Journal of Antimicrobial Chemotherapy (2001) **48**, 269–273

JAC

Effect of amoxycillin with or without clavulanate on adenoid bacterial flora

Itzhak Brook* and Kiran Shah

Department of Pediatrics, Georgetown and George Washington Universities, Washington, DC, USA

The effect of antimicrobial therapy with amoxycillin (AMX) or co-amoxiclav (AMC) on the adenoid bacterial flora of 45 children with recurrent otitis media (ROM), scheduled for elective adenoidectomy, was studied. Patients were randomized before surgery into three groups of 15, having had either no antibiotic therapy (control), or 10 days of therapy with AMX or AMC. Core adenoid tissues were quantitatively cultured for aerobic and anaerobic bacteria. Polymicrobial aerobic–anaerobic flora was present in all instances. The predominant aerobes in all groups were α-haemolytic and non-haemolytic streptococci, *Haemophilus influenzae*, *Staphylococcus aureus*, group A β-haemolytic streptococci and *Moraxella catarrhalis*. The prominent anaerobes were *Peptostreptococcus* spp., *Prevotella* spp. and *Fusobacterium* spp. The number of isolates was significantly reduced in those treated with AMX (110; $P < 0.05$) or AMC (54; $P < 0.001$) compared with control (148). The number of bacteria per gram of tissue was lower in those treated with both antibiotics. The number of potential pathogens was lower in those treated with AMC compared with the other two groups ($P < 0.001$). The number of β-lactamase-producing bacteria (BLPB) was lower in those treated with AMC compared with those treated with AMX ($P < 0.025$) or no antibiotic ($P < 0.001$). These data illustrate the ability of AMX and AMC to reduce the bacterial load as well as potential pathogens and BLPB from the adenoids of children with ROM.

Introduction

The adenoids are believed to play a role in several infectious and non-infectious upper airway illnesses. They may be implicated in the aetiology of otitis media,[1–6] rhinosinusitis,[1,4,7,8] adenotonsillitis[9] and chronic nasal obstruction.[10,11]

The cores of adenoids from children with recurrent otitis media (ROM) contain polymicrobial aerobic and anaerobic flora similar to the flora found in adenoids from patients without any pathology.[12] However, the concentration of most of the aerobic and anaerobic bacteria and the number of potential pathogens (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*) and the number of β-lactamase-producing bacteria (BLPB) is higher in adenoids from patients with ROM.[12]

Adenoidectomy is often performed in children who suffer from ROM to alleviate the obstruction of large adenoids.[1–3] This study was designed to investigate the effect of amoxycillin (AMX) or co-amoxiclav (AMC) therapy on the potential pathogens as well as the aerobic and anaerobic bacterial flora of core adenoid tissues in children with ROM who were scheduled for elective adenoidectomy.

Materials and methods

Patients

Forty-five children (31 males) participated in the study (mean age 4 years and 11 months; range 3–6.5 years). All were defined as suffering from ROM by having had at least six episodes of acute suppurative otitis media in the past 2 years. They underwent adenoidectomy and bilateral or unilateral tympanoplasty with tube insertion because of ROM.

Patients known to have received antimicrobial therapy or to have had any infection during the previous month, or those patients known to be allergic to AMX or AMC were excluded from this study. This was determined by review of medical records and a questionnaire completed by the

*Correspondence address. PO Box 70412, Chevy Chase, MD 20813-0412, USA.
Tel: +1-301-295-2698; Fax: +1-301-295-6503; E-mail: dribrook@yahoo.com

parents. Informed written consent was obtained from the parent(s) or guardian and the study was approved by the institutional Human Use Committee.

Study design

The patients were randomized using a table of random numbers into three treatment groups with 15 patients in each. Patients in group 1 received therapy with oral AMX 40 mg/kg/day every 8 h for 10 days; those in group 2 received oral AMC 40 mg/kg/day every 8 h for 10 days; and those in group 3 (controls) received no antibiotics. The distribution of the patients' age, sex and previous antimicrobial therapy was similar in the three groups. Following their medical and otolaryngological examination, the patients were scheduled for an elective adenoidectomy 2–6 weeks later. They were given the medication and instructed to start taking the medication 12 days before surgery and to discontinue therapy 48 h before the procedure. Patient compliance with administration was checked by inspection for unused medication. All patients complied with the regimen of therapy. No side effects were noted following therapy, except for mild diarrhoea, which occurred in one child each in groups 1 and 2.

