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Amoxicillin+clavulanic acid in community acquired pneumonia: Past, present, and future from an Indian perspective

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ABSTRACT

Community acquired pneumonia (CAP) is a major health problem in India with high morbidity and mortality. The threat posed by this infection is further intensified by the continued emergence of resistance to the currently available antibiotics. With a heritage of more than 24 years in India, amoxicillin + clavulanic acid is one of the most common antibiotics used for CAP. It was developed with an intent to sustain the efficacy of amoxicillin which was challenged due to the emergence of the beta-lactamase producing microorganism. Over a period, it has been included in national and international guidelines for the treatment of CAP. To assure the highest probability of clinical cure and to combat development of resistance: It is imperative for amoxicillin + clavulanic acid to reaffirm itself. Optimization of the PK/PD and higher dose of amoxicllin + clavulanic acid will tackle the burden of the future difficult to manage respiratory infections.

Key words: Amoxicillin; Amoxicillin + clavulanic acid; Antimicrobial resistance; Antibiotic resistance; Antimicrobial resistance; CAP; Community acquired pneumonia; Pneumonia

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INTRODUCTION

Community-acquired pneumonia (CAP) is a major health issue worldwide, with increased mortality burden on developing countries.[1] The annual incidence of CAP in India is 4 million cases, out of which 20% require hospitalization. The mortality rate in the intensive care unit is 25%, while in the outpatient setting, it is 1–5%.[2] The morbidity and mortality rates are high due to various factors such as diverse age range, comorbid conditions, patient non-compliance, and diagnostic challenges.[3] The overall success rate in positively identifying the causative pathogen in CAP has been <50%.[4,5]

India contributes nearly 23% of global pneumonia burden and 36% WHO regional burden in patients under 5 years. Cross-sectional studies from tertiary teaching hospitals provide most of the data for adults. A study from Mumbai reported that severe CAP reached 19% of all patients and *Streptococcus pneumoniae* and Gram-negative bacteria (*Pseudomonas aeruginosa* and *Klebsiella pneumoniae*) had increased occurrence in severe pneumonia.[6] The most common bacterial cause of the upper and lower RTIs is *S. pneumoniae*.[7] It accounts for two-thirds of all cases of bacterial pneumonia.[8]

The early administration of antibiotics helps prevent mortality in severe pneumonia.[9] Since timing is an important

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consideration while treating CAP; the initial treatment of CAP is empiric. The selection of antibiotics is an important consideration for the treatment. In a joint consensus of Indian Chest Society (ICS) and the National College of Chest Physicians (NCCP), the regimen recommended for non-ICU, inpatient CAP includes β-lactam antibiotics (cefotaxime, ceftriaxone, or amoxicillin+clavulanic acid) plus a macrolide.[10]

From the late 1960s, antimicrobial resistance in CAP therapy came into existence.[11] Due to alarming increase in antibiotics resistance, combination antibiotic therapies were introduced to achieve a better outcome.[12,13] From the past decade, amoxicillin+clavulanic acid, a broad-spectrum antibiotic, is included in the empirical treatment of CAP. This combination proved to be a potent broad-spectrum antibiotic with a wide coverage of β-lactamase-producing pathogens and a favorable pharmacokinetic/pharmacodynamics (PK/PD) profile.[14] As per a drug utilization study on antibiotics use conducted in India, amoxicillin+clavulanic acid is one of the most prevalent combination antibiotics used for the lower respiratory tract infection in India.[15]

With a heritage of more than two decades in India, amoxicillin+clavulanic acid is one of the most common antibiotics prescribed, primarily for CAP and recommend amoxicillin+clavulanic as first-line therapy for outpatient CAP.[16] Favorable PK/PD profile of amoxicillin+clavulanic acid demonstrated excellent clinical efficacy against a wide range of bacterial infections. The objective of this article is to review the role of amoxicillin+clavulanic acid in the management of CAP patients by exploring its role in the past, present, and future.

PAST: DOSAGE DEVELOPMENT OF AMOXICILLIN+CLAVULANIC ACID BASED ON PK/PD RELATIONSHIP

Amoxicillin: An antibiotic with good oral absorption. The discovery of clavulanic acid, a β-lactamase inhibitor, and its combination with amoxicillin has furthered its clinical application as it can act against organisms that produce β-lactamase enzyme. The adult oral formulation introduced in 1980 in the UK and 1981 in India as clavulanic acid 250 mg/125 mg (2:1), three times daily. This dose achieves maximum concentration in serum (Cmax) of 3.3 mg/L with time (T) > minimum inhibitory concentration (MIC) of 40% dosing interval. For maximum bacteriological efficacy of amoxicillin, a T>MIC of 30–40% of dosing interval is required.[14]

To counteract the increase in pathogen MICs and to maintain T>MIC, an increase in dose unit, dose frequency, and/or improved pharmacokinetics was achieved. In the year 1982 first in Germany and 1986 in the US, amoxicillin+clavulanic acid 500 mg/125 mg (4:1) 3 times daily was registered.[14] The dosage (4:1) achieved Cmax of 7.2 mg/L in 1.5 h, with T>MIC of 43% dosing interval. The formulation showed susceptibility for *Haemophilus influenzae* and *Moraxella catarrhalis*, while Gram-negative and Gram-positive anaerobes were found to be resistant.[14,17] For better action and control against more severe diseases caused by strains that were non-susceptible to penicillin, amoxicillin+clavulanic acid 875 mg/125 mg (7:1), 3 times daily and 1000 mg/125 mg (8:1), 3 times daily regimen doses were introduced.[14,18]

