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Amoxicillin/Clavulanic Acid

A Review of its Use in the Management of Paediatric Patients with Acute Otitis Media

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Data Selection

Sources: Medical literature published in any language since 1980 on amoxicillin/clavulanic acid and otitis media, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'amoxicillin/clavulanic acid' and 'otitis media'. EMBASE search terms were 'amoxicillin/clavulanic acid' and 'otitis media'. AdisBase search terms were 'amoxicillin clavulanic acid' and 'otitis media'. Searches were last updated 17 Dec 2002.

Selection: Studies in patients with acute otitis media who received amoxicillin/clavulanic acid. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: acute otitis media, AOM, amoxicillin/clavulanic acid, pharmacodynamics, pharmacokinetics, therapeutic use, antibacterial.

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Summary

Abstract

Amoxicillin/clavulanic acid (Augmentin®, Augmentin ES-600™)[1] is a well established, orally administered combination of amoxicillin (a semisynthetic antibacterial agent) and clavulanic acid (a β-lactamase inhibitor).

Amoxicillin/clavulanic acid shows good activity against the main pathogens associated with acute otitis media (AOM), including penicillin-susceptible and -intermediate strains of *Streptococcus pneumoniae*, and β-lactamase producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis.* It has moderate activity against penicillin-resistant *S. pneumoniae*; a high-dose formulation has been developed with the aim of providing better coverage for penicillin-resistant strains.

Amoxicillin/clavulanic acid (conventional formulations, mostly 40/10 mg/kg/day in three divided doses) produced clinical response rates similar to those of oral cephalosporin comparators and similar to or significantly greater than those for intramuscular ceftriaxone in randomised trials in paediatric patients with AOM (mean age ≈2 to 5 years). Clinical response rates were generally similar for amoxicillin/clavulanic acid and macrolide comparators (mean patient age ≈1 to 6 years), although significantly better clinical and bacteriological responses were seen versus azithromycin in one randomised trial (mean patient age ≈1 year).

The high-dose formulation of amoxicillin/clavulanic acid (90/6.4 mg/kg/day in two divided doses) eradicated a high proportion of penicillin-resistant *S. pneumoniae* (penicillin MICs 2 or 4 mg/L) in a large noncomparative trial in children with AOM (upper limit of the US indication for *S. pneumoniae* is 2 mg/L).

Amoxicillin/clavulanic acid is generally well tolerated. A low total incidence of adverse events (3.6%) and no serious events were reported from a large paediatric postmarketing study. The most frequently reported adverse events in children are mild gastrointestinal disturbances. Diarrhoea is generally less frequent with twice-daily than with three-times-daily treatment. The new high-dose formulation showed similar tolerability to a conventional twice-daily formulation (45/6.4 mg/kg/day) in a well controlled trial.

Conclusions: Amoxicillin/clavulanic acid is a well established broad-spectrum antibacterial treatment which is effective and well tolerated in the treatment of AOM in paediatric patients. The high-dose combination should prove valuable in treating AOM caused by penicillin-intermediate and -resistant *S. pneumoniae* (approved in the US for penicillin MIC ≤2 mg/L). Based on recent recommendations and the available data, high-dose amoxicillin/clavulanic acid can be considered a treatment of choice for recurrent or persistent paediatric AOM (after failure of amoxicillin alone) where involvement of resistant pathogens is suspected.

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

Antibacterial Activity

Amoxicillin/clavulanic acid is a well established antibacterial agent which is active against a wide range of Gram-positive and Gram-negative bacteria, including the main causative pathogens of paediatric acute otitis media (AOM). The addition of clavulanic acid extends the spectrum of amoxicillin to include β-lactamase-producing pathogens such as *Haemophilus influenzae* and *Moraxella catarrhalis*. Amoxicillin/clavulanic acid shows good *in vitro* activity against penicillin-susceptible and -intermediate strains of *Streptococcus pneumoniae* (median minimum inhibitory concentration against 90% of isolates [MIC_{90}] 0.03 and 1 mg/L), but more moderate activity against penicillin-resistant *S. pneumoniae* (median MIC_{90} 4 mg/L) [National Committee for Clinical Laboratory Standards breakpoints for amoxicillin/clavulanic acid are: susceptible ≤2/1, intermediate 4/2 and resistant ≥8/4 mg/L]. Median amoxicillin/clavulanic acid MIC_{90} values for penicillin-susceptible, -intermediate and -resistant strains of *Streptococcus pneumoniae* were lower than those for cefpodoxime, cefuroxime, azithromycin and clarithromycin.

Amoxicillin/clavulanic acid and MIC_{90} values against β-lactamase-positive or -negative strains of *H. influenzae* (median MIC_{90} 2 and 1 mg/L) were broadly similar to that for cefuroxime and markedly lower than those for azithromycin or clarithromycin, but higher than for cefpodoxime.

In a single study, the amoxicillin/clavulanic acid MIC_{90} against β-lactamase-positive *M. catarrhalis* (0.5 mg/L) was lower than that for cefpodoxime and cefuroxime but greater than that for azithromycin and clarithromycin. Amoxicillin/clavulanic acid had the lowest MIC_{90} value of any of the agents evaluated against β-lactamase-negative isolates of *M. catarrhalis* in this analysis.

In a rat model of pneumonia that evaluated the activity of amoxicillin/clavulanic acid against penicillin-resistant strains of *S. pneumoniae*, a dosage equivalent to 45/6.4 mg/kg/day was only fully effective against strains with a MIC of 2 mg/L, whereas a dosage equivalent to 90/6.4 mg/kg/day significantly reduced bacterial numbers in the lungs for strains with amoxicillin MIC values of 2 or 4 mg/L.

Pharmacokinetic Properties

The oral bioavailability of amoxicillin is about 70 to 90% and maximum serum concentrations occur within 60 to 90 minutes of administration. Clavulanic acid shows more variable oral bioavailability of 31 to 99%. Serum concentration profiles for amoxicillin and clavulanic acid are broadly similar in infants and children regardless of formulation/dosage ratio.

Amoxicillin/clavulanic acid provides appropriate drug exposure against penicillin-susceptible strains of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* (based on the time, as a proportion of the dose interval, for which plasma drug concentration exceeded the MIC_{90} [T > MIC]). In an analysis based on the published literature for selected agents used to treat AOM, amoxicillin (40 mg/kg/day in three divided doses) had the highest overall coverage of any oral agent for penicillin-intermediate strains of *S. pneumoniae* (T > MIC_{90} = 59%) and was the only oral agent to provide adequate coverage for penicillin-resistant *S. pneumoniae* (T > MIC_{90} = 46%). Other agents evaluated were cefprozil, cefuroxime, cefpodoxime, loracarbef, cefaclor and cefixime.

Amoxicillin and clavulanic acid are well distributed into most body tissues and extracellular fluids, including middle-ear mucosa and middle-ear effusions in children. Effective antibacterial concentrations of both drugs are achieved in the middle ear.

Like most other β-lactam antibacterial agents, a large proportion of

amoxicillin (50 to 80%) is primarily excreted unchanged in the urine within 6 hours of administration. Clavulanic acid appears to undergo more extensive metabolism with only 20 to 60% of unchanged drug eliminated in this way. The mean elimination half-lives of amoxicillin and clavulanic acid are each about 1 hour, and the mean total clearance of both is about 25 L/h in healthy adult volunteers.

Therapeutic Efficacy

The most common pathogens isolated by tympanocentesis in trials in patients with AOM were *Staphylococcus pneumoniae, H. influenzae* and *M. catarrhalis* (*S. pyogenes* and *Staphylococcus aureus* were less commonly detected).

Amoxicillin/clavulanic acid 300 to 450 mg/day in three divided doses showed good clinical efficacy (88% of patients assessed as cured) in two postmarketing studies in 3048 children ≤14 years of age with AOM.

Amoxicillin/clavulanic acid 45/6.4 or 70/10 mg/kg/day in two divided doses produced similar clinical response rates to 40/10 or 60/15 mg/kg/day in three divided doses in infants and children with AOM in three multicentre, randomised, single-blind trials.

Amoxicillin/clavulanic acid (mostly 40 mg/kg/day in three divided doses) produced clinical response rates similar to those for oral cephalosporin comparators (cefuroxime axetil, cefdinir, cefaclor, cefixime, cefpodoxime proxetil, cefprozil and ceftibuten) in numerous multicentre, randomised AOM trials (mean patient age ≈2 to 5 years). Clinical response rates were similar to (two trials) or significantly greater than (one trial) those for intramuscular ceftriaxone. For comparators assessed in more than one trial, clinical response rates were 74 to 88% with amoxicillin/clavulanic acid versus 70 to 86% with cefuroxime axetil, 82 to 95% versus 74 to 95% with intramuscular ceftriaxone and 86 and 90% versus 80 and 91% for cefdinir.

Clinical response rates were generally similar for amoxicillin/clavulanic acid (mostly 40mg/kg/day in three divided doses) and the macrolide antibacterials azithromycin (86 to 100% vs 70 to 100%) and clarithromycin (92 to 97% vs 90 to 96%) [mean patient age ≈1 to 6 years], although a significantly higher response was seen for amoxicillin/clavulanic acid compared with azithromycin in a single randomised trial. Significantly greater bacteriological efficacy with amoxicillin/clavulanic acid was also reported in the latter study.

Successful bacterial eradication, including that of penicillin-resistant *S. pneumoniae*, was demonstrated with the new high-dose formulation of amoxicillin/clavulanic acid (90/6.4 mg/kg/day in two divided doses) in a multicentre noncomparative trial in 521 children with AOM aged between 3 and 48 months (mean ≈1.6 years). Pathogens were eliminated from 96% of bacteriologically evaluable patients. This included 91% (published data) or 94% (data from package insert) of patients with penicillin-resistant *S. pneumoniae* (penicillin MICs 2 or 4 mg/L). For patients with baseline-isolate penicillin MICs of 2 mg/L (the upper limit of the US indication for *S. pneumoniae*) eradication rates were 19 of 20 (published) and 19 of 19 (package insert).

High-dose (90/6.4 mg/kg/day) and conventional (45/6.4 mg/kg/day) amoxicillin/clavulanic acid regimens given in two divided doses produced similar clinical response rates (84 and 79% of patients had persistent clinical cure with no recurrence) in a double-blind multicentre study designed primarily to assess tolerability (n = 453).

Tolerability

Amoxicillin/clavulanic acid is generally well tolerated. The most frequently re-

ported adverse events are gastrointestinal (GI) disturbances, including diarrhoea, nausea, vomiting and indigestion. The incidence of diarrhoea was significantly reduced (one study) or tended to be lower (two studies) for twice-daily compared with three-times-daily amoxicillin/clavulanic acid regimens in randomised single-blind studies

In randomised trials in paediatric patients with AOM, amoxicillin/clavulanic acid generally produced total adverse event rates that were not significantly different from those of cephalosporin comparators (range 3.1 to 63% vs 3.4 to 44%). In the majority of studies, total and GI adverse event rates were significantly higher with amoxicillin/clavulanic acid than with macrolide comparators, although most used a three-times-daily amoxicillin/clavulanic acid regimen (which tends to cause more diarrhoea). Total adverse event rates ranged from 3.7 to 51% for amoxicillin/clavulanic acid and from 2 to 32% for macrolide comparators.

No serious adverse events and a low total incidence of events (3.6%) were reported during postmarketing surveillance of 3048 children aged ≤14 years with AOM who received amoxicillin/clavulanic acid 300 to 450 mg/day in three divided doses.

High-dose amoxicillin/clavulanic acid (90/6.4 mg/kg/day in two divided doses) had a similar tolerability profile to a conventional twice-daily regimen (45/6.4 mg/kg/day in two divided doses) in a randomised, double-blind trial in 408 children with AOM. Adverse events were reported in a total of 50.2 and 47.3% of patients, with protocol-defined diarrhoea in 11 and 8.8%. The most frequently reported adverse events in 521 children treated with the high-dose formulation in a noncomparative trial were diaper rash (4.0%), diarrhoea (3.6%), vomiting (2.3%) and other rash (1.3%). Events probably or possibly related to the medication were documented in 14% of patients.

Dosage and Administration

Amoxicillin/clavulanic acid is available in a range of formulation and dosage combinations, including oral suspension, chewable tablets and tablets. The standard regimen for paediatric patients aged 3 months or above is 45/6.4 mg/kg/day in two divided doses for 10 days. In the US, conventional formulations of amoxicillin/clavulanic acid (maximum amoxicillin : clavulanic acid ratio 7 : 1) are indicated for the treatment of AOM caused by β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*.

