Review Article

Amoxicillin / Clavulanate : A Cornerstone Antibiotic for Treatment of Infections in Paediatrics

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Infections are currently the greatest cause of disease Worldwide, with community-acquired infections having the most essential role. The growing resistance to antibiotics further intensifies the threat of infections, which remains a significant issue even after 50 years, necessitating the introduction of combination antibiotic therapies to achieve better treatment outcomes. Since its inception, patients of all ages, particularly newborns, children and adults, have extensively utilized the amoxicillin/clavulanate combination. The addition of clavulanic acid to amoxicillin widened the scope to encompass strains that produce beta-lactamases in addition to other bacterial species. The increasing prevalence of antibiotic resistance necessitates higher antibiotic doses for effective treatment of infections. Amoxicillin/clavulanate plays a crucial role in the treatment of a variety of infections, particularly Respiratory Tract Infections, in adults and children globally; this is due to the development of increased dosage schedules and improved formulations. Amoxicillin/clavulanate is frequently recommended by international and national prescribing guidelines for the management of community-acquired infections. The ATLAS and SOAR susceptibility investigations, which demonstrate that the susceptibility of the common respiratory pathogens, S. pneumoniae and H influenzae, remains strong, supported these recommendations in India. Inadequate or early discontinuation of antibiotic therapy may result in recurrent infections, treatment failure and the emergence of antibiotic resistance. Therefore, healthcare providers and caregivers need to ensure that paediatric patients complete their prescribed course of amoxicillin/clavulanate to enhance its therapeutic advantages while reducing the risk of resistance. The present review article is intended to give comprehensive information about amoxicillin/clavulanate and its use in pediatric infections in outpatient settings.

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Infections continue to be one of the major causes of morbidity and mortality in the paediatric age group, around the World. As a result, both in newborns and children, antibiotics are among the most frequently recommended drugs[1]. The first natural antibiotic in the 20th century was penicillin, discovered by Fleming in 1928. The first β-lactamase inhibitor- clavulanic acid was derived from Streptomyces clavuligerus. The years that followed (1940-1970), are referred to as "the golden era" of antibiotic evolution because of the significant increase in the rate of antibiotic discovery that occurred during this time[1,2]. Since its introduction in the 1970s, amoxicillin has become the most popular penicillin, both alone and in combination with clavulanic acid[3]. Streptomyces clavuligerus was used to isolate the first β-lactamase inhibitor, clavulanic acid. It is referred to as a "suicide inhibitor" because of its ability to inactivate β-lactamase via secondary chemical interactions and complex formation[1,4].

Editor's Comment :

- The amoxicillin/clavulanate combination remains a widely used antibiotic in paediatric outpatient care for various infections, including URTIs, UTIs, AOM and CAP.
- According to the WHO AWaRe classification, amoxicillin/clavulanate is categorized in the "Access group," making it a first or second choice for treating common infections while minimizing antibiotic resistance.
- Its effectiveness in managing resistance and maintaining treatment efficacy in children underscores its ongoing importance in outpatient care.

Amoxicillin/clavulanate is a cornerstone antibiotic in primary care settings and Emergency Departments across the nation. It is a proportionate composite of two different medicines: amoxicillin and clavulanic acid[3]. This combination is used as a broad-spectrum antibiotic for treatment against a variety of bacterial infections as clavulanic acid effectively inhibits the β-lactamase enzyme and enhances the antibacterial activity of amoxicillin[4]. Although amoxicillin and

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ampicillin share the same spectrum of activity and potency, amoxicillin demonstrated superior oral absorption, resulting in a plasma exposure that is almost double that of ampicillin[5,6].

Amoxicillin is an analog of penicillin and exhibits identical activity against gram-negative bacteria and Gram-positive bacteria, including *Salmonella spp, Shigella spp, Borrelia species, Enterococcus species, Corynebacterium diphtheria, Moraxella catarrhalis, Haemophilus influenzae, Listeria monocytogenes, Streptococcus species, Klebsiella pneumoniae* and *Escherichia coli*. Additionally, with the addition of clavulanic acid, the spectrum is widened to cover all the strains of the above-mentioned microorganisms and includes *methicillin-sensitive Staphylococcus aureus (MSSA), Capnocytophaga canimorsus*, *Pasteurella multocida, Proteus species, Neisseria species,* among others[7,8].

