Management of
Acute Otitis Media &
Community Acquired Pneumonia
in pediatric patients:
Problems and Challenges of PRSP

Agenda

1. Burden of Antimicrobial Resistance (AMR)
2. AOM–prevalence
3. Etiological organisms
4. Mechanism of Resistance
5. Concept of Minimum Inhibitory Concentration (MIC) and its clinical importance
6. Definition of Penicillin Resistant Streptococcus pneumoniae (PRSP)
7. PRSP prevalence –Global and India
8. Challenges of sample collection in AOM
9. Rationale Concepts
10. Summary

WHO: 'AMR – one of the biggest threats to global public health'

WHO Fact sheet, July 2020:

'AMR is an increasingly serious threat to global public health. It requires action across all government sectors and society. The misuse and overuse of antimicrobials is accelerating this process.' WHO 2018[1]

WHO listed AMR as one of the ten threats to Global Health in 2019[2]

Mortality from antimicrobial resistance is comparatively higher in African and Asian continent[3]

Community acquired RTIs:
AOM
CAP
ABRS

Major pathogens for CARTIs:
Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis.

WHO, World Health Organization; AMR, antimicrobial resistance; AOM-Acute Otitis Media;
CAP-Community Acquired Pneumonia; ABRS-Acute Bacterial Rhinosinusitis; CARTIs:Community Acquired Respiratory Tract Infections

1. WHO AMR Fact sheet 2018. Available at https://www.who.int/en/news-room/fact-sheets/detail/antibiotic-resistance. Accessed 19/07/2019.
2. https://www.who.int/emergencies/ten-threats-to-global-health-in-2019. Accessed 01/12/2019.
3. O'Neill J; The Review on Antimicrobial Resistance;2014;1-20

AOM prevalence- Indian data

Author	Location	Study population	AOM incidence /prevalence %
Chadha et al (2014) [North Indian study]	Urban slums, non-slum urban and rural areas of Delhi	3000 children of age 0 to 15 years (door to door survey)	0.4 % prevalence
Lokhande et al (2016) [Western India study]	Government College and Hospital, Ambajogai, Maharashtra	504 clinically diagnosed cases of AOM	ASOM, max incidence is seen in 0-10 years age group; 43.71%; ASOM cases - 33.13% (167 out of 504 AOM cases) Bilateral ASOM cases - 12/167 (7%)
Bandopadhyay et al (2005) [Eastern India study]	Urban slum of Kolkata and a rural area of Hooghly	627 primary school children (rural 145, urban 482)	Middle ear pathology was found to be present in 20% and 12.6% among rural and urban students respectively
Kumari et al (2016) [Southern India study]	Hyderabad	All the patients referred with ear problems to MAA ENT Hospitals, Hyderabad, Telangana State, from 2004 to 2014 (2602 OM patients including children and adults)	Prevalence: Acute suppurative otitis media (17.6%)

Chadha SK, Gulati K, Garg S, Agarwal AK. Comparative prevalence of otitis media in children living in urban slums, non-slum urban and rural areas of Delhi. Int J Pediatr Otorhinolaryngol. 2014 Dec;78(12):2271-4. doi: 10.1016/j.ijporl.2014.10.032. Epub 2014 Oct 31. PMID: 25465454.
Ujwala A. Lokhande and Suresh L. Akulwar. 2016. Study of Profile of Otitis Media: A Study from Maharashtra, India.*Int.J.Curr.Microbiol.App.Sci.* 5(12): 349-354. doi: http://dx.doi.org/10.20546/ijcmas.2016.512.037
Bandyopadhyay R, Sengupta A, Dasgupta A, Biswas R, Mukherjee S, Biswas AB. A comparative study of common ear morbidity pattern among the primary school children of an urban slum of Kolkata and rural area of Hooghly. J Indian Med Assoc. 2005 Aug;103(8):428, 430-2. PMID: 16363198.
Kumari MS;Egyptian Journal of Ear, Nose, Throat and Allied Sciences;2016;17;57-62

Etiological micro-organisms

Q. How many cases of AOM are caused by viruses?

- Respiratory viruses have been detected in approximately 25% of middle ear fluids of children with AOM[1]

Q. What is the most important bacterial pathogen in AOM ?

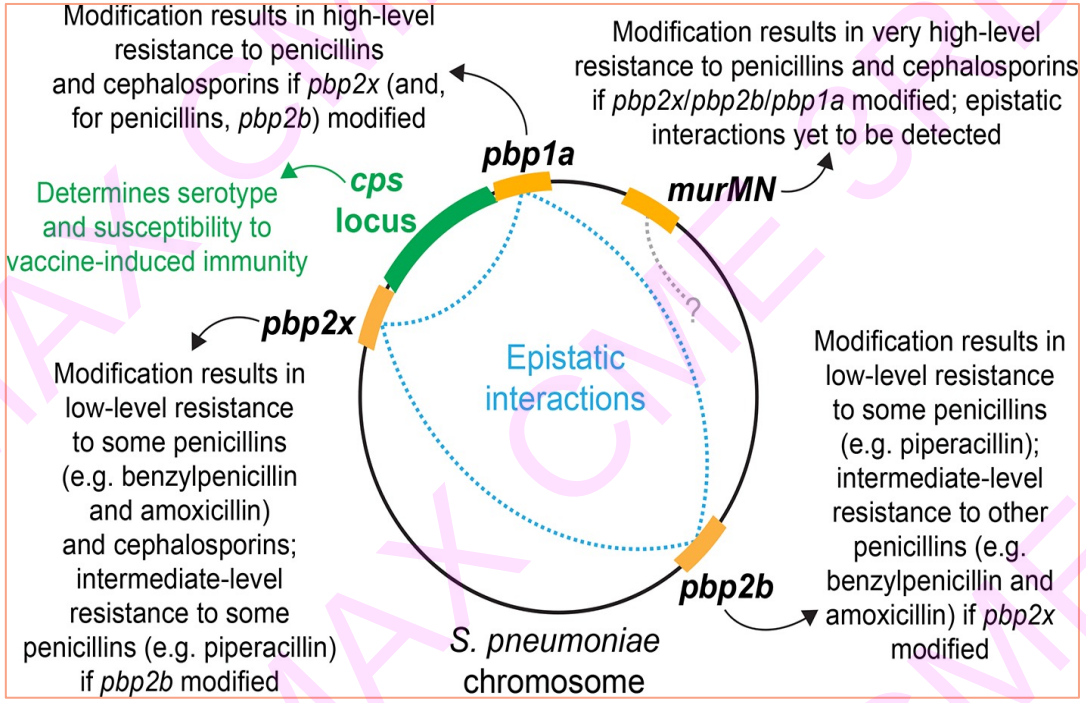
- Studies using tympanocentesis have consistently found S. pneumoniae to be the most important bacterial cause, isolated in up to 35% of cases[2]

Increasing prevalence of antimicrobial resistance remains a global problem complicating the management of CARTIs

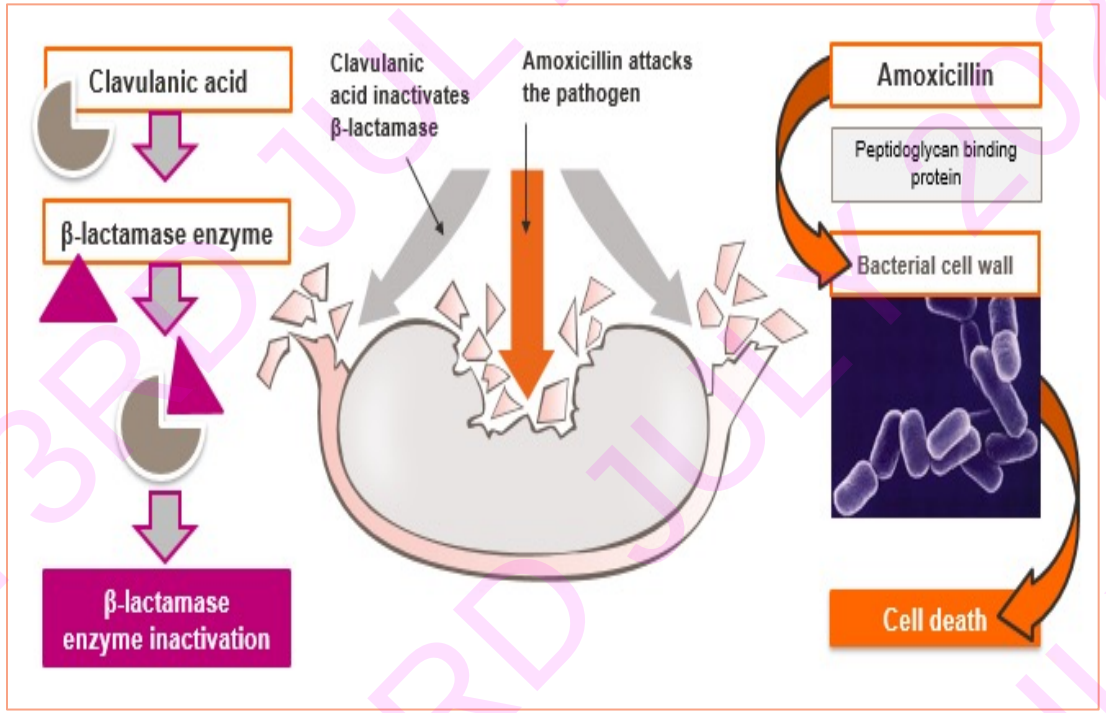
1. Klein JO. Otitis Externa, Otitis Media, and Mastoiditis. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Eighth Edition. Elsevier;2014
2.Rubin MA, Gonzales R and Sande MA. Pharyngitis, Sinusitis, Otitis, And Other Upper Respiratory Tract Infections. In: Harrison's Infectious Diseases. Third Edition. McGraw Hill; 2010.