In the year 2003, Jacobs et al., established the Alexander Project involving Africa, East Europe, West Europe, Far East countries, Middle East countries, Latin America, and USA for continuing surveillance to test the susceptibility of isolates of *S. pneumoniae*, *H. influenzae*, *and M. catarrhalis* involved in community-acquired respiratory tract infections (CA-RTI). The study reported amoxicillin+clavulanic acid susceptibility of 95.5%, 98.1%, and 100% for *S. pneumoniae* (n=8882), *H. influenzae* (n=8523), and *M. catarrhalis* (n=874), respectively, based on Clinical and Laboratory Standard Institute (CLSI-formerly NCCLS) guidelines, respectively.[19]

Drug utilization pattern studies were conducted to understand the use of antibiotics for infectious diseases. A study was conducted in outpatient and inpatients of University Hospital in New Delhi. The patients included were taking antibiotics for the upper respiratory tract infections. The most frequently prescribed antibiotics were β-lactams (45.52%) followed by quinolones (26.31%). The study concluded that amoxicillin+clavulanic acid (21.74%) was among widely consumed penicillin.[20] Another similar study showed that the most widely used antibiotic therapy for pediatrics to treat pneumonia was amoxicillin+clavulanic acid.[21,22,23] Although there are currently many new anti-bacterial compounds available, the development of higher dosing regimens and pharmacokinetically-enhanced formulations of amoxicillin+clavulanic acid continues to play an important role in the treatment of a wide range of infections, particularly those of the respiratory tract.

PRESENT SCENARIO OF AMOXICILLIN+CLAVULANIC ACID IN CAP IN INDIA

India reports the highest mortality rate globally for children below 5 years of age due to CAP. For outpatient

cases, it is <5%; it rises to 10% in admitted ward patients and can exceed 30% in patients admitted to intensive care unit.[24,25] The most likely pathogens causing CAP are: *S. pneumoniae*, *H. influenzae*, *Staphylococcus aureus*, *Streptococcus Pyogenes,* and atypical pneumonia pathogens (*Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*).[12,16,25] The pathogens responsible for disease in outpatient population are *atypical pathogens and H. influenzae*, while *S. pneumoniae* remains the highest.[1,16,25,26]

The major driver for antimicrobial resistance (AMR) is the inappropriate use of antibiotics by the consumers and prescribers. The tripartite interaction between pathogens, antibiotics, and the host can help in determination of drug resistance.[27] The WHO suggests that AMR is occurring due to genetic changes and is getting accelerated due to overuse and misuse of antibiotics.[28] Although pneumococcal resistance is prevailing across the globe; however, in India, penicillin-resistant pneumococci remains on the lesser side.[29] MIC of penicillin for pneumococci resistant strains is 2 μg/mL or more. Among various mechanisms of antibiotic resistance, the mechanism of chromosomal mutations through transformation led to penicillin resistance. Considering the resistance of typical pathogen, that is, *S. pneumoniae*; Australia reported first penicillin resistant *S. pneumoniae* (PRSP) in year 1976 and later, reported across the globe.[30] The literature reported PRSP ranges from 4.6% to 50.7% in India for penicillin (oral) based on EUCAST criteria.[31-34] During PRSP development, the most of the penicillin resistant and susceptible *S. pneumoniae* strains were susceptible to carbapenems and fluoroquinolones.[35] *S. pneumoniae* and *H. influenzae* remain among a major cause of various community-acquired respiratory tract infections. The authors reported the high level of resistance against cotrimoxazole for *H. influenzae* (67.3%) and *S. pneumoniae* (81.8%) in Indian school children.[36] A recent review showed mycoplasma being the fastest evolving bacteria with high rate of mutations and has developed resistance to β-lactams, tetracyclines, quinolones, and macrolides.[37]

Chawla et al., conducted a study to evaluate the emerging resistance of *S. pneumoniae*, the author reported a high level of resistance to cotrimoxazole (36%) followed by tetracycline (38%), cefotaxime (30%), penicillin (14%), ciprofloxacin (14%), and erythromycin (14%).[31] Another study conducted to determine the AMR demonstrated similar trends; maximum resistance to cotrimoxazole (66.4%), followed by erythromycin (35.1%), tetracycline (34.3%), and fluoroquinolones (levofloxacin) with 5.2%.[38] Based on the Asian Network for Surveillance of Resistant Pathogens, an increasing trend of anti-microbial resistance is noted to erythromycin of around 73% against *S. pneumoniae*.[39] The amoxicillin+clavulanic acid combination remains one of the first-line antimicrobials as recommended by CDC[40] and shows susceptibility against *S. pneumoniae* with MIC ≤2 mcg/mL.[41] Although amoxicillin+clavulanic acid has been prescribed widely all around the world, it remains susceptible against *S. pneumoniae* and *H. influenzae*. Recommended antibiotics for outpatient settings in CAP (Table 1) based on Guidelines for diagnosis and management of community- and hospital-acquired pneumonia in adults: Joint ICS/NCCP(I) recommendations.[10]

For the inpatient population, the recommended regimen is combination of a β-lactam plus a macrolide (preferred β-lactams include cefotaxime, ceftriaxone, and amoxicillin/clavulanate acid).[10]

As discussed earlier, increased antimicrobial resistance poses a limited choice of antibiotics for severe infections. Survey of antibiotic resistance during 2012–14 monitored respiratory pathogens and antibiotic resistance in the Middle East, Africa, Latin America, Commonwealth of Independent States, and Asia. A total of 1326 respiratory isolates of *S. pneumoniae, S. pyogenes*, *M. catarrhalis, and H. influenzae* (520 from Thailand, 493 from India, 175 from South Korea, and 138 from Singapore) were analyzed, which accounted for 220, 696, and 410 isolates for pediatric, adult, and elderly patients, respectively.[34]

The objective of the survey was to evaluate the susceptibility of community-acquired respiratory tract infection isolates (Table 2). The MIC was determined using gradient strip (E test). MIC susceptibility criteria used were those of CLSI.