Amoxicillin/clavulanate is orally administered to treat Upper Respiratory Tract Infections (URTI), Community-acquired Pneumonia (CAP), Acute Otitis Media (AOM) as well as Urinary Tract Infections (UTIs). Amoxicillin/clavulanate is available in various formulations including multiple-dose formulations for adults and paediatrics in different parts of the World.[6] Oral formulations of this antimicrobial are available as immediate or extended-release tablets, chewable tablets or reconstituted suspensions. Taking it with food improves its absorption and reduces adverse GI symptoms[9-11]. Amoxicillin 250 mg and potassium clavulanate 125 mg strength tablets are not recommended in paediatric patients, due to a higher amount of clavulanate than other strengths[1,3]. The initial ratio for an amoxicillin-clavulanic acid combination, due to clavulanic acid's high affinity for ß-lactamases, was set at 4:1, administered in a three times daily dosage regimen; ratios of 2:1, 7:1, 14:1, and 16:1 are currently available in different countries[12]. To make it more palatable in the paediatric population, oral suspension can be flavored. It is necessary to maintain a consistent amoxicillin-to-clavulanate ratio because clavulanic acid does not require substantial quantities to effectively inhibit ß-lactamase enzymes (Table 1). The reconstituted solution must be stored in the refrigerator and well-shaken prior to use to increase the durability and potency[3,11].

Table 1 — *Ratio of amoxicillin/potassium clavulanate of varying strengths in oral suspension and tablet* [12]

Amoxicillin/ Potassium clavulanate (Oral Suspension)	Amoxicillin/ Potassium clavulanate (Oral Tablet)
• 125 mg /31.25 mg per 5 mL (4:1) • 200 mg /28.5 mg per 5 mL (7:1) • 250 mg /62.5 mg per 5 mL (4:1) • 400 mg /57 mg per 5 mL (7:1) • 600 mg/42.9 mg per 5 mL (14:1) (The extended-release formulation cannot be used in place of other immediate-release strengths).	• 250mg/125 mg (2:1) • 500mg/125mg (4:1) • 875mg/125 mg (7:1) • 200 mg/28.5 mg (chewable) • 400 mg/57 mg (chewable) • 1000mg/62.5mg (The extended-release 12 hr formulation cannot be used in place of other immediate release strengths).

Pharmacokinetics (PK) and Pharmacodynamics (PD) Characteristics of Amoxicillin/Clavulanate:

Amoxicillin/clavulanate both exhibit good oral absorption from the Gastrointestinal tract (about 60% oral bioavailability). Both components ie, amoxicillin and clavulanic acid had similar PK parameters after oral administration and they did not affect the PK parameters of each other[6,13,14]. Following oral ingestion, amoxicillin/clavulanate exhibits a half-life of approximately 1.3 hours for amoxicillin and 1 hour for clavulanate. Both components of the drug have low levels of binding to proteins in the bloodstream, with amoxicillin being bound to serum proteins by around 18% and clavulanate by approximately 25%. Overall, amoxicillin/clavulanate is known to distribute effectively throughout various tissues in the body[6].

Antimicrobial Resistance and Antibiotic Susceptibility of Respiratory Pathogens : Insights from Global Surveillance Studies

Anti-microbial Resistance (AMR) is primarily caused by the improper use of antibiotics by doctors and patients. Drug resistance can be determined with the help of the tripartite interaction between the host, antibiotics and pathogens[15,16]. As per World Health Organization (WHO), AMR is caused by genetic alterations and is accelerated by antibiotic misuse and overuse[17]. *Streptococcus pneumoniae (S pneumoniae*) strains can have "intermediate" or "high" penicillin resistance. *Penicillin-resistant Streptococcus pneumoniae* (PRSP) isolates typically have minimum inhibitory concentrations (MIC) ≥2 to 4 µg/mL; isolates with MICs ≥4 or MIC ≥8 µg/mL are uncommon even though there are regional variations in resistance rates. Paediatric patients who fail to benefit from the initial therapy or who have recently taken antibiotics (within the last two to four weeks) for any other indication frequently have strains of *S pneumonia* with both intermediate and high-level penicillin resistance (PISP/PRSP)[18,19].