Mechanism of resistance to Penicillin group

S. pneumoniae



H.influenzae, Moraxella catarrhalis



Resistance to β-lactams in S. pneumoniae is due to sequential alterations in PBPs like PBP1A, PBP2B PBP2X

Amoxicillin inhibits the enzyme transpeptidase, thus disrupting the cell wall synthesis thereby exerting its bactericidal action.

Potassium clavulanate bind to the β-lactamase and irreversibly blocks the enzyme's activity, enabling the penicillin to produce its bactericidal effect.

Dewé TCM, D'Aeth JC, Croucher NJ. Genomic epidemiology of penicillin-non-susceptible Streptococcus pneumoniae. Microb Genom. 2019 Oct;5(10):e000305

MIC and its importance in clinical practice[1]

Minimum inhibitory concentrations (MICs) : Lowest concentration of an antimicrobial that inhibits the visible growth of a microorganism after overnight incubation

Clinical implementation of MIC values

1. It guide physicians in the treatment of patients
2. Indicates what concentration of antimicrobial agent would successfully treat an infection
3. Used by diagnostic laboratories to confirm resistance,
4. It is also a research tool to ascertain the *in vitro* activity of novel antimicrobials

1. Andrews JM. Determination of minimum inhibitory concentrations. J Antimicrob Chemother. 2001 Jul;48 Suppl 1:5-16. doi: 10.1093/jac/48.suppl_1.5. Erratum in: J Antimicrob Chemother 2002 Jun;49(6):1049. PMID: 11420333.

How to define PRSP?

Clinical and Laboratory Standards Institute(CLSI) defines MIC breakpoints for *S. pneumoniae* susceptibility to penicillin

Clinical syndrome and route of administration	MIC-Minimum Inhibitory concentration		
	MIC Breakpoints in µg/mL by Susceptibility category		
	Susceptible	Intermediate	Resistant
Penicillin parenteral (non-meningitis)	≤ 2	4	≥ 8
Penicillin parenteral (meningitis)	≤ 0.06	–	≥ 0.12
Penicillin (oral penicillin V)	≤ 0.06	0.12–1	≥ 2
Amoxicillin (non-meningitis)	≤ 2	4	≥ 8
Amoxicillin-clavulanate (non-meningitis)	≤ 2/1	4/2	≥ 8/4

https://clsi.org/ CLSI breakpoints. Accessed on 16th Jan 2022

PRSP rate in India currently ranging from 3.8% to 30.4%[2]

PRSP incidence is rising globally[1]

Surveillance data indicate high prevalence of PRSP strains appearing worldwide:

54.8% in Korea,
43.2% in Hong Kong,
38.6% in Taiwan,
71.4% in Vietnam

Study period	Location	Ery*	Tet†	Lev‡	Cot§	Pen‖	Reference
1993-97	Multicentric	4.2	-	-	56.3	1.3	[21]
1996-2009 (in phases)	Multicentric	1.3-17.4	-	0	-	3.8-30.4	[1]
2011-15	Multicentric	39	-	-	85	8	[7]
2012-15	Multicentric	40	-	0	100	20	[22]
2013-15	Multicentric	32	45	7	48	11.2	[11]
1996-97	Vellore	8	32	-	44	16	[23]
1996-2000	Puducherry	4.6	12.6	-	36	7.3	[10]
2007-10	New Delhi	20	34.9	-	83.3	5	[24]
2007-11	Vellore	13.6	-	1.2	87.3	4.5	[9]
2007-13	Vellore	30	-	0	96	5	[25]
2009-11	Bangalore	12.5	-	5	77.5	35	[26]
2009-11	Bangalore	28	-	4	44	3	[27]
2014-17	Puducherry	34.9	34.4	5.5	66.7	10.8	This study

[Table/Fig-8]: Antimicrobial resistance profiles observed in studies from India [1,7,9-11,21-27].
The percentage of intermediate susceptible and resistant isolates shown. Table depicts duration of the studies and their corresponding locations.
*Erythromycin; †Tetracycline; ‡Levofloxacin; § Trimethoprim – sulphamethoxazole; || Penicillin

1. Jae-Hoon S, Jung S, Ko KS. High prevalence of antimicrobial resistance among clinical streptococcus pneumoniae isolates in Asia (an ANSORP study). Antimicrob Agents Chemother. 2004;48:2101–7.
2. Peela et al. Antimicrobial Resistance in Clinical Isolates of Streptococcus Pneumoniae: Mechanisms and Association with Serotype Patterns. Journal of Clinical and Diagnostic Research, 2018, Nov, Vol-12(11): DC17-DC21. DOI: 10.7860/JCDR/2018/37414.12287

PRSP prevalence in India

Author	Year	Location	Study population	Isolates studied	Resistance report
Shariff et al[1]	2013	VP chest institute, Delhi	Children + Adults (2 to 77 years of age)	126 *S.pneumoniae* isolates (40 isolates were from children 2 to 12 years	Five (5%) isolates (2 CSF, 2 NP plus 1 sputum,) showed resistance to penicillin.
Ravikumar et al[2]	2014	KIMS, Bangalore	3 months to 5 yeas old children	53 pneumococcal isolates from nasopharynx	Penicillin intermediate susceptibility was seen in 17% (9 samples)
Nagaraj et al[3]	2017	St. John's medical college hospital, Bangalore	U5 children with fever 171 samples (164 blood, 2 pleural fluids, 5 CSF)	14 pneumococcal isolates	2 out of 14 (14.3%) reported resistance to penicillin
Chawla et al[4]	2010	KMC, Manipal	Adults 15 – 75 years having CA-LRTI	50 *S.pneumoniae* respiratory isolates (Sputum and BAL)	4% PRSP and 10% PISP. The PRSP also showed MDR

1. Shariff M, Choudhary J, Zahoor S, Deb M. Characterization of Streptococcus pneumoniae isolates from India with special reference to their sequence typesJ Infect Dev Ctries. 2013;7:101-9. doi: 10.3855/jidc.2553.
2. Kumar KLR, Ashok V, Ganaie F and Ramesh AC. Nasopharyngeal carriage, antibiogram & serotype distribution of Streptococcus pneumoniae among healthy under five children. Indian J Med Res. 2014; 140:216-20
3. Nagaraj S, Kalal BS, Manoharan A, Shet A. Streptococcus pneumoniae serotype prevalence and antibiotic resistance among young children with invasive pneumococcal disease: experience from a tertiary care center in South India.Germs. 2017;7:78-85. doi: 10.18683/germs.2017.1112. eCollection 2017 Jun.
4. Chawla K, Gurung B, Mukhopadhyay C, and Bairy I. Reporting Emerging Resistance of Streptococcus pneumoniae from India. J Glob Infect Dis.2010; 2:10–14.

Why relatively low rate of PRSP is seen in India ?
Challenge in diagnosis of PRSP : Aural swabs

- Specimen of choice for AOM is MEF obtained via Tympanocentesis, however it is challenging due to the invasive nature of the procedure and difficulty in obtaining consent from parents[3]
- There is no consensus guidelines recommending the routine use of tympanocentesis, though it can help guide appropriate antimicrobial therapy [2]
- Aural swabs remain the most common specimen received for AOM [2,4]
- Aural swabs are useful only when there is a draining myringotomy tube or if there is existing otorrhea, obtained after meticulously cleaning the EAC[1]
- Correlation with oto-pathogen is too low with Nasopharyngeal cultures to be allowed as a substitute for MEF sample[5]

1. Akanmode AM, Winters R. Tympanocentesis. [Updated 2020 Nov 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021
2. Pichichero ME. Acute otitis media: Part I. Improving diagnostic accuracy. Am Fam Physician. 2000 Apr 01;61(7):2051-6.
3. Dongen et al, Pediatr Infect Dis J. 2013 May; 32(5):549-52,
4. Miller MJ. A Guide to Specimen Management in Clinical Microbiology. March 2017. DOI: 10.1128/9781555819620
5. Kaur R, Czup K, Casey JR and Pichichero ME. Correlation of nasopharyngeal cultures prior to and at onset of acute otitis media with middle ear fluid cultures. BMC Infectious Diseases 2014.14:article640