S. pneumoniae susceptibility: Intravenous (IV) penicillin (95.4%) followed by amoxicillin+clavulanic acid which demonstrated >90% susceptibility followed by oral

Table 1: Doses of recommended antibiotics for outpatient setting in CAP in adults[10]

Antibiotic	Doses
Amoxicillin	0.5–1 g thrice daily (orally or IV)
Co-amoxiclav	625 mg thrice a day or 1 g twice daily (orally)/1.2 g trice daily (IV)
Azithromycin	500 mg daily (orally or IV)
Ceftriaxone	1–2 g twice daily (IV)
Cefotaxime	1 g thrice daily (IV)
Cefepime	1–2 g 2–3 times a day (IV)
Ceftazidime	2 g thrice daily (IV)
Piperacillin-tazobactam	4.5 g 4 times a day (IV)
Imipenem	0.5–1 g 3–4 times a day (IV)
Meropenem	1 g thrice daily (IV)

Table 2: MIC and susceptibility results based on CLSI breakpoints for *S. pneumoniae, H. influenzae,* and *M. catarrhalis* in India for different antibiotics[34]

Class	*S. pneumoniae* (% susceptibility)	*H. influenza* (% susceptibility)	*M. catarrhalis* (% susceptibility)
Cephalosporins	Cefuroxime (75.2%) Cefpodoxime (67.1%)	Cefixime (97.0%) Cefuroxime (99.3%) Cefpodoxime (97.0%)	Cefuroxime (81.4%)
Penicillin	Penicillin (oral) (49.3%) Pen IV (95.4%) AMC (91.8%)	Ampicillin (91.1%) AMC (97.0%)	AMC (98.4%)
Macrolides	Clarithromycin (54.8%) Erythromycin (57.4%) Azithromycin (66.3%)	Clarithromycin (66.7%) Azithromycin (94.7%)	-
Quinolones	Ofloxacin (77.2%) Levofloxacin (85.8%)	Ciprofloxacin (76.3%) Ofloxacin (80.7%) Levofloxacin (85.2%)	Ciprofloxacin Levofloxacin
Other	SXT (32.9%)	SXT (23.0%)	-

AMC: Amoxicillin+clavulanic acid, SXT: Cotrimoxazole, *S. pneumonia*: *Streptococcus pneumonia*, *H. influenza*: *Haemophilus influenzae*, *M. catarrhalis*: *Moraxella catarrhalis*

penicillin (49.3%). *S. pyogenes* isolates showed 100% susceptibility to most of the commonly prescribed antibiotics. Amoxicillin+clavulanic presented maximum susceptibility of 98.4% for *M. catarrhalis*. For all *H. influenzae* isolates, susceptibility to amoxicillin+clavulanic acid was >95.0%. Overall, the survey reports susceptibility of amoxicillin+clavulanic acid between 93% and 100% for pathogens responsible for CAP.[34]

Another study also analyzed the antibiotic susceptibility pattern of *S. pneumoniae* isolates mostly from cases of CA-RTI, collected from different hospitals in Thanjavur, South India. A total of 105 isolates of S. *pneumoniae* were recovered from January 2014 till June 2014. Table 3 shows MIC and susceptibility results for *S. pneumoniae* for different antibiotics. The results of MIC concluded that amoxicillin+clavulanic acid demonstrated 100% susceptibility (MIC<0.5–0.25).[42]

Government of India launched a "National Program on Containment of Antimicrobial Resistance" of 5-year plan with an objective to establish AMR surveillance system to generate quality data on AMR.[43] Indian council of medical research (ICMR) collected data on commonly prescribed antibiotics from eminent physicians and clinical microbiologists across the country. The guidelines recommend amoxicillin+clavulanic acid; first-line therapy for outpatient CAP with/without comorbidities as the pneumococcal resistance in non-meningeal isolates is low in India. The rationale behind the combination therapy is to increase the spectrum, act against atypical pathogens, and decrease mortality.[16] ICS and NCCP recommended β-lactam (cefotaxime, ceftriaxone, or amoxicillin+clavulanic acid) plus a macrolide for CAP.[41] As per international guidelines, the empiric treatment includes combination therapy of amoxicillin+clavulanic and macrolides for outpatient

Table 3: Susceptibility results for *Streptococcus pneumoniae* for different antibiotics based on E-Test method[42]

Antibiotics	n	Susceptible (%)
Amoxicillin+clavulanic acid	105	100
Ceftriaxone	105	100
Penicillin (Oral)	85	80.9
Erythromycin	58	55.2
Ciprofloxacin	89	84.7

adults of CAP with comorbidities.[44] In 2015, Kotwani et al., listed amoxicillin+clavulanic antibiotic combination to be the most commonly used among the β-lactams Penicillin group, for treating CAP.[45]

To what started to be a 2:1 ratio of amoxicillin to clavulanic acid, amoxicillin concentration has been increased to 4:1, then to 7:1 for more potent antimicrobial and better pharmacokinetic activity for severe infections and for treating resistant strains.[46] Amoxicillin+clavulanic acid dose ratios like 4:1 and 7:1 are available in adult and pediatric suspension.[47] The combination (7:1) was designed to improve convenience and compliance to change the therapy from thrice daily to twice daily and combination is advisable to children aged 2 months and above. The efficacy of many oral drugs has reduced due to drug resistant *S. pneumoniae* isolates. To deal with the issues, pharmacokinetically enhanced formulations of amoxicillin+clavulanic acid was developed as amoxicillin+clavulanic acid extended release (ES) and sustained release.[47,48]

