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The Role of Beta-Lactamase-Producing-Bacteria in Mixed Infections I Children

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Abstract

Beta-lactamase-producing bacteria (BLPB) can play an important role in polymicrobial infections. They can have a direct pathogenic impact in causing the infection as well as an indirect effect through their ability to produce the enzyme beta-lactamase. BLPB may not only survive penicillin therapy but can also, as was demonstrated in *in vitro* and *in vivo* studies, protect other penicillin-susceptible bacteria from penicillin by releasing the free enzyme into their environment. This phenomenon occurs in upper respiratory tract, skin, soft tissue, surgical and other infections. The clinical, *in vitro,* and *in vivo* evidence supporting the role of these organisms in the increased failure rate of penicillin in eradication of these infections and the implication of that increased rate on the management of infections is discussed.

Penicillins have been the drugs of choice for the treatment of a variety of bacterial infections in children. However, within the past six decades, an increased resistance to these agents has been observed. In addition to organism long known to resistant beta-lactamases, such as *Staphylococcus aureus* and *Enterobacteriaceae,* other previously susceptible bacteria became increasingly resistant to these agents due to several mechanisms including the production of the enzyme beta-lactamase (BL). These organisms include aerobic and facultative bacteria such as *Haemophilus influenzae, Moraxella catarrhalis,* as well as anaerobic Gram-negative bacilli (AGNB, i.e. *Bacteroidesfragilis* group, pigmented *Prevotella* and *Porphyromonas, Prevotellabivia,* and *Prevotella disiens*) and *Fusobacterium* spp.) [1-3].

Beta-lactamase-producing bacteria (BLPB) can have an important clinical role in clinical infections. These bacteria can be pathogenic in their own merit as well as have an indirect effect through their ability to produce the enzyme BL into their surroundings. BLPB may not only survive penicillin therapy but also may shield other beta-lactame-susceptible bacteria from these agents by releasing the enzyme into their surroundings (Figure 1) [4].

Keywords: Beta-Lactamase; Penicillin; Anaerobic bacteria; *Haemophilus influenza*; *Moraxella catarrhalis*; *Staphylococcus aureus*

Indirect Pathogenicity of BLPB

In vivo and *in vitro* studies

Animal studies illustrated the ability of BL to effect the treatment of polymicrobial infections. BL producing by AGNB protected a penicillin-sensitive *Fusobacterium necrophorum* [5]and Group A beta hemolytic streptococci (GABHS) [6] from penicillin therapy in rodents. The combination of penicillin and clavulanate (a BL inhibitor), or clindamycin which are active against both GABHS and AGNB, were effective in eradicating the polymicrobial infection [7]. Resistance of GABHS to penicillin increased when it was co-inoculated with *S. aureus* [8]*, Haemophilus parainfluenzae,* [9] or *B. fragilis* [10].

Beta-lactamase production in clinical infections

The activity of the enzyme BL in polymicrobial infections was demonstrated in several studies. Penicillins were inactivated by purulent abscesses exudates [11,12] and in experimental *B. fragilis* infection [13].

BL was detected in specimens of clinical abscesses and mixed infections. These include abdominal infections[12] empyema,[14], cerebrospinal fluid [15], abscesses [16], ear aspirates of acute and chronic otitis media [17,18], and aspirates obtained from acutely and chronically inflamed maxillary sinuses. Many of these infections did not respond to penicillins therapies and were surgically drained [19].

Clinical studies

The recovery of penicillin-sensitive bacteria mixed with BLPB in patients who have failed to respond to beta-lactam therapy illustrate the ability of BLPB to "shield" a penicillin-susceptible or cephalosporin-susceptible micro-organism from these agents.

The appearance of BLPB in the oral cavity was associated with the administration of penicillin [20]. The selection of these agents following antimicrobial therapy may account for many of the clinical failures after penicillin therapy [21]. BLPB were isolated in 75 (40%) of 185 children with orofacial and respiratory infections who failed penicillin therapy [22].

