

The Effects of Treatment of Acute Otitis Media With a Low Dose vs a High Dose of Amoxicillin on the Nasopharyngeal Flora

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Objective: To compare the effects on the nasopharyngeal flora of therapy of acute otitis media in children with either a low dose or a high dose of amoxicillin.

Design: Retrospective study.

Patients: Of 50 children diagnosed as having acute otitis media, 25 received a low dose of amoxicillin (45 mg/kg/d) (group 1) and 25 received a high dose of amoxicillin (90 mg/kg/d) (group 2) for 10 days, and both groups were evaluated.

Intervention: Antimicrobial treatment.

Results: Before therapy, potential pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*) were isolated from the nasopharynx of 15 children in group 1 (60%) and 13

in group 2 (52%). The number of penicillin-susceptible isolates was equally reduced after both therapies. However, an increase was noted in the recovery of *S aureus* only in group 2 (from 2 to 6 organisms). A greater eradication rate of interfering organisms following therapy was noted in group 2 (from 86 to 36) than in group 1 (from 92 to 60) ($P < .001$). These organisms include α -hemolytic streptococci, and *Peptostreptococcus* and *Prevotella* species.

Conclusions: The oral flora at the end of therapy with a high dose of amoxicillin is more depleted of organisms with interfering capability than following treatment with a low dose of amoxicillin. These changes may contribute to the greater recovery rate of patients infected with *S aureus* who received a high dose of amoxicillin.

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THE NASOPHARYNX OF healthy children is colonized by nonpathogenic aerobic and anaerobic organisms,¹ some of which have the ability to interfere with the growth of potential pathogens.² Interfering organisms are less often isolated from the nasopharynx of otitis media-prone children than in healthy controls.²⁻⁴ These organisms include the aerobic α -hemolytic streptococci (AHS) (mostly *Streptococcus mitis* and *Streptococcus sanguis*), anaerobic streptococci (*Peptostreptococcus anaerobius*), and *Prevotella melaninogenica*.^{4,5} Conversely, colonization by potential respiratory pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* increases considerably in otitis media-prone children and in the general population of young children during respiratory illness.⁵ Nasopharyngeal flora with interfering capability may inhibit colonization or growth of potential pathogens in the host and may play a role in preventing ear infections.^{1,3}

Administration of antimicrobial agents can affect the composition of the nasopharyngeal bacterial flora.⁶ Oral flora organisms with interfering capability are generally susceptible to amoxicillin. These include aerobic and anaerobic streptococci, as well as penicillin-susceptible *P melaninogenica*.

Amoxicillin is considered to be the standard treatment for acute otitis media in children. An increase in the daily dose of amoxicillin from 45 mg/kg to 90 mg/kg was introduced in 2000 to better eradicate penicillin-resistant *S pneumoniae*.⁷ This study compared the effects on the nasopharyngeal flora of therapy of acute otitis media in children with either a low dose or a high dose of amoxicillin.

METHODS

Children diagnosed as having acute otitis media and treated with amoxicillin were included in this retrospective study. Acute otitis media was diagnosed (as previously defined⁷) as the presence of abrupt onset of disease, irritability,

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Table. Potential Pathogens Recovered From the Nasopharynx of Patients Treated With a Low Dose or High Dose of Amoxicillin^a

Potential Pathogen	Group 1 (Low Dose: Amoxicillin, 45 mg/kg/d) (n=25)		Group 2 (High Dose: Amoxicillin, 90 mg/kg/d) (n=25)	
	Before Therapy	After Therapy	Before Therapy	After Therapy
<i>Streptococcus pneumoniae</i> ^b	7 (3)	3 (2)	8 (3)	2 (1)
<i>Haemophilus influenzae</i> (non-type B)	5 (3)	2 (2)	7 (3)	3 (3)
<i>Moraxella catarrhalis</i>	5 (5)	4 (4)	4 (4)	3 (3)
<i>Staphylococcus aureus</i>	1 (1)	2 (2)	2 (2)	6 (6)
Total	18 (12)	11 (10)	21 (12)	14 (13)

^aData are given as number (number of those resistant to penicillin).