Concept I

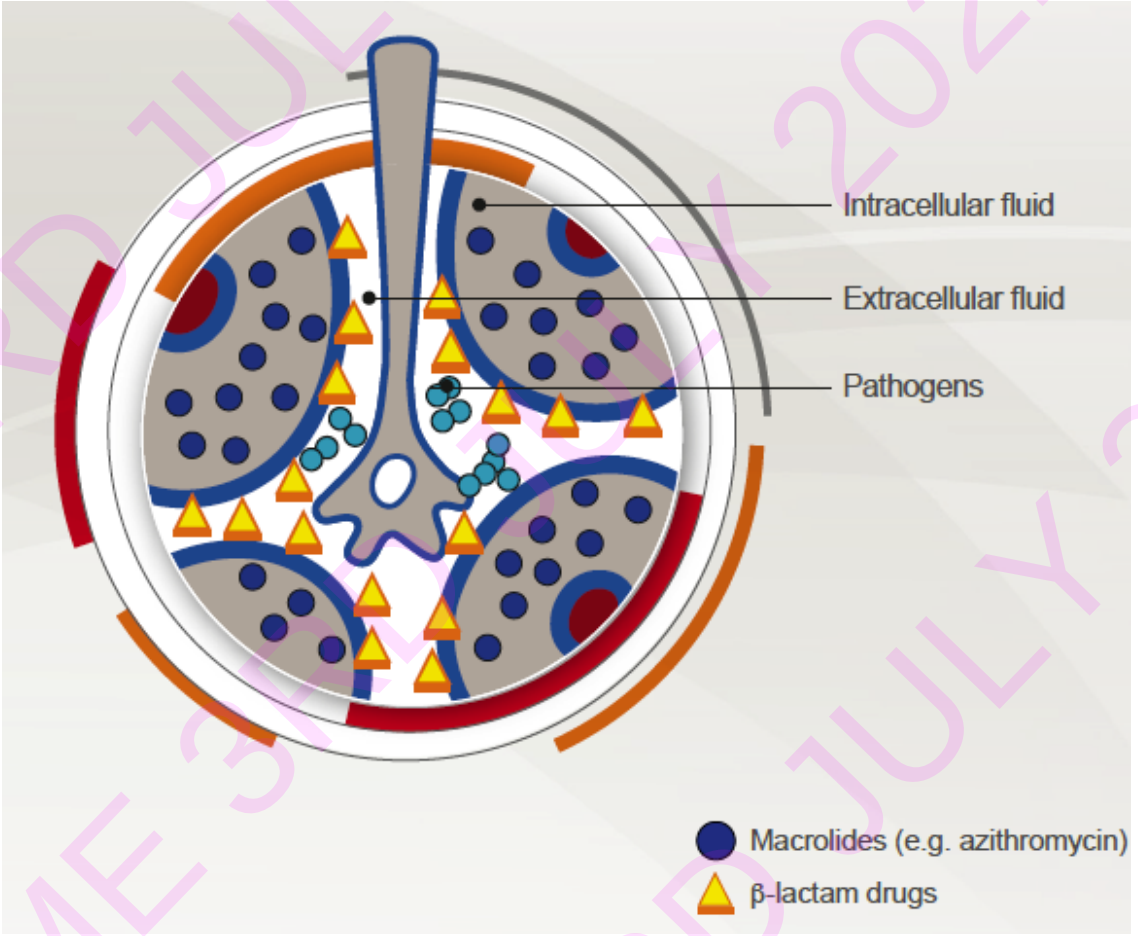
For effective eradication of pathogens, adequate penetration of antibiotics is needed for achieving sufficient concentration in the middle ear fluid in the management of AOM

Concept 1:

For effective eradication of pathogens, adequate penetration of antibiotics is needed for achieving sufficient concentration in the middle ear fluid in the management of AOM

Rationale for achieving optimal antibacterial efficacy

- During AOM most pathogenic bacteria are seen in the extracelluar MEF where β-lactam antibiotics (e.g. amoxicillin-clavulanate) also concentrate
- Other antibiotics, e.g. macrolides such as azithromycin, are found mainly within the cells
- The effective eradication of pathogens by amoxicillin-clavulanate is the result of adequate penetration into the MEF

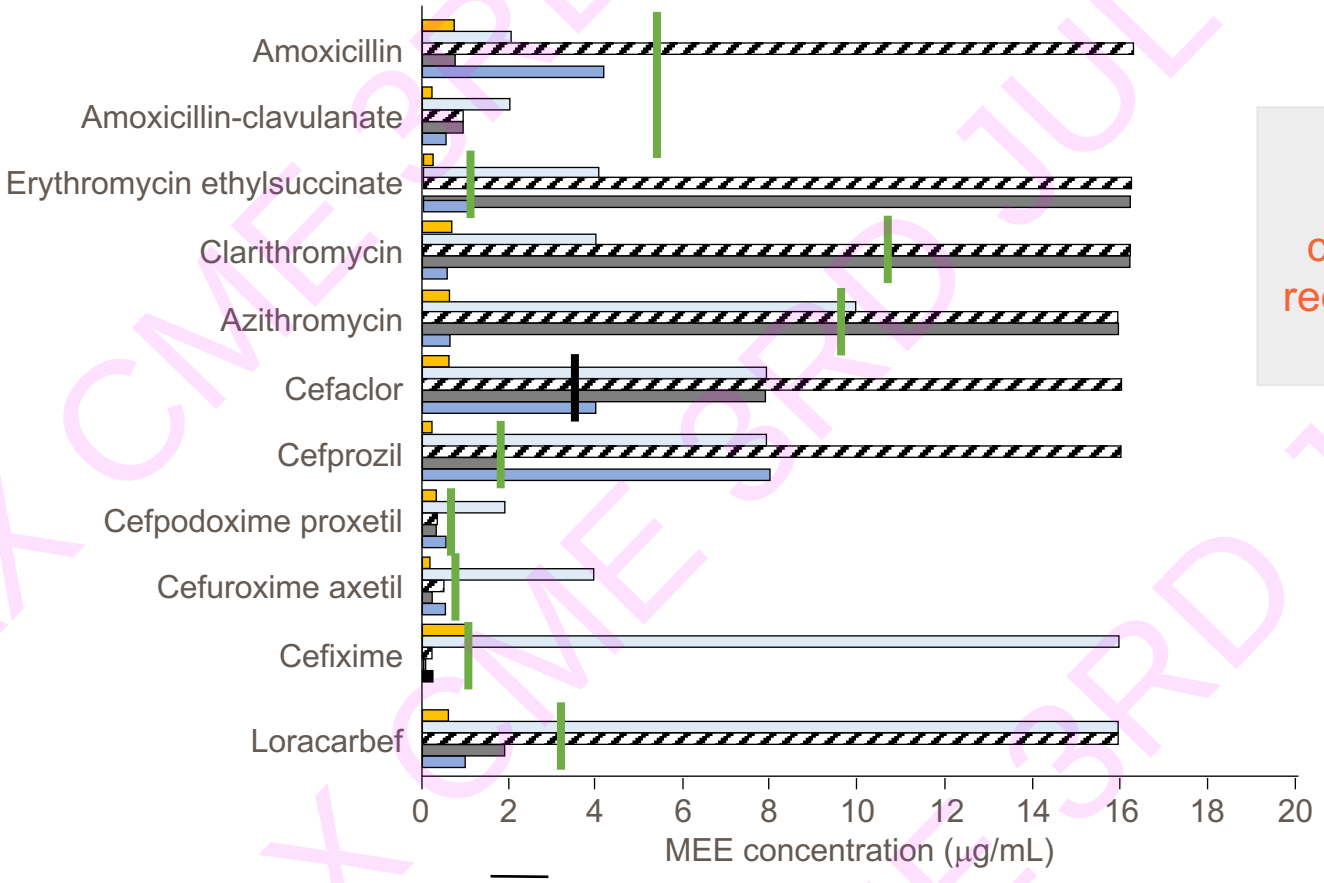


Dagan R, *et al. Lancet Infect Dis* 2002;2:593–604.

AOM, acute otitis media; MEF, middle ear fluid. *The illustration has been independently created by GSK from information available in the publication.*

Comparison of antibiotics concentration at the site of infection

MIC_{90} values of antibiotics for AOM pathogens relative to concentration of drug in MEE



For optimal antibacterial efficacy, adequate concentration of antibiotic is required, well above the MIC_{90} of key pathogens

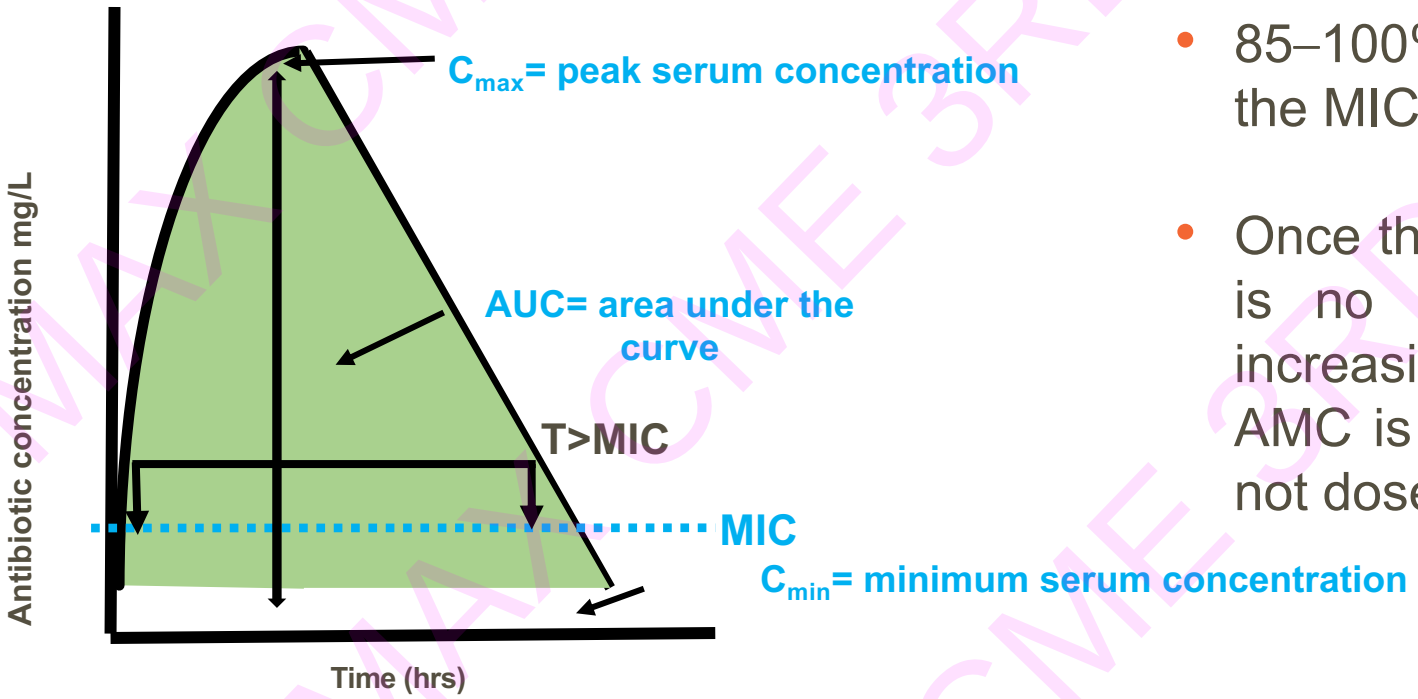
MEE, middle ear effusion; MIC_{90}, minimum inhibitory concentration needed to inhibit growth of that pathogen by 90%; AOM, acute otitis media

Block SL, *et al.* Diagnosis and management of acute otitis media. 3rd ed. P186.

