Current Opinion in the Management in Acute Otitis Media

Abir K. Bhattacharyya Consultant ENT Surgeon & Hon. Senior Lecturer in Otolaryngology St. Bartholomews and Royal London Hospitals & Medical School London.

Sudip Ghosh Resident in ENT, West Suffolk Hospital, Hardwick Lane, Bury St. Edmunds Suffolk, U.K.

The use of antibiotics in the treatment of Acute Otitis Media (AOM) remains controversial, as reflected by the state of recent papers^{1,2,3,4} on the management of this very common condition. The benefits of antibiotic treatment on short term and long term outcomes remain unproved; uncertainty exists over whether antibiotics prevent rare complications and studies on prevention of poor outcome in high-risk groups following antibiotic treatment are lacking.

It is broadly believed that community-based services would usually favour the use of antibiotics, especially in the U.K. and U.S.^{5,6,7} though not in the Netherlands⁸. The hospital departments would be advocating its use whilst dealing with treatment failures, high-risk groups and the treatment of the complications of acute otitis media.

Conservative therapy

The mainstay of conservative therapy has been analgesics-Non-steroidal anti-inflammatory

Abstract

The management of Acute otitis media has been a subject of controversy. This paper discusses the current opinion on the subject including a review of recent literature. The use and choice of antibiotics reflects the wide variation in opinion for both first line and second-line therapy. The role of tympanocentesis and prophylactic treatment is discussed. The introduction of vaccines holds new promise on the prevention of Acute otitis media. Factors affecting outcome influence the management plan especially in recurrent cases, high risk groups and treatment failures.

Key words

Acute Otitis Media, Management, Antibiotics, Tympanocentesis, Vaccines.

Drugs (NSAIDs) and paracetamol. A recent study by Bertin et al.⁹ has demonstrated the superiority of ibuprofen over paracetamol for pain relief, and analgesics were generally more effective compared to placebos. However the relative contraindication of prescribing ibuprofen to children would limit its use. The use of antihistaminics and decongestants, although traditional, has fallen into disrepute.¹⁰ Nasal decongestant drops too, are no longer popular.¹¹

The choice of antibiotics

There has been widespread acceptance for oral amoxycillin as the drug of first choice in AOM^{12,13,14} despite adverse side-effects like gastro-intestinal upsets in young children. This could be administered effectively per-rectally¹⁵ although gastro-intestinal problems were not circumvented, and compliance would be an added problem.

Penicillin-sensitive patients can be given erythromycin, cefixime¹⁶ or trimethoprim-sulphamethoxazole combinations. In a recent study¹⁷ a single intramuscular

dose of ceftriaxone was equal in efficacy to 10 days of oral co-trimoxazole. But the rare yet serious complications seen with the sulphonamide component such as pancytopenia, leucopenia and Steven-Johnson syndrome makes co-trimoxazole unsuitable as a first-line agent. Hence erythromycin remains popular in the U. K. as a second-line choice for those allergic to penicillin.

The majority of studies on the use of antibiotics in the treatment of AOM in recent literature compared the efficacies of different agents. Current trials include newer macrolides, Azithromycin and Clarithromycin, Amoxycillin-Clavulanate and Cefixime, for the treatment of beta-lactamase producing organisms i.e. *Haemophilus influenzae* and *Moraxella catarrhalis*. The recent emergence of penicillin resistant strains of *M. catarrhalis* and *H. influenzae* have caused concerns over the use of amoxycillin as the first-line agent for AOM in younger children.^{18, 19} Indeed, numerous trials have been carried in recent years to assess the suitability of newer macrolides^{20, 21, 22, 23} compared to amoxycillin-clavulanate and cefixime²⁴ as second-line agents; no single agent has been established to be distinctly superior over the others.