The Survey of Antibiotic Resistance (SOAR) during 2012-14 conducted in various regions analyzed respiratory isolates of *H influenzae, M catarrhalis, S pneumoniae* and *S pyogenes*[15,23]. The survey

revealed that amoxicillin/clavulanate demonstrated high susceptibility rates for *M catarrhalis*, *H influenzae*, and pathogens causing CAP (Table 2)[15,23]. Various breakpoints were utilized in the analysis of the new SOAR data including Clinical and Laboratory Standards Institute (CLSI), the dose-specific European Committee on Antimicrobial Susceptibility Testing (EUCAST) and PK/PD breakpoints[24].

A global AMR surveillance program with a fully searchable database is called Antimicrobial Testing Leadership and Surveillance (ATLAS). It covers the susceptibilities of a variety of bacterial and fungal pathogens to various antimicrobials and is available for general access to all. CLSI and EUCAST breakpoints are used to examine ATLAS data. Accessible susceptibility data for India is only available for a limited subset of *S. pneumoniae* isolates from 2019 (n = 11) and *H Influenzae* isolates from 2016 (n = 23) and 2019 (n = 37) (Table 3)[25].

Another SOAR study, conducted by Torumkuney, *et al* in Greece between 2014 and 2016 and published in 2018, (Table 3) concluded that these drugs are ineffective as monotherapy for community-acquired Respiratory Tract Infections due to the high prevalence of macrolide resistance among *S pneumoniae* and clarithromycin's reduced activity against *H influenzae*[26]. Amoxicillin/clavulanate, on the other hand, has shown excellent in vitro activity and is safe for use in paediatric patients, in contrast to equally effective fluoroquinolones[26].

Amoxicillin/clavulanic Acid (AMC); Antimicrobial Testing Leadership and Surveillance (ATLAS); Community-acquired Respiratory Tract Infections (CA-RTI); Clinical and Laboratory Standards Institute (CLSI); European Committee on Antimicrobial Susceptibility Testing (EUCAST); Pharmacokinetic/pharmacodynamic (PK/PD); Survey of Antibiotic Resistance (SOAR); Sulfamethoxazole/trimethoprim (SXT); (% susceptibility is based on CLSI breakpoints).

Uses in Paediatric Outpatient Department (OPD):

Initial dosage strengths for paediatric formulations were 20/5 or 40/10 mg/kg/day in three separate doses[6]. Currently, the recommended paediatric dosage for Mild to Moderate infections is 25/3.6 mg/kg/day divided into two doses, while for severe infections, 45/6.4 mg/kg/day or 90/6.4 mg/kg/day (divided into two doses) is suggested[6,22]. Table 3 presents the indications and dosage regimens for amoxicillin/clavulanate based on guidelines from the US Food and Drug Administration (FDA) and the European Medicines Agency summary of product characteristics (SmPC).

Table 2 — *Comparative description of SOAR and ATLAS study*[23-26]