Concept 2:

Pharmacokinetic/ Pharmacodynamic concept

PK/PD target for Amoxicillin clavulanic Acid

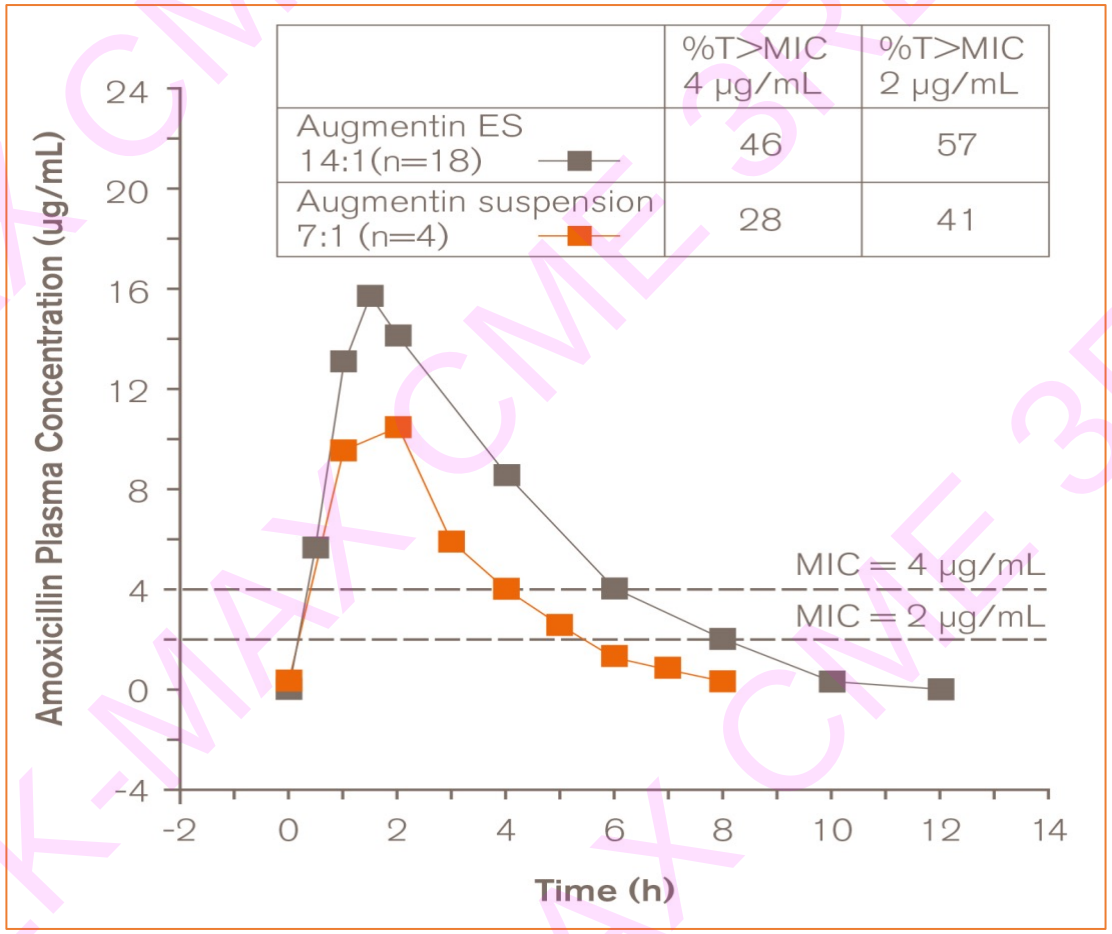


- 85–100% cure rate when serum levels exceed the MIC for >40% of the dosing interval
- Once the concentration is above the MIC there is no increase in the rate of killing with increasing concentrations of antibiotic since AMC is a time-dependent killing antibiotic and not dose dependant.

Craig WA, Andes D. *Paed infect Dis* 1996;15(3):255–259.

MIC, minimum inhibitory concentration;
PK/PD, pharmacokinetic/pharmacodynamic.

Comparing PK/PD of Augmentin ES and Augmentin DDS to cover MIC of 4 µg/ml



Mean plasma concentration-time profile for amoxicillin following AMC suspension (45/6.4 mg/kg/day) and high dose AMC (90/6.4 mg/kg/day)

T>MIC = time above minimum inhibitory concentration; MIC= Minimum Inhibitory Concentration.. PRSP, PRSP, Penicillin-resistant Streptococcus pneumoniae. PK, Pharmacokinetics. PD, Pharmacodynamics

Augmentin ES achieves a **prolonged T>MIC** of more than 41% for an MIC of 4 µg vs 28% for 7:1 Augmentin 45/6.4 mg/kg/day

Augmentin ES

with **better PK/PD**

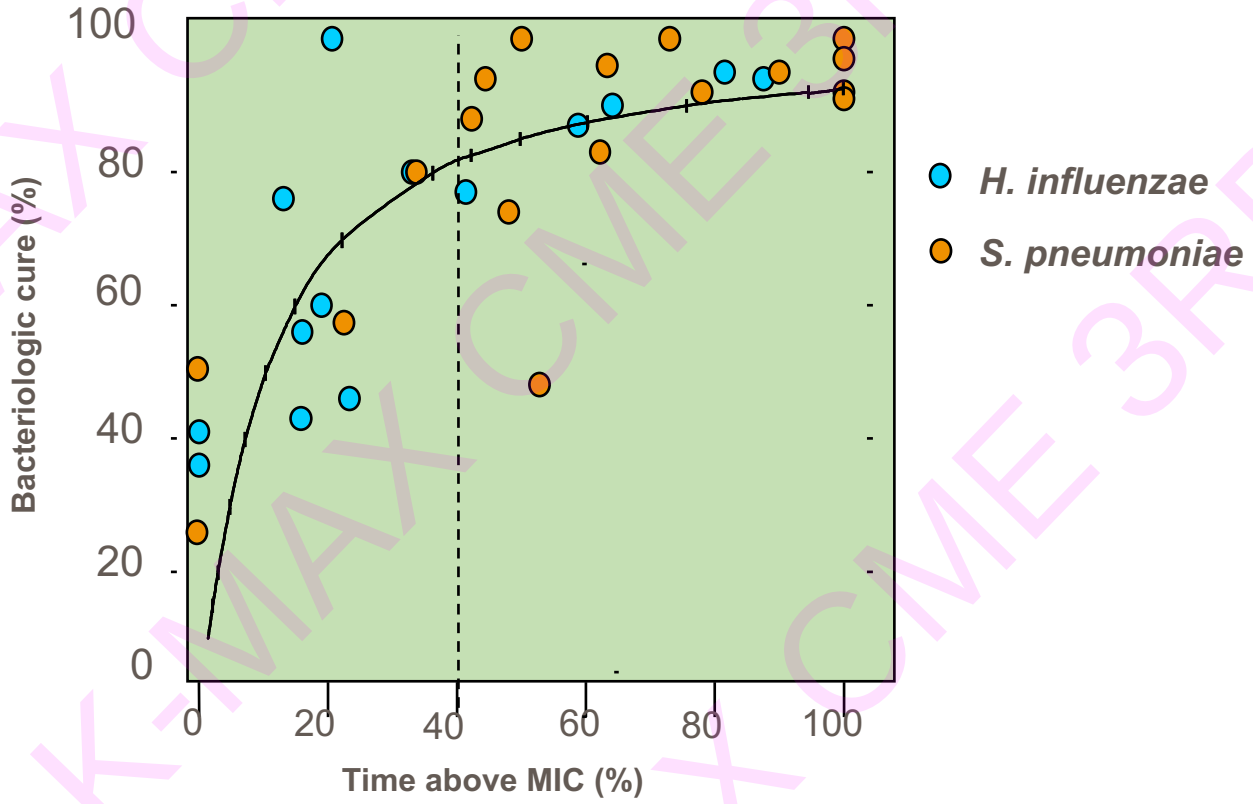
Superior & Reliable

Eradication of PRSP

GSK Data on file. 2016N290462_00, 2016.

White A, *et al. JAC* 2004;53(Suppl. S1):i3–i20

Relation of Amoxicillin time above MIC and Bacteriological cure in AOM



Clinical studies in AOM patients treated with amoxicillin have shown that a bacterial cure of 85–100% is achieved if mean plasma concentration is above the MIC for ≥40% of the dosing interval

AOM, acute otitis media; MIC, minimum inhibitory concentration.

Craig WA, Andes D. *Paed Infect Dis* 1996;15(3):255–259.