To simplify the treatment and reduce the volume, amoxicillin+clavulanic acid ES, also known as high-dose pediatric formulation, is recommended to overcome the infections caused due to PRSP and designed with high doses of amoxicillin.[47] The ES formulation provides

serum concentrations >4 μg/mL (>40% of the dosing interval).[49] The combination is available in different doses and formulation in India for various age groups. Table 4 presents the dosages and formulations for different age groups in the lower respiratory tract infections (LRTI).[50-53]

The combination has been prescribed since late 1980s in different dosages and formulations globally. A worldwide survey of clinical experience of combination was conducted by Croydon in 1989 with 9700 patients. The clinical trials reported highest incidence (13.1%) of gastrointestinal events where diarrhea was among most common with an incidence rate of 4.1% followed by nausea (3.0%) and vomiting (1.8%). There are some other adverse reactions reported with amoxicillin+clavulancic acid such as mucocutaneous candidiasis, dizziness, headache, skin rash, urticaria, and a moderate rise in AST and/or ALT.[54] The safety is evaluated and reviewed time to time. The largest review including 32,440 patients revealed a case fatality of 44 patients, however, not related to amoxicillin+clavulanic acid. The most common adverse event reported with an incidence of 8.4% in gastrointestinal system organ class; diarrhea (3.4%) is the most common.[14,50-52] In another meta-analysis including 45 studies involving amoxicillin+clavulanic and amoxicillin with various therapeutic indications demonstrated maximum incidence of diarrhea with amoxicillin+clavulanic acid.[55] Despite increasing dose of amoxicillin in the combination, the drug still holds a better safety profile from its existence to date in the market. Amidst this background, amoxicillin+clavulanic acid has secured an exemplary place. In our opinion, amoxicillin+clavulanic acid has potential to remain an agent of choice for CAP in India as per recently revised guidelines.[16]

FUTURE OF AMOXICILLIN+CLAVULANIC ACID

In the present review, we have discussed most common typical and atypical pathogens causing CAP and the recommended treatment options. The atypical pathogens responsible for CAP such as mycoplasma, chlamydia, and legionella contributed to 30–40% disease burden across the globe.[56] The resistance against these organisms along with unresolved challenges of diagnosis and treatment poses future risk on the health-care system and the disease outcome.[57] As per the WHO surveillance report, non-susceptibility to penicillin has been detected in all WHO regions.[58] Globally, the resistance against macrolides had increased since 2000 with emergence in parts of Asia.[59] The development of resistance among macrolides in *S. pneumoniae* is due to methylation of ribosomal macrolide target sites and drug efflux.[60]

Further, antibiotic resistance is a multifaceted issue, and factors such as self-medication, absence of diagnostic tools, over-the-counter use, inadequate storage, or even use of expired drugs contribute to the prevalence.[61] There is an increasing trend in resistance to both first line and broad spectrum-antibiotics. In a recent study conducted in India to assess the pattern of antibiotic resistance in CAP patients (165 respiratory isolates). The study reported that amoxicillin+clavulanic acid and levofloxacin were effective against *S. pneumoniae* with ~20% resistance. The resistance against *H. influenzae* was reported to be 6%, 13%, and 23% in cefuroxime, azithromycin, and amoxicillin+clavulanic acid, respectively. The incidence of β-lactamase production has been reported in 20–35% of the isolates of H. influenzae.[2]

Antimicrobial stewardship is defined as a set of coordinated interventions designed to measure and improve the appropriate use of antibiotics by promoting the selection of the optimal choice, dose, duration, and route of the antibiotic which, in turn, lead to improved patient outcomes and decreased adverse effects. ICMR 2019 guidelines focus on steps of rational antibiotic use as mentioned in Table 5.[62]

As discussed earlier in this review, the antibiotics are the mainstay of the treatment of CAP; however, the challenges for a successful outcome are early diagnosis

Table 4: Amoxicillin+clavulanic acid different dosages and formulations in India

	Dosage and Formulation (Children less than 12 Years)	Dosage and Formulation (Adults and Children over 12 years)	Indication
Amoxicillin + clavulanic acid	• 5 mL twice daily; dry drug solution suspension • 30 mg/kg eight hourly; Intravenous (I.V.) injection	• One tablet 3 times a day; 375 mg Tablet for mild-moderate infections • Two Tablet 3 times a day; 375 mg Tablet for severe infections • 1.2 g 8 hourly; I.V. injection • One tablet twice daily; 625 mg for mild-moderate infections • One tablet thrice daily; 625 mg for severe infection	• Pneumonia • Upper Respiratory Tract Infections • Genitourinary tract infections • Skin and soft-tissue infections • Bone and joint infections • Dental infections

Table 5: Steps of rational antibiotic use (2019 ICMR guidelines on antimicrobial use)[62]

Steps	Description
Step 1	Making a clinical diagnosis
Step 2	Limiting empiric antibiotic therapy to genuine seriously ill patients
Step 3	Know your bugs
Step 4	Choose the appropriate antibiotic
Step 5	De-escalation/modification
Step 6	Stop antibiotics in the following clinical situations
Step 7	Reduce the duration of therapy
Step 8	Optimize PK-PD parameters

The table has been adapted from ICMR-AMSP guidelines. AMR: Antimicrobial resistance, DDD: Defined daily dose, DOT: days of therapy, VAP: Ventilator-associated pneumonia, CME: Continuing medical education, AMS: Antimicrobial stewardship, AMSP: Antimicrobial stewardship program, HCP: Health-care professionals. Source: ICMR-AMSP guidelinehttp://iamrsn.icmr.org.in/images/pdf/AMSP_Guidelines_final.pdf

and start of appropriate medical management. The resistance to amoxicillin+clavulanic acid, although not quantified, might be the due presence of alternate classes of β lactamases (B, C, and D) that are not susceptible to the inhibitory action of amoxicillin+clavulanic acid and any modification of the protein target of amoxicillin resulting in decreased affinity and therefore reduced response.[63]

