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High-Dose amoxicillin supported with clavulanic acid as empirical therapy in acute otitis media

Sandeep Lahiry[1], Krunal Dalal[2], Ashwini Pawar[3], Bhavesh Kotak[4]

[1]Medical Advisor (Anti-infectives), [2]Therapy Area Lead (Anti-infectives), [3]Head Medical Affairs, [4]Country Medical Director, GlaxoSmithKline Pharmaceuticals, India

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ABSTRACT

An increase in the daily dose of amoxicillin from 45 mg/kg to 90 mg/kg was introduced in late 2000 to respond to increasing presence of penicillin-resistant Streptococcus pneumoniae (PRSP) in Acute Otitis Media (AOM) and in other respiratory infections. The basis for this recommendation is a well understood mechanism of resistance among PRSP as well as established safety profile of amoxicillin with known tolerance to high doses. The addition of a standard dose of clavulanic acid provides protection against resistance present in other pathogens involved in AOM and other respiratory infections. A formulation of high dose of amoxicillin with standard dose of clavulanic acid has been developed to meet the increasing needs for efficacy against bacteria with growing antibiotic resistance. While, on the one hand, there is continued empirical use of standard/lower dose of amoxicillin (45 mg/kg/day) or a second- or third-generation cephalosporin in AOM, on the other hand, there is evidence of a rise in intractable cases (relapses or first-line therapy failures). In addition to this, an evolving disease bacteriology and regional variation in antibiotic susceptibility are determinants of clinical outcome in AOM. The current paper discusses the unmet areas and explains rationale behind guideline-directed empirical high-dose amoxicillin supported with clavulanic acid in AOM.

Keywords: Acute otitis media; Amoxicillin; Amoxicillin/clavulanic acid; Penicillin-resistant *Streptococcus pneumoniae* (PRSP); Otitis prone; Efficacy; Relapse

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INTRODUCTION

Failure to respond to empirical therapy in acute otitis media (AOM) is increasingly common; especially in children.[1-3] Inappropriate antibiotic selection/usage and resistant pathogens like penicillin-resistant *Streptococcus pneumoniae* (PRSP) are implicated in most cases of treatment failure in compliant patients.[1-3] Several studies indicate that the spread of resistant pathogens is much greater for Asian countries.[2, 4-9]

Penicillin resistance among strains of *Streptococcus pneumoniae* (*S. pneumoniae*) may be either 'intermediate' or 'high' (**Table 1**). Although resistance rates differ between one region and another, usually PRSP isolates have minimum inhibitory concentrations (MIC) ≥ 2 to 4 μg/mL; isolates with MICs ≥ 4 or MIC ≥ 8 μg/mL are rarely observed. Strains of *S. pneumonia* with both intermediate and high-level penicillin-resistance (PISP/PRSP) are commonly isolated from children who fail initial therapy or who received antibiotics recently (previous two to four weeks) for any other indication.[1,2] PRSP strains cause three times higher incidence of intractable AOM compared to penicillin-sensitive *S. pneumoniae* (PSSP), as they are more likely to multidrug resistant (MDR).[1-4] This could explain why the efficacy of other antimicrobial classes such as cephalosporins and macrolides may be compromised in PISP/PRSP infections. As a result, in certain cases, PISP/PRSP strains can cause serious complications

Address for Correspondence:
Dr Sandeep Lahiry, GlaxoSmithKline Pharmaceuticals Limited, Dr. Annie Besant Road, Worli, Mumbai- 400030.
E-mail id: sandeep.s.lahiry@gsk.com

Table 1: MIC breakpoints for amoxicillin/clavulanic acid (oral) based on 2020 European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Organism	Susceptibility Breakpoints (mg/mL)	
	Sensitive ≤	Resistant >
Haemophilus influenzae	0.001[1]	2[1]
Moraxella catarrhalis	1[2]	1[2]
Staphylococcus aureus	Note[3,4]	Note[3,4]
Streptococcus A, B, C, G	Note[5]	Note[5]
Streptococcus pneumoniae	0.5[1,6]	1[1,6]

[1,2]The reported values are for amoxicillin concentrations. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/l.
[3]Most staphylococci are penicillinase producers, and some are methicillin resistant.
[4]Ampicillin susceptible S. saprophyticus are mecA -negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a β-lactamase inhibitor).
[5]The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility except for phenoxymethylpenicillin and isoxazolylpenicillins for streptococcus group B.
[6]The oxacillin 1 µg disk screen test or a benzylpenicillin MIC test shall be used to exclude β-lactam resistance mechanisms.

including mastoiditis, bacteremia, meningitis and auditory sequelae, therefore, empirical therapy in AOM must cover/eradicate pathogens like PISP/PRSP.