^bAll *S pneumoniae* resistant to penicillin were intermediately resistant.

and the presence of middle ear effusion determined by pneumatic otoscopy. Included in the analysis were the first 25 consecutive patients who received 10 days of treatment with a low dose (45 mg/kg/d) (group 1) and the first 25 who received a high dose (90 mg/kg/d) of amoxicillin (group 2) and were monitored with cultures as outlined in this section. An additional 24 children who failed to come to the follow-up visit or complete their treatment were not included. We initiated the routine administration of a high dose of amoxicillin after 2000. All patients who received the low dose of amoxicillin were treated from November 1, 1998, through February 15, 1999. The patients given the higher dose were treated from November 1, 2000, through February 15, 2001. None of these patients had received heptavalent pneumococcal vaccine. The patients' ages were similar in both groups and ranged from 10 to 65 months (mean age, 29 months), and 32 were males. Excluded from analysis were those who had received antimicrobial therapy in the previous 3 months, attended a day care center, and had an underlying illness or facial anomalies. The study was presented to the institutional review board (IRB) and was granted an IRB exemption.

Nasopharyngeal cultures were obtained prior to therapy and on a follow-up visit 2 to 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. The cultures were processed for the recovery of potential pathogens and 3 types of organisms known to possess inhibitory activity: AHS and *Peptostreptococcus* and *Prevotella* species. The inhibitory activity of the 3 types of organisms, known to possess inhibitory activity, was tested as previously described⁸ against 1 strain each of a recent clinical isolate of *S pneumoniae*, *H influenzae*, *M catarrhalis*, and *Staphylococcus aureus*. Processing of specimens, identification of organisms, and determination of β -lactamase production was performed as previously described.⁸

Minimal inhibitory concentration (MIC) values of penicillin and amoxicillin were determined by the broth microdilution method following the guidelines of the National Committee for Clinical Laboratory Standards with cation-adjusted Mueller-Hinton broth (Difco Laboratories, Detroit, Michigan) supplemented with 5% lysed horse blood for *S pneumoniae* and *Streptococcus pyogenes*.⁸ Intermediate resistance to penicillin was defined as an MIC of 0.1 to 1.0 μ g/mL, and high resistance to penicillin was defined as an MIC of at least 2.0 μ g/mL.

Compliance with therapy was assessed by inspection of the unused medicine after completion of treatment. Patients who failed to take more than 2 doses or who failed to return their medicine bottles were excluded from analysis. Patients were evaluated clinically 2 to 4 days after completion of therapy. Statistical significance was calculated using the χ^2 test.

RESULTS

After completion of therapy, 19 (76%) of the patients in group 1 and 21 (84%) of those in group 2 were considered clinically cured (symptom free). Persistence of middle ear fluid without inflammation was present in 9 (36%) of those in group 1 and in 7 (28%) of those in group 2.

Before therapy, 18 potential pathogens (*S pneumoniae*, *H influenzae*, *M catarrhalis*, and *S aureus*) were isolated from the nasopharynx of 15 patients in group 1 (60%), and 21 potential pathogens were isolated from the nasopharynx of 13 patients in group 2 (52%). The number of potential pathogens was equally reduced after both therapies (**Table**). However, an increase was noted in the recovery of *S aureus* in group 2 (from 2 to 6). All *S aureus* isolates were resistant to penicillin through production of β -lactamase but susceptible to methicillin. However, this change was not statistically significant ($P > .5$).

Differences between the groups were noted in the recovery of organisms with interfering capability following therapy. Prior to therapy, a total of 94 interfering organisms were isolated from group 1, and 88 interfering organisms were recovered from group 2 (**Figure**). Following therapy, the number of interfering organisms declined in group 1 from 92 to 60, whereas in group 2 the number was reduced from 86 to 36 ($P < .001$).

