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β-Lactam Failure in Treatment of Two Group G *Streptococcus dysgalactiae* subsp. *equisimilis* Pharyngitis Patients▽

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We 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, we focus on failure of beta-lactam therapy, a phenomenon that is well described for pharyngitis due to *Streptococcus pyogenes*. Therefore, these case reports add to our knowledge of pharyngitis caused by non-*S. pyogenes* streptococci.

CASE REPORT

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 anti-streptolysin O titers. Group G beta-hemolytic *Streptococcus dysgalactiae* subsp. *equisimilis* (>100 colonies) was isolated from the throat. MICs were as follows: amoxicillin, 0.03 mg/liter; clarithromycin, 0.12 mg/liter; levofloxacin, 0.25 mg/liter; moxifloxacin, 0.25 mg/liter; doxycycline, 0.5 mg/liter; and clindamycin, 0.25 mg/liter. No nonhemolytic streptococcal colonies were detected. A concurrent diagnosis of infectious mononucleosis was excluded.

The patient was treated with 10 days of amoxicillin (1,000 mg every 12 h) and had prompt relief of symptoms within few days of starting antibiotic therapy. About 2 weeks later she had persistently elevated anti-streptolysin O titers, and the same organism (11 to 50 colonies) was isolated from throat cultures. The patient was treated with 10 days of amoxicillin-clavulanic acid (1,000 mg every 12 h).

Fifteen days later, anti-streptolysin O titers were persistently elevated and the same isolate of *S. dysgalactiae* subsp. *equisimilis* (11 to 50 colonies) was cultured from the throat. 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-hemolytic and nonhemolytic streptococci, and anti-streptolysin O titers were no longer elevated.

A 31-year-old male patient had an acute exudative tonsillopharyngitis, with enlarged tonsils, enlarged tender anterior cervical lymph nodes, and increased anti-streptolysin O titers. Temperature was not elevated (37°C). Throat culture was positive for group G beta-hemolytic *Streptococcus dysgalactiae* subsp. *equisimilis* (>100 colonies). MICs were as follows: amoxicillin, 0.03 mg/liter; clarithromycin, 0.12 mg/liter; levofloxacin, 0.5 mg/liter; moxifloxacin, 0.25 mg/liter; doxycycline, 1 mg/liter; and clindamycin, 0.5 mg/liter. No nonhemolytic streptococcal colonies were observed. A concurrent diagnosis of infectious mononucleosis was excluded.

The patient was treated with 10 days of amoxicillin (1,000 mg every 12 h), which led to a rapid disappearance of symptoms (within few days of starting therapy). About 10 days later he had persistently elevated anti-streptolysin O titers, and the same organism (11 to 40 colonies) was detected in throat cultures. The patient was treated with 10 days of amoxicillin-clavulanic acid (1,000 mg every 12 h).

Fifteen days later, anti-streptolysin O titers were persistently elevated and the same isolate of *S. dysgalactiae* subsp. *equisimilis* (11 to 45 colonies) was cultured from the throat. The patient 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-hemolytic and nonhemolytic streptococci. Anti-streptolysin O titers were no longer 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, Italy) (4). Each swab was inoculated onto three plates: the first plate was incubated at 37°C in an aerobic atmosphere, the second plate was incubated at 37°C in an anaerobic atmosphere, and the third plate was incubated at 37°C in an atmosphere of 5% CO_2. 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 sheep blood agar (Biolife, Italy) at 37°C in an aerobic atmosphere. Their Lancefield group was established serologically as G by

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latex agglutination (Slidex Strepto Plus; bioMérieux) with group A, B, C, D, F, and G antisera. The beta-hemolytic group G isolate was identified as *S. dysgalactiae* subsp. *equisimilis* by use of the Vitek 2 automatic system for biochemical identification of bacteria and yeasts (Biomérieux).

Nonhemolytic streptococci were not detected. No *Streptococcus salivarius* colonies were detected. This was important because the growth of beta-hemolytic streptococcal colonies is inhibited in the vicinity of bacteriocin-producing *S. salivarius* colonies, especially when beta-hemolytic colonies are present in small numbers, as in the carrier state (13).

MICs were determined by the broth microdilution method recommended by the CLSI (formerly NCCLS) (23).

Bacteria are associated with 30% of tonsillopharyngitis cases in children and 10% of tonsillopharyngitis cases in adults. *Streptococcus pneumoniae*, *Neisseria* spp., *Corynebacterium* spp., *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* (16) have been implicated as causes of sporadic pharyngitis.

Streptococcus pyogenes (Lancefield group A) may result in elevated anti-streptolysin O titers and is most frequently responsible for streptococcal tonsillopharyngitis (14, 28, 31) and nonsuppurative sequelae, such as rheumatic fever (including heart inflammation and Sydenham's chorea), reactive arthritis, glomerulonephritis, and erythema marginatum. *Streptococcus 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, group C and G beta-hemolytic streptococci may result in elevated anti-streptolysin 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).

In particular, *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 found as a cause of bacteremia, endocarditis, pneumonia, 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 and capable of causing suppurative infections, and it has had 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 *S. agalactiae* infection of the pharynx and tonsils should be questioned about oral-genital sexual contact shortly before the onset of tonsillopharyngitis. Furthermore, colonization by the organism in the throat may be due to contamination from a distant bodily site, and patients with tonsillopharyngitis may have infections at other sites, such as the 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, nonhemolytic variants (9, 13) have been isolated both from silent carriers and from disease outbreaks. Nonhemolytic variants of *S. pyogenes* have been known to cause nonsuppurative sequelae (13) of streptococcal infections, such as rheumatic fever. Therefore, nonhemolytic streptococci should not necessarily be dismissed as nonpathogens, especially when detected in cultures from patients with clinical symptoms of tonsillopharyngitis or rheumatic fever, erythema marginatum, reactive arthritis, or glomerulonephritis.

Patients with groups A, C and G tonsillopharyngitis are usually treated with 10 days of oral amoxicillin (adults, 1,000 mg every 12 h; children, 50 mg/kg/day in two or three divided doses) or clarithromycin (adults, 500 mg every 12 h 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 (24), and this may result in penicillin failure (27, 32). Similarly, on the basis of the two clinical cases we described, we believe that *S. dysgalactiae* subsp. *equisimilis* is both an extracellular and intracellular pathogen; we think that 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 h for at least 10 days; children, 15 mg/kg/day in two divided doses for at least 10 days) (22, 25, 33). If resistance to macrolides is documented (33), then doxycycline (adults, 100 mg/day for at least 10 days), levofloxacin (adults, 500 mg/day for at least 7 to 10 days), moxifloxacin (adults, 400 mg/day for at least 5 to 10 days), or clindamycin (adults, 150 mg every 6 h for at least 10 days; children, 8 to 20 mg/kg/day in three divided doses for at least 10 days) should be administered.

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