Nutshell

- PRSP rate & MIC has been gradually rising in India
- Aural swab is not done routinely so true reflection of PRSP is not possible
- For Amoxicillin = Bacterial cure of 85–100% is achieved if mean plasma concentration is above the MIC for ≥40% of the dosing interval
- Adequate penetration & PK/PD profile of antibiotics are very important factors to select the antibiotic

Pediatric perspective on the use of high dose amoxicillin-clavulanic acid in the management of Acute otitis media

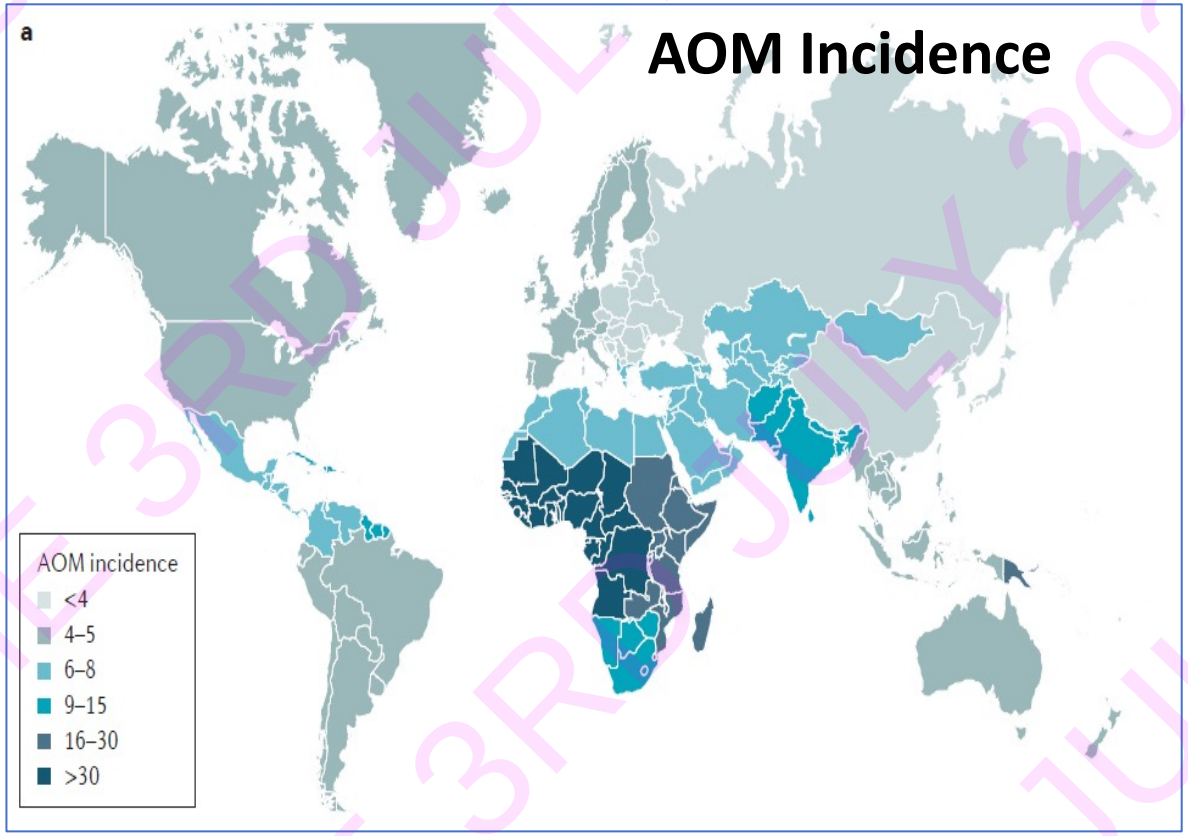
Agenda

1. AOM prevalence Global
2. AOM prevalence- India – Age wise
3. PRSP prevalence in children-2 studies
4. Nasopharyngeal colonization
5. Definition of recurrent and persistent AOM
6. AOM resistance bugs impact
7. Risk factors for persistent and recurrent disease
8. Suitable empirical therapy
9. Guidelines
10. Concepts

Global burden of Acute Otitis Media in children

- New cases of AOM globally is estimated to be 709 million with 51% of cases in children less than 5 years of age

- Peak incidence occurs in the first year of life at 45.3 new episodes per 100 children per year



Incidence rate estimates (per 100 people) in 2005 based on data from 39 papers conducted in six WHO regions.

Schilder AGM, Chonmaitree T, Cripps AW, Rosenfeld RM, Casselbrant ML and Haggard MP *et al.* Otitis media. Nat Rev Dis Primers. 2016 Sep 8;2(1):16063. doi: 10.1038/nrdp.2016.63.

AOM prevalence in India age-wise

Prevalence in preschool children is highest in <2 yrs

Author (year); n	Study population	Age group	Avg. AOM prevalence %
Singhi et al (1992); n = 100	100 febrile children (presentation to pediatric emergency with fever less than 3 days)	1m – 3 yr	5
Sophia et al (2010); n = 800	pre-school children in rural India*	< 1 yr	12.5
		1 – 2 yr	13.3
		2 – 3 yr	8.7
		3 -4 yr	7.6
		4-5 yr	9.1

1. S. Singhi, V. Kohli, A. Ayyagiri. Bacteremia and bacterial infections in highly febrile children without apparent focus. Indian Pediatr., 29 (1992), pp. 1285-1289
2. Sophia A, Isaac R, Rebekah G, Brahmadathan K, Rupa V. Risk factors for otitis media among preschool, rural Indian children. Int J Pediatr Otorhinolaryngol. 2010 Jun;74(6):677-83. doi: 10.1016/j.ijporl.2010.03.023. Epub 2010 Apr 22. PMID: 20416956.

Drug resistant *S. pneumoniae* : Growing concern

Balaji *et al* 2015

Pneumococcal serotypes associated with invasive disease in under five children in India & implications for vaccine policy

Specimens: Blood, CSF, Pleural fluid(PF)

Result of Antimicrobial susceptibility test to S.pneumoniae

- 110 isolates (96.4%) were non-susceptible to co-trimoxazole
- 35 isolates (30%) were non-susceptible to erythromycin
- **Six isolates (5.2%) were non-susceptible to penicillin**

Increase in the trend of penicillin resistant IPD serotypes from 1.3% in 1999 to 5.2% in 2015

PISP-Penicillin Intermediate Streptococcus pneumoniae
PRSP-Penicillin-resistant Streptococcus pneumoniae

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4669863/

Ravikumar *et al* 2013

Circulating Serotypes and Trends in Antibiotic Resistance of Invasive *Streptococcus Pneumoniae* from Children under Five in Bangalore

Two-year hospital-based study at tertiary care hospital; 45 invasive pneumococcal isolates in U5 children (2-year study)

Out of all isolates–
22.5% were PISP
12.5% were PRSP
} Total = 14/40 ie. 35% resistant
20% were multidrug resistance

Specimens: blood-36,CSF-3,PF-1

Clinically,
- 25 (62.5%)- pneumonia,
- 11(27.4%)-bacteremia,
- 4 (10%)-meningitis.

Penicillin resistance was associated with a lower age .
[Higher in age group of 28 days-20 months (78.5%), followed by that of 21-40 months (21.5%)]

Ravi kumar et al 2013. DOI: 10.7860/JCDR/2013/6384.3741

Recurrent or Persistent Acute Otitis Media

What is meant by recurrent AOM?

Recurrent AOM : Three or more well documented and separate AOM episodes in preceding 6 months or 4 or more episodes in preceding 12 months with at-least 1 episode in the past 6 months[1]

What is meant by persistent AOM?

Persistent AOM : It is manifested by persistence of symptoms and signs of middle ear infection (treatment failure and/or relapse of AOM within 1 month of completion of antibiotic therapy[2]

1. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131:e964-e999
2. Pichichero ME. Recurrent and persistent otitis media. Pediatr Infect Dis J.2000;19:911-6

Dramatic rise in AOM prevalence due to resistant bugs

- Most AOM pathogens have been long susceptible to β-lactam antibiotics including amoxicillin, but the rise of resistant pathogens like PRSP and β-lactamase producing *H. influenzae & Moraxella Catarrhalis* is posing serious global health issues[1].

- 90-100% of *M catarrhalis* isolates and 40-50% of *H influenzae* isolates produce beta-lactamases[2,3]

- Otitis media caused by H. influenzae is associated with non-typeable strains in the majority of patients. H. influenzae is the primary pathogen in the unique conjunctivitis-AOM syndrome[4]

1. McGee L, McDougal L, Zhou J, et al. Nomenclature of major antimicrobial-resistant clones of Streptococcus pneumoniae defined by the pneumococcal molecular epidemiology network. J Clin Microbiol. 2001;39:2565-71.
2. Jacobs MR, Bajaksouzian S, Zilles A, Lin G, Pankuch GA, Appelbaum PC. Susceptibilities of Streptococcus pneumoniae and Haemophilus influenzae to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 U.S. surveillance study. Antimicrobial Agents and Chemotherapy. 1999;43(8):1901–1908. [PMC free article] [PubMed] [Google Scholar]
3. Jacobs MR, Felmingham D, Appelbaum PC, et al. The Alexander project 1998-2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. Journal of Antimicrobial Chemotherapy. 2003;52(2):229–246. [PubMed] [Google Scholar]
4. Klein JO. Otitis Externa, Otitis Media, and Mastoiditis. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 2015;767-773.e1. doi:10.1016/B978-1-4557-4801-3.00062-X

Risks associated with AOM resistance

PRSP could be a major cause of Relapse or Initial treatment failure of AOM

PRSP can cause 3 times intractable AOM compared to penicillin sensitive strains

PRSP usually have MIC of more than 2 to 4 µg/ml

Recurrent AOM occurs in first several years of life in approximately 20 to 30% of the pediatric population.

PRSP strains are commonly isolated from children who have failed therapy or received antibiotics recently for any other indication or AOM

PRSP strains are more likely to be multi- drug resistant limiting the efficacy of cephalosporin and macrolides

AOM: Acute Otitis Media, PISP: Penicillin Intermediate *S. Pneumoniae*

Asian Network for Surveillance of Resistant Pathogens (ANSORP) Study : prospective surveillance study of 2,184 *S. pneumoniae* isolates collected from patients with pneumococcal infections from 60 hospitals in 11 Asian countries from 2008 to 2009. In India, in 1996, total numbers of clinical isolate types were 996 whereas in 2009-11 total numbers of isolates were 2184.