COMMENT

This study compared the effects of 2 therapeutic regimens of amoxicillin therapy—a low dose of 45 mg/kg/d and a high dose of 90 mg/kg/d—on the nasopharyngeal flora in children with acute otitis media. It illustrates that at the end of therapy, the oral flora in patients given a high dose of amoxicillin is more depleted of organisms with interfering capability than in those given a low dose of amoxicillin.

Although both regimens are effective against penicillin-susceptible *S pneumoniae*, a high dose of amoxicillin has greater efficacy against penicillin-resistant *S pneumoniae*, as well as other normal flora organisms, including those with inhibitory activity against pathogens (eg, AHS, anaerobic streptococci, and penicillin-susceptible *Prevotella* species).

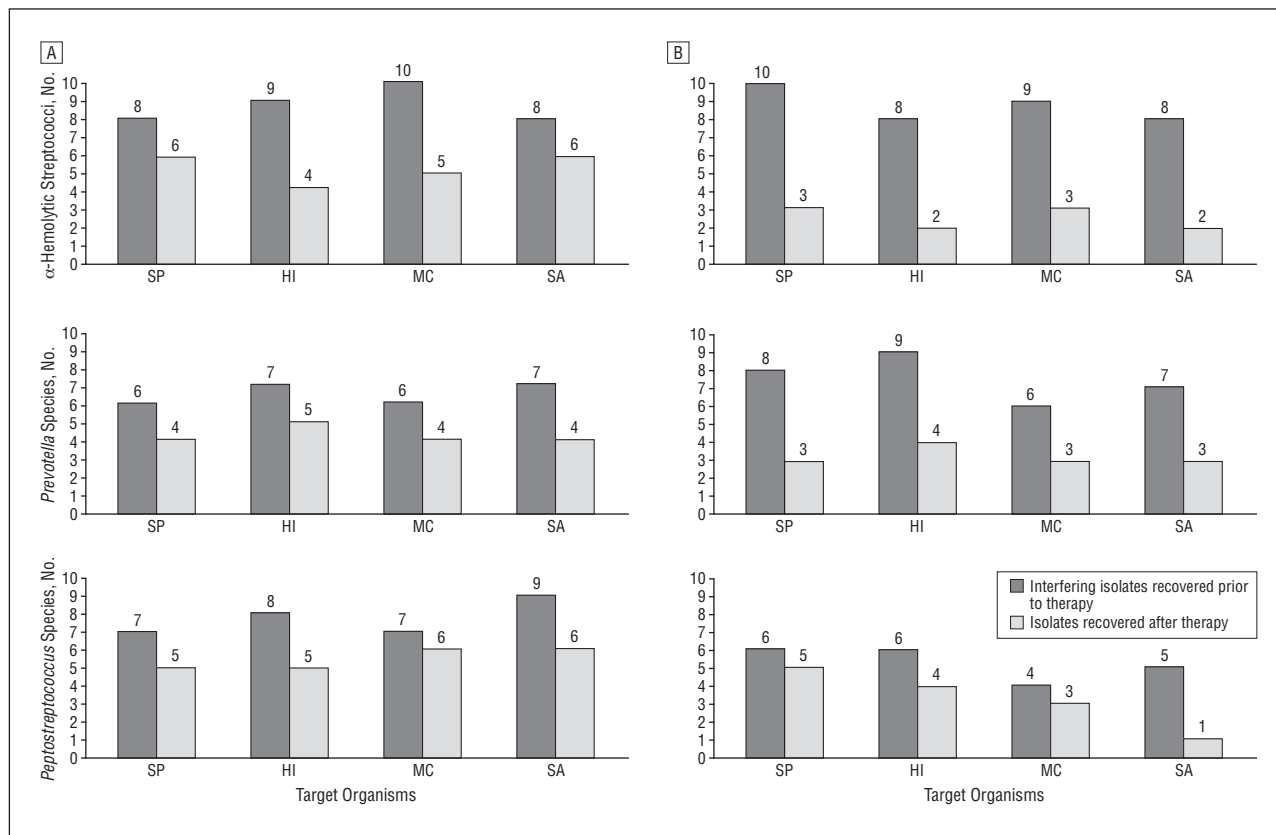


Figure. Effect of antimicrobial therapy on the recovery of interfering bacteria capable of interfering with the growth of potential pathogens in children treated with either (A) a low dose (45 mg/kg/d) (n=25) or (B) a high dose (90 mg/kg/d) (n=25) of amoxicillin. A, A change from 92 organisms before treatment to 60 after treatment is shown; B, the change is from 86 organisms before treatment to 36 after treatment. HI indicates *Haemophilus influenzae*; MC, *Moraxella catarrhalis*; SA, *Staphylococcus aureus*; SP, *Streptococcus pneumoniae*.

The higher recovery of *S aureus* from patients who received a high dose of amoxicillin may be the result of the greater reduction of organisms that are capable of interfering with this potential pathogen. The recent resurgence in the recovery of methicillin-resistant *S aureus* (MRSA) may be associated with the increased use of the higher dose of amoxicillin for the treatment of respiratory infections.⁹ Uehara et al¹⁰ found AHS less often in the oral cavity of newborns colonized with MRSA than in newborns who were MRSA free. The inhibitory activity of these AHS was through the production of hydrogen peroxide.¹¹ These data suggest that AHS may play a role in prevention of colonization with MRSA.

We¹² compared the effects of 2 types of antimicrobial therapies, amoxicillin-clavulanate and cefdinir, on the nasopharyngeal flora of children with acute otitis media. Although both agents are effective against penicillin-susceptible or penicillin-resistant potential pathogens (*S pneumoniae*, *H influenzae*, and *M catarrhalis*), they have selective activity against members of the nasopharyngeal bacterial flora. The oral flora at the end of amoxicillin-clavulanate therapy was found to be more depleted of aerobic and anaerobic organisms with interfering capability than following cefdinir therapy. The differences between the 2 therapy groups persisted for at least 60 days. A faster reacquisition of potential pathogenic bacteria occurred in those treated with amoxicillin-clavulanate than in those treated with the cephalosporin.