	SOAR (2012-2014)	SOAR (2014-2016)	ATLAS (2016 and 2019)
Objectives	To provide susceptibility data for CA-RTI pathogens like *S. pneumoniae*, *S. pyogenes*, *H. influenzae*, *M. catarrhalis*	To determine antimicrobial susceptibility in isolates of *S. pneumoniae* and *H. influenzae* in CA-RTI patients	To review the AMR in India and initiatives addressing it. An initiative to minimize further rises in AMR and to improve patient outcomes
Countries	India, Singapore, South Korea, Thailand	Greece	India
Susceptibility assessed	CLSI, EUCAST, PK/PD breakpoints	CLSI, EUCAST, PK/PD breakpoints	CLSI, EUCAST breakpoints
Test Strains	*S. pneumoniae*, *S. pyogenes*, *H. influenzae*, *M. catarrhalis*	*S. pneumoniae and H. influenzae*	Analysis was done based on the data available from *S. pneumoniae*, *H. influenzae* isolates
Antibiotics	AMC, Penicillin, Fluoroquinolones, Macrolides, SXT	Amoxicillin, AMC, Ampicillin, Azithromycin, Cephalosporins, Penicillin, Fluoroquinolones, SXT	Penicillin (oral), Penicillin (IV), Ceftriaxone, Erythromycin, Levofloxacin, AMC, Azithromycin
Results	1. *S. pneumoniae* isolates (*n*=219) AMC- 91.8% (susceptibility) Azithromycin- 66.3% Clarithromycin-54.8% Levofloxacin-85.8% 2. *H. influenzae* isolates (*n*=135) AMC- 97% (susceptibility) Ampicillin-91.1% Clarithromycin- 66.7% SXT-23.0% 3. *M. catarrhalis* AMC- 98.4%	1. *H. influenzae* AMC-100% Ceftriaxone-100% Ampicillin- 84.6% Clarithromycin- 61.5% SXT-71.2% 2. *S. pneumoniae* AMC-94.9% Amoxicillin- 94.9% Azithromycin- 49.5% SXT-83.8%	1. *H. influenzae (n= 23 in 2016), (n=37 in 2019)* AMC-100% (2016) AMC-100% (2019) Azithromycin- 91.9% (2019) Levofloxacin-91.3% (2016) Levofloxacin- 81.1% (2019) 2.*S. pneumoniae (n=11)* was not tested against AMC but for Levofloxacin- 81.8% Erythromycin- 27.3% susceptibility was observed

AMC- amoxicillin/clavulanic acid; ATLAS- antimicrobial testing leadership and surveillance; CA-RTI: community-acquired respiratory tract infections; CLSI- clinical and laboratory standards institute; EUCAST- european committee on antimicrobial susceptibility testing; PK/PD- pharmacokinetic/pharmacodynamic; SOAR- survey of antibiotic resistance; SXT- sulfamethoxazole/trimethoprim; (% susceptibility is based on CLSI breakpoints)

Table 3 — *Summary of product characteristics (SmPC) for amoxicillin/clavulanate, as per US FDA and EMA recommendations*[6]

	US FDA	EMA
Indications	Lower Respiratory tract infections (LRTIs), Otitis media, and Sinusitis are caused by β-lactamase-producing strains of *H. influenzae and M. catarrhalis*	Acute bacterial sinusitis
	Skin and Skin structure infections caused by β-lactamase producing strains of *S. aureus, E. coli, Klebsiella spp.*	Acute Otitis Media
	Urinary Tract Infections caused by β-lactamase producing strains of *E. coli, Klebsiella spp.*, and *Enterobacter spp.*	Acute exacerbations of chronic bronchitis (AECB)
	Acute otitis media due to -*S. pneumoniae* (penicillin MICs ≤ 2 mcg/mL) -*H. influenzae* (including beta-lactamase–producing strains), -or *M. catarrhalis* (including beta-lactamase-producing strains)	Community-acquired pneumonia (CAP)
		Cystitis
		Pyelonephritis
		Skin and Soft Tissue Infections (SSTIs) like cellulitis, animal bites, several dental abscesses with spreading cellulitis
		Bone and joint infection, especially osteomyelitis
Dosage	For children weighing less than 40 kg: • Neonates and infants aged < 12 weeks. Based on the amoxicillin component, 30 mg/kg/day divided q12 hr (125 mg/5 ml suspension is recommended) • Pediatric Patients > 12 weeks and older. For severe infections like otitis media, sinusitis, and lower respiratory tract infections: 45 mg/kg/day divided q12 hr or 40 mg/kg/day divided q8 hr based on the amoxicillin component • Oral Suspension for children weighing less than 40 kgs: 90 mg/kg/day divided every 12 hours, administered for 10 days	For children weighing less than 40 kg: • 20mg/5mg/kg/day to 60mg/15 mg/kg/day is given in three divided doses based on the amoxicillin component
	For children weighing more than 40 kg: • Should be dosed as per adult regimen- -50 mg q12 hr or 250 mg q8 hr -875 mg q12 hr or 500 mg q8 hr for more severe infections	For children weighing more than 40 kg: • Should be dosed as per adult regimen- - 500 mg/125 mg q8 hr -875 mg/125 mg q12 hr -875mg/125 mg q8 hr for more severe infections like otitis media, sinusitis, LRTIs, and UTIs

