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REVIEW

Overcoming penicillin failures in the treatment of Group A streptococcal pharyngo-tonsillitis

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Summary The causes of penicillin failure in eradicating Group A beta-hemolytic streptococcal pharyngo-tonsillitis (GABHS PT) are described. These include the presence of beta-lactamase producing bacteria that "protect" Group A beta-hemolytic streptococci (GABHS) from penicillins; the absence of bacteria that interfere with the growth of GABHS; co-aggregation between GABHS and *Moraxella catarrhalis*; and the poor penetration of penicillin into the tonsillar tissues and the tonsillopharyngeal cells. The use of antimicrobials that can overcome and modulate these phenomena and achieve better cure of the infection is described.

Contents

1. Introduction

Despite its excellent *in vitro* efficacy, the frequently reported inability of penicillin to eradicate Group A beta-hemolytic streptococci (GABHS) from patients with acute and relapsing pharyngo-tonsillitis (PT) is cause for concern. Over the past 50 years, the rate of penicillin failure has consistently increased from about 7% in 1950 to almost 40% in 2000 [1].

Various explanations exist for the failure of penicillin to eradicate GABHS PT (Table 1). One possibility is the poor penetration of penicillin into the

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Table 1 Possible causes for antibiotic failure in therapy of GABHS tonsillitis

• Bacterial interactions
- The presence of beta-lactamase-producing organisms that ''protect'' GABHS from penicillins
- Co-aggregation 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 penicillin 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

tonsillar tissues as well as into the epithelial cells [2]. Other explanations relate to the bacterial interactions between GABHS and other members of the pharyngo-tonsillar bacterial flora. For example, it is hypothesized that beta-lactamase secreted by beta-lactamase-producing bacteria (BLPB), which colonize the pharynx and tonsils, may ''shield'' GABHS from penicillins [3]. Another possibility is the co-aggregation between *Moraxella catarrhalis* and GABHS, which can facilitate colonization by GABHS [4]. Normal bacterial flora can interfere with the growth of GABHS [5], and the absence of such competitive bacteria makes it easier for GABHS to colonize and invade the pharyngo-tonsillar area.

The bacterial flora that colonize the tonsils and pharynx, in health as well as in illness, contain over 600 different strains of aerobic and anaerobic bacteria, and more than 10 [8—11] bacteria/ml of secretion. Anaerobic bacteria outnumber their aerobic counterparts by a ratio of 10:1—100:1 [6]. Group A beta-hemolytic streptococci interact with these other organisms in a synergistic or antagonistic fashion [7]. These interactions can involve sharing of metabolites, exchange of genetic material, and influence of extra-cellular enzymes and other compounds produced by some bacteria on their partners.

The pharyngo-tonsillar area is also repeatedly infected by viral agents that can act synergistically with potential bacterial pathogens and normal flora. Such interactions have been demonstrated in other respiratory tract infections [8]. Pharyngo-tonsillitis occurs in a heavily colonized location, and should be considered as a potential polymicrobial infection.

This review describes the mechanisms by which bacterial interactions contribute to the failure of penicillins to eradicate GABHS from the acutely infected pharyngo-tonsillar area, possibly resulting in clinical and bacterial failure. Also discussed are therapeutic modalities that can overcome these causes of failure.

2. The role of intracellular survival of gabhs and poor penetration of penicillin into the tonsils

Strains of GABHS have been demonstrated to internalize within epithelial cells both *in vitro* and *in vivo* in recent studies [9]. The internalization-associated gene, prtF1/sfbI, has been identified more from patients with eradication failure of GABHS than has been recovered from patients with successful eradication [10]. Since penicillins penetrate mammalian cells poorly, intracellular survival of GABHS possibly allows the pathogens to persist despite antibiotic treatment [11].

The intracellular niche may therefore protect GABHS strains from penicillin that is not in high intracellular concentration. In support of this hypothesis, GABHS strains were shown to survive 4—7 days within cultured epithelial cells. Thus, internalization and intracellular survival represent a novel explanation for penicillin eradication failure.

Marouni et al. [12], compared the survival of GABHS strains from cases of eradication failure and eradication success, using an epithelial cell culture model. ''Eradication failure'' strains showed significantly increased intracellular survival, compared to the 'eradication success' strains. These results demonstrate how an intracellular reservoir of GABHS may play a role in the etiology of antibiotic eradication failure.

Kaplan et al. [2], recently examined the viability of intracellular GABHS in a human laryngeal epithelial cell line (HEp-2epithelial cell) after exposure to antibiotics (penicillin V, erythromycin, azithromycin, cephalothin, and clindamycin) that are commonly recommended for GABHS therapy. Three techniques were used to study antibiotic killing of ingested GABHS: (1) electron microscopy examination of ultrathin sections of internalized GABHS; (2) qualitative determination of intra-epithelial cell antibiotic; and (3) special stain evaluation of intracellular GABHS viability within antibiotic-treated epithelial cells. Group A beta-hemolytic streptococci survived intracellularly despite exposure of the GABHS-infected epithelial cells to penicillin. Cephalothin (a cephalosporin) and clindamycin were more effective than penicillin in killing