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Bacterial interference in the nasopharynx following antimicrobial therapy of acute otitis media

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The effect on the nasopharyngeal bacterial flora of therapy for 10 days with co-amoxiclav or cefprozil was studied in 50 children with acute otitis media. Before therapy, potential pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*) were isolated in 14 (56%) of those treated with co-amoxiclav and 15 (60%) of those treated with cefprozil. Following therapy, the reduction in the number of these pathogens was the same in the two groups. However, differences between the groups were noted in the recovery of organisms with interfering capability, namely α-haemolytic streptococci, *Peptostreptococcus anaerobius* and *Prevotella melaninogenica*. Fifty interfering organisms were recovered from each group before therapy. After therapy with co-amoxiclav or cefprozil their number declined to 11 and 42, respectively ($P < 0.001$).

Introduction

The nasopharynx of normal children is generally colonized by relatively non-pathogenic aerobic and anaerobic organisms,[1] some of which can interfere with the growth of potential pathogens.[2] These non-pathogenic organisms include the aerobic α-haemolytic streptococci (mostly *Streptococcus mitis* and *Streptococcus sanguis*),[3] anaerobic streptococci (*Peptostreptococcus anaerobius*) and *Prevotella melaninogenica*.[4] Carriage of potential respiratory pathogen such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* is significantly higher in children prone to otitis media and in the general population of young children during respiratory illness.[5]

Administration of antimicrobial agents can influence the composition of nasopharyngeal flora.[6] Members of the oral flora with interfering capability are generally susceptible to amoxycillin. These include aerobic and anaerobic streptococci, as well as penicillin-susceptible *P. melaninogenica*. Co-amoxiclav is also effective against β-lactamase-producing *P. melaninogenica*. In contrast, all of these organisms are relatively resistant to second- and third-generation cephalosporins.[7]

This study was designed to compare the effects of co-amoxiclav and cefprozil on the nasopharyngeal flora of children with acute otitis media. Co-amoxiclav is a broad-spectrum antimicrobial effective against potential interfering organisms, while cefprozil is a second-generation cephalosporin that is potentially less inhibitory towards these organisms.

Patients and methods

Children diagnosed with acute otitis media and treated with either co-amoxiclav or cefprozil were included in the study. The patients included in the analysis were the first 25 consecutive patients who received co-amoxiclav and the first 25 who received cefprozil, completed their course of therapy and were monitored for cultures as outlined below. No randomization of antimicrobial agents was done. The choice of antimicrobial was made by the examining physician at his discretion. The age of patients was similar in the two groups and ranged from 8 months to 5 years (mean 2 years, 4 months) and 32 were male.

Pharyngeal cultures were obtained before therapy and on a follow-up visit 2–4 days after completion of 10 days of antimicrobial therapy. These were obtained with calcium alginate swabs that were immediately plated into media supportive of the growth of aerobic and anaerobic bacteria. The collectors of cultures and the microbiologist were blinded to the patients' therapy. Specimens were processed, organisms identified and β-lactamase production determined as previously described.[8]

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Three types of organism known to have inhibitory activity were studied, namely α-haemolytic streptococci, *P. anaerobius* and *P. melaninogenica*. Their inhibitory activity was tested, as previously described,[8] against one strain each of recent clinical isolates of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*.

Patients received co-amoxiclav 40 mg/kg/day divided into three doses, or cefprozil 30 mg/kg/day divided into two doses. Both drugs were administered for 10 days. Compliance with therapy was assessed using a dosage card and by inspecting unused medicine after completion of treatment. Patients who failed to take more than two doses or who failed to return their medicine bottles and dosage cards were excluded from the study. Patients were evaluated clinically 2–4 days after completion of therapy. Statistical significance was calculated using the χ^2 test.

Results

After completion of therapy, 22/25 (88%) of the patients treated with co-amoxiclav and 21/25 (84%) of those treated with cefprozil were considered clinically cured. Persistence of middle ear fluid without inflammation was present in 10/25 (40%) of those treated with co-amoxiclav and 8/25 (36%) after cefprozil.

Before therapy (Table), potential pathogens were isolated from the nasopharynx of 14 (56%) of those treated with co-amoxiclav and 15 (60%) of those treated with cefprozil. Following therapy, the number of potential pathogens was reduced equally by the two therapies.

Differences between the groups were noted in the recovery of organisms with interfering capability following therapy. Fifty interfering organisms were recovered from each group before therapy (Figure). Five (50%) of the ten *P. melaninogenica* isolates were β-lactamase-producers. Following co-amoxiclav therapy, the number of interfering organisms declined to 11, while following cefprozil treatment their number was reduced to 42 ($P < 0.001$).

Discussion

This study compared the effects of co-amoxiclav and cefprozil therapy on the nasopharyngeal flora in children. While both agents are effective against penicillin-susceptible or -resistant pathogens (*S. pneumoniae*, *H. influenzae* and *M. catarrhalis*), they have selective activity against members of the oral flora. We found that after co-amoxiclav therapy the oral flora is more depleted of organisms with interfering potential, than following cefprozil therapy. This presumably reflects the broad-spectrum efficacy of co-amoxiclav, which is active against α-haemolytic streptococci, anaerobic streptococci and penicillin-resistant *Prevotella* spp. Cefprozil, in contrast, is less effective against these organisms *in vitro*.[9] Another possible mechanism for the increased survival of interfering aerobic and anaerobic streptococci following cefprozil treatment is the survival of β-lactamase-producing Gram-negative anaerobic bacilli (including *P. melaninogenica*) which are resistant to cefprozil. The β-lactamase produced by these organisms shields the streptococci from β-lactam antibacterial activity.[8]

The presence of organisms with interfering potential may play a role in the prevention of respiratory infections. For example, Bernstein *et al.*[3] found significantly more colonies of α-haemolytic streptococci in the adenoids of non-otitis-prone children than in otitis-prone children. In contrast, they recovered more non-type b *H. influenzae* in the otitis-prone group than in the non-otitis-prone group.