The high-dose amoxicillin/clavulanic acid formulation allows administration at 90/6.4 mg/kg/day in two divided doses, double the previously recommended standard amoxicillin dosage for paediatric patients aged 3 months or above. It is indicated for the treatment of paediatric patients with recurrent or persistent AOM due to *S. pneumoniae* (penicillin MICs ≤2 mg/L), *H. influenzae* (including β-lactamase-producing strains), or *M. catarrhalis* (including β-lactamase-producing strains) characterised by the following risk factors: antibiotic exposure for AOM within the preceding 3 months, and either age ≤2 years or attendance at daycare.

Amoxicillin/clavulanic acid should be used cautiously in patients with hepatic impairment. Dosage adjustment is recommended for patients aged <3 months.

1. Introduction

Acute otitis media (AOM) has become the most prevalent paediatric infection requiring treatment in the US, a finding that is generally attributed to the rising use of child daycare[1] coupled with the increased susceptibility of children to upper respiratory tract infections.[2] It can be caused by bacterial or viral pathogens,[2] and although up to 80% of middle-ear infections clear spontaneously, antibacterial therapy is generally recommended in the US (although not routinely recommended in all countries) as the potential complications can be serious.[3] Culture of middle-ear effusions yields bacterial pathogens in 50 to 70% of cases, the major pathogens typically being *Streptococcus pneumoniae* 25 to 50%, *Haemophilus influenzae* nontypeable 15 to 30%, *Moraxella catarrhalis* 3 to 20%, *S. pyogenes* group A 2 to 4% and *Staphylococcus aureus* 1 to 3%.[2] These aerobes are generally considered the major pathogens for AOM. Anaerobic bacteria are not commonly isolated, but this is largely related to the culture techniques used; anaerobes, primarily Gram-positive cocci, have been recovered either alone or with aerobic bacteria from children with AOM (in up to 27% of patients[4,5]). Respiratory viral pathogens have been isolated alone or with bacterial pathogens in about 20% of patients.[2]

Amoxicillin, a broad spectrum, semisynthetic, oral antibacterial agent, is protected from β-lactamase degradation by the addition of clavulanic acid, a naturally occurring β-lactam produced by *Streptomyces clavuligerus*. The pharmacological properties and therapeutic use of combined amoxicillin/clavulanic acid (Augmentin®) in the treatment of various types of infections have been previously reviewed in *Drugs*.[6]

A panel of experts recently concluded that oral amoxicillin 80 to 90 mg/kg/day should remain the first-line antimicrobial agent for treating AOM unless resistant pathogens are suspected, in which case amoxicillin/clavulanic acid 80 to 90/6.4 mg/kg/day is recommended.[7] Alternative second-line treatments include oral cefuroxime axetil or intramuscular ceftriaxone.

The following amoxicillin/clavulanic acid formulations are available in the US as either an oral suspension (mg/5ml of reconstituted suspension) or chewable tablets (ratio of amoxicillin:clavulanic acid as shown):[8]

- 125mg/31.25mg (4 : 1)
- 200mg/28.5mg (7 : 1)
- 250mg/62.5mg (4 : 1)
- 400mg/57mg (7 : 1).

The following formulations are available as tablets:[9]

- 250mg/125mg (2 :1)
- 500mg/125mg (4 : 1)
- 875mg/125mg (7 : 1).

In addition, a new high-dose formulation (amoxicillin 600mg/clavulanic acid 43mg per 5ml; 14 : 1 ratio) [Augmentin ES-600™] has recently been approved in the US for twice-daily administration.[10]

Detailed dosage recommendations for the use of amoxicillin/clavulanic and in AOM are presented in section 6.

This article reviews data from paediatric trials of amoxicillin/clavulanic acid for AOM that used regimens and dosage ratios consistent with the conventional formulations listed above, plus data on the new high-dose formulation.

2. Antibacterial Activity

Amoxicillin/clavulanic acid has a wide spectrum of activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria. In many *in vitro* investigations, the combination was used as a standard reference against which the activity of other oral antibacterials was compared.[6] The primary rationale for combining clavulanic acid with amoxicillin is to extend the spectrum of anti-bacterial activity of amoxicillin to include strains of pathogens which commonly produce β-lactamases, such as *H. influenzae* and *M. catarrhalis*.[6] Clavulanic acid alone has only weak antibacterial properties but is a potent inhibitor of many bacterial β-lactamases to which it binds, thereby protecting amoxicillin from enzymatic degradation and rendering the resistance mechanism of such pathogens ineffective.

S. pneumoniae is the major Gram-positive pathogen, and the most common causative pathogen overall, in paediatric AOM.[11] *S. pyogenes* and *S. aureus* are less commonly isolated. Infection with *S. pneumoniae* causes concern due to the worldwide increase in penicillin resistance.[12] In a large US study, 45% of 290 *S. pneumoniae* isolates from ear effusions, tympanocentesis or other ear samples were susceptible to penicillin (minimum inhibitory concentration [MIC] <0.1 mg/L), 30% had intermediate susceptibility (MIC 0.1 to 1.0 mg/L) and 26% were resistant (MIC >1 mg/L).[12] It should be noted that the breakpoints used were different to current values (see section 2.1).

H. influenzae and *M. catarrhalis* are the most common Gram-negative pathogens cultured from middle-ear effusions from paediatric patients with AOM.[13] Although considerable variation in the percentage of β-lactamase-positive *H. influenzae* has been reported with respect to country of origin and individual centers,[14,15] worldwide estimates for isolates collected between 1998 and 2000 put the overall incidence at 17 to 19%.[15-17]

As indicated in section 1, anaerobic bacteria may also be present in AOM. Most anaerobic bacteria in AOM are β-lactamase-positive and thus susceptible to amoxicillin/clavulanic acid.[4,18]

The remainder of this section focuses on activity against the major aerobic pathogens for AOM.

2.1 *In Vitro* Activity

In vitro activity of antibacterial agents can be assessed according to the minimum inhibitory concentration required to inhibit the growth of 90% of strains tested (MIC_{90}) and interpreted using the National Committee for Clinical Laboratory Standards recommended breakpoints (2002 update[19]). The breakpoints for amoxicillin/clavulanic acid susceptibility testing are as follows: *S. pneumoniae* MIC ≤2/1 mg/L is susceptible, MIC 4/2 mg/L is intermediate and MIC ≥ 8/4 mg/L is resistant; *H. influenzae* MIC ≤4/2 is susceptible and ≥8/4 is resistant. Penicillin susceptibility breakpoints for *S. pneumoniae* are as follows: penicillin MIC ≤0.06 mg/L is susceptible, 0.12 to 1 mg/L is intermediate, ≥2 mg/L is resistant.

Table I summarises MIC_{90} data for amoxicillin/clavulanic acid and oral antibacterial agents against bacteria that may be causative in paediatric AOM. Comparators have been selected on the basis of their use in clinical trials of amoxicillin/clavulanic acid (see section 4). Because the susceptibility of pathogens to antibacterial agents is changing continuously, only investigations conducted since mid-1996 are included in this section. MIC values were determined using standard agar or broth dilution techniques. Most studies in table I investigated the activity of amoxicillin/clavulanic acid against bacterial isolates from the US, Europe and Canada. Some isolates from South America, Saudi Arabia, South Africa and Hong Kong have also been included. The MIC is an absolute value and is defined as the lowest concentration of antibacterial tested which completely inhibits visible growth of the inoculum in broth or on agar (usually after 20 to 24 hours of incubation). It should be noted that the comparisons made between various antibacterial agents in this section are based only on the MIC_{90} values and do not take into account their respective breakpoints.

2.1.1 Gram-Positive Bacteria

Amoxicillin/clavulanic acid was highly active against penicillin-susceptible *S. pneumoniae* in several studies conducted in Europe or the US. The MIC_{90} for amoxicillin/clavulanic acid was 0.03 mg/L in four studies (two from Spain,[20,24] one from the Netherlands[26] and one from the UK[14]), ≤0.06 mg/L in a European study[21] and ≤0.125 mg/L in a US study.[12] Amoxicillin/clavulanic acid also showed good activity against isolates of *S. pneumoniae* that were intermediately susceptible to penicillin; the median MIC_{90} was 1 mg/L for amoxicillin/clavulanic acid, compared with 2, 4, >16 and >32 mg/L for cefpodoxime, cefuroxime, azithromycin and clarithromycin, respectively.

For penicillin-resistant *S. pneumoniae* (penicillin MIC ≥2 mg/L), the median MIC_{90} was 4 mg/L for amoxicillin/clavulanic acid[12,14,20,21,24,26] (current amoxicillin/clavulanic acid breakpoint for in-

Table I. *In vitro* antibacterial activity of amoxicillin/clavulanic acid compared with that of other antibacterial agents against Gram-positive and Gram-negative pathogens. Combined data taken from at least three reviews (unless otherwise stated) evaluating >500 clinical isolates collected from mid-1996 onwards.[12-14,20-28] Ratio of amoxicillin:clavulanic acid was 2 : 1[12,14,20,22] or not stated; the concentration of clavulanic acid was not reported for any study

Pathogen	Range (median[a]) of MIC_{90} values [mg/L] and no. of isolates[b]					References
	amoxicillin/ clavulanic acid	cefpodoxime	cefuroxime	azithromycin	clarithromycin	
Gram-positive bacteria						
Streptococcus pneumoniae (penicillin-susceptible)[c]	0.03–0.125 (0.03)	0.06–≤0.125[d] (≤0.125)	0.06–≤0.25 (0.12)	≤0.12–0.25 (≤0.125)	≤0.125–>16 (0.25)	12,14,20,21,24,26
	n = 6152	n = 3356	n = 6107	n = 3800	n = 3845	
S. pneumoniae (penicillin-intermediate)[e]	0.5–2 (1)	2-2[d] (2)	2–4 (4)	4–≥16 (>16)	2–≥64 (>32)	12,14,20,21,24,26
	n = 1800	n = 1207	n = 1763	n = 1470	n = 1507	
S. pneumoniae (penicillin-resistant)[f]	4–8 (4)	4–8[d] (8)	8 (8)	>16–≥64 (≥16)	>16–≥64 (≥64)	12,14,20,21,24,26
	n = 1409	n = 624	n = 1366	n = 1030	n = 1073	
Staphylococcus aureus (methicillin-susceptible)	2[g] (NR)	4[g] (NR)	2[g] (NR)			23,25
	n = 1290	n = 84	n = 84			
S. aureus (methicillin-resistant)	>16[g] (NR)	>256[g] (NR)	>256[g] (NR)			23,25
	n = 401	n = 16	n = 16			
Streptococcus pyogenes	≤0.03[g] (NR)	<0.06[g] (NR)	<0.06[g] (NR)		4[g] (NR)	23,24
	n = 42	n = 19	n = 19		n = 42	
Gram-negative bacteria						
Haemophilus influenzae (All)[h]	1–2 (2)	0.25–0.25[d] (0.25)	2–2 (2)	2[g] (NR)	16-16[d] (16)	13,14,24,28
	n = 4050	n = 1287	n = 4008	n = 1077	n = 1119	
H. influenzae β-lactamase-positive	1/2-4[d] (2)	<0.03–0.12[d] (0.12)	1–2 (1)	4–4[d] (4)	16–16[d] (16)	22,23,27
	n = 1828	n = 550	n = 1902	n = 1828	n = 1828	
H. influenzae β-lactamase-negative	1/0.5-2[d] (1)	<0.03–0.25[d] (0.25)	1–4 (2)	2–4[d] (4)	16–16[d] (16)	22,23,27
	n = 2405	n = 1087	n = 2439	n = 2405	n = 2405	
Moraxella catarrhalis (All)[h]	0.12–0.25 (0.25)	2[g] (NR)	2–2 (2)	0.03–≤0.12 (≤0.12)	≤0.12–≤0.25 (0.125)	13,14,24,27
	n = 1650	n = 503	n = 1616	n = 1616	n = 1650	
M. catarrhalis β-lactamase-positive	0.5[g] (NR)	2[g] (NR)	2[g] (NR)	0.12[g] (NR)	0.12[g] (NR)	22
	n = 687	n = 687	n = 687	n = 687	n = 687	
M. catarrhalis β-lactamase-negative	0.03[g] (NR)	0.25[g] (NR)	0.5[g] (NR)	0.12[g] (NR)	0.12[g] (NR)	21
	n = 39	n = 39	n = 39	n = 39	n = 39	

a The median of an even number of values has been reported as the higher of the two.

b Total number of isolates from all studies evaluated.

c Penicillin MIC ≤0.06 mg/L.[19]

d Results from two studies.

e Penicillin MIC 0.12-1 mg/L.[19]

f Penicillin MIC ≥2 mg/L.[19]

g Data as reported from a single study (not a median value).

h Includes both β-lactamase-positive and -negative pathogens.