Penicillin non susceptible/resistant strain has increased in India from 3.8% in 1996 to 30.4% in 2009

1. Leibovitz E, Raiz S, Piglansky L, et al. Resistance pattern of middle ear fluid isolates in acute otitis media recently treated with antibiotics. Pediatr Infect Dis J 1998;17:463-9.
2. Mamishi S, Moradkhani S, Mahmoudi S, Hosseinpour-Sadeghi R, Pourakbari B. Penicillin-Resistant trend of Streptococcus pneumoniae in Asia: A systematic review. Iran J Microbiol. 2014;6:198-210.
3. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131:e964-e999.
4. Jaiswal N, Singh M, Das RR, et al. Distribution of serotypes, vaccine coverage, and antimicrobial susceptibility pattern of Streptococcus pneumoniae in children living in SAARC countries: a systematic review. PloS one. 2014;9:e108617.

Risk factors of recurrent / persistent AOM

- Acute otitis media in the first 6 months of life[1]
- Age less than 3 years[1]
- Parental smoking[1]
- Day-care attendance[1]
- Antimicrobial exposure for AOM within the previous three months[2]
- Allergy or atopy[3]
- Upper respiratory tract infections[3]
- Low socio-economic status[3]
- Tonsillar and adenoid hypertrophy[3]
- Artificial feeding[3]

1. M E Pichichero. Recurrent and persistent otitis media. Pediatr Infect Dis J. 2000;19:911-6.doi: 10.1097/00006454-200009000-00034.
2. Klein OJ. Amoxicillin/clavulanate for infections in infants and children: past, present and future.Pediatr Infect Dis J.2003;22:S139-48.doi: 10.1097/00006454-200308001-00005.
3. Zhang Y, Xu M, Zhang J, Zeng L, Wang Y, Zheng YQ. Risk factors for chronic and recurrent otitis media-a meta-analysis.PLoS One. 2014 Jan 23;9(1):e86397. doi: 10.1371/journal.pone.0086397. eCollection 2014.

Can amoxicillin remain a suitable empiric AOM therapy?

- PSSP/PRSP data is **sparse**, as tympanocentesis is rarely done in routine clinical practice.
- Because of low PRSP prevalence, aural isolates mostly belong to PSSP (MIC < 0.1 ug/mL). PSSP group respond well to amoxicillin or AMC at 45 mg/kg/day[1,2]
- However, amoxicillin (45mg/kg/day) does not cover high risk pathogens like PRSP & other beta-lactamase producing pathogens like *H. influenzae* & *Moraxella*[1,2].
- Additionally, children are at high risk of PRSP due to[3]
    - High nasopharyngeal carriage rate of pneumococcus during the first years of life (20% to 50%).
    - Pneumococcus undergoes genetic transformation and can acquire DNA from other streptococci; during asymptomatic nasopharyngeal carriage, selection of resistant pneumococcus occurs especially in children, because they carry pneumococcus more often and for longer periods.
    - Frequent exposure to antibiotics, particularly penicillin.

AOM: acute otitis media; PRSP: penicillin-resistant *S. pneumoniae*; MIC: minimum inhibitory concentration; AMC:, amoxicillin-clavulanate. PSSP

1. Song JH, Jung SI, Ko KS, Kim NY, Son JS, Chang HH, et al. High prevalence of antimicrobial resistance among clinical Streptococcus pneumoniae isolates in Asia (an ANSORP study). Antimicrob Agents Chemother 2004;48:2101-7.
2. Veeraraghavan B, Kurien T. Penicillin resistant Streptococcus pneumoniae in India: Effects of new clinical laboratory standards institute breakpoint and implications. Indian J Med Microbiol 2011;29:317-8
3. Cillóniz C, Garcia-Vidal C, Ceccato A, Torres A. Antimicrobial Resistance Among Streptococcus pneumoniae. Antimicrobial Resistance in the 21st Century. 2018 Mar 7:13–38. doi: 10.1007/978-3-319-78538-7_2. PMCID: PMC7122384.

Rationale for high dose AMC as empiric AOM therapy

- ***PRSP*** has no response to conventional dosages of amoxicillin (40–50 mg/kg/day).
- Only high dose amoxicillin (80-90 mg/kg/day) provides **elevated MEF antibiotic levels** that surpasses MIC of PISP/PRSP to achieve maximal bacterial killing.
- Non typeable H. influenzae(**NTHi)** is the etiologic agent in 23 to 67% AOM cases. About 50% of *H. influenza* and 100% *M. catarrhalis* are *β*-lactamase positive.
- In contrast to PRSP, AOM caused by *H. influenza* or *M. catarrhalis* requires a *β*-lactamase inhibitor such as clavulanic acid, a second- or third-generation cephalosporin, or other types of antibiotics.
- Therefore, a high dose of amoxicillin combined with clavulanic acid is effective for PISP/PRSP and is also effective against *β*-lactamase-positive bacteria.

- Jacobs MR, Bajaksouzian S, Zilles A, Lin G, Pankuch GA, Appelbaum PC. Susceptibilities of Streptococcus pneumoniae and Haemophilus influenzae to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 U.S. surveillance study. Antimicrobial Agents and Chemotherapy. 1999;43(8):1901–1908. [PMC free article] [PubMed] [Google Scholar]
- Jacobs MR, Felmingham D, Appelbaum PC, et al. The Alexander project 1998-2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. Journal of Antimicrobial Chemotherapy. 2003;52(2):229–246. [PubMed] [Google Scholar]

AAP/AAFP 2013 recommendations on AOM

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.

1st line

Amoxicillin
Dose: 80-90 mg/kg/day)

OR

Amoxicillin Clavulanate
Dose: 90 mg/kg/day)

Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131:e964-e999

Indian National Treatment Guidelines for Antimicrobial Use in Infectious Diseases 2016 (National Centre for Disease Control)

Drug of choice for presumptive therapy

Disease	Microorganisms	Suggested regimen	Alternate	Remarks
Acute otitis media	*S. pneumoniae* *H. influenzae* *Morexella catarrahalis*	Amoxicillin+clavulanate 90/6.4mg /kg/day bid or cefpodoxim /cefuroxime axetil 250mg BD	Ceftriaxone 50mg/kg I/M for 3 days	Treat children <2 years If >2 years, afebrile and no ear pain- consider analgesics and defer antibiotics Duration of treatment If age <2 years: 10 days If age >2 years : 5-7 days

https://ncdc.gov.in/WriteReadData/l892s/File622.pdf

Nutshell

- Treatment of AOM is more challenging in younger children and developing countries
- There is an increasing trend of resistant organisms in AOM
- PRSP can cause more intractable AOM compared to penicillin sensitive strains
- High dose amoxicillin (80-90 mg/kg/day) provides elevated MEF antibiotic levels to achieve maximal bacterial killing
- Guidelines AAP/AAFP also recommends the use of high-dose AMC

Study evidences on the use of high dose amoxicillin-clavulanic acid in the management of acute otitis media

Amoxicillin clavulanic acid (90 mg/kg) : High dose paediatric formulation

- Augmentin ES-**Double dose of amoxicillin (90 mg/kg/day compared with 45 mg/kg/day for the standard 7:1 Augmentin syrup) but the same dose of clavulanic acid**
- Augmentin ES was developed using clinical studies in AOM and PK/PD concepts to provide improved eradication of PRSP with penicillin MICs ≤4 µg/mL[1,2]
- Augmentin ES was approved by the US FDA in 2001 for the treatment of children with recurrent or persistent OM in two divided doses.[1]
- Increasing the dose of amoxicillin further extends the antibacterial coverage to include most penicillin-resistant strains, including those with elevated amoxicillin MICs (up to 4 µg/mL)

1. White A, *et al. JAC* 2004;53(Suppl. S1):i3–i20.
2. Easton J, *et al. Drugs* 2003;63(3):311–340.
3. Augmentin ES GDS, version 24, 13 June 2019.

AOM, acute otitis media; PRSP, penicillin-resistant *S. pneumoniae*; MIC, minimum inhibitory concentration; FDA, Food and Drug Administration; LRTI, lower respiratory tract infection; SSTI, skin and soft tissue infection; UTI, urinary tract infection; OM, otitis media; PK/PD, pharmacokinetic/pharmacodynamic.

Comparison of Amoxicillin clavulanic acid paediatric oral formulations

T>MIC over 24 hour dosing interval for Augmentin oral formulations

AMC formulations	Amoxicillin C_{max}	T>MIC (%) MIC 1 µg/mL	T>MIC (%) MIC 2 µg/mL	T>MIC (%) MIC 4 µg/mL
Paediatric oral formulations				
400/57 mg/5 mL suspension **(7:1) [45/6.4 mg/kg/day given BD]**	10.9	50	41	-
ES suspension **(14:1) [90/6.4 mg/kg/day given BD]**	15.8	61	50	41

BD, twice daily; TDS, three times daily; MIC, minimum inhibitory concentration.