Nearly half of antibiotics are prescribed in an outpatient setting for the treatment of URTIs, CAP, and AOM, which are common Respiratory Tract Infections as well as UTIs[6,27].

Treatment of Acute Otitis Media (AOM) :

AOM, a common childhood infection, arises commonly following acute URTIs and is the most prevalent reason for paediatric clinic visits and antibiotic prescriptions[20]. Immediate antibiotic therapy is advised for patients under 2 years with bilateral AOM, severe symptoms, spontaneous perforation, or recurrent episodes. In cases of uncertainty, antibiotic treatment may be considered for infants under 2 years with severe symptoms[27-30]. Table 4 lists the antibiotics in accordance with children's age and clinical characteristics. In children with penicillin allergy, macrolides or cephalosporins can be used[27,30].

In severe cases, the approved dose of amoxicillin is 80-90 mg/kg/day. However, for children weighing above 20 kg, this may exceed the typical clinical dose of 1500 mg/day for adults. Therefore, a daily dosage of 1500 mg amoxicillin is considered acceptable for children over 20 kg[20]. In children at low risk of colonization by resistant Streptococcus pneumoniae, 2 doses of amoxicillin alone or amoxicillin/clavulanate are indicated, whereas 3 doses are recommended for children at high risk[27]. The American Academy of Paediatrics & American Academy of Family Physicians (AAP/AAFP) Guidelines recommended high-dose amoxicillin/clavulanate (90/6.4 mg/kg/day in 2 divided doses) as the preferred empirical treatment for AOM (approved 2013, reaffirmed 2019)[19]. Antibiotic treatment is recommended for 10 days in paediatric patients who are susceptible to adverse effects (under 2 years old and/or with spontaneous otorrhea). The duration of therapy can be reduced to 5 days, in children older than 2 years, without the risk of adverse evolution[27].

Treatment of Community-acquired Pneumonia (CAP) :

Community-acquired pneumonia has a high morbidity and mortality rate and is a significant public health problem in India[15]. Based on the limited information available, it was suggested to take the following course of action: Children who have been vaccinated with pneumococcal conjugate vaccine and exhibit mild symptoms, do not require immediate antibiotic treatment, instead close monitoring is advised. The thorough evaluation of clinical, epidemiological, radiological, and laboratory data strongly suggests a viral infection. Therefore, timely evaluation is recommended and a careful follow-up should be ensured. In all other circumstances, antibiotic treatment is still recommended[27,31,32].

Table 4 — *Recommended therapy in children with AOM, UTI, URTI and community-acquired pneumonia*[27,31,32]