MIC_{90} = minimum concentration required to inhibit growth of 90% of tested strains; **NR** = not reported.

termediate isolates is 4 mg/L[19]). Cefpodoxime and cefuroxime had a median MIC_{90} of 8 mg/L for penicillin-resistant *S. pneumoniae* whereas azithromycin and clarithromycin were inactive with median MIC_{90} values of ≥16 and ≥64 mg/L. The new high-dose (14 : 1) formulation of amoxicillin/clavulanic acid has been developed with the general aim of providing an effective agent for *S. pneumoniae* isolates that are nonsusceptible to penicillin. The US indication for this formulation is limited to recurrent or persistent AOM due to *S. pneumoniae* with a penicillin MIC of ≤2 mg/L, which includes some penicillin-resistant isolates (breakpoint for penicillin-resistant is ≥2 mg/L [see also section 6.1]).

Amoxicillin/clavulanic acid had lower median MIC_{90} values against isolates of *S. pneumoniae* (penicillin-susceptible, -intermediate and -resistant strains) than relevant comparators in the studies in table I. The median MIC_{90} values for amoxicillin/clavulanic acid ranged from 0.03 to 4 mg/L, compared with ≤0.125 to 8 mg/L for cefpodoxime, 0.12 to 8 mg/L for cefuroxime, ≤0.125 to ≥16 mg/L for azithromycin and 0.25 to ≥64 mg/L for clarithromycin (see table I).[12,14,20,21,24,26]

In a single small study, amoxicillin/clavulanic acid was active against *S. pyogenes*,[23,24] with an MIC_{90} of ≤0.03 mg/L compared with <0.06 mg/L for cefpodoxime and cefuroxime (table I). Against methicillin-susceptible *S. aureus*, amoxicillin/-clavulanic acid and cefuroxime inhibited 90% of the isolates at 2 mg/L compared with 4 mg/L for cefpodoxime.[23,25] The same three agents were inactive against methicillin-resistant *S. aureus*: MIC_{90} values were >16 mg/L for amoxicillin/clavulanic acid and >256 mg/L for cefpodoxime and cefuroxime.[23,25]

2.1.2 Gram-Negative Bacteria

Amoxicillin/clavulanic acid showed good activity against β-lactamase-positive or -negative strains of *H. influenzae*, with median MIC_{90} values of 2 or 1 mg/L, respectively.[22,23,27] The median MIC_{90} for amoxicillin/clavulanic acid was lower than that for cefuroxime (2 mg/L) for β-lactamase-negative strains but higher than that of cefuroxime (1 mg/L) for β-lactamase-positive strains (table I). Cefpodoxime had median MIC_{90}s of 0.12 and 0.25 against β-lactamase-positive and -negative strains in this analysis.

Amoxicillin/clavulanic acid and clarithromycin showed good activity against *M. catarrhalis* (both β-lactamase-positive and -negative strains) in four studies (n = 1650).[13,14,24,27] In three studies (US, Canada and worldwide), azithromycin exhibited significant activity (MIC_{90} 0.03 to 0.12 mg/L) against β-lactamase-positive and -negative strains of this pathogen.[13,14,27] Some of the data reported in this section are from the SENTRY antimicrobial surveillance programme in the United States and Canada[13] and Europe,[25] and from the Alexander Project 1996 to 1997.[14]

2.2 Activity *In Vivo*

The reported MIC values of antibacterial drugs are a useful indicator of their activity against specific pathogens, but because the interaction between pharmacodynamic and pharmacokinetic parameters (e.g. the time that serum drug concentrations remain above the MIC of a given pathogen) is also important, *in vivo* activity against specific pathogens should also be considered.[29] A previous review included information on general *in vivo* activity of amoxicillin/clavulanic acid,[6] but as this review is specific to AOM, only *in vivo* activity against relevant pathogens, reported since 1998, is included.

The potential for twice-daily administration and a higher ratio of amoxicillin to clavulanic acid were indicated by results from two animal studies of *S. pneumoniae*-induced respiratory tract infection.[30,31]

The time (as a percentage of the dose interval) that the plasma amoxicillin concentration remained above the amoxicillin MIC (T > MIC) in mice that had received total dosages of between 2.5 and 1280 mg/kg/day every 4, 6, 8 or 12 hours for 2 days correlated well with bacterial killing in a murine pneumonia model.[30] If T > MIC was less than 20%, there was no significant decrease in bacterial numbers in the lungs. Bacterial killing was

maximal above a T > MIC of 35 to 40%. Based on this information, an amoxicillin/clavulanic acid dosage equivalent to 500/125mg 3 times daily or 875/125mg twice daily was used in a rat model. At the end of treatment, bacterial numbers in the lungs were significantly reduced with both regimens ($p < 0.01$).[30]

In a rat model of pneumonia produced by penicillin-resistant *S. pneumoniae*, amoxicillin/clavulanic acid was administered at dosages equivalent to 45/6.4 or 90/6.4 mg/kg/day in divided doses every 12 hours for three days. At the end of treatment, the 90/6.4mg equivalent dosage significantly reduced bacterial numbers in the lungs for strains with amoxicillin MIC values of 2 or 4 mg/L ($p < 0.01$), whereas the 45/6.4mg dosage equivalent was only fully effective against strains with an MIC of 2 mg/L.[31] These results indicated that the efficacy of amoxicillin/clavulanic acid could be extended to include more resistant strains of *S. pneumoniae* by increasing the amoxicillin component, supporting the development of the new high-dose formulation.

Two *in vivo* studies reported that amoxicillin/-clavulanic acid was superior to comparators in animal models of *S. pneumoniae*- and *H. influenzae*-induced respiratory tract infection.[32,33] The *in vivo* efficacy of amoxicillin/clavulanic acid (10 : 1 ratio) and cefuroxime was assessed using low (5 mg/kg) and high (20 mg/kg) doses in a gerbil model of AOM induced by β-lactamase-positive *H. influenzae*.[32] Only high-dose amoxicillin/clavulanic acid significantly reduced the number of culture-positive specimens (91.7 vs 36.7% for high-dose cefuroxime) and results for all treatment groups were correlated with the ratio of middle-ear antibiotic concentration to the MIC. Another study compared the bacteriological efficacy of erythromycin, clarithromycin and azithromycin with that of amoxicillin/clavulanic acid in rats with *S. pneumoniae*- or *H. influenzae*-induced respiratory tract infections.[33] Azithromycin (equivalent to 500 and 250mg once daily) was significantly less effective than amoxicillin/clavulanic acid (equivalent to 500/125mg twice daily) against *S. pneumoniae* ($p < 0.01$) and *H. influenzae* ($p < 0.05$). Clarithromycin (equivalent to 250 or 500mg twice daily) was significantly less effective than amoxicillin/clavulanic acid against *H. influenzae* ($p < 0.01$) but both were highly effective against *S. pneumoniae*. Erythromycin (dosage not reported) was also significantly less effective against *H. influenzae* than amoxicillin/clavulanic acid (significance or efficacy against *S. pneumoniae* not reported).

The *in vivo* activity of amoxicillin 7 mg/kg or amoxicillin/clavulanic acid 7/1.75 mg/kg (4 : 1) every 8 hours for 1 and 4 days was assessed in a model of *S. pnemoniae* infection in the thighs of mice rendered neutropenic by cyclophosphamide.[34] A high correlation was observed between the MIC of amoxicillin with or without clavulanic acid (0.03 to 5.6 mg/L) and both the change in $\log_{10}$ colony-forming units (CFU)/thigh at 24 hours and 4-day survival (coefficient of determination = 95%). A reduction of ≥1 $\log_{10}$ in CFU/thigh at 24 hours was consistently observed when amoxicillin concentrations exceeded the MIC for 25 to 30% of the dose interval.

3. Overview of Pharmacokinetic Properties

The pharmacokinetic profiles of amoxicillin and clavulanic acid have previously been reviewed in detail in *Drugs*[6] and elsewhere.[35] This section therefore provides an overview of these pharmacokinetic data together with information from more recent studies where relevant.

The pharmacokinetics of amoxicillin and clavulanic acid have been investigated in small numbers of infants and children with AOM and in larger numbers of healthy adult volunteers.

3.1 Absorption

Both amoxicillin and clavulanic acid are well absorbed into the systemic circulation after administration of oral suspension or tablet formulations of amoxicillin/clavulanic acid (data reviewed previously[6,35]). Coadministration of the two agents did not affect the pharmacokinetic properties of

either drug in single-dose studies conducted in healthy volunteers and in children.[6,35]

After administration of oral suspension, tablet or capsule formulations of amoxicillin/clavulanic acid, amoxicillin is rapidly absorbed from the GI tract. The oral bioavailability of amoxicillin is about 70 to 90% and maximum serum concentrations (C_{max}) occur within 60 to 90 minutes of administration (reviewed by Galvez-Mugica et al.[36]). In contrast, clavulanic acid shows more variable oral bioavailability (31 to 99%).[37]

The absorption of orally administered amoxicillin from capsule, tablet or suspension formulations of amoxicillin/clavulanic acid is not affected by the presence of gastric acid. The relative bioavailability of clavulanic acid was reduced when an oral dose of amoxicillin/clavulanic acid was taken 30 or 150 minutes after the start of ingestion of a high-fat meal in one study.[8]

Serum concentration profiles of amoxicillin and clavulanic acid are broadly similar in adults, infants and children after administration of various formulations, including a chewable tablet and a suspension.[6,35,37,38] Steady-state pharmacokinetic parameters of amoxicillin and clavulanic acid administered as 40/10 mg/kg/day (given in three divided doses) or as 45/6.4 mg/kg/day (given in two divided doses) to children aged >1 year are shown in table II (data reviewed by Reed[35]).

Mean C_{max} values of amoxicillin and clavulanic acid after single oral 400/57mg doses of amoxicillin/clavulanic acid chewable tablets were similar to those achieved after single oral doses of the 400/57mg (per 5ml) suspension formulation (6.67 vs 6.94 for amoxicillin, 1.03 vs 1.10 mg/L for clavulanic acid).[8] Area under the serum concentration-time curve values (from 0 to infinity) were also similar (amoxicillin: 17.29 mg • h/L [suspension] vs 17.24 mg • h/L [tablet]; clavulanic acid 2.34 mg • h/L [suspension] vs 2.17 mg • h/L [tablet]). After single 5ml doses of 250 mg/5ml or single 10ml doses of 125 mg/5ml amoxicillin/-clavulanic acid suspension (concentrations of clavulanic acid/5ml not reported), mean C_{max} values of 6.9 mg/L for amoxicillin and 1.6 mg/L for clavulanic acid were achieved about 1 hour after administration.[8]

Craig and Andes[39] reviewed pharmacodynamic/pharmacokinetic relationships for various antibacterial agents used for AOM, noting that available data suggest 80 to 85% efficacy when T > MIC is 40 to 50% of the dose interval (based on

Table II. Summary of steady-state pharmacokinetic parameters of amoxicillin and clavulanic acid in children aged >1 year who received multiple doses of amoxicillin/clavulanic acid administered as different oral formulations[a] (reviewed by Reed[35])

Drug	C_{max} (mg/L)	t_{max} (h)	AUC[b] (mg/h • L)	$t_{1/2}$ (h)
Amoxicillin				
After 40/10 mg/kg/day in three divided doses[c]	7.3	2.1	18.6	1.0
After 45/6.4 mg/kg/day in two divided doses[d]	12	1.3	35.2	1.2
Clavulanic acid				
After 40/10 mg/kg/day in three divided doses[c]	2.7	1.6	5.5	0.9
After 45/6.4 mg/kg/day in two divided doses[d]	5.5	1.2	13.3	1.0

a A dosage of amoxicillin 45 mg/kg and clavulanate 3.2 mg/kg administered in two divided doses (90/6.4 mg/kg/day) is referred to in the original reference, but values of pharmacokinetic parameters were not reported for this formulation.

b Over the dose interval.

c Dosages were amoxicillin 13.2 mg/kg plus clavulanic acid 3.3 mg/kg in three divided doses.

d Dosages were amoxicillin 22.5 mg/kg plus clavulanic acid 3.2 mg/kg in two divided doses.