Currently, many clinicians recommend empirical use of high-dose of amoxicillin/clavulanic acid (AMC) as empirical therapy in AOM, mostly where PRSP and other resistant pathogens are suspected.[10-18] The justification for the use of AMC not only relates to its efficacy, but also to its well-defined safety profile, low cost and acceptable taste.[10,11,14] In fact, the American Academy of Pediatrics & American Academy of Family Physicians (AAP/AAFP) Guidelines on Diagnosis and Management of AOM (endorsed 2013, reaffirmed 2019) also recommends high-dose AMC (at 90/6.4 mg/kg/day in 2 divided doses) as preferred empirical treatment in AOM.[3] The basis for this recommendation is a broader spectrum of AMC than amoxicillin, that may be a better initial/empiric antibiotic in AOM. This is true, especially in children who have taken amoxicillin in the previous 30 days, those for whom coverage for *Haemophilus influenzae* (NTHi), *Moraxella catarrhalis* (*M. catarrhalis)* is desired, or children with concurrent purulent conjunctivitis or a history of recurrent AOM unresponsive to amoxicillin[19,20] (**Table 2**).

Time above MIC (T>MIC) is also a major determinant to clinical cure of AOM.[18] Data suggest high-dose AMC at 90/6.4 mg/kg/day may provide antibiotic concentrations sufficient to kill PRSP with MICs ≤ 4 µg/mL.[19,20] This regimen also showed T>MIC of 38% for an PRSP MIC of 4 µg/mL, in contrast to 23% of T>MIC provided by the standard/lower dose of AMC at 45/6.4 mg/kg/day (in 2 divided doses).[19,20] Hence, therapy in AOM should preferably be initiated with high-dose AMC at 90/6.4 mg/kg/day of amoxicillin using 14:1 formulation (given in 2 divided doses).

CLINICAL BACTERIOLOGY IN OTITIS MEDIA DUE TO RESISTANT PNEUMOCOCCI

Acute otitis media with or without effusion in children is mostly bacterial in 50% to 90% of cases.[1-3] Most pathogens have been long susceptible to β-lactam antibiotics including amoxicillin, but the rise of PISP/PRSP and other resistant microbes such as β-lactamase producing or non-producing ampicillin-resistant *H. influenzae* (BLPNAR or BLNAR) is posing serious global health issues. Surveillance data indicate high prevalence of PRSP strains appearing worldwide, ranging up to 43.7% in India, 54.8% in Korea, 43.2% in Hong Kong, 38.6% in Taiwan, 71.4% in Vietnam, 29.3% in Japan, 12% in US and 2% in Germany.[21,22] Most resistant strains belong to pneumococcal serotypes 6A, 6B, 9V, 14, 15A, 19F, 19A, and 23F, the so-called 'pediatric serotypes' – a nomenclature standardized by the Pneumococcal Molecular Epidemiology Network.[23]

The resistance to β-lactams in *S. pneumoniae* is due to sequential alterations in essential high molecular weight penicillin binding proteins (PBPs), particularly PBP1A, PBP2B and PBP2X.[24-29] It is the extent of these alterations like homologous recombination of PBP with the PBP genes of β-lactam-resistant oral streptococci, epigenetic interactions etc. that determine the range and concentrations of β-lactams to which the genotype is non-susceptible (**Figure 1**).

Nevertheless, the exact mechanism(s) responsible for the differing pharmacodynamic interactions between PISP/PRSP versus amoxicillin during sub-MIC phase post dosing remains unknown. It is possible that the observed differences are related to the degree of PBP alterations and ability to recover after the drug levels fall below the MIC.[24-26] It is possible that PISP without extensive PBP alterations may be able to recover much more rapidly during the post-antibiotic period compared to PRSP. This could explain why PISP regrowth is observed shortly after the drug falls below the MIC.[24-26]

Interestingly, studies of natural immunity to pneumococcal infections shows that majority of children respond to an infection by *S. pneumoniae* by making antibody to capsular polysaccharide antigens (PCP) although approximately 50% children show subnormal levels of anti-PCP IgG2 antibody against middle-ear infections of *S. pneumoniae.*[30-37] In particular, the protective antibody response was found to be type-specific and poorly immunogenic in children ≤ 2 years old.[30,31] In children who had recurrent otitis media caused by *S. pneumoniae* or NTHi, a subnormal response to PspA, PCP-IgG2, and P6 have been elucidated during

Table 2: AAP/AAFP recommended antibiotic treatment for Acute Otitis Media (endorsed 2013; reaffirmed 2019)