Further, the development and better understanding of PK/PD characteristics led to optimum dosing regimens and to combat the AMR. The β lactam antibiotics exhibit time-dependent killing without persistent effects. Hence, to maintain the serum drug concentration above MIC for at least 40–50% of dose interval can successfully kill the pathogens. The studies demonstrated that among β-lactams amoxicillin+clavulanic acid, high dose (14:1) achieves MIC ≥40% of dosing interval against PRSP.[64] Second, the researchers focused on eradication of pathogens rather than an outcome of clinical cure as a parameter of efficacy of antibacterial agents and a step further to prevent the AMR.[35] In this era of AMR, based on PK/PD parameters and susceptibility data, it is crucial to choose an antimicrobial agent against CAP infections. Optimization of the dose of amoxicillin+clavulanic acid based on PK/PD to maximize bacterial eradication promises the highest probability of clinical cure and it may reduce the development and spread of resistance.[65-67] For majority of oral formulations, the unit dose of clavulanate has remained as 125 mg and 3.2 mg/kg for pediatrics (250–375 mg and 6.4–10 mg/kg daily dose). This strength is adequate to inhibit the clinically relevant target β-lactamases and to protect the amoxicillin component.[68] The researchers reported a good lung penetration of the combination and the amoxicillin achieves enough concentration in lung mucosa to inhibit CAP pathogens.[69]

To increase convenience and patient compliance over thrice a day regimen, twice daily formulations of 500/125 mg and 875/125 mg regimens are available with T>MIC of 26%.[70] As discussed earlier in this review that PRSP is increasing progressively and to maximize the elimination of PRSP and to increase the efficacy, a target T>MIC of >40% was set. To achieve the desired T>MIC values, few factors were considered:

1. Increase in the dose of amoxicillin+clavulanic acid
2. Increase in peak plasma concentration
3. Improvement in PK.

Community-acquired respiratory tract infections and reduction of susceptibility against key antibiotics posed a significant challenge in the treatment of CAP. In addition, the above-mentioned factors could lead to an increase in adverse events if the dose of amoxicillin+clavulanic acid was increased. To overcome these problems, bilayer tablet was introduced, which had one layer of immediate releasing amoxicillin/clavulanate (562.5 mg amoxicillin and 62.5 mg clavulanate) and another layer of sustained-release amoxicillin (437.5 mg amoxicillin).[70] This pharmacokinetically enhanced, ES, high-dose adult 2000/125 mg (16:1) twice daily formulation has been developed to permit coverage of more bacterial strains as compared to conventional dosing. It is available in US, some EU countries and India for the treatment of CAP, acute bacterial sinusitis, or acute exacerbation of chronic bronchitis due to β-lactamase-producing bacteria (e.g., *H. influenzae* or *M. catarrhalis*) and could be useful in CAP management in India.[71,72] The recommended dose of ES formulation of amoxicillin+clavulanic acid is 90/6.4 mg/kg/day especially in PRSPs. A study conducted by Prabhudesai et al., assessed the efficacy and safety of ES amoxicillin+clavulanic acid in patients with CAP in India. At the end of the study, ES amoxicillin+clavulanic acid showed 97.16% success rate for *S. pneumoniae* and only 13% patients reported at least one adverse event; diarrhea was most frequent AE. No deaths were reported on, and after therapy and ES amoxicillin/clavulanate was found to be safe.[73]

There has been the introduction of drugs in empirical treatment of resistant TB that acts on other bacteria and shows favorable results. Amoxicillin+clavulanic acid, which remained on TB reserve drug lists (by the WHO), has shown potential *in vitro* and *in vivo* effectiveness in resistant TB.[74] The efficacy is further proven by a team of researchers in Indian Institute of Science. They found that TB bacterium, when comes to proximity with amoxicillin+clavulanic acid, produces sub-lethal amount of reactive oxygen species (ROS), and by increasing the ROS levels, this resistance can be overcome.[75]

The benefit-risk assessment of amoxicillin+clavulanic acid continues to be favorable, provided official guidelines on appropriate use of antibacterial agents are followed, and consideration is given to the local prevalence of resistance. During the period under review, no withdrawal, revocation, rejection, suspension, or failure to obtain a renewal of a marketing authorization due to safety concerns was reported.

CONCLUSION

If the crises of increasing AMR and scanting antibiotic pipeline continue unabated, we must deal with increased mortality rates due to severe infections. Researchers are focusing to reappraise the impact and sustainability of existing antibiotics and exploring their role in patient lives. Amoxicillin+clavulanic acid drug molecule continues to provide opportunities for the future modifications that may provide more efficacious and well tolerated safe compounds. Optimization of ratio and dose of amoxicillin+clavulanic acid based on PK/PD characteristics, it remained a pioneer in tackling a wide range of infections, particularly those of the respiratory tract in both adults and children worldwide. With a heritage of more than 24 years in India, amoxicillin+clavulanic acid is one of the most common antibiotics prescribed, primarily for respiratory tract infections. The combination still preserved its place as first line therapy for outpatient CAP with maintaining high sensitivity among pathogens responsible for the disease. To assure the highest probability of clinical cure and to combat development of resistance, it is imperative for amoxicillin+clavulanic acid to reiterate itself.