Microbiology

Following adenoidectomy, the adenoids were placed in a sterile container and promptly taken to the microbiology laboratory, where the surface of the right adenoid was cauterized with a heated scalpel and an incision was made through the area, cutting the adenoid in half. A biopsy of the core of the adenoid was obtained, weighed, homogenized and inoculated into media appropriate for the growth of aerobic and anaerobic bacteria for quantitative determination of growth. The method used could detect $>10^2$ cfu per gram of tissue.[13]

Aerobic and anaerobic bacteria were identified as described previously using conventional methods.[13,14] β-Lactamase activity was determined using five colonies of each morphological type for all isolates by using the Cefinaz disc (BBL, Cockeysville, MD, USA).

Statistical analysis

The data from each patient consisted of the total number of isolates, pathogens and BLPB categories for which the subject was positive. When the three groups were compared at the same time using a randomization test,[15] 15 000

Table I. Aerobic and facultative organisms isolated from the core of excised adenoids from 45 children with ROM

	No. of isolates (cfu ± S.D.)[a]		
Organism	AMX therapy ($n = 15$)	AMC therapy ($n = 15$)	control ($n = 15$)
Gram-positive cocci			
S. pneumoniae	3 (6.8±1.2)	–	4 (7 ± 1.1)
α-haemolytic streptococcus	9 (4.1 ± 1.1)	8 (5.2 ± 0.2)	13 (5.4 ± 0.6)
non-haemolytic streptococcus	8 (4.4 ± 0.5)	9 (3.8 ± 0.6)	14 (4.8 ± 0.7)
β-haemolytic streptococcus			
group A	2 (4.8 ± 0.5)	1 (3.7)	2 (7.6 ± 0.8)
group F	1 (4.4)	1 (4.1)	1 (6.0)
Staphylococcus aureus	6 (4.2 ± 0.7)	2 (4.2 ± 0.4)	7 (7.4 ± 1.4)
Staphylococcus epidermidis	1 (3.6)		
Gram-positive bacilli			
Lactobacillus spp.	2 (4.5 ± 0.4)	2 (3.8 ± 0.5)	2 (5.2 ± 0.8)
diphtheroid spp.	4 (3.6 ± 0.5)	3 (4.8 ± 0.6)	3 (4.8 ± 0.5)
Gram-negative bacilli			
M. catarrhalis	7 (7.1 ± 0.8)	1 (4.0)	8 (6.4 ± 0.6)
H. influenzae			
type b	2 (5.2 ± 0.4)	1 (4.8)	2 (7.1 ± 0.5)
non-type b	10 (7.2 ± 0.8)	2 (5.3 ± 0.1)	12 (7.5 ± 1.0)
Haemophilus parainfluenzae	1 (6.6)	–	2 (6.6 ± 0.4)
Eikenella corrodens	1 (5.8)	–	1 (5.2)
Escherichia coli	–	1 (6.2)	
Total	56	31	72

[a]Mean number of organisms per gram, expressed as $\log_{10}$ cfu ± S.D.

random permutations were used; when two groups were compared, 10 000 random permutations were used.

Results

Polymicrobial aerobic–anaerobic flora were present in all instances. The predominant aerobic isolates in all three groups were α-haemolytic and non-haemolytic streptococci, β-haemolytic streptococci, *H. influenzae*, *Staphylococcus aureus* and *M. catarrhalis*. The anaerobic bacteria most commonly recovered in all groups were *Peptostreptococcus* spp., *Prevotella* spp. and *Fusobacterium* spp.

One hundred and forty-eight organisms (9.87 isolates per specimen, 72 aerobes and 76 anaerobes) were cultured from the control group, 110 (7.3 isolates per specimen, 56 aerobes and 54 anaerobes) were isolated from the AMX group and 54 (3.6 isolates per specimen, 31 aerobes and 23 anaerobes) were recovered from the AMC group (Tables I and II). Patients treated with antimicrobials had fewer isolates recovered than those who received no therapy (Tables I and II). A significant reduction in the number of isolates compared with the control group occurred in those treated with AMX (110; $P < 0.05$) or AMC (54; $P < 0.001$). However, the number of isolates recovered in patients treated with AMC (54) was significantly lower than those treated with AMX (110) ($P < 0.005$).

The number of bacteria in adenoid tissue varied between 10^3 and $10^{8.2}$ cfu/g. The number of anaerobic bacteria exceeded the number of aerobic bacteria in the ratio of 1:100 (Tables I and II). The number of cfu per gram of tissue was 10–1000 times lower in those treated with AMX, and 100–10 000 times lower in those treated with AMC.