The target T>MIC for efficacy for Augmentin is set at 40%

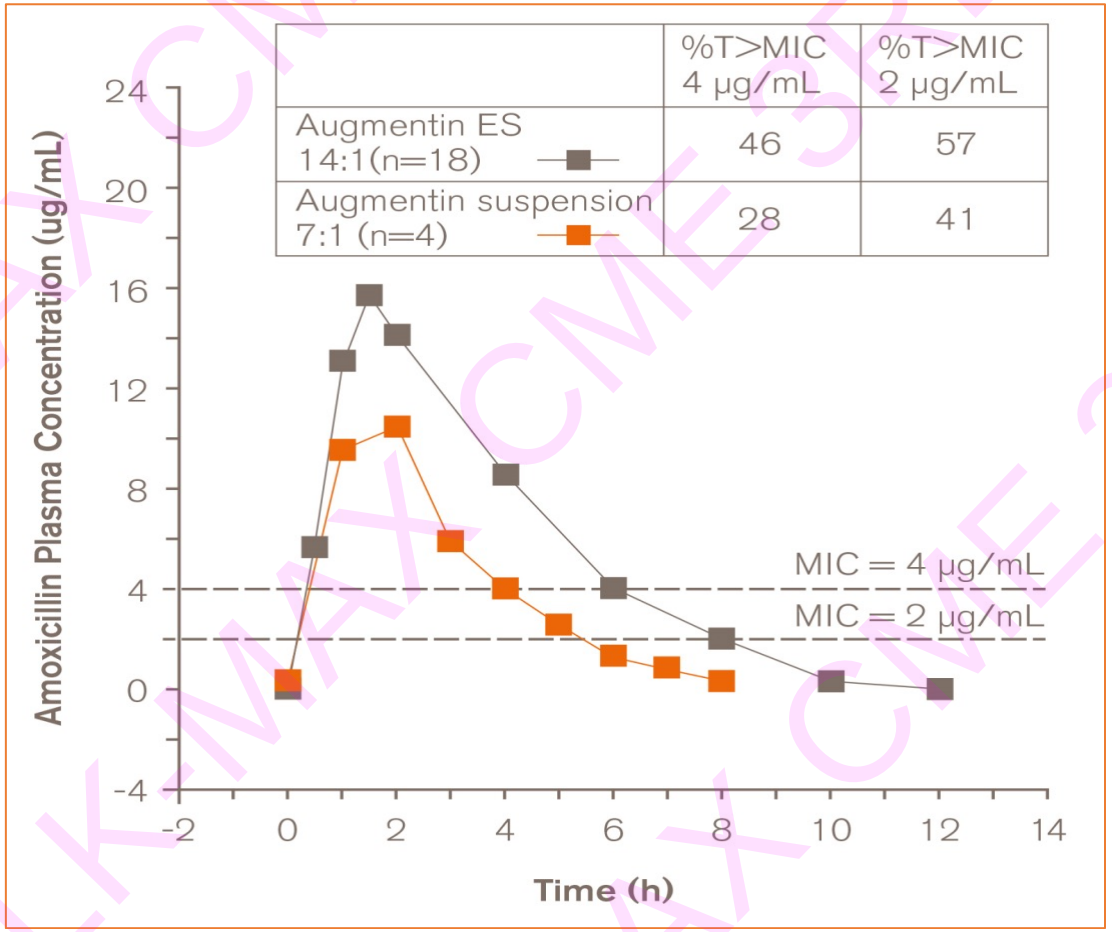
All oral Augmentin formulations achieve maximum eradication of pathogens with MICs ≤1 µg/mL

Augmentin 7:1, achieves maximum eradication of pathogens with MICs up to 2 µg/mL

Only Augmentin ES achieves maximum eradication of pathogens with MICs 4 µg/mL

White A, *et al. JAC* 2004;53(Suppl. S1):i3–i20.
Jehl F, Klossek JM, Peynegre R, Serrano E, Castillo L, Bobin S, et al. [Sinusal penetration of amoxicillin-clavulanic acid. Formulation 1 g./125 mg., twice daily versus formulation 500 mg./125 mg., three times daily]. Presse Med. 2002;31(34):1596–1603. pmid:12426976

Comparing PK/PD of High dose AMC and Standard dose AMC to cover MIC of 4 µg/ml



Mean plasma concentration-time profile for amoxicillin following AMC suspension (45/6.4 mg/kg/day) and high dose AMC (90/6.4 mg/kg/day)

T>MIC = time above minimum inhibitory concentration; MIC= Minimum Inhibitory Concentration.. PRSP, PRSP, Penicillin-resistant Streptococcus pneumoniae. PK, Pharmacokinetics. PD, Pharmacodynamics

Augmentin ES achieves a **prolonged T>MIC** of more than 41% for an MIC of 4 µg vs 28% for 7:1 Augmentin 45/6.4 mg/kg/day

Augmentin ES

with **better PK/PD**

Superior & Reliable

Eradication of PRSP

GSK Data on file. 2016N290462_00, 2016.

White A, *et al. JAC* 2004;53(Suppl. S1):i3–i20

Dagan et al

Open-label, multicentre AOM study (n=521), mean age 18.6 months, including children with PRSP

Augmentin ES 90/6.4 mg/kg/day, BD,10 days

Study Objective:
Bacteriological and clinical efficacy in children with AOM

Clinical assessment: 4 -6 days; 12 -15 days; 21-25 days
Tympanocentesis: Baseline and 4 – 6 days

Efficacy assessment: Clinical response	Bacteriological assessment: Eradication of pathogens
Symptoms and otoscopic signs of acute inflammation were completely resolved/improved on Days 12–15 in 89% (263/295) of children	**Pathogens were eradicated in 96% (172/180) of 180 evaluable children with pathogens isolated at baseline who underwent repeat tympanocentesis on Days 4–6**

	Bacteriological eradication rates	
Pathogen	n/N of isolates	%
All S. pneumoniae	122/125	98
S. pneumoniae with penicillin MIC ≥2–4 µg/mL	31/34	91
H. influenzae	78/83	94

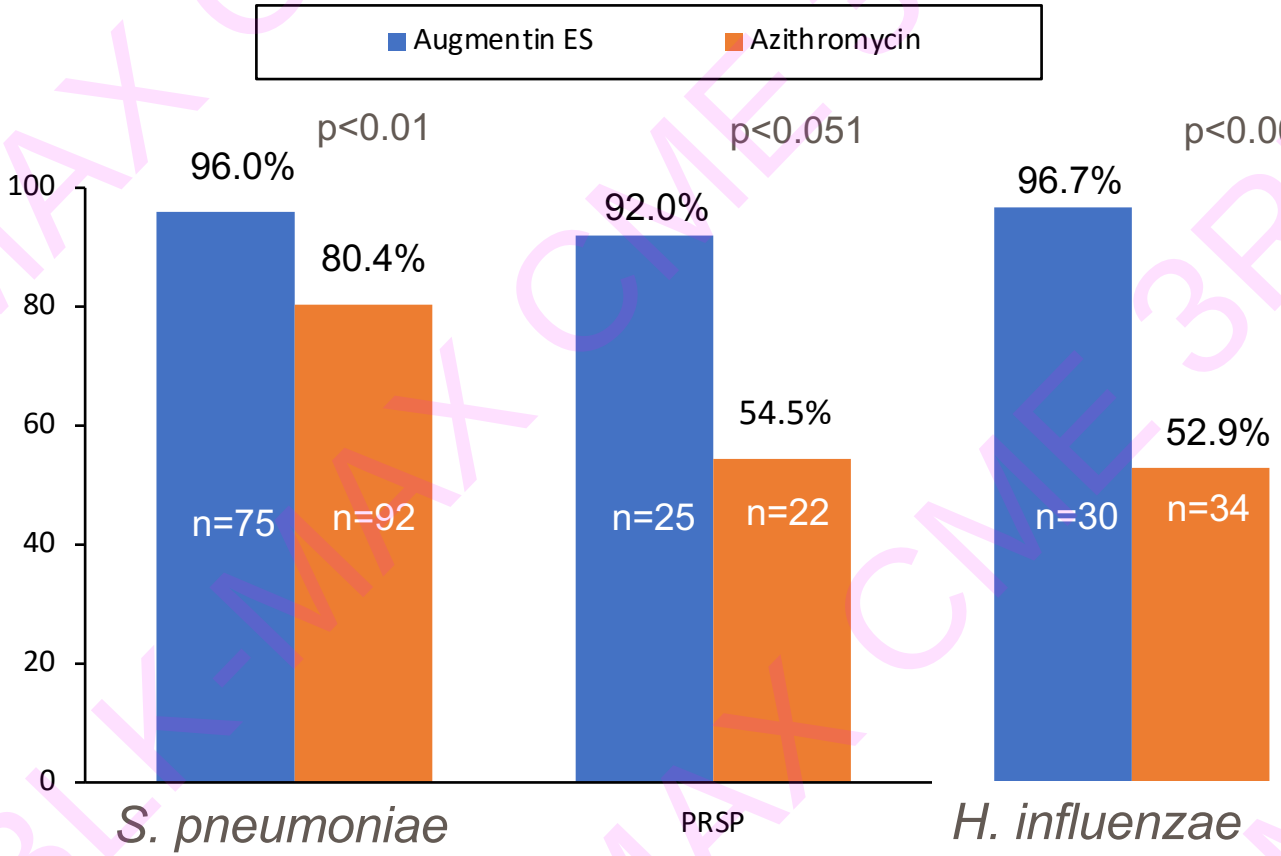
AOM, acute otitis media; MIC, minimum inhibitory concentration; PRSP, penicillin-resistant *S. pneumoniae*; BD, twice daily.

Dagan R, *et al. PIDJ* 2001;20(9):829–837.