Initial Immediate or Delayed Treatment		Therapy after Initial Treatment Failure (48-72 hrs)	
Recommended first-line treatment	**Alternative treatment (if penicillin allergy)**	**Recommended first-line treatment**	**Alternative treatment**
Amoxicillin (80 – 90 mg/kg/day in 2 divided doses)	Cefdinir (14 mg/kg/day in 1 or 2 divided doses)	Amoxicillin/clavulanic acid (90 mg/kg/day amoxicillin, with 6.4 mg/kg/day clavulanic acid [amoxicillin: clavulanic acid ratio 14:1] in 2 divided doses)[a]	Ceftriaxone, 3-day clindamycin (30 – 40 mg/kg/day in 3 divided doses) with or without third-generation cephalosporin
OR	Cefuroxime (30 mg/kg/day in 2 divided doses)	OR	Failure of second antibiotic
Amoxicillin/clavulanic acid (90 mg/kg/day amoxicillin, with 6.4 mg/kg/day clavulanic acid [amoxicillin: clavulanic acid ratio 14:1] in 2 divided doses)[a]	Cefpodoxime (10 mg/kg/day in 2 divided doses)	Ceftriaxone (50 mg IM or IV daily for 1 or 3 days)	Clindamycin (30 – 40 mg/kg/day in 3 divided doses) plus third-generation cephalosporin
	Ceftriaxone (50 mg IM or IV daily for 1 or 3 days)		Tympanocentesis[b]
			Consult specialist[b]

AAP, American Academy of Pediatrics; AAFP, American Academy of Family Physicians; IM, intramuscular; IV, intravenous. Note: Cefdinir, cefuroxime, cefpodoxime and ceftriaxone are highly unlikely to be associated with cross-reactivity with penicillin-allergy based on their distinct chemical structures.
[a]May be considered in patients who have received amoxicillin in previous 30-days or who have otitis-conjunctivitis syndrome.
[b]Perform tympanocentesis/drainage if skilled in procedure or seek consultation from otorhinologist for tympanocentesis/drainage. If tympanocentesis/drainage reveals multi-drug resistant pathogen, seek consultation with infectious-disease specialist.

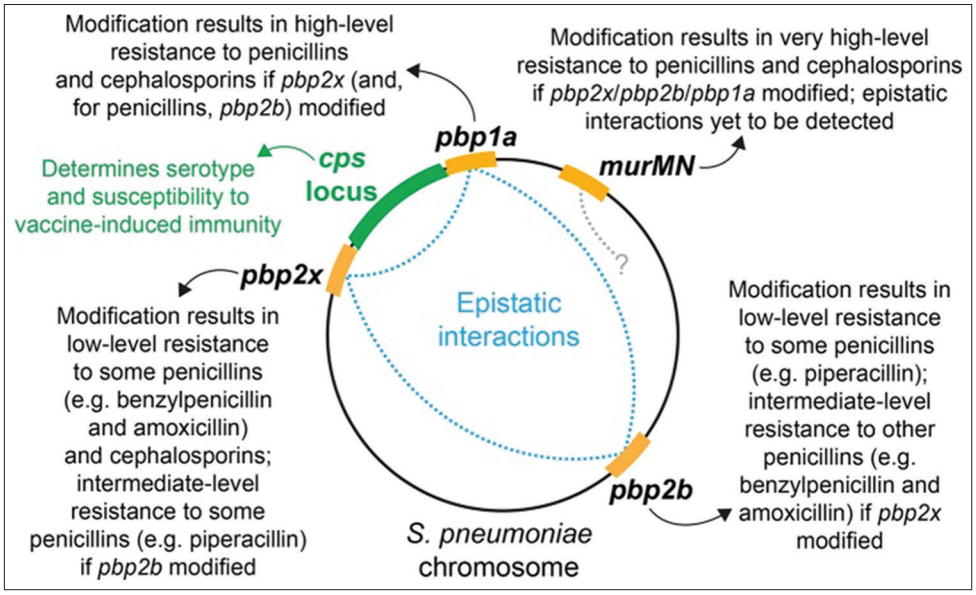

Figure 1: Summary of the genetic determinants of pneumococcal β-lactam-non-susceptibility, and their relative positioning in the bacterium's chromosome. *PISP/PRSP strains are characterized by mosaic pbp2x, pbp2b and pbp1a genes generated by interspecies recombination. It is the extent of these alterations that determine the range and concentrations of β-lactams to which the genotype is non-susceptible. The complexity of the genetics underlying these phenotypes has been the subject of both molecular microbiology and genome-wide association and epistasis analyses.*

the episodes, also causing failure of a secondary immune response on repeated challenge.[32-37] It is likely, therefore, that these children will also not respond adequately to immunization with PspA or P6 vaccines. Selective immunological derangements may therefore be more widespread than previously believed; hence effective active immunoprophylaxis against otitis media will be possible only when the mechanism of the immunological defect in otitis-prone children is understood.