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum plasma concentration; **t_{max}** = time to reach C_{max}; **$t_{1/2}$** = plasma elimination half-life.

published bacteriological data obtained before and after 2 to 7 days' treatment).

For penicillin-susceptible isolates (penicillin MIC ≤0.06 mg/L), T > MIC_{90} values for amoxicillin (125mg three times daily)/clavulanic acid (31.25mg three times daily) were 100% of the dose interval for *S. pneumoniae*, 41% for *H. influenzae* and 78% for *M. catarrhalis*. Amoxicillin had the highest overall coverage of the oral agents tested against penicillin-intermediate strains of *S. pneumoniae* (T > MIC_{90} [1 mg/L]= 59% vs 28% for cefprozil, 33% for cefuroxime and 0% for cefpodoxime, loracarbef, cefaclor and cefixime). Against penicillin-resistant *S. pneumoniae*, amoxicillin (40 mg/kg/day in three divided doses) was the only oral agent evaluated that provided adequate plasma concentrations (based on criteria mentioned above) [T > MIC_{90} {2mg/L} = 46%]. Intramuscular ceftriaxone provided a T > MIC of 100% for penicillin-susceptible, -intermediate and -resistant *S. pneumoniae*.

3.2 Distribution

Amoxicillin and clavulanic acid are well distributed into most body tissues and extracellular fluids (reviewed by Todd and Benfield[6] and Reed[35]), including middle-ear mucosa[40] and middle-ear effusions in children.[8,35,41] Effective antibacterial concentrations of both drugs are achieved in the middle ear.[35] Clavulanic acid is distributed less widely than amoxicillin because it is less lipid soluble (volume of distribution is about 25% of bodyweight).[6] In fasted children, mean concentrations of amoxicillin and clavulanic acid in middle-ear effusions were 3.0 and 0.5 mg/L, respectively, 2 hours after administration of a single 35 mg/kg dose of amoxicillin/clavulanic acid (dose of clavulanic acid not reported).[8]

High concentrations of amoxicillin were measured in middle-ear effusions of 20 evaluable infants and children aged 1 to 130 months (mean 34 months) who received high-dose amoxicillin as a component of amoxicillin/clavulanic acid (35/5 [6 patients] or 45/3.2 [14 patients] mg/kg single dose) [data for the higher dose are presented in figure 1].[41] Concentrations of amoxicillin in middle-ear effusions exceeded 1 mg/L in 18 samples (90%) and 4 mg/L in 8 samples (40%). In contrast, concentrations of amoxicillin in middle-ear effusion ranged from 0.3 to 4 mg/L in children with AOM who received single 15 mg/kg doses of amoxicillin; concentrations were <1 mg/L in 6 of 12 samples.[42]

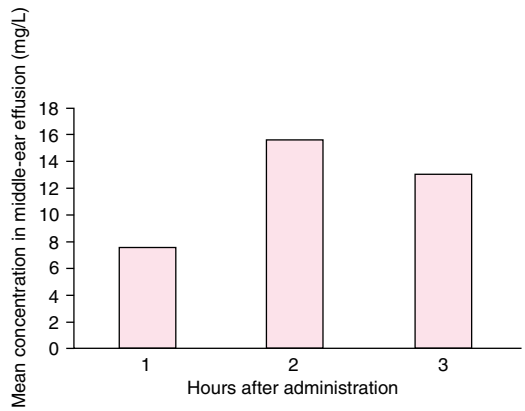

Fig. 1. Mean concentrations of amoxicillin in middle-ear effusion.[41] Infants and children aged 1 to 130 months (mean 34 months) with acute otitis media received a single 45/3.2 mg/kg dose of amoxicillin/clavulanic acid (n = 14 evaluable).

Mean maximum concentrations of amoxicillin and clavulanic acid in the middle-ear mucosa were 1 ± 0.48 μg/g and 0.4 ± 0.21 μg/g 3 hours after administration of a single oral dose of amoxicillin (875mg) and clavulanic acid (125mg) [n = 108 patients awaiting surgery].[40] Mean serum concentrations at the same timepoints were 5.8 ± 1.43 mg/L and 0.63 ± 0.2 mg/L. Twelve hours after administration, only low concentrations of amoxicillin were detected in middle-ear mucosa (mean 0.2 ± 0.12 μg/g) and serum (<0.1 ± 0.13 mg/L); at this timepoint, clavulanic acid was undetectable in both the serum and middle-ear mucosa.

Amoxicillin and clavulanic acid show relatively low binding to plasma proteins (18 to 25%).[6,8]

3.3 Metabolism and Elimination

Like most other β-lactam antibacterial agents, amoxicillin is primarily eliminated as unchanged

drug. A large proportion (50 to 80%) of an administered dose of amoxicillin is excreted unchanged in the urine within 6 hours of administration.[36] Because amoxicillin undergoes active secretion from renal tubules, coadministered probenecid competitively inhibits clearance of the drug. In contrast, clavulanic acid appears to undergo more extensive metabolism (possibly by hydrolysis followed by decarboxylation[35]) with only 20 to 60% of unchanged drug eliminated in the urine (via simple rather than active glomerular filtration[35]) within 6 hours of administration. Clavulanic acid metabolites were excreted in the urine and faeces, and also via the lungs in animal investigations.[36]

The mean elimination half-lives ($t_{1/2}$) of amoxicillin and clavulanic acid are 1.3 and 1 hour(s), respectively.[8] The time the drug concentration remained above the amoxicillin MIC of 1 mg/L was similar (values not reported) with corresponding daily dosages of amoxicillin/clavulanic acid given either 8- or 12-hourly.[8] The mean total clearance of both amoxicillin and clavulanic acid is about 25 L/h in healthy adult volunteers.[6] Renal impairment decreases the clearance of amoxicillin and, less markedly, clavulanic acid[6] [dosage reduction is required for paediatric patients aged less than 3 months, as a result of underdeveloped renal function (see section 6.1)]. Both amoxicillin and clavulanic acid are removed by haemodialysis and a supplemental dose is therefore required at the end of the dialysis session.[6]

4. Therapeutic Efficacy

The antibacterial efficacy of amoxicillin/clavulanic acid in children with AOM has been established in numerous randomised trials, most of which were single-blind or nonblind. Amoxicillin/clavulanic acid is often used as a standard reference treatment with which other oral antibacterial agents are compared.

Section 4.1 provides a review of data for 'conventional' amoxicillin/clavulanic acid formulations available in the US (see section 6.1 for further details of these formulations). Section 4.2 reviews efficacy data for the new high-dose formulation (90/6.4 mg/kg/day in two divided doses).

Analyses of efficacy were based on clinical and, in a small number of cases, bacteriological criteria in evaluable patients (unless otherwise stated). A clinical response was defined as cure (resolution of signs or symptoms) or improvement (partial disappearance or improvement of signs and symptoms). For clinical response, the major evaluation timepoint ranged between 7 and 24 days but was most commonly between 10 and 15 days from the start of treatment (generally described as the 'end-of-treatment' evaluation). Follow-up evaluations were performed in most comparative trials between 15 and 45 days from the start of treatment.

It should be noted that clinical trials of antibacterial agents for AOM are generally not powered to show significant differences in clinical response rates between treatment arms. Between 1000 and 15 000 patients would be required to show differences between a highly effective agent and one with lesser efficacy.[43] This is a result of the high spontaneous resolution rate for untreated AOM and the fact that <40% of patients with bacteriological failure present as clinical failures at the end of treatment.[44,45] In addition, assessment of clinical response 2 or more weeks after completion of treatment is of limited value because of the conflicting effects of spontaneous resolution of the initial infection and new infections. Nevertheless, the use of such endpoints in clinical trials involving much smaller patient numbers than those mentioned above is a common feature in much of the AOM literature, and relevant data for amoxicillin/clavulanic acid studies are therefore reviewed in this section. The issues above should however be borne in mind when evaluating the available data.

For the reasons above, trials that isolate bacterial pathogens from middle-ear fluid (by tympanocentesis or after spontaneous rupture of the tympanic membrane and subsequent drainage) can be considered a much more rigorous test of antibacterial efficacy in AOM (samples are required at baseline and after 4 to 6 days to properly

monitor bacterial efficacy). In addition, smaller numbers of patients are required to demonstrate meaningful differences in bacterial eradication rates.

Although tympanocentesis was performed to identify baseline pathogens in 13 of the comparative studies included in this section,[46-58] it was repeated after 4 to 6 days to confirm bacterial eradication as standard or for the majority of patients in only two studies.[48,58] Indeed, repeat tympanocentesis is rare in clinical practice.[32] Although other studies sometimes reported data for 'bacteriological' response, this was in fact presumed bacteriological response based on clinical response.

Generally, the most common pathogens isolated in trials were *S. pneumoniae, H. influenzae* and *M. catarrhalis. S. pyogenes* and *S. aureus* were less commonly identified (<7% of pathogens in two studies).[55,56]

As illustrated by data presented in section 4.1[59,60] and discussion in section 7, age and disease severity are generally inter-related (inversely) and also impact on clinical response (with lower responses for younger patients and/or more severe disease); patient age thus needs to be considered when evaluating clinical trials in AOM.

4.1 Conventional Formulations

The efficacy of oral formulations of amoxicillin/clavulanic acid (40/10 mg/kg/day in three divided doses and 45/6.4 mg/kg/day in two divided doses) in the treatment of paediatric patients with AOM has been established in numerous trials. This section focuses on the most common major antibacterial comparators in randomised trials, namely cephalosporins (e.g. cefuroxime axetil, ceftriaxone) and macrolides (azithromycin and clarithromycin) [see sections 4.1.1 and 4.1.2].

Amoxicillin/clavulanic acid showed good clinical efficacy in two postmarketing studies conducted in large numbers of patients with AOM (reported as an abstract).[61] The trials reported the efficacy of a total amoxicillin dosage between 300 and 450 mg/day administered in three divided doses (reported as a 4 : 1 ratio; dose of clavulanic acid not stated) for ≈8 days in 3048 children ≤14 years of age. At the end of treatment, 88% of the patients were assessed as cured and 11% as improved.

A three-times-daily regimen of amoxicillin/clavulanic acid produced similar clinical response rates to those with a twice-daily regimen in infants and children with AOM aged 2 months to 12 years (n = 1746) in three randomised single-blind trials.[59,62,63] Amoxicillin/clavulanic acid 40/10 mg/kg/day in three divided doses was compared with 45/6.4 mg/kg/day in two divided doses in two studies;[59,63] a third compared 60/15 mg/kg/day in three divided doses with 70/10 mg/kg/day in two divided doses.[62] Treatment was generally for 7 or 10 days although one study[59] also had a 5-day treatment arm in the twice-daily group. At the end-of-therapy assessment, clinical success (defined as clinical cure[63] or clinical cure or improvement /partial resolution[59,62]) was achieved in ≈80 to 94% of patients in the three-times-daily group and 84 to 94% of the twice-daily group (intent-to-treat analysis; 10-day regimens). The rate for those treated twice daily for 5 days was 71%.[59]

In one of the three studies mentioned above,[59] the results were stratified by age-group in a per-protocol analysis. The clinical response improved with increasing age (50.6% for <2 years, 64.7% for 2 to 5 years, 76.8% for 6 to 12 years), although the differences were not statistically significant (p = 0.059). In a large US study, *S. pneumoniae* isolates from blood were significantly more susceptible to penicillin than those from the ear, and pneumococci from patients ≤2 years old were significantly more resistant than those from older patients.[60]

4.1.1 Comparisons with Cephalosporins

Numerous multicentre, randomised, nonblind and single-blind trials have compared the efficacy of oral formulations of amoxicillin/clavulanic acid with that of various cephalosporins (cefuroxime axetil, ceftriaxone, cefdinir, cefaclor, cefixime, cefpodoxime proxetil, cefprozil and ceftibuten) in children with AOM (aged 3 months to 12 years) [table III].