Hoberman et al

Randomized, investigator-blinded, multicenter trial conducted in AOM children

Participants – 250 in each group approximately (6 – 30 months age
AMC (90/6.4 mg/ kg/d for 10 days) versus azithromycin for 5 days



- **Results:**
- **Eradication of AOM pathogens**
- **Augmentin ES achieves significantly higher rates of eradication of AOM pathogens than azithromycin, including antibiotic-resistant pathogens[1]**

1. Hoberman A, *et al*. *PIDJ* 2005;24(6):525–532.

PRSP, penicillin-resistant *S. pneumoniae;*
AOM, acute otitis media. AMC-Amoxivillin Clavulanic acid

Hoberman et al

AMC (90/6.4 mg/kg)
Symptom resolution in children under 2 years with AOM

Young children (6 to 23 months) with AOM received Augmentin ES (n=144) or placebo (n=147), BD, 10 days

Mean AOM-SOS, Days 1–7, was lower with Augmentin ES than placebo (p<0.02)

Clinical failure rate was lower with Augmentin ES than with placebo: 4% vs 23% at or before Day 4 or 5 (p<0.001) and 16% vs 51% at or before Day 10–12 (p<0.001)

		Day 2	Day 4	Day 7	
Initial resolution of symptoms*	**Augmentin ES**	**35%**	**61%**	**80%**	**p=0.14 overall comparison**
	Placebo	**28%**	**54%**	**74%**	
Sustained resolution of symptoms†	**Augmentin ES**	**20%**	**41%**	**67%**	**p=0.04 overall comparison**
	Placebo	**14%**	**36%**	**53%**	

Augmentin ES compared to placebo had consistently more favourable short-term effects including sustained resolution of symptoms, absence of otoscopic evidence of persistent MEI and reduced rate of residual MEE

- **Children <2 yrs with AOM are less likely to have clinical failure and have lower symptom burden when treated with Augmentin ES, 10 days compared with placebo**

*Based on one AOM-SOS reading; †Based on two successive AOM-SOS readings.

Hoberman A, et al. NEJM 2011;364(2):105–115.

AOM-SOS, acute otitis media severity of symptoms score; MEI, middle ear infection; MEE, middle ear effusion; BD, twice daily.

Phase 3 trial comparing Augmentin-90 and Augmentin-45

A randomized double-blind, multicentric, comparative Study of the safety and efficacy of q 12 hrs *Augmentin*- 90/6.4 mg/kg/day and q 12 hrs *Augmentin*- 45/6.4 mg/kg/day in the treatment of acute otitis media in children

1^0 objectives	Incidence of Adverse events including PDD
2^0 objectives	Compare the clinical efficacy of Augmentin-90 and Augmentin-45 at end of therapy

Study Population: 453 children with age range 3 months to 12 years
Study design: Prospective, randomized, double-blind, multicenter, comparative, active controlled study

PDD, Protocol-Defined Diarrhea-Three or more watery stools in one day or two watery stools per day for two consecutive day

GSK data on file-BRL-025000/RSD-1009XZ/3,1997

Rowinski et al

Comparison on PDD between Augmentin-90 and Augmentin-45 (Rowinski et al)

PDD	Augmentin-90		Augmentin-45		
	N	%	N	%	Significance
ITT	23/218	10.6	20/222	9	1.5(-4.0% to 7.1%)
PP	21/200	10.5	18/211	8.5	2.0 (-3.7% to 7.6%)

This supports the conclusion that the rate of PDD associated with *Augmentin*-90 was no greater than that associated with *Augmentin*-45

Higher dose of amoxicillin in the Augmentin-90 formulation does not contribute to an increased incidence of diarrhea in children.

The upper limits of the 95% confidence intervals were less than the protocol specified limit of 10%.

GSK data on file-BRL-025000/RSD-1009XZ/3,1997

ITT, Intention to treat. PDD, Protocol-Defined Diarrhea . CI: Class interval

Nutshell

- High dose is proven effective clinically and bacteriologically in children with AOM by various studies
- High dose AMC offers optimum treatment of AOM, ensuring coverage of penicillin-resistant S. pneumoniae (with MIC ≤4 µg/mL) as well as β-lactamase producing H. influenzae and M. catarrhalis
- AMC reduces MEE duration, and the risk for persistent MEE and possible hearing loss, in children with AOM compared to children receiving placebo
- No increase in treatment-related AEs (including diarrhoea) compared with standard dose AMC
- Appropriate as empirical AOM treatment in persistent or recurrent cases and in patients with risk factors

Rationale for the use of high dose amoxicillin-clavulanic acid in the management of community acquired pneumonia

Disease burden-Global/Indian

- Community acquired pneumonia (CAP) contributes to about one sixth of this mortality[1]
- UNICEF: A child dies of pneumonia every 39 seconds[2]
- India contributes 20% of global mortality in U5 children (report:2015) [1]
- In India, CAP accounted for 13–16% of total annual mortality in under 5 years of age group[1]
- Indian studies reported 3.6–4.0 million episodes of CAP in U5 children in 2010 with 30.7–32.0 episodes per 1000 child-year of severe pneumonia[1]

1.Yadav K, Awasthi S. The current status of community-acquired pneumonia management and prevention in children under 5 years of age in India: a review. Therapeutic Advances in Infectious Disease. 2016;3(3-4):83-97.
2.https://data.unicef.org/topic/child-health/pneumonia/

CAP in children-etiological organisms

- Streptococcus pneumoniae – Most common cause of bacterial pneumonia in children
- Haemophilus influenzae type b (Hib) – Second most common cause of bacterial pneumonia
- S. pneumoniae causes about one-third of radiologically confirmed pneumonia in children aged <2 years
- Viruses account for 30–67% of CAP cases in childhood (UK data) and are more frequently identified in children aged <1 year than in those aged >2 years
- One-third of cases of CAP are caused by a mixed infection

CAP, community-acquired pneumonia; PCV7, pneumococcal conjugate vaccine 7; IPD, invasive pneumococcal disease; ICU, intensive care unit.

Harris M, Clark J, Coote N, et alBritish Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011Thorax 2011;66:ii1-ii23.

Pneumococcal resistance (invasive) U5 children

- Increasing emergence of resistant strains of *S. pneumoniae* is of major concern
- In India there are only few reports that show the resistance pattern in *S. pneumoniae*.
  - According to a South Indian study, Nagaraj et al conducted under 5 children with invasive pneumococcal disease and fever (40% had pneumonia)
    - Out of 171 samples were collected, out of which 14 were pneumococci isolates
    - Two out of these 14 , (14.3%) reported resistance to penicillin

Nagaraj S, Kalal BS, Manoharan A, Shet A. Streptococcus pneumoniae serotype prevalence and antibiotic resistance among young children with invasive pneumococcal disease: experience from a tertiary care center in South India.Germs. 2017;7:78-85.

Pediatric Infectious Diseases Society and the Infectious Diseases Society of America (PIDS/IDSA 2011)

Empirical therapy for the Management of presumed bacterial CAP in infants and children > 3 months of age

Child < 5 years old on OPD basis:	Child > 5 years old on OPD basis:
Amoxicillin, oral (90 mg/kg/day in 2 doses) **Alternative:** Oral amoxicillin clavulanate (amoxicillin component,90 mg/kg/day in 2 doses)	Oral amoxicillin (90 mg/kg/day in 2 doses to a maximum of 4 g/day); for children with presumed bacterial CAP who do not have clinical, laboratory, or radiographic evidence that distinguishes bacterial CAP from atypical CAP, a macrolide can be added to a b-lactam antibiotic for empiric therapy; **Alternative:** Oral amoxicillin clavulanate (amoxicillin component, 90 mg/kg/day in 2 doses to a maximum dose of 4000 mg/day

Also, if a physician **suspects Haemophilus influenza,** typeable (A-F) or non-typeable, as a causative agent for CAP with **mild infection**,

Preferred choice is Amoxicillin (75-100 mg/kg/day in 3 doses) if b-lactamase negative **or**

Amoxicillin clavulanate (90 mg/kg/day) as an Oral **Step-down** therapy

So, in a nutshell, guideline PIDS/IDSA suggests the use of high dose Amoxicillin clavulanate as an alternative therapy in presumed bacterial pediatric CAP

CAP, community-acquired pneumonia; PIDS, Pediatic Infectious Diseases Society; IDSA, Infectious Diseases Society of America; LRTI, lower respiratory tract infection.

Bradley JS, *et al. Clin Inf Dis* 2011;53(7):e25–e76.

Therapeutic justification for extrapolation of data for the use of High Dose Amoxicillin Clavulanate in the Management of CAP in children

- Key CAP pathogens are the same as those for AOM (*S. pneumoniae, H. influenzae* and *M. catarrhalis*)
- Clinical and bacteriological efficacy of Augmentin ES against *S. pneumoniae, H. influenzae* and *M. catarrhalis* (including resistant pathogens) has been established in AOM
- **European Medicines Agency (EMA) approved High dose Amoxicillin Clavulanate** for the treatment of AOM and CAP in children aged ≥ 3 months and < 40 kg BW, caused or thought likely to be caused by PRSP.
- This approval is given by **extrapolation based on PK/PD principles**, as results from AOM studies have shown that the PK/PD concept is predictive for clinical outcome in CAP
- Augmentin 7:1 is already approved in CAP, thus its use can be extended to the 14:1 ratio based on approved PK/PD data for the 14:1 ratio in children with AOM
- Safety profile of high dose AMC has also been established in AOM patients

CAP, community-acquired pneumonia; ABRS, acute bacterial rhinosinusitis; AOM, acute otitis media; PK/PD,pharmacokinetic/pharmacodynamic.

https://www.ema.europa.eu/documents/referral/losec-article-30-referral-annex-ii_en.pdf

Summary

- Pneumonia is an important cause of mortality in under 5 children especially in developing countries
- Rise in Resistant strains of Streptococcus pneumoniae is becoming an alarming concern
- Guidelines currently thus recommend using high dose of amoxicillin/amoxicillin-clavulanate (PIDS/IDSA)
- Efficacy and safety can be extrapolated to CAP in children due to sharing of etiological organisms with AOM
- EMA has approved using high dose amoxicillin-clavulanate in CAP (Extrapolated from studies in AOM based on PK/PD principles)