The total number of known aerobic pathogens (e.g. *S. pneumoniae*, *S. aureus*, β-haemolytic streptococci, *Haemophilus* spp. and *M. catarrhalis*) was lower in the AMC group compared with the two other groups ($P < 0.001$): eight potential pathogens (0.5 isolates per adenoid) were recovered from the AMC group, compared with 31 (2.1 isolates per adenoid) from the AMX group and 38 (2.5 isolates per adenoid) from the control group.

Fifty BLPB were recovered from 13 (87%) of the control group, 37 BLPB from 11 (73%) of the AMX group and nine BLBP from six (40%) of the AMC group ($P < 0.001$ compared with the control group and 0.025 compared with the AMX group) (Table III).

Table II. Anaerobic bacteria isolated from the core of excised adenoids from 45 children with ROM

Organism	No. of isolates (cfu ± S.D.)[a]		
	AMX therapy ($n = 15$)	AMC therapy ($n = 15$)	control ($n = 15$)
Gram-positive cocci			
Peptostreptococcus spp.	11 (5.8 ± 0.8)	5 (4.0 ± 0.5)	12 (6.2 ± 0.6)
microaerophilic streptococci	3 (6.2 ± 0.6)	1 (3.4)	6 (6.4 ± 0.8)
Gram-negative cocci			
Veillonella parvula	5 (6.0 ± 0.5)	2 (3.5 ± 0.3)	4 (5.4 ± 1.0)
Gram-positive bacilli			
Bifidobacterium adolescens	1 (5.5)	1 (6.3)	
Eubacterium spp.	1 (4.6)	1 (5.6)	
Propionibacterium acnes	2 (4.7 ± 1.3)	1 (3.1)	3 (5.4 ± 0.9)
Actinomyces spp.	1 (5.2)	1 (5.4)	
Gram-negative bacilli			
Fusobacterium spp.	3 (4.6 ± 0.3)	1 (3.9)	4 (7.0 ± 1.2)
Fusobacterium varium	1 (7.3)	1 (8.2)	
Fusobacterium nucleatum	7 (6.0 ± 0.7)	4 (3.6 ± 0.2)	10 (7.6 ± 1.3)
Bacteroides spp.	1 (5.2)	1 (4.1)	2 (6.8 ± 0.8)
Porphyromonas asaccharolytica	2 (5.4 ± 0.6)	1 (3.4)	3 (6.4 ± 1.0)
Prevotella melaninogenica	7 (5.8 ± 1.0)	3 (4.7 ± 0.2)	11 (7.4 ± 0.8)
Prevotella intermedia	4 (6.6 ± 1.0)	2 (5.0 ± 0.3)	7 (8.2 ± 1.2)
Prevotella oralis	2 (4.9 ± 1)	–	4 (6.2 ± 0.8)
Prevotella oris	2 (5.2 ± 0.5)	1 (5.2)	3 (7.2 ± 0.6)
Bacteroides fragilis group	1 (4.6)	1 (4.8)	3 (6.4 ± 0.4)
Total	54	23	76

[a]Mean number of organisms per gram, expressed as $\log_{10}$ cfu ± S.D.

Table III. β-Lactamase-producing bacteria isolated from the core of 45 excised adenoids

BLPB	No. of BLPB/total no. of isolates		
	amoxycillin therapy (n = 15)	co-amoxiclav therapy (n = 15)	control (n = 15)
Aerobes			
S. aureus	6/6	2/2	7/7
M. catarrhalis	7/7	1/1	8/8
H. influenzae			
type b	2/2	1/1	1/2
non-type b	6/10	2/2	8/12
H. parainfluenzae	1/1	–	1/2
aerobes subtotal	22/26	6/6	25/31
Anaerobes			
Fusobacterium spp.	2/3	1/1	2/5
F. nucleatum	4/7	1/4	6/10
Prevotella melaninogenica	3/7	0/3	7/11
P. intermedia	2/4	0/2	5/7
P. oris	1/2	0/1	2/4
B. fragilis group	1/1	1/1	3/3
anaerobes subtotal	12/24	3/12	25/40
Total	37/50 (72%)	9/18 (50%)	50/71 (70%)

Discussion

This study highlights and supports our previous observation that the core of adenoids in children with ROM contains polymicrobial aerobic and anaerobic flora that include potential respiratory pathogens as well as BLPB.[9,12] We recovered similar polymicrobial flora, although in lower numbers and with a lower frequency of pathogens and BLPB, in 'normal' adenoids.[12]

Whether the presence of these bacteria in the core of adenoids of patients with ROM contributes to any pathological process in them has not yet been determined. However, the 100- to 1000-fold increase in the number of several species of these organisms in adenoids of patients with ROM compared with 'normal' adenoids suggests that these bacteria may contribute to the inflammatory process in ROM.

