory Standards (NCCLS)-recommended broth microdilution method (24).

Bacteria are associated with 30% of tonsillopharyngitis in children and 10% of tonsillopharyngitis in adults.

\textit{Streptococcus pneumoniae, Neisseria} spp., \textit{Corynebacterium} spp., \textit{Chlamydia pneumoniae}, \textit{Mycoplasma pneumoniae} (16) have been implicated as a cause of sporadic pharyngitis.

\textit{S. pyogenes} (Lancefield group A) may result in elevated antistreptolysin O titers and is responsible most frequently for streptococcal tonsillopharyngitis (14, 28, 32) and nonsuppurative sequelae, such as rheumatic fever (including heart inflammation and Sydenham’s cornea), reactive arthritis, glomerulonephritis, erythema marginatum.
S. agalactiae (Lancefield group B) and S. dysgalactiae subsp. equisimilis (Lancefield group C or group G) (35) are frequent inhabitants of the human pharynx and tonsils, where they can adopt either a commensal or a pathogenic role (2, 3, 10, 34). In fact, groups C and G beta-hemolytic streptococci may result in elevated antistreptolysin O titers and have been known to cause exudative tonsillopharyngitis and nonsuppurative sequelae of streptococcal infections, such as glomerulonephritis and reactive arthritis (12, 19, 21).

Particularly, S. dysgalactiae subsp. equisimilis is responsible for epidemic tonsillopharyngitis in adults and children (7, 17, 20, 36) and for sporadic episodes of tonsillopharyngitis in adults (1, 5, 11, 15, 18) and can be implicated as a cause of bacteremia, endocarditis, pneumoniae and meningitis. Cases of exudative group G streptococci tonsillopharyngitis are known to be associated with contaminated food (8).

Group B beta-hemolytic streptococci do not produce streptolysin O and have never been associated with the nonsuppurative sequelae of streptococcal infections (6, 26). S. agalactiae can be invasive, capable of causing suppurative infections and has gained increasing significance as a human pathogen, causing bacteremia, meningitis, pneumonia and genitourinary tract infections, particularly in debilitated and diabetic patients. In the last years, S. agalactiae has become a common cause of bacteremia and meningitis in newborn infants, which often acquire infection from the mother’s vagina. Moreover, because of the frequent carriage of group B streptococci in the genital tract, patients with infection of the pharynx and tonsils by S. agalactiae should be questioned about oral-genital sexual contact shortly before the onset of tonsillopharyngitis. Furthermore, colonization of the organism in the throat may be due to contamination from a distant bodily site and patients with tonsillopharyngitis have infections at other sites, such as genitourinary tract and skin, from which the same organism is cultured.

Therefore, laboratories which report beta-hemolytic streptococcal isolates from the pharynx only as group A or non-group A should be encouraged to perform group identification of all beta-hemolytic
isolates to further evaluate the role of non-group A hemolytic streptococci in tonsillitis, pharyngitis and infections at other bodily sites.

Although *S. pyogenes*, *S. agalactiae* and *S. dysgalactiae* subsp. *equisimilis* are generally considered to be beta-hemolytic, non-hemolytic variants (9, 13) have been isolated both from silent carriers and from disease outbreaks. Non-hemolytic variants of *S. pyogenes* have been known to cause nonsuppurative sequelae (13) of streptococcal infections, such as rheumatic fever. Therefore, non-hemolytic streptococci should not necessarily be dismissed as nonpathogen, especially when detected in cultures from patients with clinical symptoms of tonsillopharyngitis or rheumatic fever, erythema marginatum, reactive arthritis and glomerulonephritis.

Patients with groups A, C and G tonsillopharyngitis are usually treated with 10 days of oral amoxicillin (adults: 1000 mg every 12 h; children: 50 mg/kg/day, in two or three divided doses), or clarithromycin (adults: 500 mg every 12 hours, for at least 10 days; children: 15 mg/kg/day, in two divided doses) as an alternative for patients allergic to penicillin (29, 30, 33). *S. pyogenes* has been known to penetrate into pharyngeal cells (23) and this may result in penicillin failure (27, 31). Similarly, on the basis of the two clinical cases we described, we think *S. dysgalactiae* subsp. *equisimilis* is both an extracellular and intracellular pathogen; we suppose the organism may survive inside pharyngeal and tonsillar cells or inside phagocytes, particularly in the carrier state, and this may result in penicillin failure in the treatment of tonsillopharyngitis.

Therefore, when penicillin fails, antibiotics characterized by extracellular and intracellular activity should be administered, such as clarithromycin (adults: 500 mg every 12 hours, for at least 10 days; children: 15 mg/kg/day, in two divided doses, for at least ten days) (22, 25, 33). If resistance to macrolides is documented (33), doxycycline (adults: 100 mg/day, for at least 10 days), levofloxacin (adults: 500 mg/day, for at least 7-10 days), moxifloxacin (adults: 400 mg/day, for at least 5-10 days).
or clindamycin (adults: 150 mg, every 6 hours, for at least 10 days; children: 8-20 mg/kg/day, in three divided doses, for at least 10 days) should be administered.

REFERENCES


29. **Rondini, G., C. E. Cocuzza, M. Cianflone, A. Lanzafame, L. Santini, and R. Mattina.**


**ABSTRACT**
The authors present two cases of exudative pharyngitis due to *Streptococcus dysgalactiae* subsp. *equisimilis*, Lancefield group G. While the participation of this organism as an agent of pharyngitis is well-documented, the authors focus on failure of beta-lactam therapy, a phenomenon that is well-described in pharyngitis due to *Streptococcus pyogenes*. Therefore these case reports add to our knowledge of pharyngitis caused by non-*S. pyogenes* streptococci.