Indications	Antibiotic Choice Recommended Treatment	Alternative Treatment
Acute Otitis Media **i) Mild symptoms** No otorrhea No risk factors*	**Amoxicillin** (50 mg/kg/day in 2-3 doses)	**Cefaclor** 40-50 mg/kg/day in 2 doses
ii) Severe symptoms Otorrhea Risk Factors*	**Amoxicillin + Clavulanic acid** (80-90**mg/kg/day in 2-3 doses)	**Cefuroxime axetil** (30 mg/kg/day in 2 doses) **Cefpodoxime proxetil** 8mg/kg/day in 2 doses
Acute Bacterial Rhinosinusitis (ABRS)	**Amoxicillin + clavulanic acid** **Mild**- 45 mg/kg/day in 2 doses **Severe**-90 mg/kg/day in 2 doses	**Amoxicillin :** 90 mg/kg/day in 2 doses **Cefpodoxime :** 10 mg/kg/day in 2 doses **Cefdinir :** 14 mg/kg/day in 1 or 2 doses **Levofloxacin :** 10 to 20 mg/kg/day in 1 or 2 doses
Pharyngitis	**Penicillin V –**250 mg bid or tid **Amoxicillin-** 50 mg/kg once daily	**Benzathine penicillin G (IM)** -750 mg for patients ≥27 kg) -375 mg for patients <27 kg)
UTI	**Amoxicillin/ Clavulanate** 25-45 mg/kg/day **Amoxicillin** 20 to 45 mg/kg/day	**Cefixime** 8 mg/kg/day **Cefpodoxime** 10mg/kg/day **Trimethoprim/Sulfamethoxazole** 8-10 mg/kg/day
Community-Acquired Pneumonia (CAP)- **(i) 1-3 months^**	**Oral Amoxicillin** -50-90 mg/kg/day in 2-3 doses **IV Ampicillin** **Clarithromycin-** -Oral (15mg/kg/day in 2 doses orally) - IV 4-8 mg/kg/day in 2 doses for 10-14 day **Erythromycin** -40 mg/kg/day in 3-4 doses **Azithromycin** oral -10mg/kg/day in 1 dose for 3 days	**Oral Amoxicillin/Clavulanate** (amoxicillin 50-90 mg/kg/day in 2 doses) for 7-10 days **IV Cefotaxime**- 100-150 mg/kg/day in 3 doses **IV Ceftriaxone**-50 mg/kg 1 dose per day **Benzylpenicillin** IV 200,000 U/kg/day in 4-6 doses
(ii) 3 months – 5 years	**Oral amoxicillin or IV Ampicillin** 50-90 mg/kg/day in 2-3 doses for 7-10 days	**Oral Amoxicillin/Clavulanate** (Amoxicillin 50-90 mg/kg/day in 2 doses) for 7-10 days **IV ceftriaxone** (50 mg/kg 1 Time per day) or **IV cefotaxime** (100-150 mg/kg/day in 3 doses) **Cefuroxime axetil** (30 mg/kg/day in 2 doses) **Benzylpenicillin** IV 200,000 U/kg/day in 4-6 doses, Clarithromycin **-Oral** 15mg/kg/day in 2 doses for 10-14 days **-IV** 4-8 mg/kg/day IV in 2 doses or **Oral Azithromycin** 10mg/kg/day in 1 dose for 3 days or **Cephalexin oral, IV Cloxacillin**, **Cefazolin**, and **Vancomycin,** **Erythromycin oral** or IV (40 mg/kg/day in 3-4 doses)
(iii) 5-18 years	**Oral Amoxicillin** or **IV Ampicillin** 50-90 mg/kg/day in 2-3 doses for 7-10 days ***Clarithromycin** Oral- 15mg/kg/day in 2 doses IV 4- 8 mg/kg/day in 2 doses for 10-14 days **Erythromycin**-40 mg/kg/day in 3-4 doses **Oral azithromycin**-10 mg/kg/day in 1 dose for 3 days	**IV Ceftriaxone** 50 mg/kg 1 time per day or **IV Cefotaxime** 100-150 mg/kg/day in 3 doses **Benzylpenicillin IV** 200,000 U/kg/day in 4-6 doses or **Cefalexine** oral or IV **Cloxacillin** or **Cefazoline** or **Vancomycin**

^Treatment with azithromycin, clarithromycin should be recommended in children under 6 weeks old. * In case of suspected infection by Mycoplasma pneumoniae, Chlamydia pneumoniae, or Bordetella pertussis. Staphylococcus aureus is unusual; if pleural fluid culture or haemoculture reveal S. aureus, oxacillin can be added, or vancomycin is advised in areas with methicillin-resistant S. aureus.