There has been an emerging awareness that the traditional methods of assessing clinical efficacy of an antibiotic by symptomatic response gives rise to the 'Polyanna' phenomenon (drugs with poor antibacterial activity appearing to be clinically effective in AOM and therefore not quite reliable to assess).²⁵ Most clinical trials comparing the clinical efficacy of different antibiotics have failed to show statistically significant difference between the different agents.²⁷

A number of randomised, placebo-controlled trials^{28, 29, 30, 31} have been carried out to evaluate the effectiveness of antibiotic regimes compared to the option of not using antibiotics at all in acute otitis media. Del mar and colleagues¹ have recently carried out a meta-analysis of six of these trials. They have concluded that although early use of antibiotics

did not influence resolution within 24 hours of presentation, after 2-7 days, fewer children in the antibiotic group had pain compared to those treated with placebos (9.7% vs. 14.3%). Moreover the risk of contralateral otitis media was reduced by 43%, although there was little influence on subsequent attacks of AOM or deafness. But antibiotics nearly doubled the risk of vomiting or rashes, Del Mar et al concluded that the benefits of early antibiotic use were modest. To prevent one child from experiencing pain by 2-7 days of presentation, 17 children must be treated early with antibiotics. They suggested a selective and more restricted use of antibiotics, and that looking for subgroups of children with otitis media who are going to suffer beyond one day and thus benefit most from antibiotics might be an useful of research in future.

The role of Tympanocentesis

More recently, measuring antibiotic concentrations in middle-ear fluid (MEF) has been used to assess the efficacy of antibiotic regime, especially in children who have had treatment failure in the presence of beta-lactamase.³² Several beta-lactamase stable drugs e.g. cefixime and amoxycillin-clavulanate achieve MEF concentrations well above the Minimum Inhibitory Concentration (MIC) 90-s for both beta-lactamase producing and non-producing *Haemophilus influenzae*, which was a distinct advantage over amoxycillin, as the latter failed to achieve the MIC 90 for most strains of beta-lactamase producing *H. influenzae*. But amoxycillin remains the first-line agent of choice by virtue of its superiority over amoxycillin-clavulanate or cefixime in reaching MEF levels that exceed the MIC 90 for penicillin-resistant *Streptococcus pneumoniae* at normal doses. Thus tympanocentesis with culture is the ideal method of antibiotic choice, atleast in children with multiple antibiotic-regime failures³³ to decide between first and second-line agents. Clarithromycin³⁴ has been reported to produce sustained MEF concentrations well above the MIC 90-s for most otitic pathogens with multiple oral doses.

It is possible that while empiric therapy could be restricted to first-line agents like amoxycillin, treatment of therapeutic failures with the former might be an indication to choose second-line agents based on tympanocentesis and culture in the near future. Moreover in the areas of high prevalence of beta-lactamase producing organisms, the appropriate first-line agent for empiric therapy could be chosen on the basis of clinical efficacy as predicted by MF levels.³⁵ More prospective studies are required to establish a protocol for choosing second-line antibiotics.

Prophylactic therapy for recurrent AOM

At present the sub-population of children having recurrent episodes of acute otitis media can be best managed by a number of approaches. Long-term low-dose antibiotics have proved adequate with few side-effects^{36,37}, and overgrowth of *Clostridium difficile* has never been reported.³⁸ A recent American study³⁹ however found no benefit of continuous twice-daily or once-daily amoxycillin prophylaxis over placebo in preventing new AOM episodes. The use of routine antibiotic prophylaxis over placebo in preventing new AOM episodes. The use of routine antibiotic prophylaxis was therefore discouraged in this study, keeping in view the risk of acquisition of resistant *pneumococci*.

Surgical interventions like adenoidectomy^{40,41} and insertion of ventilating tubes⁴² have also been effectively used, although long-term sequelae of the later intervention might make it seem less than ideal. More recently, Uhari et al⁴³ have reported from Finland the effectiveness of xylitol administered through chewing gums, which reduces the growth of *Streptococcus pneumoniae* in children with recurrent otitis media. There were fewer attacks as well as reduced antibiotic requirements in the above group of children.

Prevention of AOM

Preventing acute otitis media is a high-priority

area and vaccines, both against bacteriae and viruses, appear to hold considerable promise for the ultimate prevention of AOM.⁴⁴

In a recent development, Respiratory Syncytial Virus-enriched Immunoglobulin (RSVlg) has been successfully used in the prophylaxis of AOM in high-risk children.^{45,46} Although AOM develops in upto one-third of children with RSV illness, this approach appeared to have a significant impact on both RSV and non-RSV related AOM in high-risk children (e.g. broncho-pulmonary dysplasia, prematurity and heart disease). In the future, we are likely to witness significant work in the development of vaccines for the prevention of acute otitis media.