Our study compared the effect of therapy of two antimicrobials on the flora of the adenoids in patients suffering from ROM. While both AMX and AMC reduced the total number of bacteria overall, the reduction in the number of potential pathogens and BLPB was more significant following the use of AMC.

Since many of the potential pathogens (*Haemophilus* spp., *M. catarrhalis* and *S. aureus*), as well as other members of the adenoid flora produced β-lactamase, the superior efficacy of AMC may be due to its activity against BLPB. The elimination of non-pathogenic BLPB may also be beneficial, as these organisms might 'shield' penicillin-susceptible pathogens (e.g. *S. pneumoniae* and β-haemolytic streptococci) from penicillins.[16] This phenomenon might explain the survival of penicillin-susceptible bacteria such as *S. pneumoniae* in children treated with AMX in our study. The aerobic and anaerobic organisms, including BLPB, isolated from adenoids of patients with ROM are similar to those isolated from the cores of tonsils from patients with a history of recurrent inflammation attributable to either group A[17–19] or non-group A[19,20] streptococci. Antimicrobials effective against BLPB, as well as group A streptococci, were effective in eliminating recurrent tonsillitis. These agents included AMC[21,22] and clindamycin.[16,18] The increased number of BLPB in adenoids of patients with recurrent ROM may be a result of increased exposure to antimicrobial agents. The existence of BLPB, many of them anaerobes within the core of the adenoids, may explain the persistence of many pathogenic organisms in the core of adenoids, where they may be shielded from the activity of penicillins.[16] Chronically infected adenoid tissue may also be a causative factor in the recurrence of middle ear disease by causing Eustachian tube dysfunction, serving as a reservoir of pathogenic bacteria.

Recently, Kononen *et al.*[23] reported an increased recovery rate of anaerobic bacteria from the nasopharynx of children during acute otitis media episodes. The significance of these anaerobic bacteria in the pathogenesis of such episodes is uncertain. However, if these organisms play a role in the pathogenesis of acute or recurrent otitis media, reducing their number may contribute to recovery

and may prevent recurrences. Indirect evidence for the potential importance of microorganisms in adenoid hypertrophy was recently provided by Sclafani *et al.*,[24] who demonstrated a significant reduction in the need for adenotonsillectomy after 30 days of therapy with AMC compared with placebo in children with hypertrophic adenoids and tonsils. The effect of AMC therapy may be owing to its activity against aerobic and anaerobic BLPB, which are found in higher numbers in the cores of hypertrophic adenoids and tonsils.[9,12]

Further studies are warranted that would compare the efficacy of antimicrobial agents that are active against potential pathogens, as well as BLPB, with other agents that are not active against these organisms in the treatment of ROM associated with adenoid hypertrophy. Such studies may shed more light on the role of specific bacteria in this condition and could determine whether the use of antimicrobial agents is an adequate substitute for the surgical removal of adenoids.

Acknowledgements

The authors thank Drs E. M. Friedman and J. J. Kuhn for providing adenoids from their patients, L. Calhoun, J. E. Perry and J. C. Gilmore for technical support, and Sarah Blaisdell for secretarial support.

References

1. Tuohimaa, P. & Palva, T. (1987). The effect of tonsillectomy and adenoidectomy on the intra-tympanic pressure. *Journal of Laryngology and Otology* **101**, 892–6.

2. Gates, G. A., Avery, C. A., Prihoda, T. J. & Cooper, J. C. (1987). Effectiveness of adenoidectomy and tympanostomy tubes in the treatment of chronic otitis media with effusion. *New England Journal of Medicine* **317**, 1444–51.

3. Gates, G. A., Avery, C. A. & Prihoda, T. J. (1988). Effect of adenoidectomy upon children with chronic otitis media with effusion. *Laryngoscope* **98**, 58–63.

4. Fujita, A., Takahashi, H. & Honjo, I. (1988). Etiological role of adenoids upon otitis media with effusion. *Acta Otolaryngologica Supplement (Stockholm)* **454**, 210–3.

5. Tomonaga, K., Kurono, Y., Chaen, T. & Mogi, G. (1989). Adenoids and otitis media with effusion: nasopharyngeal flora. *American Journal of Otolaryngology* **10**, 204–7.