Table III. Efficacy of amoxicillin/clavulanic acid (AMC) in paediatric patients with acute otitis media. Summary of randomised, multicentre[a] trials comparing the oral suspension (reported or assumed) of AMC with various oral or intramuscular cephalosporins. All but three studies[64-66] excluded patients who had received antibacterial treatment prior to enrolment (48 hours to 2 weeks)

Reference (year of publication)	Study design	Age range	Age mean (y)	No. of pts evaluated	Treatment regimen drug, total daily dosage (mg/kg/day) and duration	Treatment regimen no. of divided doses	Clinical response[b] (% of pts)	Relapse[c] (% of pts)
Versus oral cefuroxime axetil (CFA)								
Gooch et al.[52][d] (1995)	sb	3m-12y	3.7	177	AMC 40[e] x 10 days	3	74	NR
			3.3	173	CFA 30 x 10 days[e]	NR	70	NR
McLinn et al.[53] (1994)	sb	3m-11y	2	89	AMC 40[e] x 10 days	3	74	NR
			2	146	CFA 30 x 10 days	2	77	NR
Pessey et al.[54] (1999)	nb	6m-3y	NR	205	AMC 40/10 x 10 days	3	88	NR
			NR	165	AMC 80 x 8 days	3	88	NR
			NR	203	CFA 30 x 5 days	2	86	NR
Versus intramuscular ceftriaxone (CRO)								
Al-Ghamdi et al.[67] (1999)	nb	6m-6y	1.96	115	AMC 40[e] x 10 days	3	93	NR
			2.04	77	CRO 50 x single dose	NA	91	NR
Prescribing information for CRO[66] (2000)	sb	3m-6y	NR	302	AMC 40 x 10 days	NR	82[f]	NR
			NR	296	CRO dosage not reported	NR	74	NR
Varsano et al.[68] (1997)	nb	4m-6y	2.58	106	AMC 37.5/9.4 x 10 days	3	95.3	10.9
			2.83	109	CRO 50 x single dose[g]	NA	95.4	10.6
Versus oral cefdinir (CDR)								
Adler et al.[69] (2000)	sb	6m-12y	4.7[h]	197	AMC 40[e] x 10 days	3	89.9	NR
			4.7[h]	203	CDR 14 x 10 days	2	88.7	NR
			4.5[h]	195	CDR 14 x 10 days	od	90.8	NR
Block et al.[55] (2000)	sb	6m-12y	2.8[h]	100	AMC 40/10 x 10 days	3	86	NR
			1.9[h]	101	CDR 14 x 10 days	2	80.2	NR
			1.8[h]	102	CDR 14 x 10 days	od	83.3	NR
Versus oral cefaclor (CEC)								
Subba Rao et al.[70] (1998)	sb	1-12y	4.5	105 (ITT)	AMC 20/5 x 7 days	3	91.4	NR
			4.5	112 (ITT)	CEC 20 x 7 days	3	78.6	NR
Versus oral ceftibuten (CTB)								
McLinn et al.[64] (1995)	sb	6m-8y	2.8	98	AMC 40[e] x 10 days	2	97	15[i]
			3.3	121	CTB 9 x 10 days	od	93	13[i]
Versus oral cefixime (CFM)								
Gooch et al.[65] (1997)	nb	6m-12y	4.0	138	AMC 40[e] x 10 days	3	76.8[i]	29
			3.9	148	CFM 8 x 10 days	od	75.7[i]	26
Versus oral cefprozil (CPR)								
Gehanno et al.[56] (1994)	NR	NR (mean 29m)	2.0	92	AMC 40[e] x various days[j]	3	87	6
			2.4	99	CPR 40 x various days[j]	2	84	4
Versus cefpodoxime proxetil (CPD)								
Gehanno et al.[57] (1994)	nb	3m-11y	3.1	105	AMC 40/10 x 8 days	3	40	1[k]
			2.8	118	CPD 8 x 8 days	2	60.2	0[k]

a With the exception of the trial reported by Al-Ghamdi et al.,[67] which was conducted at a single centre.
b Clinical response was generally defined as the complete or partial resolution of baseline signs and symptoms and was assesses between 10 and 24 days after the start of treatment (most commonly between days 10 and 15).
c Relapse was generally defined as complete or partial response at initial evaluation followed by deterioration within 4 days of completion of treatment.
d Pooled results of two independent studies.
e Dose of clavulanic acid not stated.
f Reported as statistically significant versus CRO (p value not reported).
g Ten pts who did not improve received a second injection after 48h.
h Median age.
i Pts evaluated 2 weeks after study completion.
j Duration of treatment was 7 to 9 days for 81 pts, 10 days for 105 pts and 11 to 16 days for 5 pts.
k Bacteriological relapse, clinical relapse not recorded.

ITT = intention-to-treat population; **NA** = not applicable (single-dose treatment); **nb** = nonblind; **NR** = not reported; **od** = once daily; **pts** = patients; **sb** = single-blind.

All studies summarised in table III were published as full papers; most used amoxicillin/clavulanic acid 40/10 mg/kg/day in three divided doses for 10 days. The dosage of clavulanic acid is noted in the tables if reported in the study. Clinical responses were evaluated between 10 and 24 days after the start of treatment.

Amoxicillin/clavulanic acid produced clinical response rates similar to those of all oral cephalosporin comparators and similar to or significantly higher than those for intramuscular ceftriaxone (table III). Relevant data are reviewed in the sections below. Amoxicillin/clavulanic acid was as effective as cefuroxime axetil for clinical cure rates in patients assessed bacteriologically at baseline (but not at endpoint for all patients) in 3 trials (patients with clinical cure were assumed to be bacteriologically cured).

Cefuroxime Axetil

In three large randomised comparisons with cefuroxime axetil,[52-54] 27 to 34% of isolated pretreatment pathogens were identified as *S. pneumoniae*, 24 to 39% were *H. influenzae* and 3 to 16% were *M. catarrhalis*.

Clinical responses ranged from 74 to 88% with amoxicillin/clavulanic acid versus 70 to 86% with cefuroxime axetil (table III). The largest trial, in 716 children with AOM (573 evaluable),[54] demonstrated similar response rates for amoxicillin/clavulanic acid 40 mg/kg/day in three divided doses for 10 days (88%), amoxicillin/clavulanic acid 80 mg/kg/day in three divided doses for 8 days (88%) and twice-daily cefuroxime axetil 30 mg/kg/day for 5 days (86%).

Clinical cure (presumed bacteriological cure) rates in the bacteriologically evaluable patients treated with amoxicillin/clavulanic acid ranged from 76 to 95% and from 81 to 90% in the patients who received cefuroxime axetil, with no statistically significant between-group differences reported.[52-54] One trial[52] found that 44% of the *H. influenzae* and 94% of the *M. catarrhalis* isolates were positive for β-lactamase production.

Ceftriaxone

Amoxicillin/clavulanic acid (40 or 37.5 mg/kg/day in three divided doses) produced clinical response rates similar to or greater than those for intramuscular ceftriaxone in randomised trials (82 to 95% response rate vs 74 to 95%)[66-68] [table III]. In the only blinded (single-blind) trial,[66] clinical cure rates were significantly higher with amoxicillin/clavulanic acid 40 mg/kg/day in three divided doses for 10 days than with single-dose intramuscular ceftriaxone (dose not reported) [82 vs 74% on day 14, 67 vs 58% on day 28; p values not reported] in 598 evaluable children aged 3 months to 6 years.

Cefdinir

Amoxicillin/clavulanic acid and oral cefdinir produced similar rates of clinical cure or improvement in two single-blind trials.[55,69] Clinical response rates were 86 and 89.9% with amoxicillin/clavulanic acid and 80.2 to 90.8% with once- or twice-daily cefdinir. Baseline tympanocentesis was performed in one of these trials:[55] among patients from whom *S. pneumoniae* was recovered, there was a significant difference in clinical response (presumed bacteriological eradication rate) 2 to 4 days after completion of treatment between amoxicillin/clavulanic acid and twice-daily cefdinir recipients (89 vs 55%; p = 0.0019). Clinical response rates for patients with *H. influenzae* were 84% for amoxicillin/clavulanic acid, 75% for once-daily cefdinir and 72% for twice-daily cefdinir. Respective rates for *M. catarrhalis* were 50, 58 and 86%.

Other Comparisons

Single randomised trials have demonstrated similar clinical response rates for amoxicillin/clavulanic acid and either cefaclor, ceftibuten, cefixime, cefprozil or cefpodoxime proxetil (table III). These studies did not assess bacteriological response.

4.1.2 Comparisons with Macrolides

Table IV summarises the results of randomised, double-blind, single-blind and nonblind trials comparing amoxicillin/clavulanic acid with mac-

Table IV. Efficacy of amoxicillin/clavulanic acid in paediatric patients with acute otitis media. Summary of randomised, multicentre[a] trials comparing the oral suspension of amoxicillin/clavulanic acid (AMC:dose of clavulanic acid not reported unless shown) with oral macrolide antibacterial agents. All studies excluded patients who had received antibacterial treatment prior to enrolment (48 hours to 2 weeks)

Reference (year of publication)	Study design	Age		No. of pts evaluated	Treatment regimen		Clinical response[b] (% of pts)	Relapse[c] (% of pts)
		range	mean (y)		drug, total daily dosage (mg/kg/day) and duration	no. of divided doses		
Versus azithromycin (AZ)								
Arguedas et al.[46] (1996)	nb	6m-12y	4.5	45	AMC 40/20 x 10 days	3	95.5	0
			3.5	47	AZ 10 x 3 days	od	100	0
Aronovitz[47] (1996)	nb	2-15y	3.8	43	AMC 40 x 10 days	3	100	21.1*
			4.3	49	AZ 10 x 1 day then 5 x 4 days	od	87.7	5.1
Dagan et al.[48] (2000)	sb	6m-4y	1.4	70	AMC 45/6.4 x 10 days	2	86**	NR
			1.3	73	AZ 10 x 1 day then 5 x 4 days	od	70	NR
Daniel[49] (1993)	nb	1-8y	4.8	54	AMC various[d] x 10 days	3	100	0
			4.4	98	AZ 10 x 3 days	od	99	1
Khurana[71] (1996)	nb	6m-12y	5.8	230	AMC ≈40 x 10 days	3	90	9
			5.5	233	AZ 10 x 1 day then 5 x 4 days	od	92.2	9.9
McLinn[72] (1996)	db	1-15y	NR	273	AMC 40 x 10 days	3	87.9	12.7
			NR	280	AZ 10 x 1 day then 5 x 4 days	od	87.5	13
Principi[50] (1995)	nb	6m-12y	4.5	198	AMC 40 x 10 days	3	93.9	NR
			4.2	215	AZ 10 x 3 days	od	92.6	NR
Schaad[73] (1993)	nb	0.6-10.2y	4.4	189	AMC 40 x 10 days	3	97.3	2.1
			4.5	192	AZ 10 x 3 days	od	93.2	3.1
Versus clarithromycin (CL)								
Aspin et al.[51] (1994)	sb	6m-12y	3.4	86	AMC 40 x 10 days	3	94	5[e]
			2.9	86	CL 15 x 10 days	2	93	7[e]
McCarty et al.[74] (1993)	sb	6m-12y	3.8	145	AMC 40 x 10 days	3	92	6
			3.9	135	CL 15 x 10 days	2	90	8
Ramet[75] (1995)	nb	5m-7y	2.4	108	AMC 21-30 x 5 days	3	97	5
			2.0	110	CL 15 x 5 days	2	96	8

a With the exception of the trial reported by Arguedas et al.,[46] which was conducted at a single centre.

b Clinical response was generally defined as the complete or partial resolution of baseline signs and symptoms and was assessed between 10 and 16 days after the start of treatment.

c Relapse was generally defined as complete or partial response at initial evaluation followed by deterioration within 4 days of completion of treatment.

d Given at a dosage according to the manufacturer's instructions for the country.

e Value includes relapse and clinical failure.

db = double-blind; **nb** = nonblind; **NR** = not reported; **od** = once daily; **pts** = patients; **sb** = single-blind; * p = 0.047, ** p = 0.023 vs AZ.

rolide antibacterial agents in the treatment of children with AOM (aged 5 months to 15 years).

All studies summarised in table IV were published as full papers; most used amoxicillin/clavulanic acid 40/10 mg/kg/day in three divided doses for 10 days. The dosage of clavulanic acid is noted in the tables if reported in the study. Clinical responses were evaluated between 10 and 24 days after the start of treatment.

Clinical response rates were generally similar for amoxicillin/clavulanic acid and either azithromycin or clarithromycin, although a significantly higher response was seen for amoxicillin/clavulanic acid compared with azithromycin in a single randomised trial in younger children[48] (in whom AOM tends to be more severe, penicillin resistance greater and overall responses somewhat lower[59,60]). Significantly greater bacteriological

efficacy with amoxicillin/clavulanic acid was also reported in the latter study.