UNDERSTANDING ANTIBIOTIC APPROPRIATENESS IN 'OTITIS-PRONE' CHILDREN

Many children experience repeated AOM episodes and reach a threshold where they are termed 'otitis prone'. The definition for this entity is varied, however the most frequently used definition (including AAP/AAFP

definition) currently is three or more episodes in six months, or four episodes within 12 months with at least one episode during the preceding six months.[3, 36]

Of late, studies on immune response to AOM have tried to explain susceptibility to an increased frequency of AOM in otitis-prone children. Preliminary data indicates that children who experience frequent AOM have an immature immune system, resembling a neonate.[38-42] Additionally, after an episode of AOM, the immune system of the otitis-prone child fails to generate an immune memory response. The child then remains susceptible to another AOM episode following antibiotic treatment, even by the same otopathogen residing in the nasopharynx that caused the preceding episode. This partly explains why children with recurrent AOM are generally treated with broader-spectrum antibiotics as additional cases of infection occur.

Thus, in order to effect a cure reliably in otitis-prone children, empirical therapy must reliably achieve good bacteriologic cure, apart from clinical cure. For this to happen, the concentration of the antibiotic in an infected site must exceed the antibiotic MIC for the organism.[43,44] Generally, antibiotic peak concentrations reaching at-least four times the MIC of the antibiotic for the organism is preferred in case there are undetected bacterial subpopulations whose MICs are one- to two-fold higher than the measured MIC.[43,44] An antibiotic concentration four times greater than the reported MIC ensures that the antibiotic level will be sufficient should these relatively more resistant strains be present in significant numbers. For instance, following oral administration of a single dose of high-dose AMC (14:1 formulation) at 45/3.2 mg/kg mg/kg to pediatric patients, sufficiently high concentrations for amoxicillin in plasma and middle ear fluid (MEF) were achieved (**Table 3**).

Table 3: Amoxicillin concentrations in plasma and middle ear fluid following administration of 45 mg/kg of 14:1 amoxicillin/clavulanic acid formulation to pediatric patients (9 months to 8 years) with AOM

Timepoint		Amoxicillin concentration in plasma (μg/mL)	Amoxicillin concentration in MEF (μg/mL)
1-hour	Mean	7.7	3.2
	Median	9.3	3.5
	Range	1.5 – 14.0 (n = 5)	0.2 – 5.5 (n = 4)
2-hour	Mean	15.7	3.3
	Median	13.0	2.4
	Range	11.0 – 25.0 (n = 7)	1.9 – 6 (n = 5)
3-hour	Mean	13.0	5.8
	Median	12.0	6.5
	Range	5.5 – 21.0 (n = 5)	3.9 – 7.4 (n = 5)

Dose administered immediately prior to eating.

The antibiotic must be also able to sufficiently clear the nasopharyngeal carriage of resistant pathogens, an outcome which is frequently measured in studies in AOM. This is because such a carriage constitutes a potential source of spread of resistant pathogens in the community.[45-47] Brook et. al demonstrated that oral flora in patients receiving high-dose amoxicillin at 90 mg/kg/day were more depleted of organisms with interfering capability compared to low-dose amoxicillin therapy at 45 mg/kg/day.[47] Although both regimens were effective against PSSP, amoxicillin at 90 mg/kg/day had greater efficacy against PRSP and other normal flora organisms, including those with inhibitory activity against pathogens e.g. aerobic α-hemolytic streptococci, anaerobic streptococci, and penicillin-susceptible *Prevotella* species.[47] It is possible that the use of higher doses of other oral antibiotics approved for the treatment of otitis media may be effective, however, no studies have yet documented the effectiveness of their use against PISP/PRSP.

RATIONALE BEHIND HIGH-DOSE AMOXICILLIN/CLAVULANIC ACID IN AOM DUE TO RESISTANT PNEUMOCOCCI: SUPPORT FROM *IN-VITRO* PHARMACODYNAMIC STUDIES

Lister et. al offered in vitro evidence in support of high-dose amoxicillin (70-90 mg/kg/day) in AOM.[48] The study assessed logarithmic-phase cultures that were exposed to peak concentrations of 3, 6 and 9 mg of amoxicillin per mL every 12 h, and measured changes in viable bacterial counts over 36 h. It was found that 6 and 9 mg/mL peak doses of amoxicillin were significantly bactericidal against all the pneumococcal strains evaluated, with greater than 3-logs of bacterial killing before regrowth initiated. Additionally, there was substantial post-antibiotic sub-MIC (PA-SME) interaction was occurring between high-dose amoxicillin and PRSP strains. The study concluded that in the absence of any host defense, high-dose amoxicillin could reliably provide MEF levels of amoxicillin within the range of 6 to 9 mg/mL sufficient to inhibit most strains of *S. pneumoniae*, including PRSP.