Outcome and factors affecting outcome

Acute otitis media is essentially a self-limited disease and a poor outcome is fortunately rare. Perforation of the tympanic membrane occurs in about one-third of cases, of which more than 90% close within one month.⁴⁷ However, a middle-ear effusion persists for upto 3 months after the acute episode in about 70% of cases. In 10% it persists even beyond this period, usually requiring myringotomy with insertion of ventilating tubes.⁴⁸ Air-conduction and inner-ear function are unaffected^{49,50} in the absence of complications, though recently hearing threshold elevation in the high-frequency range (> 8kHz) has been reported following AOM.⁵¹ Animal studies have indicated that this might be due to inner ear dysfunction. Rarely facial palsy may be the presenting feature of AOM.⁵² In most cases of facial palsy due to AOM, complete recovery is the rule, and antibiotics with myringotomy is all that is required. The risk of facial palsy in AOM seems to be highest in adults.⁵³

It is generally believed that acute mastoiditis has become very rare due to early antibiotic use.⁵⁴ However the incidence of 'masked' or latent mastoiditis as a result of protracted sub-acute otitis has gone up significantly, as a result of disease modification by increasing early antibiotic administration in AOM.⁵⁴

Intra-cranial complications like meningitis have been shown to be predisposed by cochlear abnormalities like the Mondini deformity, or dehiscent facial nerve, especially in the horizontal part.⁵⁵

In a recent Finnish study⁵⁶ of prognostic factors associated with a poor outcome of AOM, age below 2 years, history of allergic or respiratory symptoms, 6 hours or more of pre-treatment otalgia and Branhamella (Moraxella) catarrhalis in MEF were implicated with clinical failure of therapy. HIV infection and immunocompromised states are also associated with a higher incidence of complications.

Conclusions

Although the majority of cases of Acute otitis media continue to be treated by early administration of antibiotics, there is increasing awareness that the benefits of antibiotic

treatment are only modest.¹ Despite increasing penicillin resistance, amoxycillin continues to be the drug of choice, though newer macrolides (Roxithromycin, Azithromycin and Clarithromycin), Amoxycillin-Clavulanate and Cefixime appear to be promising as second-line agents. Tympanocentesis with culture of middle-ear fluid is likely to be a key investigation for rational therapy in future, especially in cases of therapeutic failure of amoxycillin. Preventing AOM is a high-priority area at present, with current research aimed at developing vaccines and conducting trials.⁴⁴ Although antibiotics have definitely improved the outcome of AOM with regard to complications, there is some concern about the rising incidence of masked or latent mastoiditis as a result of increased early antibiotic therapy.⁵⁴ More prospective studies would be needed to elucidate the best mode of management of this very common condition.

References

1. Del mar CB, Glasziou PP, Havem M. (1997) Are antibiotics indicated as initial treatment for acute otitis media? A meta-analysis. *BMJ* : 1526–9.
2. Burke P, Bain J, Robinson D, Dunleavy J. (1991) Acute red ear in Children: controlled trial of non-antibiotic treatment in general practice. *BMJ* : 303 : 558–62
3. Claessen JQ, Appelman CL, Touw Otten FW, et al. (1992) A review of clinical trials regarding treatment of acute otitis media. *Clin Otolaryngol* : 17 : 251–7
4. van Balen FAM, De Melker RA. (1996) Touw Otten FWMM. Double-blind randomised trial of coamoxiclav versus placebo for persistent otitis media with effusion in general practice. *Lancet* : 348 : 713–6
5. Froom J, Culpepper L, Grob P, et al. (1990) Diagnosis and antibiotic treatment of acute otitis media: Report from International Primary Care Network. *BMJ* : 300 : 582–6.
6. Bain J. Childhood otalgia : (1990) acute otitis media. Justification for antibiotic use in general practice. *BMJ* : 300 : 1006–7
7. Mills RP. (1990) Policies on antibiotics on of SE London general practitioners for managing AOM in children. *BMJ (Clinical Research Edition)* : 288 : 1199–1201.
8. van Buchem FL. (1987) Antibiotics for otitis media. *J R Coll Gen Pract* : 37 : 367.
9. Bertin L, Pons G, et al. (1996) A randomized, double-blind, multi-centre trial of ibuprofen versus acetaminophen and placebo for symptoms of AOM in children. *Fundam-Clin-Pharmacol*. 10(4) : 387–92.
10. Karma PH, Palva T, et al. (1987) Finnish approach to the treatment of AOM. *Annals of Otolaryngology, Rhinology and Laryngology*. : Suppl 129 : 1–19.
11. van Buchem FL, Peeters MF, van't Hoff MA. (1985) Acute otitis media : A new treatment strategy. *BMJ* : 290 : 1033–7.