The ability of the indigenous normal nasopharyngeal flora to inhibit colonization with potential pathogens has been studied previously. α-Haemolytic streptococci were found to inhibit the colonization in patients and in-vitro growth of a variety of pathogenic bacteria, including *S. pneumoniae*, Group A β-haemolytic streptococci and *S. aureus*.[8,10] The production of bacteriocin and other inhibitory substances that suppresses some bacterial growth, or utilization of nutrients in the nasopharyngeal environment essential for the potential pathogens, may explain this phenomenon.[10] Organisms other than α-

Table. Potential pathogens recovered from the nasopharynx of patients treated with co-amoxiclav or cefprozil (the number of penicillin-resistant isolates is given in parentheses)

	Co-amoxiclav ($n = 25$)		Cefprozil ($n = 25$)	
Potential pathogens	before therapy	after therapy	before therapy	after therapy
Streptococcus pneumoniae	7 (3)[a]	2 (2)	6 (3)	1 (0)
Haemophilus influenzae (non-type b)	8 (4)	1 (1)	9 (5)	3 (1)
Moraxella catarrhalis	4 (4)	0 (0)	3 (3)	1 (1)
Total	19 (11)	3 (3)	18 (11)	5 (2)

[a] All *S. pneumoniae* resistant to penicillin were intermediately resistant (MIC = 0.1–1.0 mg/L).

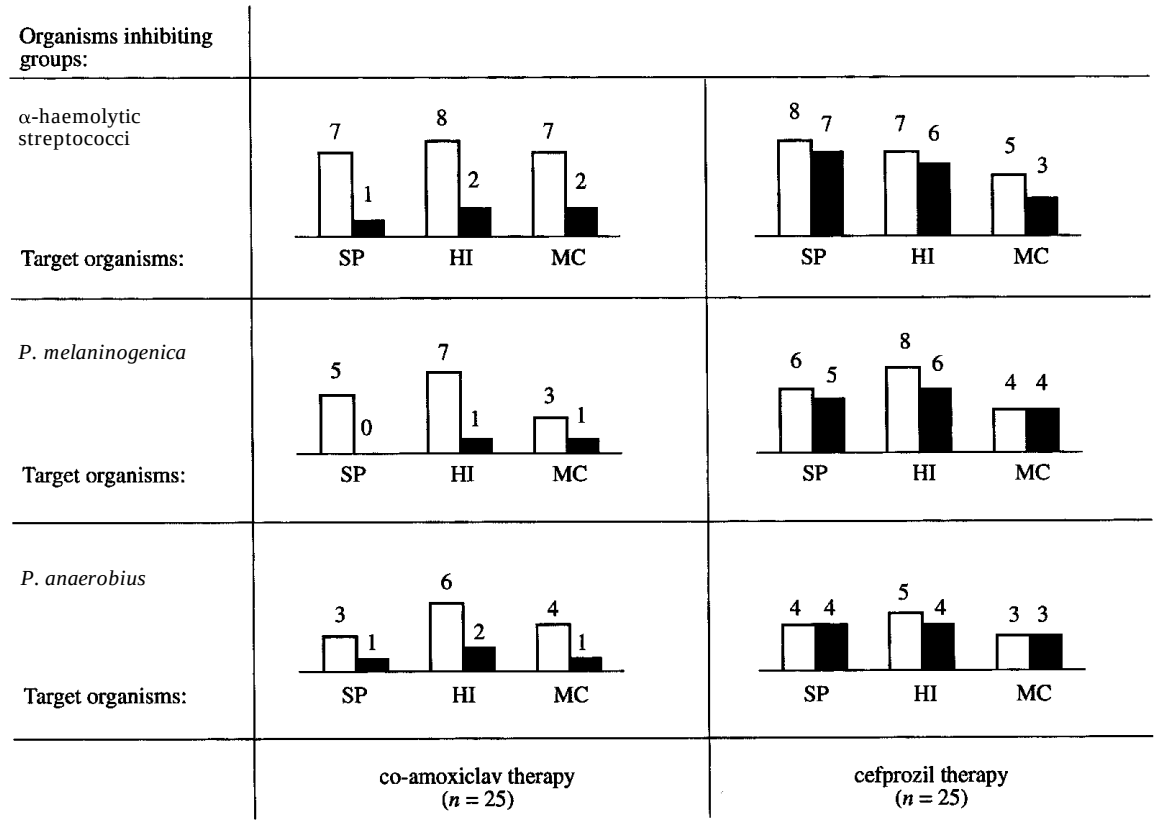

Figure. Effect of antimicrobial therapy on the recovery of bacteria capable of interfering with the growth of potential pathogens in children treated with either co-amoxiclav (n = 25) or cefprozil (n = 25) for acute otitis media. White bars, number of interfering isolates recovered before therapy; black bars, number of interfering isolates recovered after therapy. SP, *S. pneumoniae*; HI, *H. influenzae*; MC, *M. catarrhalis.*

haemolytic streptococci, such as *P. melaninogenica* and *P. anaerobius*, may also interfere with the growth of potential pathogens.[4]

This study suggests a potential beneficial effect of using an antimicrobial that acts selectively, sparing interfering organisms while inhibiting penicillin-resistant bacteria. Further studies are warranted to explore the clinical implications of these findings and how quickly such organisms recolonize the nasopharynx following therapy.

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