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REFERENCES

1. Peto L, Nadjm B, Horby P, Ngan TT, van Doorn R, Van Kinh N, et al. The bacterial aetiology of adult community-acquired pneumonia in Asia: A systematic review. Trans R Soc Trop Med Hyg. 2014;108(6):326-337.
   https://doi.org/10.1093/trstmh/tru058
2. Prasad P and Bhat S. Clinicomicrobiological study of community-acquired pneumonia. Lung India. 2017;34(5):491-492.
   https://doi.org/10.4103/lungindia.lungindia_89_17
3. Rodrigues CM and Groves H. Community-acquired pneumonia in children: The challenges of microbiological diagnosis. J Clin Microbiol. 2018;56(3):e01318-17.
   https://doi.org/10.1128/JCM.01318-17
4. Shah BA, Singh G, Naik MA, Dhobi GN. Bacteriological and clinical profile of Community acquired pneumonia in hospitalized patients. Lung India. 2010;27(2):54-57.
   https://doi.org/10.4103/0970-2113.63606
5. Acharya VK, Padyana M, Unnikrishnan B, Anand R, Acharya PR and Juneja DY. Microbiological profile and drug sensitivity pattern among community acquired pneumonia patients in tertiary care centre in Mangalore, Coastal Karnataka, India. J Clin Diagn Res. 2014;8(6):MC04-MC06.
   https://doi.org/10.7860/JCDR/2014/7426.4446
6. Eshwara VK, Mukhopadhyay C and Rello J. Community-acquired bacterial pneumonia in adults: An update. Indian J Med Res. 2020;151(4):287-302.
   https://doi.org/10.4103/ijmr.IJMR_1678_19
7. Lim WS, Macfarlane JT, Boswell TC, Harrison TG, Rose D, Leinonen M, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: Implications for management guidelines. Thorax. 2001;56(4):296-301.
   https://doi.org/10.1136/thorax.56.4.296
8. Bartlett JG, Dowell SF, Mandell LA, File TM Jr., Musher DM, and Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Clin Infect Dis. 2000;31(2):347-382.
   https://doi.org/10.1086/313954
9. Khilnani GC, Zirpe K, Hadda V, Mehta Y, Madan K, Kulkarni A, et al. Guidelines for antibiotic prescription in intensive care unit. Indian J Crit Care Med. 2019;23(Suppl 1):S1-S63.
   https://doi.org/10.5005/jp-journals-10071-23101
10. Gupta D, Agarwal R, Aggarwal AN, Singh N, Mishra N, Khilnani GC, et al. Guidelines for diagnosis and management of community and hospital-acquired pneumonia in adults: Joint ICS/NCCP(I) recommendations. Lung India. 2012;29(Suppl 2):S27-S62.
   https://doi.org/10.4103/0970-2113.99248
11. Ventola CL. The antibiotic resistance crisis: Part 1: Causes and threats. PT. 2015;40(4):277-283.
12. Lutfiyya MN, Henley E, Chang LF and Reyburn SW. Diagnosis and treatment of community-acquired pneumonia. Am Fam Physician. 2006;73(3):442-450.
13. Caballero J and Rello J. Combination antibiotic therapy for community-acquired pneumonia. Ann Intensive Care. 2011;1:48-48.
   https://doi.org/10.1186/2110-5820-1-48
14. White AR, Kaye C, Poupard J, Pypstra R, Woodnutt G and Wynne B. Augmentin (amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: A review of the continuing development of an innovative antimicrobial agent. J Antimicrob Chemother. 2004;53 Suppl 1:i3-20.
   https://doi.org/10.1093/jac/dkh050
15. Naik HG, Khanwelkar CC, Kolur A, Desai R and Gidamudi S. Drug utilization study on antibiotics use in lower respiratory tract infection. Natl J Med Res. 2013;3:334-327.
16. Indian Council of Medical Research ND. Treatment Guidelines for Antimicrobial Use in Common Syndromes. Indian Council of Medical Research ND; 2019.
17. Agency European Commission. Revision 2. A guideline on the

Summary of Product Characteristics. Enterprise and industry directorate general. September 2009