Bacterial interference has an important role in the development, prevention, and eradication of upper respiratory tract infections in children and can be modulated by antimicrobial agents. Interfering organisms were only found in 25% to 35% of children with recurrent group A streptococcal tonsillitis, acute otitis media, and sinusitis.⁴ Their absence in children with recurrent infections was most probably induced by repeated courses of antimicrobial drugs and may have contributed to a more rapid return of potential pathogens and recurrence of infections.

The ability of the indigenous normal nasopharyngeal flora to inhibit colonization with potential pathogens has been studied. α-Hemolytic streptococci were found to inhibit the colonization in patients and in vitro growth of a variety of pathogenic bacteria. These include *S pneumoniae*, group A β-hemolytic streptococci, and *S aureus*.^{4,8} The production of bacteriocin and other inhibitory substances that suppress some bacterial growth or the use of nutrients in the nasopharyngeal environment essential for the potential pathogens may explain this phenomenon.^{4,13,14}

This study illustrates the potential adverse effect of using the high dose of amoxicillin in the treatment of acute otitis media in children, which contributes to a greater reduction in the number of bacteria with interfering capability than the lower dose. Although the high dose of amoxicillin was more efficacious in eradicating penicillin-resistant *S pneumoniae*, it was also more able to eradicate many of the potentially beneficial inhibitory aero-

bic and anaerobic bacteria. The reduction in their number and subsequently their pathogen inhibitory effects might have enabled the emergence of *S aureus*. Furthermore, *S aureus*, which is generally resistant to amoxicillin, can survive amoxicillin treatment and benefits from the reduction of competitive bacteria.

That the subjects were not randomized to a low vs high dose and were recruited at different times is a limitation of this study. Further prospective studies are warranted to explore the clinical implications of these findings on the recovery of MRSA in clinical infections.

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