Oral cephalosporins in the treatment of acute otitis media

N. Principi

Clinica Pediatrica IV, Università di Milano, Milan, Italy

Clin Microbiol Infect 2000; 6 (Supplement 3): 61–63

Acute otitis media (AOM) is one of the most common diseases of infants and children; more than 90% of children younger than 3 years of age develop at least one episode of this disease and more than 40% suffer from more than one attack [1]. AOM is generally a mild disease, but, occasionally, it can lead to serious and potentially life threatening complications, such as mastoiditis, meningitis, sepsis and severe auditory sequelae [2,3].

AOM is a bacterial disease in 70%–80% of the cases and, because it is not possible to distinguish clinically those cases that have a spontaneous good prognosis from those that may evolve negatively, most of the opinion leaders in pediatric infectious diseases suggest a systematic prescription of antibiotics in all the cases. However, although AOM can spontaneously resolve in most cases, it has been demonstrated that use of antibiotics reduces the incidence of complications, prevents progression to chronic otitis media with effusion and relieves symptoms in a shorter time, thus permitting a faster return to day-care centers or to school.

Bacterial pathogens usually cultured from middle ear fluid collected by tympanocentesis during an episode of AOM are *Streptococcus pneumoniae* (S.pn.), *Haemophilus influenzae* (H.i.), *Moraxella catarrhalis* (M.c.) and *Streptococcus pyogenes* (S.p.). Amoxicillin is active against all these bacteria, and is safe, well tolerated and cheap. Therefore, it has been considered the drug of choice for AOM since its introduction on the market [4–6]. Until the beginning of the 1980s this opinion was never debated but the emergence of resistance of H.i. and M.c. posed the question of the possible substitution of amoxicillin with different antibiotics able to resist to β-lactamases. Among the possible alternatives to amoxicillin, amoxicillin-clavulanate combination, recently marketed macrolides and second- and third-generation oral cefaphalosporins were indicated [7,8]. However, use of amoxicillin-clavulanate combination was followed by an increased risk of gastrointestinal side-effects, and macrolides were considered less suitable because in some geographic areas high percentages of S.p. were resistant to these drugs. Therefore, second-and third-generation oral cephalosporins became the most commonly prescribed alternatives to amoxicillin. Several clinical trials demonstrated their efficacy, safety and tolerability in AOM. At usual therapeutic doses all these compunds were considered to have a similar clinical and microbiological efficacy and ultimate choice depends on safety, tolerability and cost considerations [6].

At the beginning of the 1990s a new problem of resistance among the AOM pathogens arose: in several countries, a significant proportion of S.pn. became penicillin resistant. As with penicillin, several other antibiotics were included in this form of resistance, and the role of second- and third-generation oral cephalosporins in the treatment of AOM was reconsidered [9–12]. Taking into account both pharmacokinetic and pharmacodynamic characteristics of all these antibiotics, it was demonstrated that most of the cephalosporins did not have properties good enough to overcome the problem of S.pn. resistance. Of particular interest is the length of time between doses during which concentrations of the various oral cephalosporins remain higher than the minimal inhibitory concentration (MIC) for the infecting pathogen. Starting from the premise that to have a significant probability of eradicating the pathogen present in the middle ear fluid an antibiotic must remain at the site of the infection at a concentration higher than the MIC for at least a period corresponding to 30%–50% of the dose interval, it was clearly demonstrated (Table 1) that only cefuroxime-axetil and, to a lesser extent, cefprozil may have a chance of being effective in AOM due to penicillin-resistant S.pn., at least when less resistant strains are involved [14].

Oral cephalosporins were also involved in a second problem concerning the therapy of AOM, that which considers the possible prescription of the antibiotic for a period of time shorter than that usually used. It is current opinion that a 10-day course is the best way to obtain a cure; however, it is difficult to maintain the antibiotic therapy for as long as this, especially in infections such as AOM, which have a very good clinical reponse in 3–4 days. As a consequence, compliance may be reduced and the risk of failure can be highly increased. So several trials evaluated shortened treatment regimens for AOM with the use of oral cephalosporins (Table 2). The collected data cannot be considered conclusive because the number of enrolled patients is small. However, an overall evalutation of the data suggests that a shortened course of therapy cannot be systematically used in AOM. With a shortened course of therapy, whatever the drug used, an

Corresponding author and reprint requests: Nicola Principi, Istituto Clinici di Perfezionamento, Clinica Pediatrica, Università di Milano, Italy
Fax.: +39 02 551 95341

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Table 1 Short-term therapy with oral cephalosporins for acute otitis media

Therapy	Age (no. of cases)	Outcome
Cefaclor 5 days vs. Amoxicillina 10 days	5 m–5 y (27)	No difference
Cefaclor 5 days vs. Cefaclor 10 days	1 m–10 y (59)	5 days less effective if perforation of eardrum
Cefuroxime 5 d vs. Amoxl + AC.Clav.10 d	3 m–12 y (242)	No difference < ADR with 5 days
Cefpodoxime 5 d vs. Cefixime 8 d	6 m–6 y (125)	No difference
Cefpodoxime 5 d vs. Amoxi + AC.Clav 8 d	4 m–4 y (111)	No difference

Modified, from [13].

Table 2 Time > MIC_{90} of oral cephalosporins vs. *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*

	S. pneumoniae			*H. influenzae*	*M. catarrhalis*
	PEN-S	PEN-I	PEN-R		
Cefaclor	44	0	0	0	35
Cefuroxime	73	33	0	33	33
Cefixime	48	0	0	88	48
Cefprozil	78	28	0	16	41
Cefpodoxime	62	0	0	82	37
Ceftibuten	5	0	0	33	20

From [15].

increased risk of failure seems possible in those cases where the tympanic membrane is perforated and in younger infants and children. In contrast, no problems are present when older children and uncomplicated cases are evaluated [16–27]. It is clear that a shortened course of antibiotic administration is a goal of antibiotic therapy because it increases compliance, thus reducing the risk of failure, it limits the development of undesirable side-effects and it reduces the economic cost of the treatment. However, it can be suggested only when there is a clear definition of which patients may really benefit from a simplified scheme of therapy and which children may have an increased risk of failure. Because this is not clearly established for AOM, it is reasonable to suggest that in correctly diagnosed AOM oral cephalosporins are given for 10 days, accurately monitoring drug administration, safety and tolerability.

In conclusion, some oral cephalosporins, such as cefuroxime axetil and cefprozil, remain the drugs of choice to treat AOM of infants and children all over the world, even in those countries where there are problems of resistance to amoxicillin, owing to production of β-lactamases by H.i. and M.c. and for modification of PBP by S.pn. Other oral cephalosporins may be valid alternatives to amoxicillin where the only problem is H.i. and M.c. resistance. In all AOMs, they must be administered for 10 days until the problem of which children might receive a shorter treatment is clearly solved. Among the various compounds of this antibiotic group the choice of the best drug to use in those cases in which clinical and microbiological efficacy can be considered quite similar has to be supported by a precise consideration of safety, tolerability and economic cost. A careful evaluation of clinical trials in which these drugs were assessed together with a precise analysis of pharmacokinetic and pharmacodynamic characteristics of each of them can differentiate the various compounds and identify those with the best cost/efficacy ratio.

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