18. Klein JO. Amoxicillin/clavulanate for infections in infants and children: past, present, and future. Pediatr Infect Dis J. 2003;22(Suppl 8):S139-S148.
https://doi.org/10.1097/00006454-200308001-00005
19. Jacobs MR, Felmingham D, Appelbaum PC, Grüneberg RN and Alexander Project Group. The Alexander Project 1998-2000: Susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. J Antimicrob Chemother. 2003;52(2):229-246.
https://doi.org/10.1093/jac/dkg321
20. Ain MR, Shahzad N, Aqil M, Alam MS and Khanam R. Drug utilization pattern of antibacterials used in ear, nose and throat outpatient and inpatient departments of a university hospital at New Delhi, India. J Pharm Bioallied Sci. 2010;2(1):8-12.
https://doi.org/10.4103/0975-7406.62695
21. Laxminarayan R and Chaudhury RR. Antibiotic resistance in India: Drivers and opportunities for action. PLoS Med. 2016;13(3):e1001974.
https://doi.org/10.1371/journal.pmed.1001974
22. Kotwani A and Holloway K. Trends in antibiotic use among outpatients in New Delhi, India. BMC Infect Dis. 2011;11:99-99.
https://doi.org/10.1186/1471-2334-11-99
23. Don D, Luise D, Da Dalt L and Giaquinto C. Treatment of community-acquired pneumonia: Are all countries treating children in the same way? A literature reviews. Int J Pediatr. 2017;2017:4239268.
https://doi.org/10.1155/2017/4239268
24. Yadav KK and Awasthi S. The current status of community-acquired pneumonia management and prevention in children under 5 years of age in India: A review. Ther Adv Infect Dis. 2016;3(3-4):83-97.
https://doi.org/10.1177/2049936116652326
25. Para RA, Fomda BA, Jan RA, Shah S and Koul PA. Microbial etiology in hospitalized North Indian adults with community-acquired pneumonia. Lung India. 2018;35(2):108-115.
https://doi.org/10.4103/lungindia.lungindia_288_17
26. Watkins RR and Lemonovich TL. Diagnosis and management of community-acquired pneumonia in adults. Am Fam Physician. 2011;83(11):1299-306.
27. Nuermberger EL and Bishai WR. Antibiotic resistance in *Streptococcus pneumoniae*: What does the future hold? Clin Infect Dis. 2004;38(Suppl 4):S363-S371.
https://doi.org/10.1086/382696
28. Antimicrobial Resistance; 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance [Last accessed on 2019 Oct 24].
29. Lalitha MK, Pai R and Manoharan A. Multidrug-resistant *Streptococcus pneumonia* from India. Lancet. 2002;359(9304):445.
https://doi.org/10.1016/S0140-6736(02)07578-5
30. Chenoweth CE, Saint S, Martinez F, Lynch JP 3rd, Fendrick AM. Antimicrobial resistance in *Streptococcus pneumoniae*: Implications for patients with community-acquired pneumonia. Mayo Clin Proc. 2000;75(11):1161-1168.
https://doi.org/10.4065/75.11.1161
31. Chawla K, Gurung B, Mukhopadhyay V and Bairy I. Reporting emerging resistance of *Streptococcus pneumoniae* from India. J Glob Infect Dis. 2010;2(1):10-14.
https://doi.org/10.4103/0974-777X.59245
32. Goyal R, Singh NP, Kaur M and Talwar V. Antimicrobial resistance in invasive and colonising *Streptococcus pneumoniae* in North India. Indian J Med Microbiol. 2007;25(3):256-259.
https://doi.org/10.1016/S0255-0857(21)02117-4
33. Verghese VP, Veeraraghavan B, Jayaraman R, Varghese R, Neeravi A, Jayaraman Y, et al. Increasing incidence of penicillin- and cefotaxime-resistant *Streptococcus pneumoniae* causing meningitis in India: Time for revision of treatment guidelines? Indian J Med Microbiol. 2017;35(2):228-236.
https://doi.org/10.4103/ijmm.IJMM_17_124
34. Torumkuney D, Chaiwarith R, Reechaipichitkul W, Malatham K, Chareonphaibul V, Rodrigues C, et al. Results from the survey of antibiotic resistance (SOAR) 2012-14 in Thailand, India, South Korea and Singapore. J Antimicrob Chemother. 2016;71(Suppl 1):i3-i19.
https://doi.org/10.1093/jac/dkw073
35. Garau J. Why do we need to eradicate pathogens in respiratory tract infections? Int J Infect Dis. 2003;7(Suppl 1):S5-S12.
https://doi.org/10.1016/S1201-9712(03)90065-8
36. Jain A, Kumar P and Awasthi S. High nasopharyngeal carriage of drug resistant *Streptococcus pneumoniae* and *Haemophilus influenzae* in North Indian schoolchildren. Trop Med Int Health. 2005;10(3):234-239.
https://doi.org/10.1111/j.1365-3156.2004.01379.x
37. Yatoo I, Parray OR, Bhat RA, Muheet, Gopalakrishnan A, Saxena A, et al. Emerging antibiotic resistance in mycoplasma microorganisms, designing effective and novel drugs/therapeutic targets: Current knowledge and futuristic prospects. J Pure Appl Microbiol. 2019;13(1):27-44.
https://doi.org/10.22207/JPAM.13.1.03
38. Peela S, Sistla S, Tamilarasu K, Krishnamurthy S and Adhisivam B. Antimicrobial resistance in clinical isolates of *Streptococcus pneumoniae*: Mechanisms and association with serotype patterns. J Clin Diagn Res. 2018;12:DC17-DC21.
https://doi.org/10.7860/JCDR/2018/37414.12287
39. Kim SH, Song JH, Chung DR, Thamlikitkul V, Yang Y, Wang H, et al. Changing trends in antimicrobial resistance and serotypes of *Streptococcus pneumoniae* isolates in Asian countries: An Asian network for surveillance of resistant pathogens (ANSORP) study. Antimicrob Agents Chemother. 2012;56(3):1418-1426.
https://doi.org/10.1128/AAC.05658-11
40. Menon R, George A and Menon U. Etiology and anti-microbial sensitivity of organisms causing community acquired pneumonia: A single hospital study. J Fam Med Prim Care. 2013;2(3):244-249.
https://doi.org/10.4103/2249-4863.120728
41. Augmentin: Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050575s037s50597s044050725s025050726s019lbl.pdf [Last accessed on 2019 Oct 24].
42. Nivas RK and Boominathan M. Antibiotic susceptibility pattern of *Streptococcus pneumoniae* in South India by using e-test techniques. Int J Sci Res. 2015;4(2):2326-2328.
43. National Programme on Containment of Anti-Microbial Resistance; 2018. Available from: https://ncdc.gov.in/index1.php?lang=1&level=2&sublinkid=384&lid=344 [Last accessed on 2019 Nov 05].
44. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infectious diseases society of America. Am J Respir Crit Care Med. 2019;200(7):e45-e67.
https://doi.org/10.1164/rccm.201908-1581ST