*Risk factors for bacterial resistance: age <3 years, daycare attendance, older siblings, and recent antibiotic therapy (<1 month).

** The dosage refers to amoxicillin.

For mild or moderate types, a course of therapy lasting 5-7 days is recommended. A prolonged duration of therapy (8–14 days) should be considered in severe and/or complicated cases and the event of suspected infection with *Mycoplasma pneumoniae*[27,33,34].

Treatment of Upper Respiratory Tract Infections (URTIs) :

URTIs pose significant public health challenges and contribute to both mortality and morbidity in developed and developing countries. In India, URTIs affect a substantial portion of the population, with prevalence rates of approximately 52%[35,36]. URTI includes acute pharyngitis, rhinosinusitis and AOM which are common in children[24]. When treating URTIs, antibiotics with broad-spectrum activity are commonly prescribed to target not only the primary pathogen, such as Pneumococcus, but also other clinically relevant colonizing bacteria like *S aureus, H influenzae*, and *M catarrhalis*. Besides amoxicillin/clavulanate, cephalosporins and macrolides are frequently recommended broad-spectrum antibiotics for treating RTI[36].

The recommended dose of amoxicillin/clavulanate is 875 mg/125 mg taken twice daily, 500 mg/125 mg taken three times daily, or 2000 mg/125 mg taken twice daily along with either doxycycline or macrolide. NICE 2019 guidelines recommend amoxicillin/clavulanate as the initial treatment of choice for severe symptoms for adults and paediatric patients aged more than a month and below 18 years[24,37].

Treatment of Urinary Tract Infections (UTIs) :

UTIs in paediatrics, primarily caused by *E coli* and other *Enterobacteriaceae*, carry the risk of complications and renal scarring[38]. A significant concern to the health of the general population is posed by the rise of extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-E) as a cause of febrile UTI[39-41]. However, recent studies indicate that amoxicillin/clavulanate retains substantial susceptibility against modern Enterobacterales causing UTIs[6].

The study by Beytur et al. suggested that if the causative agent is susceptible, amoxicillin/clavulanate may be effective for ESBL-positive UTIs. However, strains with high amoxicillin/clavulanate MICs may develop resistance during therapy[42]. Another study by Wilkowski, *et al* found that high doses of oral amoxicillin/clavulanate could overcome the resistance of ESBL-producing *K pneumoniae* strains, providing a safe and affordable substitute for carbapenems in specific UTIs[43].

Discussion

Amoxicillin/clavulanate combination remains a commonly used antibiotic in paediatric outpatient settings for various infections, including URTIs, UTIs, AOM and CAP. Despite the availability of other antibiotic options, amoxicillin/clavulanate continues to be recommended as the first-choice treatment for these paediatric infectious diseases. WHO has developed the AWaRe classification to guide antibiotic selection based on their importance in treating common infections while minimizing antibiotic resistance. Amoxicillin/clavulanate falls into the "Access" group, which includes antibiotics recommended as first or second choices for frequent infections, unlike other antibiotics like Azithromycin, Cefixime and Cefuroxime which fall under the "Watch" group. This classification highlights the continued relevance and effectiveness of amoxicillin/clavulanate in paediatric outpatient settings[44].

International and country-specific local antibiotic prescribing guidelines frequently recommend amoxicillin/clavulanate to treat community acquired-RTIs. These recommendations in India are supported by the ATLAS and SOAR susceptibility studies, which demonstrate that *S pneumoniae* and *H influenzae* are still highly susceptible RTI pathogens[24].

While these medications are generally safe and effective, they can sometimes cause adverse effects in children. Two common adverse effects encountered with amoxicillin/clavulanate in paediatric patients are low compliance and diarrhoea. Poor adherence to recommended antibiotic treatment may cause worsening of patients' health or delays in recovery. Additionally, it might cause a rise in hospital admissions and expenses, in addition to the emergence of antibiotic-resistant bacteria[45].