12. Mills RP. (1984) Policies on antibiotics of SE London GPs for AOM. *BMJ* : 288 : 1199-1201.
13. Giebenk GS. Canafax DM. (1991) Antimicrobial treatment of otitis media. *Seminars on Respiratory Infections*. ; 6 : 85-93.
14. Bluestone CD. (1990) Rationale for anti-microbial therapy of otitis media. In *Update on Otitis media*, Ed. JD Nelson. London . New York. RSM Services.pp 23-32.
15. Bergstrom BK. Bertilson SO. Movin G. (1988) Clinical evaluation of rectally-administered ampicillin in AOM. *Jour of Internat'l Medical Research*. 16 : 376-85.
16. Gooch WM-3rd. Blair E. Puopolo A. et al. (1996) Effectiveness of five-day therapy with cefuroxime axetil suspension for treatment of AOM. *Paediatr-Inf-Dis-J*. Feb : 15(2) : 157-64.
17. Barnett ED. Teele DW. Kleine JO. et al. (1997) Comparison of ceftriaxone and co-trimoxazole for AOM. *Paediatrics*. jan : 99 (1) : 23-8.
18. Block SL. (1997) Causative pathogens, antibiotic resistance and therapeutic considerations in AOM. *Paedtr-Inf-Dis-J*. April ; 16 (4) : 449-56.
19. Jacobs MR. (1996) Increasing importance of antibiotic-resistant *Strep. Pneumoniae* in AOM. *Paedtr-Inf-Dis-J*. Oct ; 15 (10) : 940-3.
20. McCarty J. (1996) A multi-center trial of Azithromycin for treatment of AOM. *Paedtr-Inf-Dis-J*. Sept, 15 (9) Suppl. S10-14.
21. Arguedas A. Loaiza C. Rodriguez F. Herrera ML. Mohs E. (1997) Comparative trial of 3 days of Azithromycin vs. 10 days of Clarithromycin in the treatment of AOM with effusion. *J Chemotherapy*. Feb ; 9 (1) : 44-50.
22. Khurana CM. A multi-center open-label comparison of azithromycin and amoxycillin-clavulanate for the treatment of AOM in children attending daycare or school. (1997) *Diagn-Microbiol-Infect-Dis*. Jan-Feb ; 27 (1-2) : 35-9.
23. McInn S. (1996) A multi-center double-blind comparison of azithromycin and amoxycillin for the treatment of AOM in children. *paedtr-Inf-Dis-J*. 15 (9 Suppl) : S 20-3.
24. Gooch WM3rd. Philips et al. (1997) Comparison of Safety, efficacy and acceptability of cefixime and amoxycillin-clavulanate in AOM. *paedtr-In-Dis-J*. 16 (2 Suppl.) S 21-24.
25. Marchant CD. Carlin SA. Johnson CE. Shurin PA. (1992) Measuring the comparative efficacy of antibacterial agents for AOM : the 'Polyanna' phenomenon. *J of paediatrics*. 120 : 72-77.
26. Sorri M. Alho OP. Oja H. Dynamic multi-variate modelling (1996) day-care and consultation rate for AOM. *Acta Otolaryngol-Stockh*. 116 (2) : 299-301.
27. Cohen R. (1997) The antibiotic treatment of AOM and sinusitis in childhood. *Diagn-Microbiol-Infect-Dis-J*. jan-Feb ; 72-77.
28. Thalín A. Denert O. et al . (1985) Is penicillin necessary in the treatment of AOM ? In : *Proceedings of the Int. Conference on acute and secretory otitis media part 1* ; Jerusalem Israel 17-22 Nov. Amsterdam : Kugler Publ. 441-6.
29. Burke P. Bain J. Robinson D. Dunleavy J. (1991) Acute red ear in children : controlled trial of non-antibiotic treatment in general practice . *BMJ* : 303 : 558-62.
30. van Buchem FL. Dunk HJHN. van't Hof MA. (1981) Therapy of AOM : Myringotomy, Antibiotics or neither? A double-blind study in children. *lancet* ; ii : 883-7.
31. Mygind N. Meistrup-Larsen KI. et al. (1981) Penicillin in AOM : a double-blind placebo-controlled trial *Clin Otolaryngol*. 6 : 5-13.
32. Kaleida PH. Caselhrant ML. et al (1991) Amoxycillin or Myringotomy or both for AOM : results of a randomized clinical trial. *Paediatrics* ; 87 : 466-74.