Azithromycin

Clinical response rates in patients treated with amoxicillin/clavulanic acid for 10 days ranged from 86 to 100% compared with 70 to 100% in recipients of azithromycin (the most common amoxicillin dosage was 40 mg/kg/day in three divided doses; clavulanic acid dosage was not stated in most cases) [see table IV].[46-50,71-73]

In the four largest, randomised, multicentre trials,[50,71-73] all of which randomised ≈200 patients or more to each treatment arm, amoxicillin/clavulanic acid and azithromycin produced similar rates of clinical cure or improvement in the signs and symptoms of AOM. One of these trials is the only available double-blind comparison between these drugs.[72] None of the trials reported any significant rigorous bacteriological eradication data.

A randomised, multicentre, investigator-blind study[48] in 143 (evaluable) children assessed both clinical and bacteriological response with amoxicillin/clavulanic acid (45/6.4 mg/kg/day in two divided doses for 10 days) and azithromycin (10 mg/kg as a single dose on day 1, then 5 mg/kg for 4 days).

Tympanocentesis was performed at baseline to identify pathogens and repeated in evaluable patients on days 4 to 6 to confirm bacterial eradication from middle-ear fluid. The distribution of baseline pathogens, isolated either as a single pathogen or with other pathogens, was similar between the two treatment groups. *H. influenzae* (33% produced β-lactamase, similar prevalence between treatment groups) was isolated from 106 patients, *S. pneumoniae* from 74 patients and *M. catarrhalis* (all produced β-lactamase) from 8 patients.

Overall clinical response was significantly better with amoxicillin/clavulanic acid than azithromycin (86 vs 70%, p = 0.023). In addition, as indicated in figure 2, repeat tympanocentesis on day 4 to 6 showed that amoxicillin/clavulanic acid was significantly more likely to eradicate all bacterial pathogens than azithromycin (54 of 65 [83%] vs 35 of 71 [49%], p = 0.001).

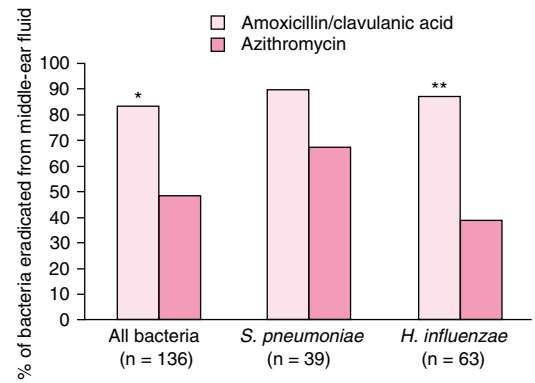

Fig. 2. Bacterial eradication confirmed by tympanocentesis in patients with acute otitis media treated with amoxicillin/clavulanic acid 45/6.4 mg/kg/day in two divided doses for 10 days, versus azithromycin 10 mg/kg single dose for 1 day, then 5 mg/kg once daily for 4 days.[48] * p = 0.001, ** p = 0.0001 vs azithromycin.

Amoxicillin/clavulanic acid also eradicated significantly more *H. influenzae* as a single pathogen than azithromycin (87 vs 39%; p = 0.0001), and tended to be more successful against *S. pneumoniae* (18 of 20 [90%] vs 13 of 19 [68%]; not statistically significant). At follow-up on days 22 to 28, both culture-positive treatment groups had similar rates of clinical success (although there was a nonsignificant trend towards a higher success rate against *H. influenzae* infection with amoxicillin/clavulanic acid [81%] than with azithromycin [58%]).

Baseline bacteriological data and eradication rates at endpoint (based largely on clinical response) were reported from a randomised nonblind comparison with azithromycin in patients with a mean age of ≈4 years.[50] Baseline pathogens isolated by tympanocentesis from 57 bacteriologically evaluable patients (including four with more than one pathogen) were *S. pneumoniae* (n = 20), *H. influenzae* (n = 15), *S. pyogenes* group A (n = 14) and others (n = 12). Elimination of these pathogens occurred in 25 of 26 children treated with amoxicillin/clavulanic acid (96.2%) and in 29 of 31 patients who received azithromycin (93.5%). Overall, clinical response was recorded in 186 of

198 patients who received amoxicillin/clavulanic acid (93.9%) compared with 199 of 215 patients treated with azithromycin (92.5%). In a subgroup of patients <2 years old, clinical response was recorded in 45 of 49 (92%) and 50 of 61 (82%) patients, respectively.

Relapse rates, generally defined as complete or partial response at initial evaluation followed by deterioration within 4 days of completion of treatment, were similar for amoxicillin/clavulanic acid and azithromycin in 4 out of 5 studies that reported relapse data.[49,71-73] In the other study,[47] relapse occurred in 8 of 38 (21%) patients who received amoxicillin/clavulanic acid compared with 2 of 39 (5%) of patients treated with azithromycin (p = 0.047).

Clarithromycin

Amoxicillin/clavulanic acid produced similar clinical response rates to clarithromycin in three randomised, multicentre trials (two single-blind and one nonblind) in children aged between 5 months and 12 years.[51,74,75] Clinical response rates ranged from 92 to 97% in amoxicillin/clavulanic acid recipients compared with 90 to 96% in patients who received clarithromycin (each administered for 5 or 10 days). In one of these studies,[74] a subgroup analysis in patients with a history of recurrent AOM showed that cure or improvement was achieved in 93% of patients who received amoxicillin/clavulanic acid versus 85% in recipients of clarithromycin, although this did not reach statistical significance. In another, which was investigator-blind,[51] baseline tympanocentesis was performed on all patients, recovering pathogens from 76%; the most common pathogens were *S. pneumoniae* (39%), *H. influenzae* (27%) and *M. catarrhalis* (8%). Among patients with baseline bacteriological data, the clinical success rate was 96 vs 91% respectively.

There were no significant differences between amoxicillin/clavulanic acid and clarithromycin in relapse rates in any of the trials in table IV.

4.2 High-Dose Formulation

The new high-dose formulation of amoxicillin/clavulanic acid (administered at 90/6.4 mg/kg/day in two divided doses for 10 days) was developed with the general aim of providing an agent for the treatment of AOM caused by penicillin-non-susceptible pathogens. The US indication for this formulation specifies *S. pneumoniae* isolates with a penicillin MIC of ≤2 mg/L, which covers penicillin-intermediate pathogens but also overlaps with the bottom of the breakpoint for penicillin-resistant isolates (penicillin MIC ≥2 mg/L) [see section 6.1 for further details].

Successful bacterial eradication, including that of penicillin-resistant *S. pneumoniae*, has been demonstrated in patients treated with the high-dose formulation in a multicentre non-comparative trial in 521 children with AOM aged between 3 and 48 months (mean ≈1.6 years). Patients received twice-daily treatment for 10 days. Slightly different bacteriological datasets are available from the published report[58] and from the US package insert for the high-dose formulation[10] (see table V).

Baseline tympanocentesis isolated pathogens in 68% of patients as follows: *H. influenzae* (n = 197), of which 37% produced β-lactamase; *S. pneumoniae* (n = 159), 28% of which were penicillin resistant (penicillin MIC ≥2 mg/L) [includes 37 patients infected with both *H. influenzae* and *S. pneumoniae*]; *M. catarrhalis* (n = 30), all producing β-lactamase; *S. pyogenes* (n = 17).[58] Repeat tympanocentesis on days 4 to 6 was performed irrespective of baseline pathogen in three centres, only if baseline pathogen was *S. pneumoniae* in 22 centres, and on all patients withdrawn from day 4 onwards due to clinical failure (total n = 180 patients).[58]

By days 4 to 6, pathogens were eliminated from 96% of bacteriologically evaluable patients overall.[58] Individual eradication rates were as follows:

- 98% for any *S. pneumoniae* (with or without *H. influenzae*)[10,58] [see table V]
- 94% (78 of 83)[58] or 93% (75 of 81)[10] for *H. influenzae*

- 100% (11 of 11[10] or 3 of 3[58]) for *M. catarrhalis*.

For patients with *S. pneumoniae* alone, the eradication rate was 99% (92 of 93), whereas for those with *S. pneumoniae* plus *H. influenzae* it was 91% (29 of 32).[58]

High-dose amoxicillin/clavulanic acid produced successful bacterial eradication in ≥95% of patients with *S. pneumoniae* with a baseline penicillin MIC of 2 mg/L (penicillin-resistant and within the US indication i.e. penicillin MIC ≤2 mg/L).[10,58] For baseline isolates with a penicillin MIC of 4 mg/L (penicillin-resistant and outside the US indication), the eradication rate was 86% (table V). Overall eradication rates for any penicillin-resistant *S. pneumoniae* (penicillin MIC 2 or 4 mg/L) were 91%[58] and 94%.[10]

Clinical cure or improvement was achieved in 89% of evaluable patients on days 12 to 15 and in 71% of patients on days 25 to 28 (figure 3).[58]

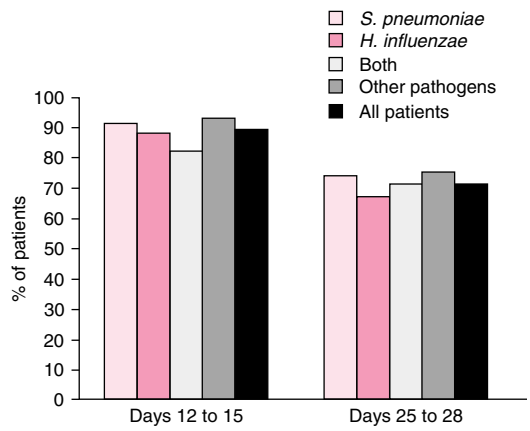

Fig. 3. Clinical success rates (clinical cure or improvement) in children with acute otitis media after treatment with high-dose amoxicillin/clavulanic acid. Evaluable patients had baseline pathogens isolated by tympanocentesis (n = 295 at days 12 to 15 and 287 at days 25 to 28). Data from a noncomparative trial in 521 children aged between 3 and 48 months. All patients received amoxicillin/clavulanic acid 90/6.4 mg/kg/day in two divided doses for 10 days.[58]

Table V. Eradication of *Streptococcus pneumoniae* in children with acute otitis media treated with high-dose amoxicillin/clavulanic acid.[10,58] Data from a multicentre noncomparative trial in which 521 children aged 3 to 48 months received amoxicillin/clavulanic acid 90/6.4 mg/kg/day in two divided doses for 10 days. Tympanocentesis was carried out at baseline and at days 4 to 6

S. pneumoniae penicillin susceptibility at baseline	Eradication rate	
	published paper[58]	package insert[10]
MIC ≤0.25 mg/L (penicillin susceptible or intermediate)[a]	83/83 (100%)	
MIC 0.5-1.0 mg/L (penicillin-intermediate)	5/5 (100%)	
MIC 2 mg/L (penicillin-resistant)[b]	19/20 (95%)	19/19 (100%)
MIC 4 mg/L (penicillin-resistant)[b]	12/14 (86%)	12/14 (86%)
All *S. pneumoniae*	122/125 (98%)	121/123 (98%)

a 0.25 mg/L falls within penicillin-intermediate range (0.12-1 mg/L) but breakpoint for susceptible isolates is ≤0.06 mg/L. Data grouped for ≤0.25 mg/L with no further breakdown into susceptible or intermediate.

b US indication for the high-dose formulation is for *S. pneumoniae* with a penicillin MIC of ≤2 mg/L.

MIC = minimum inhibitory concentration.

An analysis of potentially confounding factors in this study showed that children who had penicillin-resistant *S. pneumoniae* isolates were significantly younger than those without such isolates (mean age 12.8 vs 19.1 months, p = 0.003). They were also more likely to have received antibacterial therapy in the 3 months prior to the study (80 versus 39%, p = 0.001).[58]

Similar clinical response rates were seen with high-dose (90/6.4 mg/kg/day) and conventional (45/6.4 mg/kg/day) amoxicillin/clavulanic acid regimens both administered in two divided doses in a double-blind multicentre study designed primarily to assess tolerability (see section 5) [efficacy was a secondary endpoint].[76] 453 children with AOM aged 3 months to 12 years were treated for 10 days. 84 and 79% of patients in each group achieved persistent clinical cure with no recurrence at follow up. Almost 98% of patients in the study were considered to be compliant (80 to 120% compliance). This trial did not report data on bacteriological efficacy.