6. Ruokenen, J., Sandelin, K. & Makinen, J. (1979). Adenoids and otitis media with effusion. *Annals of Otology, Rhinology and Laryngology* **88**, 166–71.

7. Fukuda, K., Matsune, S., Ushikai, M., Imaura, Y. & Ohyama, M. (1989). A study of the relationship between adenoid vegetation and rhinosinusitis. *American Journal of Otolaryngology* **10**, 214–6.

8. Wilson, T. G. (1965). The aetiology of chronic rhinitis and sinusitis in children. *Laryngology and Otology* **79**, 365–83.

9. Brook, I. (1981). Aerobic and anaerobic bacteriology of adenoids in children: a comparison between patients with chronic adenotonsillitis and adenoid hypertrophy. *Laryngoscope* **91**, 377–82.

10. Klein, G. L., Timmas, R. & Ziering, R. W. (1984). Obstructive sleep apnea presenting as mouth breathing in a five year old. *Immunology and Allergy Practitioner* **6**, 59–61.

11. Schiffman, R., Faber, J. & Eidelman, A. L. (1985). Obstructive hypertrophic adenoids and tonsils as a cause of infantile failure to thrive: reversed by tonsillectomy and adenoidectomy. *International Journal of Pediatric Otorhinolaryngology* **9**, 183–7.

12. Brook, I., Shah, K. & Jackson, W. (2000). Microbiology of healthy and diseased adenoids. *Laryngoscope* **110**, 994–9.

13. Murray, P. R., Baron, E. J., Pfaller, M. A., Trenover, P. C. & Yolken, R. H. (1999). *Manual of Clinical Microbiology*, 7th edn. American Society for Microbiology, Washington, DC.

14. Summanen, P., Baron, E. J., Citron, D. M., Strong, C. A., Wexler, H. M. & Finegold, S. M. (1993). *Wadsworth Anaerobic Bacteriology Manual*, 5th edn. Star Publishing, Belmont, CA.

15. Edgington, E. S. (1987). *Randomization Tests*, 2nd edn. Marcel Dekker, New York.

16. Brook, I. (1984). The role of β-lactamase-producing bacteria in the persistence of streptococcal tonsillar infection. *Review of Infectious Diseases* **6**, 601–7.

17. Brook, I., Yocum, P. & Friedman, E. M. (1981). Aerobic and anaerobic bacteria in tonsils of children with recurrent tonsillitis. *Annals of Otology, Rhinology and Laryngology* **90**, 261–3.

18. Brook, I. & Hirokawa, R. (1985). Treatment of patients with a history of recurrent tonsillitis due to group A beta-hemolytic streptococci: a prospective randomized study comparing penicillin, erythromycin and clindamycin. *Clinical Pediatrics (Philadelphia)* **24**, 331–6.

19. Kielmovitch, I. H., Keleti, G., Bluestone, C. D., Wald, E. R. & Gonzalez, C. (1989). Microbiology of obstructive tonsillar hypertrophy and recurrent tonsillitis. *Archives of Otolaryngology, Head and Neck Surgery* **115**, 721–4.

20. Brook, I. & Yocum, P. (1988). Comparison of the microbiology of group A and non-group A streptococcal tonsillitis. *Annals of Otology, Rhinology and Laryngology* **97**, 243–6.

21. Brook, I. (1989). Treatment of patients with acute recurrent tonsillitis due to group A beta-haemolytic streptococci: a prospective randomized study comparing penicillin and amoxycillin/clavulanate potassium. *Journal of Antimicrobial Chemotherapy* **24**, 227–33.

22. Kaplan, E. L. & Johnson, D. R. (1988). Eradication of group A streptococci from the upper respiratory tract by amoxicillin with clavulanate after oral penicillin V treatment failure. *Journal of Pediatrics* **113**, 400–3.

23. Kononen, E., Kanervo, A., Bryk, A., Takala, A., Syrjanen, R. & Jousimies-Somer, H. (1999). Anaerobes in the nasopharynx during acute otitis media episodes in infancy. *Anaerobe* **5**, 237–9.

24. Sclafani, P., Ginsburg, J., Shah, K. & Dolitsky, J. N. (1998). Treatment of symptomatic chronic adenotonsillar hypertrophy with amoxicillin/clavulanate potassium: short- and long-term results. *Pediatrics* **101**, 675–81.

Received 2 January 2001; returned 7 March 2001; revised 30 April 2001; accepted 3 May 2001