The continued suppression of PRSP growth through PA-SME interactions with penicillins both *in vitro* and *in vivo* were also described by other investigators.[48-50] Odenholt-Tornqvist et al. observed a similar 3- to 6-h PA-SME suppression of *S. pneumoniae* growth *in vitro* by penicillin when cultures were exposed to concentrations 0.1 to 0.3 times the MIC during the post-antibiotic phase.[49] In a rabbit model of meningitis, Sande et al. reported a post-antibiotic effect of 6 to 12 h for amoxicillin against *S. pneumoniae*.[50] However, when β-lactamase was injected at the site of infection, no post-antibiotic effect was observed,

suggesting that continued suppression of bacterial growth was the result of sub-inhibitory levels of amoxicillin or PA-SME interactions.

Andes et al. reported 1-log or greater net reductions in *S. pneumoniae* bacterial counts in a neutropenic mouse thigh model after three consecutive 8-h amoxicillin dosing intervals.[51] These net reductions in bacterial counts were observed despite amoxicillin levels remaining above the MICs for the challenge strains for only 25 to 30% of each dosing interval. In comparison, Lister et. al had shown a 1.5- to 2-log net reduction in bacterial counts of the resistant strains was observed at 36 h with the 6 mg/mL dose, despite amoxicillin levels remaining above the MICs for the resistant strains for only 2.5 to 4 h (20% to 35% of the dosing interval).[47]

Overall, *in-vitro* data suggests that PA-SME interactions play an important role in the pharmacodynamics of amoxicillin against most *S. pneumoniae* isolates. High-dose amoxicillin levels was able to sustain PISP/PRSP inhibition when MEF concentrations remained above the MICs, including the post-antibiotic phase.

RATIONALE BEHIND HIGH-DOSE AMOXICILLIN/CLAVULANIC ACID IN OTITIS MEDIA DUE TO RESISTANT PNEUMOCOCCI: SUPPORT FROM CLINICAL STUDIES

Summary of clinical studies using high-dose AMC in the treatment of pediatric otitis media (acute/recurrent) is depicted in **Table 4**.

Table 4: Efficacy of high-dose amoxicillin/clavulanic acid in otitis media. Summary of clinical studies comparing high-dose AMC (dose of amoxicillin & clavulanic acid component shown) with other antibiotics/placebo in the treatment of AOM (acute/recurrent)

Author (year of publication)	Study design	Age range	Sample size	Treatment regimen (drug, total daily dose in mg/kg/day and duration)	No. of divided doses	Clinical response at EOT[a] (% patients)	Clinical response at EOS[b] (% patients)	Relapse[c] (% patients)	Reference
Pessey (1999)	NB	6m – 3y	573	AMC 40/10 x 10 days	3	88	NR	NR	59
				AMC 80 (7:1) x 8 days	3	88			
				CFA 30 x 5 days	2	86			
Dagan (2001)*	NB	< 24m	521	AMC 90/6.4 x 10 days	2	89	71	NR	10
Arietta (2003)+	DB		304	AZT 20 x 3 days	od	86	72	NR	12
				AMC 90/6.4 x 10 days	2	84	61		
Piglansky (2003)*	NB	3m – 22m	50	AMC 80 (7:1) x 10 days	3	86	80	20	11
Sher (2005)+	DB	6m – 7y	354	GTF 10 x 10	od	84.7	63.7	13.6	60
				AMC 90/6.4 x 10	2	78.6	63.2	16.1	
Hoberman (2005)*	SB	6m – 30m	731	AMC 90/6.4 x 10 days	2	91	79.2	NR	61
				AZT 10 x Day 1	od	81	71		
				AZT 5 x Day 2-5					
Arguedas (2005)	DB	6m - 30m	331	AMC 90/6.4 x 10 days	2	84	77.4	0.78	62
				AZT 30 x single dose	NA	84	76.9	0.76	
Casellas (2005)	SB	6m – 48m	331	AMC 80 (7:1) x 10 days	2	98	95.1	NR	13
				AMS 80 (4:1) x 10 days	2	98	94.1		
Block (2006)*	SB	6m – 6y	318	AMC 90/6.4 x 10 days	2	90	NR	4.4	14
				CFD 14 x 10 days	2	86		4.8	
Arguedas (2011)*	DB	3m – 48m	902	AMC 90/6.4 x 10 days	2	92	89.4	21.7	63
				AZT[ex] 60 x single dose	NA	80	91	15.4	
Hoberman (2011)*	DB	6m – 23m	291	AMC 90/6.4 x 10 days	2	80	67	4	64
				Placebo x 10 days	2	74	53	23	
Casey (2012)*	SB	6m – 24m	330	AMC 80 (7:1) x 10 days	2	87	NR	NR	16
				CFD 14 x 5 days	2	71			
Hoberman (2016)	DB	6m – 23m	520	AMC 90/6.4 x 10 days	2	91	NR	19	65
				AMC 90/6.4 x 5 days	2	88		28	
Hoberman (2017)	NB	6m – 23m	40 (Ph 1)	AMC 90/3.2 x 10 days	2	86	NR	11	17
			72 (Ph 2)	AMC 80/2.85 x 10 days	2	89		12	