5. Tolerability

5.1 Conventional Formulations/ General Tolerability

Amoxicillin/clavulanic acid is generally well tolerated: most adverse events are mild and transient. A previous review of amoxicillin/clavulanic acid in *Drugs*[6] identified the main adverse effects (in adults and children) as gastrointestinal (GI) disturbances, including diarrhoea, nausea, vomiting and indigestion (each <5% incidence); the frequency of these events appeared to be related to the dosage of clavulanic acid.

In the studies summarised in table III (see section 4.1.1), the total incidence of adverse events ranged from 3.1 to 63% for amoxicillin/clavulanic acid recipients versus 3.4 to 44% in those treated with various cephalosporins. There were no significant differences in total event rates except in a single nonblind comparison of amoxicillin/clavulanic acid 40 mg/kg/day in three divided doses (clavulanic acid dosage not reported) and cefixime 8 mg/kg/day once daily,[65] in which 63 versus 44% of patients experienced adverse events ($p = 0.001$), mainly diarrhoea and vomiting.

Amoxicillin/clavulanic acid generally produced significantly higher total and GI adverse event rates than macrolide comparators in the trials summarised in table IV (section 4.1.2). It should be noted that most of these trials used a three-times-daily amoxicillin/clavulanic acid regimen; such regimens appear to cause a higher incidence of diarrhoea than twice-daily regimens (see elsewhere in this section). Total adverse event rates ranged from 3.7 to 51% for amoxicillin/clavulanic acid and from 2 to 32% for macrolide comparators.

Significantly higher total adverse event rates were reported for amoxicillin/clavulanic acid in five comparisons with azithromycin[47,48,71-73] (1.8- to 3.4-fold difference in three large studies[71-73]). In the largest study,[72] which was also the only double-blind comparison with azithromycin, 31 and 9% of amoxicillin/clavulanic acid and azithromycin recipients had adverse events ($p < 0.0001$). Significantly higher total and/or individual GI event rates or discontinuation resulting from GI events were reported in six studies;[46,48,50,71-73] in the large double-blind study, 29% of amoxicillin/clavulanic acid recipients and 8% of azithromycin recipients had GI adverse events ($p < 0.001$).[72]

Total adverse event rates and rates for diarrhoea were significantly higher with amoxicillin/clavulanic acid than with clarithromycin in two of the three trials summarised in table IV[51,75] [51 vs 32%[51] and 42 vs 31%[74] for total events, 40 vs 12%[51] and 32 vs 12% for diarrhoea ($p \leq 0.015$)]. In the third trial,[75] vomiting was significantly more common with amoxicillin/clavulanic acid than with clarithromycin (11 vs 3.5%, $p = 0.04$).

The incidence of diarrhoea was significantly reduced (one study) or tended to be lower (two studies) for twice-daily compared with three-times-daily amoxicillin/clavulanic acid regimens in randomised single-blind studies (total n = 1746)[59,62,63] (figure 4) [see also section 5.1.1 for compliance data]; these studies demonstrated similar efficacy between such regimens (see section 4.1).

Amoxicillin/clavulanic acid 40/10 or 60/15 mg/kg/day (4 : 1) in three divided doses and 45/6.4 or 70/10 mg/kg/day (7 : 1) in two divided doses were administered for 7 or 10 days to children aged 2 months to 12 years with AOM (a 5-day 45/6.4 mg/kg/day treatment group was also evaluated in one study[59]). Diarrhoea was reported in 10.3 to 26.7% of patients who received three-times-daily 4 : 1 regimens compared with 6.7 to 9.6% of patients treated with twice-daily 7 : 1 regimens (fig. 4). In the largest study, the incidence of diarrhoea was ≈3-fold higher with three-times- than with twice-daily treatment ($p < 0.0001$).[59] The percentage of patients with diarrhoea was greatest on days 2 and 3 after the start of treatment.[62] GI adverse events, including diarrhoea, can be reduced by taking amoxicillin/clavulanic acid with food.[77]

No serious adverse events were reported during postmarketing surveillance of 3048 children aged ≤14 years with AOM who received amox-

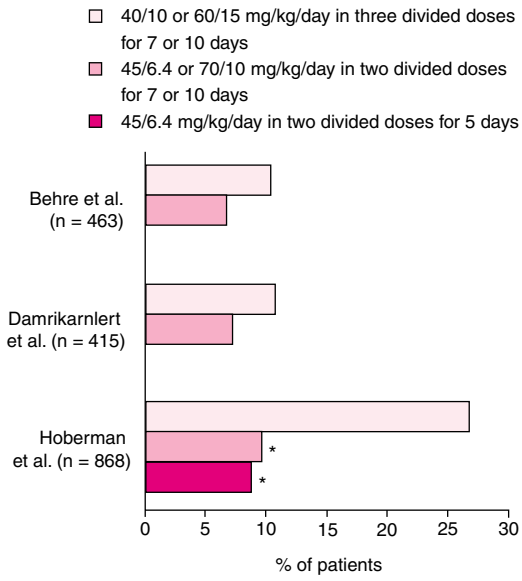

Fig. 4. Gastrointestinal tolerability of twice- and three-times-daily amoxicillin/clavulanic acid in paediatric patients with acute otitis media. Incidence of diarrhoea reported in three randomised, single-blind studies comparing amoxicillin/clavulanic acid 40/10 or 60/15 mg/kg/day in three divided doses with 45/6.4 or 70/10 mg/kg/day in two divided doses in 1746 children aged 2 months to 12 years.[59,62,63] * $p < 0.0001$ compared with three-times-daily administration.

icillin/clavulanic acid 300 to 450 mg/day in three divided doses (mostly as the 4 : 1 suspension, clavulanic acid dosage not reported) [reported as an abstract[61]]. There were 161 adverse events (type of event not reported) in 118 patients (3.6%), 34 of which were assessed as related or probably related to the medication.

Pseudomembranous colitis resulting from overgrowth of *Clostridium difficile* has been reported with most antibacterial treatments, including amoxicillin/clavulanic acid, and severity can range from mild to life threatening (see also section 6.2).[8]

Serious and occasionally fatal hypersensitivity reactions have been reported in patients receiving penicillin and are more likely to occur in patients with a history of penicillin hypersensitivity or multiple-allergen sensitivity (see also section 6.2).[8]

Among patients who had received amoxicillin/-clavulanic acid, rare or infrequent adverse events related to drug treatment included changes in liver function tests[9] and cholestatic jaundice.[78] Occasionally hypersensitivity reactions have been reported including erythema multiforme,[79] Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, serum sickness-like syndrome and hypersensitivity vasculitis.[9]

5.1.1 Compliance and Acceptability

Compliance rates were higher for twice-daily compared with three-times-daily amoxicillin/clavulanic acid regimens in randomised clinical trials reviewed in section 4.1.[62,63] The difference in the proportion of patients with at least 80% compliance during 7 to 10 days' treatment (83 vs 73% in both studies) was statistically significant in one trial[62] (statistical analysis not reported in the other[63]).

Amoxicillin/clavulanic acid suspension is available in two fruit flavours.[8,10] In randomised trials that assessed acceptability of different oral suspensions used in the treatment of AOM, amoxicillin/clavulanic acid was not as well accepted for taste/smell and/or acceptability as cefixime[65,80] or cefdinir,[81] although neither of these agents is recommended in Centers for Disease Control (CDC) guidelines[7] as a primary treatment option after failure of amoxicillin alone or where resistant pathogens are involved (see also sections 1 and 7).

5.2 High-Dose Formulation

The incidence of adverse events with twice-daily administration of high-dose amoxicillin/-clavulanic acid 90/6.4 mg/kg/day was not significantly different from that with a conventional twice-daily 45/6.4 mg/kg/day regimen in a randomised, double-blind trial in 408 children with AOM (figure 5).[76] Most events were mild.

Adverse events were reported in a total of 50.2 and 47.3% of patients receiving the high-dose and conventional twice-daily formulations. The most common adverse events overall with the high-dose formulation were coughing (36.4 vs 20.9%) and GI

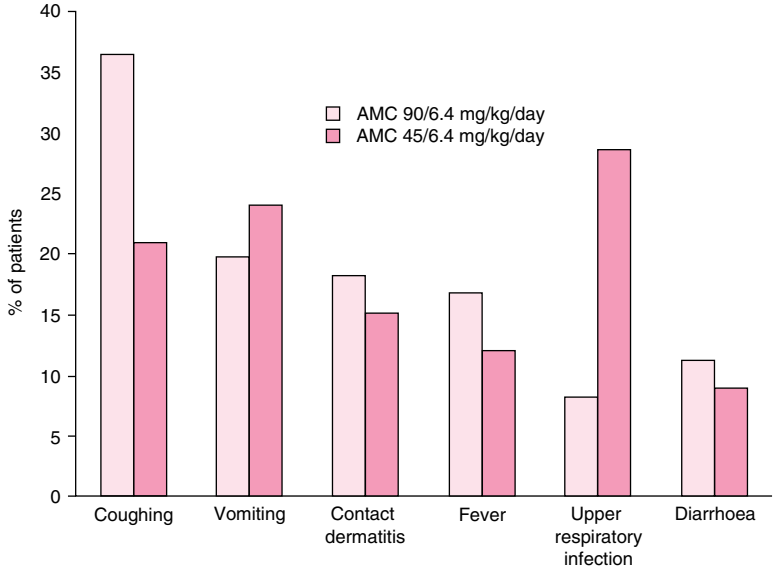

Fig. 5. Tolerability of high-dose and conventional twice-daily amoxicillin/clavulanic acid (AMC) regimens. Most frequently reported adverse events in a randomised, double-blind multicentre study comparing amoxicillin/clavulanic acid 45/6.4 mg/kg/day with 90/6.4 mg/kg/day in two divided doses in 408 paediatric patients with acute otitis media (per-protocol analysis).[76]

effects. Vomiting occurred in 19.7 versus 23.9% of patients receiving the high-dose and conventional regimens. Protocol-defined diarrhoea (≥3 watery stools/day or 2 watery stools/day for 2 consecutive days) occurred in 11 and 8.8% of patients.

In a noncomparative multicentre trial in which 521 children with AOM were treated with the high-dose formulation (90/6.4 mg/kg/day in two divided doses for 10 days), adverse events probably or possibly related to the medication were documented in 14% of patients.[58] Adverse events were mainly mild to moderate: the most frequently reported were diaper rash (4.0%), diarrhoea (3.6%), vomiting (2.3%) and other rash (1.3%). The incidence of protocol-defined diarrhoea (at least 3 watery stools/day or at least two watery stools/day for two consecutive days), as indicated from caregiver's notebooks, was 12.5%.

6. Dosage and Administration

Information in this section is based on US prescribing information for amoxicillin/clavulanic acid.[8-10]

6.1 Recommended Regimens

As discussed in section 1, a range of conventional amoxicillin/clavulanic acid formulations is available in the US.[8,9]

Recommended amoxicillin/clavulanic acid treatment regimens for children with AOM are summarised in table VI. The standard regimen (patients aged 3 months or above) is 45/6.4 mg/kg/day in two divided doses for 10 days. Standard formulations of amoxicillin/clavulanic acid are indicated for the treatment of AOM caused by β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*.[8,9]

The high-dose formulation of amoxicillin/clavulanic acid allows administration at 90/6.4 mg/kg/day in two divided doses, double the previously recommended standard amoxicillin dosage for paediatric patients aged 3 months or above (table VI). It is indicated for the treatment of paediatric patients with recurrent or persistent AOM due to *S. pneumoniae* (penicillin MICs ≤2 mg/L), *H. influenzae* (including β-lactamase-producing strains) or *M. catarrhalis* (including β-lactamase-

Table VI. Dosage and administration of amoxicillin/clavulanic acid in paediatric patients with acute otitis media: recommended formulations and dosages from US prescribing information

	Formulation type	Composition	Dosage (based on amoxicillin component)[a]
Conventional formulations[8,9]			
Paediatric pts aged ≥3mo	Oral suspension or chewable tablets	200mg/28.5mg (7 : 1) or 400mg/57mg (7 : 1)	45 mg/kg/day in two divided doses (q12)[b]
	Oral suspension or chewable tablets	125mg/31.25mg (4 : 1) or 250mg/62.5mg (4 : 1)	40 mg/kg/day in three divided doses (q8h)[b]
Paediatric pts weighing >40kg	Tablets		500mg q12h[c]
	Tablets		250mg q8h[c]
Neonates and infants aged <3mo	Oral suspension	125mg/31.25mg (4 : 1)	30 mg/kg/day in two divided doses (q12h)
High-dose formulation[10]			
Paediatric pts aged ≥3mo	Oral suspension	600mg/42.9mg (14 : 1)	90 mg/kg/day in two divided doses (q12h)

a Recommended treatment duration is 10 days.[8,10]

b The twice-daily regimen is recommended over the three-times-daily one, as it produces significantly less diarrhoea.

c 875mg q12h or 500mg q8h for more severe infections.

pts = patients; **qxh** = every x hours.

producing strains) characterised by the following risk factors: antibiotic exposure for AOM within the preceding 3 months, and either age ≤2 years or attendance at daycare.[10]

The US package insert notes that AOM resulting from *S. pneumoniae* alone can be treated with amoxicillin[10] and that the high-dose formulation is not indicated for AOM associated with *S. pneumoniae* strains with a penicillin MIC ≥4 mg/L.[10]

6.2 General Considerations and Precautions

General considerations and precautions for amoxicillin/clavulanic acid are summarised below.[8-10]

Amoxicillin/clavulanic acid can be taken without regard to meals. However, absorption of clavulanic acid is enhanced when administered at the start of a meal. Administration at the start of a meal is recommended to minimise the potential for GI adverse events.

