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PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

Penicillin Failure in the Treatment of Streptococcal Pharyngo-Tonsillitis

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Abstract The inadequate penetration of penicillins into the tonsillar tissues and tonsillar surface fluid and microbiologic interactions between Group A beta-hemolytic streptococci (GABHS) and other pharyngo-tonsillar bacterial flora can account for their failure in eradicating GABHS pharyngo-tonsillitis (PT). These interactions include the presence of beta-lactamase producing bacteria (BLPB) that "shield" GABHS from penicillins, the absence of bacteria that interfere with the growth of GABHS, and the coaggregation between GABHS and *Moraxella catarrhalis*. In the treatment of acute tonsillitis, the use of cephalosporins can overcome these interactions by eradicating aerobic BLPB, while preserving the potentially interfering organisms and eliminating GABHS. In treatment of recurrent and chronic PT, the administration of clindamycin or amoxicillin-clavulanatecan eradicates both aerobic and anaerobic BLPB, as well as GABHS.

Keywords Tonsillitis · Group A streptococci · Penicillin · Interference · Cephalosporins · Clindamycin · Beta-lactamase

Despite its excellent in vitro efficacy, the inability of penicillin to eradicate Group A beta-hemolytic streptococci (GABHS) from patients with acute and recurrent pharyngo-tonsillitis (PT) is a concern, since the rate of penicillin failure has increased from about 7 % to almost 40 % [1].

The explanations for the failure of penicillin (see Table 1) include penicillin's poor penetration of into the tonsillar tissues, including the tonsillar epithelial cells [2]; the protection of GABHS by beta-lactamase-producing bacteria (BLPB) [3]; the coaggregation between *Moraxella catarrhalis* and GABHS, which can enhance the colonization by GABHS [4]; and the absence of competitive and interfering normal flora, which makes it easier for GABHS to colonize and invade the pharyngo-tonsillar area [5, 6].

This article describes the bacterial interactions that can lead to the failure of penicillin to eradicate GABHS from acute or recurrent PT and the therapeutic approaches that can overcome these causes of failure.

Intracellular Survival of GABHS Due to the Inadequate Penetration of Penicillin into the Tonsils

In vitro and in vivo studies have illustrated that GABHS strains can survive inside tonsillar epithelial cells and become "internalized" [7]. An internalization-associated gene, prtF1/sfbI, was found more frequently in GABHS recovered from patients who failed penicillin therapy than in those who did not [7]. Since penicillin penetrates mammalian cells poorly, the intracellular survival of GABHS may be possible [8]. This is supported by the ability of GABHS to survive for 4–7 days within cultured epithelial cells [9]. Strains from patients who were "eradication failures" showed significantly increased intracellular survival, as compared with the "eradication success" strains [9].

Intracellular GABHS survived penicillin but were killed by cephalothin, clindamycin, and macrolides, all able to penetrate intracellularly [2]. Penicillin's failure to eradicate GABHS may, therefore, be the result of its inability to eradicate intracellular GABHS, as well as its failure in maintaining sufficient concentration within the tonsillar fluid [10].

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Table 1 Causes for antimicrobials failure in the treatment of GABHS pharyngo-tonsillitis

- Bacterial interactions
  - The presence of beta-lactamase–producing bacteria that "protect" GABHS from penicillins
  - Coaggregation between GABHS and *M. catarrhalis*
  - Absence of members of the oral bacterial flora capable of interfering with the growth of GABHS (through production of bacteriocins and/or competition on nutrients)
- Poor penetration of penicillins into the tonsillar cells and tonsillar surface fluid (allowing intracellular survival of GABHS)
- Resistance (i.e., erythromycin) or tolerance (i.e., penicillin) to the antibiotic used
- Inappropriate dose, duration of therapy, or choice of antibiotic
- Poor compliance
- Reacquisition of GABHS from a contact or an object (i.e., toothbrush or dental braces)
- Carrier state, not disease

Beta-lactamase-Producing Bacteria

Treatment with penicillin has created in a shift in the oro-pharyngeal flora by selecting for beta-lactamase-producing strains of *Haemophilus* spp., *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), *M. catarrhalis*, anaerobic Gram-negative bacilli (e.g., pigmented *Prevotella*, *Porphyromonas*), and *Fusobacterium* spp. [11, 12]. These organisms are typically recovered from those who were recently treated with beta-lactam antibiotics [3, 11].

An association has been found between the failure of patients to respond to penicillin and the preexistence of BLPB among their pharyngo-tonsillar flora [12]. A correlation was noted between the rate of recovery of BLPB in healthy children and the rate of amoxicillin failure to eradicate GABHS [13]. Over 75 % of tonsils removed as a result of recurrent tonsillitis harbor BLPB [14–20]. Free beta-lactamase was present in the core of most of those tonsils [21]. Antibiotics effective against GABHS, as well as BLPB, achieved a higher success rates in eradication of acute and recurrent GABHS PT [22–26]. These antimicrobials included cephalosporins, clindamycin, lincomycin, macrolides, and amoxicillin-clavulanate.

Bacterial Interference

A microbial balance occurs in the oro-pharynx between potential pathogens and the normal flora [27–30].