AMC, Amoxicillin/clavulanic acid; AZT, Azithromycin; AMS, Amoxicillin/sulbactam; CFA, Cefuroxime axetil; CFD, Cefdinir; AZT[ex], Azithromycin extended-release; NB, Non blind; SB, single blind; DB, double blind; NA, not applicable; NR, Not reported; RR, Relative Risk; CI, Confidence interval; EOT, End of therapy; EOS, End of study; OD, Once daily; NA, Not applicable; NR, Not recorded

[a,b]Clinical cure at EOT & EOS in AOM was defined in terms of complete resolution of signs and symptoms, based on otoscopic and/or clinical findings (measured in clinically evaluable patients)

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

+Indication: Recurrent AOM

*Studies favoring high-dose amoxicillin/clavulanic acid as preferred antibiotic therapy in AOM at EOT

Before the introduction of pneumococcal vaccines, preferred therapy in AOM was amoxicillin at standard/lower doses (40-50 mg/kg/day). It remained effective in eradication of about one-third of the current mix of otopathogens.[34] Over the years, the diminished presence of PSSP under vaccine-induced selection pressure changed over time, and incidence of PISP/PRSP increased. An increase in the daily dose of AMC from 45 mg/kg to 90 mg/kg (based on amoxicillin component) was thus introduced in late 2000 to better eradicate PISP/PRSP. However, clinical therapy in AOM remains controversial, as many clinicians continue to prefer standard/lower dose AMC or a second- or third-generation cephalosporin with β-lactamase stability as empirical therapy in AOM, despite rise in intractable cases (relapse or treatment failures).[52-55] This is because amoxicillin, with or without clavulanic acid, has one of the lowest MICs for *S. pneumoniae* among available β-lactams and in doses of 40 to 50 mg/kg/day continues to exceed the MIC of most PSSP/PISP.[52-55] In fact, studies involving children with acute or chronic ear infections have found that following single doses of 13 to 15 mg/kg of amoxicillin, the mean concentration of the drug in the MEF ranged from 2.8 to 5.6 μg/mL. [56-58]

Of late, several studies have proven the beneficial effect of high-dose AMC in pediatric AOM (**Table 4**).[10-17, 59-65] Additionally, several studies have shown that high-dose amoxicillin, with or without clavulanic acid, achieved levels in the MEF that exceed the MICs of most PISP/PRSP strains.[66-69] In all such studies, patients tolerated the higher dosage without any significant increase in side effects including diarrhea or gastrointestinal intolerance. Craig et. al determined that amoxicillin (at a 13.3 mg/kg dose) was the only orally available drug regime studied that could exceed the MICs of PISP/PRSP for 40% or more of the dosing interval,[44] unlike for a variety of β-lactams, where bacteriological cure rate of 85% to 100% is observed when serum concentrations exceeded the MIC for at least 40% of the dosing interval.

Dagan et. al [10] assessed bacteriologic and clinical efficacy of high-dose AMC (90/6.4 mg/kg/day for 10 days) in 521 pediatric patients (3 to 50 months) with AOM. Pathogens were eradicated from 172 (96%) bacteriologically evaluable children. Overall 78 (94%) isolates of *H. influenzae* and 122 (98%) isolates of *S. pneumoniae* were eradicated, including 31 (91%) PRSP isolates (penicillin MICs 2 to 4 μg/mL). Symptoms and otoscopic signs of acute inflammation were completely resolved or improved on Days 12 to 15 in 263 (89%) clinically evaluable children with bacteriologically documented AOM.