In an Indian Real-World prospective study done by Jaydeep Chaudhary, *et al*, it was found that the production method of amoxicillin impacts the quality of the resulting antibiotic formulation. The study further showed that a biocatalytic or enzymatic method of preparation was found superior and 81.25% of clinicians believed that Good Manufacturing Practices (GMP) played a critical role in the occurrence of gastrointestinal side effects[45]. This study proved that the attributes of the antibiotic depend upon the manufacturing process and can have a direct influence on the antibiotic efficacy, side effects and hence compliance to treatment.

Compliance as we are aware may be affected by the dosage, duration, palatability, formulation, side effects and cost of the medication. Children's medication compliance varies widely, between 11%

to 93%[46-48]. There exists a strong perception among healthcare practitioners that all antibiotic courses must be completed as that would limit the risk of relapse and selection of resistant organisms. A study conducted by Chan, *et al* reported that over 30% of individuals non-adherent to antibiotic therapy showed a high prevalence of antibiotic resistance. In a similar Indian survey, clinicians agreed that non-adherence to oral antibiotic treatment poses a challenge and AMR was reported as a key consequence. It was perceived that a 60 ml dosage (instead of the commonly available 30 ml dosage) of amoxicillin/clavulanate addressed the challenges observed with non-compliance to antibiotic therapy completion[45]. Extended-release formulations of amoxicillin/clavulanate can provide sustained release of the medication over a longer period. This can help reduce fluctuations in drug concentration in the body and minimize GI side effects like diarrhoea. In randomized single-blind studies, twice-daily amoxicillin/clavulanic acid regimens were considerably less likely to cause diarrhoea than three times-daily regimens[11]. Importance of GMP of amoxicillin/clavulanate is crucial for treatment outcomes ie, safety and effectiveness.

In a large non-comparative trial involving children with AOM, the administration of a high-dose formulation of amoxicillin/clavulanate (90/6.4 mg/kg/day in 2 divided doses) demonstrated substantial efficacy against penicillin-resistant *S pneumoniae* strains (with penicillin MICs of 2 or 4 mg/L, surpassing the maximum threshold limit of the US indication for *S pneumoniae* is 2 mg/L)[11]. Amoxicillin and clavulanic acid in sufficient doses are effective against ß-lactamase-positive bacteria as well as susceptible-to-medium-resistant *S pneumoniae*. For these reasons, oral amoxicillin is commonly recommended by clinicians, with or without a β-lactamase inhibitor, unless patients have allergies to penicillin[20]. Dagan, *et al* conducted a study to evaluate the efficacy of a high dosage of amoxicillin/clavulanate (90/6.4 mg/kg/day) in treating AOM. The results demonstrated that this particular formulation was highly effective against *H influenzae*, eliminating the pathogen in 94.0% of patients (78 out of 83) within 4-6 days[22,49].

The clinical use of amoxicillin/clavulanate in UTI is questionable given the increased prevalence of ESBLs Worldwide. Oral cephalosporins such as ceftibuten, cefpodoxime and cefixime are less susceptible to ESBLs and stable to OXA-1 as compared to amoxicillin, making them potential alternatives when used in conjunction with clavulanate for treatment of UTIs. To treat UTIs caused by ESBL-producing *Klebsiella spp and E coli* amoxicillin/clavulanate can be used in conjunction with third-generation oral cephalosporins such as cefpodoxime or ceftibuten[6].

In real-world evidence, physicians prescribe antibiotics based on their knowledge of the disease's pathogenesis, the course of the illness, the responsible pathogens, the severity of the condition, and pharmacological expertise[20].

Conclusion

In conclusion, amoxicillin/clavulanate remains a relevant and valuable antibiotic in the management of paediatric infections in outpatient settings. Its broad-spectrum activity, good PK properties and high susceptibility rates against common respiratory pathogens make it a preferred choice for the therapeutic management of URTIs, AOM, CAP and UTIs in paediatric patients. However, to preserve the effectiveness of antibiotics and prevent the development of antimicrobial resistance, it is crucial to exercise caution in their utilization. This cautious approach helps to safeguard the potency of these medications for future use.

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