Probenecid decreases renal tubular secretion of amoxicillin and coadministration of these drugs is not recommended.

Because of the risk of potentially fatal anaphylactic reactions (see also section 5.1), careful enquiries should be made regarding any prior history of hypersensitivity to penicillins, cephalosporins or other allergens before starting treatment with amoxicillin/clavulanic acid. The drug is contraindicated in patients with a history of allergic reactions to any penicillin.

The possibility of pseudomembranous colitis should be considered for patients presenting with diarrhoea during treatment (see also section 5.1).

Amoxicillin/clavulanic acid should be used cautiously in patients with hepatic dysfunction. It is contraindicated in those with a previous history of amoxicillin/clavulanic acid-associated cholestatic jaundice/hepatic dysfunction.

Physicians should be alert to the possibility of bacterial or fungal superinfections during treatment.

7. Place of Amoxicillin/Clavulanic Acid in the Management of Acute Otitis Media in Paediatric Patients

AOM is now the leading indication for outpatient antibacterial use in the US,[7] with more than a quarter of the estimated 120 million annual prescriptions for oral agents written for this indication.[1] Children are affected more frequently than adults because they have an increased susceptibility to upper respiratory infections and shorter more

horizontal eustachian tubes which are prone to obstruction.[2]

Almost 90% of children have experienced at least one episode of AOM by the age of 5 years, the peak incidence occurring in infants aged 6 to 24 months.[2] Recurrent and severe disease are also more common in younger children (<2 years).[2,59] Morbidity associated with AOM includes frequent recurrences which may affect language development and school performance.[82]

Although AOM resolves spontaneously (typically within 7 to 10 days) in 70 to 80% of cases, the small proportion of patients needing antibacterial therapy cannot be quickly identified,[3] and the consequences of withholding treatment can be serious, including sensorineural hearing loss, mastoiditis and meningitis.[83]

The treatment of AOM is complicated by the changing patterns of resistance to antimicrobial agents among the primary pathogens. Resistance occurs by a variety of adaptive mechanisms. Although the ability to produce β-lactamase renders most strains of *M. catarrhalis* and certain strains of *H. influenzae* resistant to amoxicillin,[52] this is largely overcome by the addition of clavulanic acid, or use of a β-lactamase stable antimicrobial agent.[84] In order to overcome resistance in these pathogens, a β-lactam antibacterial agent should be administered at a dosage which maintains the drug concentration above the MIC of the strain at the site of infection for >40% of the dose interval.[85]

Clinicians are facing a rapid rise in the incidence of drug-resistant *S. pneumoniae*, the pathogen most likely to cause AOM and also most likely to cause severe symptomatology and complications.[3,11] Studies have shown considerable geographical variation in resistance patterns of this pathogen. During 1997 to 1998, 6223 isolates of *S. pneumoniae* were collected from 153 sites in nine countries. Reduced susceptibility to penicillin ranged from 7.8% of isolates in Germany to 66.5% in France.[86] If resistant pathogens are present but not eradicated by first-line antibacterial agents, overgrowth of the resistant bacteria can occur, promoting superinfection which is refractory to treatment.[87]

The primary mechanism of resistance to penicillin involves chromosomally mediated alterations in one or more of the six known penicillin-binding proteins; higher resistance is conferred by a higher number of alterations.[84] Pneumococcal strains that are resistant to three or more separate classes of antibacterial agents are considered to be multidrug resistant.[88] Several reviews[11,89,90] noted that prior antibacterial treatment increased the risk of subsequent infection with resistant pathogens, highlighting the need to choose an effective first-line antibacterial agent to decrease the selective pressure on the bacteria.

Studies in children with AOM have reported that in the age group ≤2 years old, there is a significantly lower clinical response rate with antibacterial treatment (pathogens not determined).[59] *S. pneumoniae* infection in this age group was found to be significantly more resistant to penicillin than that in older children,[60] and in another study, children with penicillin-resistant *S. pneumoniae* were significantly younger than those with intermediate or susceptible isolates and more likely to have received antibacterial treatment in the preceding 3 months.[58] The lower success rate in this age group may be related to reduced penicillin susceptibility or to host factors that increase the risk of recurrent AOM.

Although some strains of *S. pneumoniae* are documented as β-lactam nonsusceptible by *in vitro* studies, this should not be assumed to correlate with clinical ineffectiveness, and to minimise the progression of resistance among pneumococci, treatment with effective β-lactams is still recommended.[88]

A 1999 review by a group of experts convened by the CDC concluded that oral amoxicillin at standard (40 or 45 mg/kg/day) or high (80 to 90 mg/kg/day) dosages should remain the first-line antimicrobial agent for treating AOM, although the higher dosage level was preferred.[7] Amoxicillin/clavulanic acid 80 to 90 mg/kg/day (with clavulanic acid at 6.4 mg/kg/day) was rec-

ommended in cases of treatment failure after 3 days of therapy or when resistant pathogens are suspected (oral cefuroxime axetil and intramuscular ceftriaxone are also listed as the major alternatives).[7] Increasing the dosage to 80 to 90 mg/kg/day increases middle-ear fluid concentrations for at least 3 hours after the dose and will generally be effective against penicillin-intermediate and some penicillin-resistant strains of *S. pneumoniae* (MICs 0.1 to 1 and ≥2 mg/L).[41,84] Activity against resistant strains of this pathogen is not reliably provided by oral cephalosporins or macrolide antibacterial agents.[84]

Amoxicillin/clavulanic acid has a broad spectrum of antibacterial activity against both aerobic and anaerobic bacteria implicated in AOM. It has good *in vitro* activity against the main causative pathogens associated with AOM, including penicillin-susceptible and -intermediate strains of *S. pneumoniae*, and β-lactamase producing strains of *H. influenzae* and *M. catarrhalis.* It was also active *in vitro* against *S. pyogenes* and *S. aureus* (less commonly implicated in AOM). Amoxicillin/clavulanic acid had lower MIC_{90} values against penicillin-susceptible, -intermediate and -resistant isolates than cefpodoxime, cefuroxime, azithromycin and clarithromycin (see section 2, table I).

Available *in vitro* data suggest only moderate activity against penicillin-resistant *S. pneumoniae* (see section 2.1.1). However, the high-dose formulation of amoxicillin/clavulanic acid provides a much higher amoxicillin dosage (administered at 90/6.4 mg/kg/day twice daily) than conventional formulations with the aim of providing coverage for penicillin-nonsusceptible strains. The approved US indication includes penicillin-intermediate and some -resistant *S. pneumoniae* (penicillin MIC ≤2 mg/L, see section 6.1). The high-dose formulation proved effective in eradicating a high proportion of penicillin-resistant *S. pneumoniae* isolates (albeit in a small number of patients in total) in a large noncomparative trial (section 4.2). Clinical response rates were similar for the high-dose formulation and a conventional twice-daily amoxicillin/clavulanic acid regimen in a double-blind trial designed primarily to assess tolerability (section 4.2). It should be noted that the high-dose formulation is the only antibacterial treatment currently indicated specifically for children with recent exposure to antibacterial AOM treatment combined with the additional risk factors of either very young age (2 or below) or attendance at daycare; these patients present a significant challenge to successful treatment.

The time that plasma concentrations of an antibacterial agent remain above the MIC of a pathogen (T > MIC) seems to be as accurate as middle-ear fluid concentrations in predicting bacteriological efficacy of β-lactam and most macrolide antibacterial agents in AOM.[39] Based on T > MIC_{90} data reviewed in section 3.1 (published in 1996), amoxicillin/clavulanic acid provided suitable times of exposure (i.e. >40% of the dose interval) against ≥90% of strains for penicillin-susceptible *H. influenzae* and *M. catarrhalis* and for penicillin-susceptible, -intermediate and -resistant strains of *S. pneumoniae*. It provided the highest exposure of any oral agent evaluated against penicillin-intermediate *S. pneumoniae* and was the only such agent to provide adequate exposure for penicillin-resistant *S. pneumoniae*.

The antibacterial efficacy of a drug is not only dependent on bacterial susceptibility and the T > MIC but also on relevant tissue penetration and the ratio between the peak concentration in the middle-ear fluid and the MIC of the pathogen.[39] Amoxicillin and clavulanic acid are both well absorbed and distributed into the middle-ear mucosa and middle-ear effusions, and effective antibacterial concentrations of both drugs are achieved in the middle ear (see section 3).

Amoxicillin/clavulanic acid administered as conventional formulations produced clinical response rates similar to those for oral cephalosporin comparators and similar to or significantly greater than those for intramuscular ceftriaxone in randomised trials in paediatric patients with AOM (see section 4.1.1). In addition, clinical response rates were generally similar for amoxicillin/

clavulanic acid and macrolide comparators, although significantly better clinical and bacteriological responses were seen versus azithromycin in a single randomised trial (see section 4.1.2). It should be remembered that there are limitations to assessment of clinical response in AOM and bacteriological assessment is the most rigorous test of efficacy (see introduction to section 4). However, tympanocentesis is rarely repeated during or after treatment (and indeed was rare in the trials reviewed in section 4). Bacterial eradication is often presumed, based on clinical results. It should also be remembered that the mean age of the patients studied may influence the outcome as spontaneous resolution of disease is higher in children >2 years old.

Amoxicillin/clavulanic acid is generally well tolerated (section 5). In comparative trials, the most frequently reported adverse events were mild GI disturbances, including diarrhoea, nausea, vomiting and indigestion. Diarrhoea in patients treated with amoxicillin/clavulanic acid is attributed largely to the clavulanic acid element and is generally less frequent with twice-daily than with three-times-daily treatment (section 5.1). A low total incidence of adverse events (3.6%) and no serious events were reported from a large postmarketing study (section 5).

With the exception of a single nonblind comparison versus cefixime, in which the total incidence of adverse events was significantly higher for amoxicillin/clavulanic acid than for cefixime, there were no significant differences in total adverse event rates between amoxicillin/clavulanic acid and a range of cephalosporin comparators (see section 5.1). Amoxicillin/clavulanic acid was associated with significantly higher total adverse event rates than macrolide comparators in most trials, contributed to mainly by significantly more GI events (section 5.1). It should be noted that, unlike amoxicillin/clavulanic acid, these comparators are not recommended in the CDC guidelines[7] as second-line therapies after treatment failure with amoxicillin alone or as first-line therapy where resistant pathogens are involved.

Amoxicillin/clavulanic acid suspension is available in two fruit flavours and can be administered twice daily, either as conventional formulations or the newer high-dose formulation.

In summary, amoxicillin/clavulanic acid is a well established broad-spectrum antibacterial treatment which is effective and well tolerated in the treatment of paediatric patients with AOM. The high-dose combination of amoxicillin/clavulanic acid should prove valuable in treating AOM caused by penicillin-intermediate and -resistant *S. pneumoniae* (approved in the US for penicillin MIC ≤2 mg/L). Based on recommendations from recent guidelines and the available body of data, high-dose amoxicillin/ clavulanic acid can be considered a treatment of choice for recurrent or persistent paediatric AOM (after failure of amoxicillin alone) where involvement of resistant pathogens is suspected .

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