33. Harrison CJ. (1997) Using antibiotic concentrations in middle-ear fluids to predict potential clinical efficacy. *Pediatr-Inf-Dis-J* ; 16 (2 Suppl) : 16 (2 Suppl) : S 12 -16
34. Gan VN. McCarty JM. Chu SY. Carr R. (1997) Penetration of Clarithromycin into MEF of children with AOM. *Paediatr-Inf-Dis-J* ; 16 (1) : 39-43.
35. Bocazzi A. Careddu P. AOM in Paediatrics (1997) Are there rational issues for empiric therapy ? *paediatr-Infect-Dis-J*. 16 (Suppl 3) : S 56-9.
36. Paradise JL. (1992) Antibiotic prophylaxis for recurrent AOM . *Annals of Otolology, Rhinology and Rhinology Suppl*. 155; 33-6.
37. Lundgren K. Ingvarsson L. AOM in Sweden . *Drugs*. 31 Suppl. 3 ; 125-30.
38. Cohen R. (1997) The antibiotic treatment of AOM and sinusitis in children . *Diagn-Microbiol-Infect-Dis*. 27 (1-2) : 35-9.
39. Roark R. (1997) Berman S. Continuous once-daily or twice-daily amoxycillin prophylaxis compared with placebo for children with recurrent AOM. *Paediatr-Inf-Dis-J* 16 (4) 376-81.
40. Bluestone CD. (1994) Surgical management of otitis media. *paediatr-Inf-Dis-J* ; 3 : 392-6.
41. Magnuson B. Falk B. (1984) Diagnosis and management of Eustachian tube malfunction . *Otol Clinics of N America* ; 17 : 659-71
42. Gonzalez C. Arnold JE. et al. (1986) Prevention of recurrent AOM : Chemoprophylaxis vs. Tympanostomy tubes. *Laryngoscope* 96 : 1330-4.
43. Uhari M. Kontiokari T. et al. (1996) Xylitol chewing gum in prevention of AOM : Double -blind randomized trial . *BMJ* 313 (7066) : 1180-4.
44. Heikkinen T. Ruuskanen O. New prospects in prevention of otitis media. (1996) ; *Ann Med*. 28 (1) : 23-30.
45. Harrison C.J. (1996) The other effect of intravenously administered respiratory syncytial virus enriched immunoglobulin for prophylaxis : less AOM . *J paediatrics* : 129 (2) : 214-9.
46. Simoes EA. Groothuis JR. et al.(1996) Respiratory Syncytial Virus-enriched globulin for the prevention of AOM in high-risk children. *J Paediatrics*. 129 (2) : 214 -9.
47. Berger G. (1989) nature of spontaneous tympanic membrane perforation in AOM in children . *J of Laryngol and Otol*. 103 : 1150-3.
48. Nakajima Y. (1989) Hatori Y. Clinical observation of AOM in children. *J of the ORL Society of Japan*. 92 : 347-52.
49. Holmberg K. Axelsson A. et al (1985) Comparison of tympanometry and otomicroscopy in AOM during healing. *Scandinavian Audiology*. 14 : 191-9
50. Haggard M. Hughes E. Screening children's hearing. A review of literature and the implications of Otitis Media. London HMSO p.23.
51. Margolis RH. (1991) Hunter LL. Audiologic evaluation of the Otitis Media patient. *Otol Clinics of N America* . 24 : 877-99.
52. Henderson PE. Baldone SC. (1989) Facial nerve palsy secondary to AOM. *J. of the American Osteopathic Association* . 207 -10
53. Eilefsen B. Bonding P. (1996) Facial palsy in AOM. *Clin Otolaryngol*. 21 (5) : 393-5
54. Faye Lund H. (1989) Acute and latent mastoiditis. *Journal of laryngology and Otolology*. 103 : 1158-60.
55. Barcz DV. Wood RP. et al. (1985) Sub-arachnoid space : middle-ear pathways and recurrent meningitis. *American Journal of Otolology*. 6 : 157-63.
56. Jero J. Virolainen A. Prognosis of AOM (1997) Factors associated with poor outcome. *Acta-Otolaryngol-Stockh*. 117 (2) : 278-83.