Long-term effects on the nasopharyngeal flora of children following antimicrobial therapy of acute otitis media with cefdinir or amoxycillin-clavulanate

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The effect on the nasopharyngeal bacterial flora of 10 days of amoxycillin-clavulanate or cefdinir antimicrobial therapy was studied in 50 children with acute otitis media. Before therapy, 17 potential pathogens (Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis) were isolated from the nasopharynx of 14 (56%) of those treated with amoxycillin-clavulanate, and 20 potential pathogens were recovered from 15 (60%) of those treated with cefdinir. Following therapy, at days 12–15, the number of potential pathogens was reduced to a similar extent with both therapies, to three in those treated with amoxycillin-clavulanate and two in those treated with cefdinir. However, the number of potential pathogens rebounded faster in those treated with amoxycillin-clavulanate as compared with cefdinir in the two subsequent specimens taken at days 30–35 and 60–65 (12 and 18 in the amoxycillin-clavulanate group, and six and nine in the cefdinir group, \( P < 0.01 \) and \( P < 0.001 \), respectively). Differences between the groups were also noted in the recovery of organisms with interfering capability. Immediately following amoxycillin-clavulanate therapy, the number of interfering organisms declined from 54 to 13, while following cefdinir treatment their number was reduced from 59 to 39 (\( P < 0.001 \)). The differences between the two therapy groups persisted in the two later specimens taken at days 30–35 and 60–65 (25 and 38 in the amoxycillin-clavulanate group, and 52 and 51 in the cefdinir group, \( P < 0.001 \) and \( P < 0.05 \), respectively). This study illustrates the potential beneficial effect of using a narrow-spectrum antimicrobial that selectively spares the interfering organisms while eliminating pathogens. The benefit of such therapy is the prevention of reacquisition of pathogenic bacteria in the nasopharynx. In contrast, utilization of a broad-spectrum antimicrobial is associated with prolonged absence of inhibitory organisms and rapid recolonization with pathogens.

Introduction

The nasopharynx of normal children is colonized by non-pathogenic aerobic and anaerobic organisms (Mackowiak, 1982), some of which have the ability to interfere with the growth of potential pathogens (Brook, 2000). Interfering organisms are isolated less often from the nasopharynx of otitis-media-prone children than normal controls (Brook, 2000; Bernstein et al., 1994). These organisms include the aerobic alpha-haemolytic streptococci (AHS, mostly Streptococcus mitis and Streptococcus sanguinis), anaerobic streptococci (Peptostreptococcus anaerobius) and Prevotella melaninogenica (Murray & Rosenblatt, 1976). Conversely, colonization by potential respiratory pathogens such as Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis increases significantly in otitis-media-prone children and in the general population of young children during respiratory illness (Faden et al., 1991). Nasopharyngeal flora with interfering capability may therefore inhibit colonization or growth of potential pathogens in the host and may play a role in preventing ear infections (Mackowiak, 1982; Bernstein et al., 1994).

Administration of antimicrobial agents can affect the composition of the nasopharyngeal bacterial flora (Foote & Brook, 1989). Oral flora organisms with interfering capability are generally susceptible to amoxycillin. These include aerobic and anaerobic streptococci, as well as penicillin-susceptible Pre. melaninogenica. Amoxycillin-clavulanate is also effective against beta-lactamase-producing Pre. melaninogenica. In contrast, these organisms are relatively resistant to the second- and third-generation cephalosporins (Brook & Gilmore, 1993).

This study compared the effects on the nasopharyngeal flora of two antimicrobial therapy for acute otitis media in children. One antimicrobial was amoxycillin-clavulanate,
which is a wide-spectrum antimicrobial that is effective also against potential interfering organisms, and the other agent was cefdinir, a third-generation cephalosporin, which is a lesser inhibitor of these organisms.

**Methods**

Children diagnosed with acute otitis media and treated with either amoxycillin-clavulanate or cefdinir were included in this retrospective study. Included in the analysis were the first 25 patients who received amoxycillin-clavulanate and the first 25 who received cefdinir, and who also completed their course of therapy and had cultures as outlined below. The choice of the antimicrobial was made at the discretion of the examining physician. Patient age was similar in both groups and ranged from 6 months to 6 years (mean 2 years and 4 months), and 32 were males. Excluded from the analysis were those who had received antimicrobial therapy in the previous 3 months or the 2 month follow-up period, attended a day care centre, and those with an underlying illness or facial anomalies. The study was granted Institutional Review Board approval.

Nasopharyngeal cultures were obtained prior to therapy and on a follow-up visit 2–4 days after completion of 10 days of antimicrobial therapy and at follow-up visits on days 30–35 and days 60–65. These were obtained with calcium alginate swabs that were immediately plated onto media supportive of the growth of aerobic and anaerobic bacteria. The microbiologists were blinded to the patients’ therapy. The cultures were processed for the recovery of potential pathogens, and the types of organisms known to possess inhibitory activity: AHS, Peptostreptococcus and Prevotella species. The inhibitory activity of the organisms known to possess inhibitory activity was tested against one strain each of potential pathogens and the other agent which is a wide-spectrum antimicrobial that is effective also against potential interfering organisms, and the other agent was cefdinir, a third-generation cephalosporin, which is a lesser inhibitor of these organisms.