The normal flora employs several mechanisms that interfere with colonization and subsequent infection by potential pathogens. These include competition for nutrients and the production of antibiotic-like substances called *bacteriocins*, which kill other bacteria [31]. Organisms that are capable of interfering with the growth of potential bacterial pathogens are present in over 85 % of healthy children. In contrast, only 25 %–30 % of children who suffer from recurrent upper respiratory tract bacterial infections (including PT) harbor interfering bacteria [28–30].

The predominant interfering organisms are gamma- and alpha-hemolytic streptococci (AHS), *Peptostreptococcus* spp., and *Prevotella* spp. They play a homeostatic role in the pharyngo-tonsillar area by preventing colonization and subsequent infection by GABHS [28–30].

Therapeutic colonization of the nasopharynx with interfering AHS prevented relapsing GABHS PT [30–34]. The judicious use of antimicrobials can preserve the normal interfering flora [35]. Oro-pharyngeal flora are generally more susceptible to amoxicillin with and without clavulanate and are relatively resistant to the extended spectrum and second- and third-generation cephalosporins [36].

The use of narrow-spectrum antimicrobial selectively spares interfering organisms while eliminating pathogens [1]. The advantage of such treatment is the prevention of reacquisition of pathogens in the oro-pharynx. In contrast, administration of broad-spectrum antimicrobials is associated with prolonged absence of interfering organisms and a rapid recolonization with potential pathogens.

Coexistence of BLPB and Bacterial Interference

The coexistence of BLPB and the absence of interfering organisms were demonstrated in children who failed penicillin therapy of acute GABHS PT [28] or became GABHS carriers [37].

Before therapy, interfering AHS were recovered in 37 % of cured children, and BLPB were detected in 5 % [28]. After therapy, inhibiting AHS were recovered in 82 %, and BLPB were detected in 13 %. In contrast, before therapy, AHS were isolated in 7 % of those who failed penicillin, and BLPB were recovered from 64 %. After therapy, AHS were recovered in 29 %, and BLPB were recovered in 93 %. These findings show that the absence of interfering AHS and the presence of BLPB are associated with penicillin failure in treating GABHS PT.

Interfering organisms were more frequently recovered in non-GABHS carriers than in GABHS carriers [37]. This was observed in healthy children as well as those recently treated for symptomatic GABHS PT with penicillin that failed to eradicate GABHS. A higher rate of recovery of BLPB was observed only in GABHS carriers who were treated with penicillin for GABHS PT.

Coaggregation Between *M. Catarrhalis* and GABHS

A mutual symbiotic enhancement exists between GABHS and other organisms [38]. Such synergy may also occur in

PT. An example of such synergy is the ability of *M. catarrhalis* to increase GABHS adherence to human epithelial cells through species-specific coaggregation [4].

An association between the isolation of GABHS and *H. influenzae* or *M. catarrhalis* was also observed in patients with PT and between GABHS and *M. catarrhalis* from healthy children [39]. The increased recovery of *H. influenzae* and *M. catarrhalis* in association with GABHS may be due to a synergy between these organisms [39]. The ability of *H. influenzae* and *M. catarrhalis* to produce the beta-lactamase, which can inactivate the penicillin in the tonsillar tissues [3], may protect these organisms, as well as GABHS, from eradication and contribute to the failure of penicillin treatment.

An indirect support for the importance of the synergy between GABHS and *H. influenzae* and *M. catarrhalis* is the better efficacy, as compared with penicillin, of antimicrobials active against these organisms. These include the second-generation, extended-spectrum, and third-generation cephalosporins [40, 41], as well as amoxicillin-clavulanate [23, 24]. Their superiority may be due to their efficacy against GABHS, as well as beta-lactamase-producing *H. influenzae* and *M. catarrhalis*.

Implications of Microbiological Interactions for Therapy

Penicillin is still recommended as the antibiotic of choice for GABHS PT [42], although other antibiotics are more effective in the bacteriological eradication and clinical cure of acute and recurrent GABHS PT [23–26, 43]. Macrolides and cephalosporins are more effective than penicillin in acute GABHS PT [40, 41], while lincomycin, clindamycin, and amoxicillin-clavulanate are more effective in relapsing GABHS PT [22–24, 43]. The goal of the treatment of PT in those who failed penicillin therapy is also to eradicate the BLPB that protect GABHS from penicillin, while preserving any "protective" interfering organisms (e.g., AHS). Cephalosporins have been successful in eradicating GABHS better [40] and, in some instances, even faster [41] and in less time [44] (5–7 days, as compared with 10) than penicillin. The explanation for the superiority of cephalosporins is their ability to eradicate GABHS while preserving the interfering organisms and eliminating aerobic BLPB [35, 45, 46].

Several clinical studies have demonstrated the superiority of lincomycin, clindamycin, and amoxicillin-clavulanic acid over penicillin in the treatment of recurrent PT [23, 24, 43, 44–56]. These antimicrobial agents are effective against aerobic, as well as anaerobic, BLPB and GABHS in eradicating recurrent tonsillar infection. However, no studies have shown them to be superior to penicillin in the treatment of acute tonsillitis.

Better understanding of the microbiological causes of penicillin's failure to eradicate GABHS can lead to greater success in managing the infection.

Conflict of Interest No potential conflicts of interest relevant to this article were reported.

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