Piglansky et. Al[11] evaluated the bacteriologic and clinical efficacy of high-dose AMC as first line therapy in AOM. Fifty culture-positive patients, age 3 to 22 months (median, 9 months; 77% <1 year) were treated with high-dose AMC (80 mg/kg/day three times a day for 10 days). MEF culture was sent at enrollment and on Days 4 to 6 of therapy. Eradication was achieved in 41 (82%) patients for 54 (83%) pathogens: 22 (92%) *S. pneumoniae,* 21 (84%) β-lactamase-negative *H. influenzae,* 8 (62%) β-lactamase-positive *H. influenzae*, 2 (100%) *S. pyogenes* and 1 (100%) *M.catarrhalis.* It was concluded that due to good clinical efficacy overall, high-dose AMC would be an appropriate choice as first line empiric therapy for AOM, followed by a β-lactamase-stable drug in the event of therapy failure. Similarly, Casey et. Al[16] compared the clinical efficacy of high-dose AMC (80 mg/kg/day for 10 days) to cefdinir (14 mg/kg/day for 5 days therapy) in pediatric AOM. Out of 330 children (6 to 24 months) evaluated, clinical cure rates were higher for AMC group (86.5% versus 71.0%, $p = 0.001$).

Hoberman and Dagan et al[61] examined treatment of bacterial AOM in children 6 to 30 months of age with high-dose AMC (90/6.4 mg/kg/day in 2 divided doses for 10 days) versus azithromycin (10 mg/kg for 1 day followed by 5 mg/kg/d for 4 days). Clinical assessments were performed at the on-therapy (Day 4-6), end-of-therapy (EOT, day 12-14) and follow-up (FU, Day 21-25) visits. Clinical success rates were higher in AMC group at on-therapy (94.9% versus 88%; $p < 0.05$); EOT (90.5% versus 80.9%; $p < 0.01$) and FU visit (80.3% versus 71.1%, $p < 0.05$). At the on-therapy visit, higher proportion of pre-therapy pathogens were eradicated in AMC group (94.2% versus 70.3%; $p < 0.001$). High-dose AMC eradicated 96.0% of *S. pneumoniae* (92.0% cases of PRSP) and 89.7% of *H. influenzae* (85.7% cases of β-lactamase-positive NTHi). Corresponding rates for azithromycin were 80.4% (54.5% cases of *S. pneumoniae*) and 49.1% (100% cases for *H. influenzae* (all $p < 0.01$ for between-drug comparisons). In summary, high-dose AMC was clinically and bacteriologically more effective than azithromycin among children with bacterial AOM, including cases caused by PRSP and β-lactamase-positive NTHi.

Hoberman and Paradise et al[64] in a randomized, placebo-controlled trial assigned 291 children between 6 to 23 months of age, with AOM to receive high-dose AMC (90/6.4 mg/kg/day) or placebo for 10 days and measured symptomatic response and rates of clinical failure. Results indicated children who received AMC, 35% had initial resolution of symptoms by day 2, 61% by Day 4, and 80% by Day 7; among children who received placebo, 28% had initial resolution of symptoms by Day 2, 54% by Day 4, and 74% by Day 7 ($p = 0.14$ for all comparison). The rate of clinical failure was lower among the children treated with high-dose AMC than among those who received placebo: 4% versus 23% at or before the visit on Day 4 or

5 ($p< 0.001$) and 16% versus 51% at or before the visit on Day 10 to 12 ($p< 0.001$).

CURRENT RECOMMENDATIONS ON ANTIBIOTIC THERAPY IN AOM

According to AAP/AAFP, high-dose AMC is the preferred empirical treatment in AOM, especially in children who have taken amoxicillin in the previous 30 days, those with concurrent conjunctivitis, or those for whom coverage for β-lactamase–positive NTHi and *M. catarrhalis* or PISP/PRSP is desired. The recommended formulations and dosages of AMC as per US prescribing information is depicted are **Table 5**.