**Results**

Before therapy, 17 potential pathogens (*S. pneumoniae, H. influenzae* and *M. catarrhalis*) were isolated from the nasopharynx of 14 (56 %) of those treated with amoxycillin-clavulanate, and 20 potential pathogens were recovered from 15 (60 %) of those treated with cefdinir. Following therapy, at days 12–15, the number of potential pathogens was reduced to a similar extent with both therapies, to three in those treated with amoxycillin-clavulanate and two in those treated with cefdinir. However, the number of potential pathogens rebounded faster in those treated with amoxycillin-clavulanate as compared with cefdinir in the two subsequent specimens taken at days 30–35 and days 60–65 (12 and 18 in the amoxycillin-clavulanate, and six and nine in the cefdinir group, *P* < 0.01 and *P* < 0.001, respectively) (Table 1, Fig. 1).

Following therapy, differences between the groups were also noted in the recovery of organisms with interfering capability. Immediately following amoxycillin-clavulanate therapy, the number of interfering organisms declined from 54 to 13, while following cefdinir treatment their number was reduced from 59 to 39 (*P* < 0.001) (Table 1, Fig. 2). The differences between the two therapy groups persisted in the two later specimens taken at days 30–35 and days 60–65 (25 and 38 in the amoxycillin-clavulanate group, and 52 and 51 in the cefdinir group, *P* < 0.001 and *P* < 0.05 respectively).

Fifty-four of the 111 (49 %) interfering *Prevotella* species isolates produced beta-lactamase.

**Table 1. Potential pathogens and interfering organisms recovered from the nasopharynx of children treated with amoxycillin-clavulanate and cefdinir**

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of organisms isolated a given number of days after start of antimicrobial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amoxycillin-clavulanate therapy (<em>n</em> = 25)</td>
</tr>
<tr>
<td></td>
<td>0 days</td>
</tr>
<tr>
<td>Potential pathogens</td>
<td></td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>8</td>
</tr>
<tr>
<td><em>H. influenzae</em> (non-type B)</td>
<td>5</td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>4</td>
</tr>
<tr>
<td>Total pathogens</td>
<td>17</td>
</tr>
<tr>
<td>Interfering organisms</td>
<td></td>
</tr>
<tr>
<td>Alpha-haemolytic streptococci</td>
<td>22</td>
</tr>
<tr>
<td><em>Prevotella</em> species</td>
<td>16</td>
</tr>
<tr>
<td><em>Peptostreptococcus</em> species</td>
<td>16</td>
</tr>
<tr>
<td>Total interfering organisms</td>
<td>54</td>
</tr>
</tbody>
</table>
ment is the survival of beta-lactamase-producing Gram-

negative anaerobic bacilli (including Prevotella species)
which are resistant to cefdinir. The beta-lactamase produced
by these organisms can ‘shield’ the aerobic and anaerobic streptococci from cefdinir (Brook, 2001).

The presence of organisms with interfering potential may
play a role in the prevention of respiratory infections.
Bernstein et al. (1994) found a significantly greater number
of colonies of AHS in the adenoids of non-otitis-prone
children as compared to otitis-prone children. In contrast,
they concomitantly recovered a higher number of non-type b
H. influenzae in the otitis-prone group as compared to the
non-otitis-prone group. These findings suggest the potential
protective nature of AHS with inhibitory activity in prevent-
ing otitis media. The ability of the indigenous normal
nasopharyngeal flora to inhibit colonization with potential
pathogens has been studied. AHS were found to inhibit the
colonization in patients and the in vitro growth of a variety
of pathogenic bacteria, including S. pneumoniae, group A beta
haemolytic streptococci and Staphylococcus aureus (Brook &
Gober, 1995; Brook, 1999). The production of bacteriocin
and other inhibitory substances that suppress some bacterial
growth, or utilization of nutrients in the nasopharyngeal
environment essential for the potential pathogens, may
explain this phenomenon (Brook, 2001). Organisms other
than AHS, such as Pre. melaninogenica and Pep. aerobius,
may also interfere with the growth of potential pathogens
(Murray & Rosenblatt, 1976; Brook, 1999).

This study suggests a potential beneficial effect of using a
narrow-spectrum antimicrobial that selectively spares the
interfering organisms while eliminating pathogenic bacteria.
The benefit of such therapy is the prevention of reacquisition
of pathogenic bacteria in the nasopharynx. In contrast,
utilization of a broad-spectrum antimicrobial is associated
with prolonged absence of inhibitory organisms and rapid
recolonization with pathogens. Further prospective studies
are warranted to explore the clinical implications of these
findings and find out if the recolonization with potential
pathogens is associated with recurrence of ear and other
infections.

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References