Aerobic and anaerobic BLPB may account for penicillin failure to eradicate GABHS tonsillitis [8,9,21-31]. These BLPB may protect GABHS from penicillin by inactivating the antibiotic. (Figure 1) BLPB were isolated in 37 of 50 tonsils (74%) excised from children who failed penicillin therapy. These findings were confirmed in other studies. [29-31] Free BL was detected in the tonsillar tissues in 33 of 39 (85%) tonsils that contained BLPB [28].
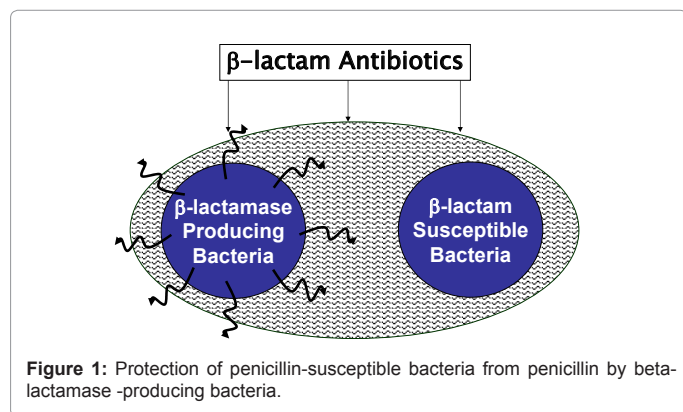
BLPB appeared in the oropharynx following penicillin therapy [32-34]. BLPB were recovered in 3 of 21 (14%) of children before to penicillin therapy, and in 10 of 21 (48%) after one course of penicillin [33]. In a study of 26 children who were treated with penicillin for seven

Figure 1: Protection of penicillin-susceptible bacteria from penicillin by beta-lactamase -producing bacteria.

days 11% had BLPB before therapy which increased to 45% at the end of the treatment, and the incidence was 27% three months later [34]. These BLPB were also recovered from household members of children who were repeatedly treated with penicillin, suggesting their possible transfer within a family [33].

Chemoprophylaxis of 20 children with recurrent otitis media with amoxicillin increased the recovery rate of BLPB from 20 % to 100% after six month [35]. No change took place in the isolation of BLPB in 20 children treated with sulfisoxazole.

An association has been observed between the presence of BLPB even before treatment of acute GABHS tonsillitis and the outcome of 10-day oral penicillin ttratment [36]. A correlation was also found between the rate of isolation of BLPB in healthy children and the rate of amoxicillin inability to eradicate GABHS infection [37]. A high failure rate of penicillins in eradication of GABHS in pharyngo-tonsillitis in the community can serve as sensitive indicator for a high prevalence rate of BLPB in that community.

The detection of a high level of BL in saliva reflects colonization with many BLPB [38]. Antimicrobial treatment can select for resistant bacterial strains that could sorvive in the nasopharynx to re-appear in new ear and sinus infection [39].

Therapeutic implications of beta-lactamase production

The presence of BLPB in mixed infection requires the administration of antimicrobials against these organisms as well as the other pathogens. The high failure rate of penicillin therapy in infections where of BLPB are also recovered emphasizes the importance of this therapeutic approach [21,22].

An infection where this approach has been successful is recurrent GABHS tonsillitis [40-55]. Treatment with antimicrobials effective against aerobic and anaerobic BLPB as well as GABHS were more effective in eradicating the infection and prevented elective tonsillectomy [47] compared to penicillin. These antimicrobials include cephalosporins [56,57], lincomycin [40-43], clindamycin [44-49] and amoxicillin/clavulanate [53].

BLPB colonized over 83% of the adenoids of children suffering from chronic adeno-tonsillitis [55] which may explain the persistence of many pathogens including *Streptococcus pneumoniae*. The number of potential pathogens and BLPB were lower in those treated with amoxicillin/clavulante [58] or clindamycin [59]. Similarly amoxicillin/

clavulante was superior to amoxicillin in curing the infection (92% vs 64%) and reducing the number of potential pathogens and BLPB in children with acute otitis media [60].

Clindamycin superiority of to penicillin in the treatment of lung abscesses was demonstrated in two studies [61,62]. This superiority was probably due to its ability to eradicate the BLPB present in lung abscess.

Antimicrobials active against anaerobic BLPB (ticarcillin/clavulanate or clindamycin with ceftazidime) were superior to an agent without such coverage (ceftriaxone) in the treatment of aspiration or tracheostomy-associated pneumonia in 57 children [63].

This findings illustrate that the successful management of polymicrobial infections is enhanced by antimicrobials capable of eradicating both aerobic and anaerobic BLPB. This therapeutic approach is effective in managing infections such as tonsillitis where BLPB are part of the normal flora at the infection site.

Further studies are warranted to explore and ascertain the efficacy of therapeutic modalities that target polymicrobial infections evolving BLPB that had not yet been studied. These include skin and soft tissue and bone and joint infections. Antimucrobials such as carbapenems and the newer quinolones should also be evaluated in the management of such infections.

The growing recovery rate of methicillin-resistant *S. aureus* (MRSA) in the tonsillar [64] as well as other respiratory infections [65] may contribute to the difficulty in eradicating GABHS as well as other non-BLPB pathogens with penicillins and other antimicrobials that are ineffective against this organism. Because most of the MRSA isolated in respiratory infections were also BLPB their presence may interfere with the eradication of GABHS by penicillin. MRSA that is also able to produce BL can survive treatment with beta-lactam antibiotics and continue to protect non-BLPB from penicillins through the production of the enzyme BL.

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