Alternative initial antibiotics include cefdinir (14 mg/kg per day in 1 or 2 doses), cefuroxime (30 mg/kg per day in 2 divided doses), cefpodoxime (10 mg/kg per day in 2 divided doses), or ceftriaxone (50 mg/kg, administered intramuscularly). It is important to note that alternative antibiotics vary in their efficacy against AOM pathogens. For example, recent US data on *in vitro* susceptibility of *S. pneumoniae* to cefdinir and cefuroxime are 70% to 80%, compared with 84% to 92% amoxicillin efficacy.[70-75] In vitro efficacy of cefdinir and cefuroxime against *H. influenzae* is approximately 98%, compared with 58% efficacy of amoxicillin and nearly 100% efficacy of AMC.[76]

Macrolides, such as erythromycin and azithromycin, have limited efficacy against both *H. influenzae* and *S. pneumoniae*.[72-75] Clindamycin lacks efficacy against *H. influenza*.[72, 76,77] Clindamycin alone (30-40 mg/kg/day in 3 divided doses) may be used for suspected PRSP; however, the drug will likely not be effective for the MDR serotypes.[72,76,77] Several of these choices of antibiotic suspensions are barely palatable or frankly offensive and may lead to avoidance behaviors or active rejection by spitting out the suspension.[72-75]

In the patient who is persistently vomiting or cannot otherwise tolerate oral medication, even when the taste is masked, ceftriaxone (50 mg/kg, administered intramuscularly in 1 or 2 sites in the anterior thigh, or intravenously) has been demonstrated to be effective for the initial or repeat antibiotic treatment of AOM.[78,79] Although a single injection of ceftriaxone is approved by the US FDA for the treatment of AOM, results of a double tympanocentesis study (before and 3 days after single-dose ceftriaxone) by Leibovitz et al[79] suggest that more than 1 ceftriaxone dose may be required to prevent recurrence of the middle ear infection within 5 to 7 days after the initial dose.

The 2016 Indian National Treatment Guidelines for Antimicrobial Use in Infectious Diseases also recommends high-dose AMC as preferred empiric therapy in AOM, especially in patients who have received penicillin in the past one month, or if non-responding to amoxicillin.[80] Alternate agents include cephalosporins like Cefpodoxime, Cefuroxime, and Ceftriaxone. In case of penicillin allergy, Cefidinir or macrolides can be used.[80]

COMMENT

The biologic and immunologic basis of the otitis-prone condition in children points to new areas for research and alternative treatments, especially in intractable AOM where resistant pathogens, especially PISP/PRSP continue to dominate. These organisms show PBP protein gene mutation and response to standard/lower doses of amoxicillin, ampicillin, cephalosporin and macrolides is poor. Moreover, levels of protective antibodies against pneumococcal or NTHi antigens are subnormal in young children, without an age-dependent rise in levels in otitis prone individuals. Therefore, current guidelines, recommend high-dose AMC not only as first-line treatment in AOM, but also in case non-responders to initial therapy

Table 5: Dosage and administration of amoxicillin/clavulanic acid in pediatric patients with acute otitis media (US prescribing information)

Formulation/age group	Formulation type	Composition (amoxicillin/ clavulanic acid, ratio)	Dosage (based on amoxicillin component)[1]
Conventional formulations			
Age > 3m	Oral suspension or chewable tablets	200/28.5mg (7:1) or 400/57mg (7:1)	45mg/kg/day q12h[2]
	Oral suspension or chewable tablets	125/31.25mg (4:1) or 250/62.5mg (4:1)	40mg/kg/day q8h[2]
Weight >40kg	Tablets		500mg q12h[2]
	Tablets		250mg q8h[3]
Age < 3m (Neonates & infants)	Oral suspension	125/31.25mg (4:1)	30mg/kg/day q12h
High-dose formulation			
Age ≥ 3m	Oral suspension	600/42.9mg (14:1)	90mg/kg/day q12h

qxh, every x hours. [1]Dosage based on amoxicillin component[3,c]. [2]The twice-daily regimen is recommended over the three-times-daily one, as it produces significantly less diarrhoea. [3]875mg q12h or 500mg q8h for more severe infections

or whose illness relapses quickly after discontinuing antibiotics. The low toxicity of amoxicillin also suggests that the increase in its daily dose (without proportionate increase in clavulanic acid) is unlikely to adversely affect tolerability. In this regard, clinicians should consider using AMC 14:1 formulation at 90/6.4 mg/kg/day (in 2 divided doses) as empirical therapy in AOM.

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Author's Contribution:
SL, KD - Conceptualized and designed the study, literature search, prepared first draft of the manuscript, critical revision of the manuscript;
SL, AP- Conceptualized the study, Interpretation, critical revision of the manuscript; **AP, BK-** Concept of the study, literature search, review of the study.

Work attributed to:
Medical & Regulatory Affairs, GlaxoSmithKline Pharmaceuticals (India).

Orcid ID:
Dr. Sandeep Lahiry - https://orcid.org/0000-0002-6919-0530
Dr. Krunal Dalal - https://orcid.org/0000-0001-5189-7469
Dr. Ashwini Pawar - https://orcid.org/0000-0003-1884-2399
Dr. Bhavesh Kotak - https://orcid.org/0000-0003-0992-1028

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