45. Kotwani A, Kumar S, Swain PK, Suri JC and Gaur SN. Antimicrobial drug prescribing patterns for community-acquired pneumonia in hospitalized patients: A retrospective pilot study from New Delhi, India. Indian J Pharmacol. 2015;47(4):375-382. https://doi.org/10.4103/0253-7613.161258
46. Navarro AS. New formulations of amoxicillin/clavulanic acid: A pharmacokinetic and pharmacodynamic review. Clin Pharmacokinet. 2005;44(11):1097-115. https://doi.org/10.2165/00003088-200544110-00001
47. Behre U, Burrow HM, Quinn P, Cree F and Harrison HE. Efficacy of twice daily dosing of amoxycillin/clavulanate in acute otitis media in children. Infection 1997;25:163-6.
48. Odenholt I, Cars O and Lowdin E. Pharmacodynamic studies of amoxicillin against Streptococcus pneumoniae: Comparison of a new pharmacokinetically enhanced formulation (2000 mg twice daily) with standard dosage regimens. J Antimicrob Chemother. 2004;54(6):1062-1066. https://doi.org/10.1093/jac/dkh484
49. Piglansky L, Leibovitz E, Raiz S, Greenberg D, Press J, Leiberman A, et al. Bacteriologic and clinical efficacy of high dose amoxicillin for therapy of acute otitis media in children. Pediatr Infect Dis J. 2003;22(5):405-413. https://doi.org/10.1097/01.inf.0000065688.21336.fa
50. GSK Pharmaceuticals. AUGMENTIN 375. Adapted from Augmentin Oral GDS 26 and Augmentin TID Tablets and Suspension IPI 16 dated 13 June 2019. AUG-375/PI/IN/2019/02. Revised 14th October 2019. Accessed Nov 2020.
51. GSK Pharmaceuticals. AUGMENTIN XR. AUG-TAB/PI/IN/2018/02 NDA 50-785/S-007.10 Sep 2018. Accessed Nov 2020.
52. GSK Pharmaceuticals. AUGMENTIN INTRAVENOUS. AUG-IV/PI/IN/2017/03 12-Dec-2017. Revised 7th November 2017. Accessed Nov 2020.
53. GSK Pharmaceuticals. AUGMENTIN DDS. AUG-DDS/PI/IN/2018/01 29 October 2018. Accessed Nov 2020.
54. GSK Pharmaceuticals. AUGMENTIN 625/1g DUO Prescribing Information. Version: AUG-TAB/PI/IN/2019/02. NDA 50-726/S-019. Accessed Nov 2020.
55. Gillies M, Ranakusuma A, Hoffmann T, Thorning S, McGuire T, Glasziou P, *et al*. Common harms from amoxicillin: A systematic review and meta-analysis of randomized placebo-controlled trials for any indication. CMAJ. 2015;187(1):E21-E31. https://doi.org/10.1503/cmaj.140848
56. Thibodeau KP and Viera AJ. Atypical pathogens and challenges in community-acquired pneumonia. Am Fam Physician. 2004;69(7):1699-706.
57. Kang J. Challenges from atypical pathogens in diagnosis and treatment of community-acquired pneumonia. Community Acquired Infection. 2015;2(2):29-31. https://doi.org/10.4103/2225-6482.159216
58. World Health Organization. Antimicrobial Resistance Report on Global Surveillance Geneva: World Health Organization; 2014. Available from: https://www.who.int/antimicrobial-resistance/publications/AMR_report_Web_slide_set.pdf?ua=1 [Last accessed on 2020 Aug 06].
59. Wunderink RG and Yin Y. Antibiotic resistance in community acquired pneumonia pathogens. Semin Respir Crit Care Med. 2016;37(6):829-838. https://doi.org/10.1055/s-0036-1593753
60. Nayar S, Hasan A, Waghray P, Ramananthan S, Ahdal J and Jain R. Management of community-acquired bacterial pneumonia in adults: Limitations of current antibiotics and future therapies. Lung India. 2019;36(6):525-533. https://doi.org/10.4103/lungindia.lungindia_38_19
61. Mamishi S, Moradkhani S, Mahmoudi S, Hosseinpour-Sadeghi R and Pourakbari B. Penicillin-resistant trend of *Streptococcus pneumoniae* in Asia: A systematic review. Iran J Microbiol. 2014;6(4):198-210.
62. Treatment Guidelines for Antimicrobial Use in Common Syndromes 2019. Indian Council of Medical Research (ICMR); 2019. https://www.icmr.nic.in/sites/default/files/guidelines/Treatment_ guidelines_2019_final.pdf. [Last accessed on Nov 2020]
63. Sandoz. Co-Amoxiclav 500/125 mg Tablets Prescription only Medicine. Available from: https://www.medicines.org.uk/emc/product/6544/smpc [Last accessed on 2019 Oct 31].
64. Craig WA. Overview of newer antimicrobial formulations for overcoming pneumococcal resistance. Am J Med. 2004;117(Suppl 3A):16S-22S. https://doi.org/10.1016/j.amjmed.2004.07.004
65. Dagan R, Klugman K, Craig WA and Baquero F. Evidence to support the rationale that bacterial eradication in respiratory tract infection is an important aim of antimicrobial therapy. J Antimicrob Chemother. 2001;47(2):129-140. https://doi.org/10.1093/jac/47.2.129
66. Cars O. The hidden impact of antibacterial resistance in respiratory tract infection. Steering an appropriate course: Principles to guide antibiotic choice. Respir Med. 2001;95(Suppl A):S20-S25; discussion S26-S27. https://doi.org/10.1016/S0954-6111(01)90024-1
67. Ball P, Baquero F, Cars O, File T, Garau J, Klugman K, et al. Antibiotic therapy of community respiratory tract infections: strategies for optimal outcomes and minimized resistance emergence. J Antimicrob Chemother. 2002;49(1):31-40. https://doi.org/10.1093/jac/49.1.31
68. Cooper CE, Slocombe B and White AR. Effect of low concentrations of clavulanic acid on the *in-vitro* activity of amoxycillin against beta-lactamase-producing *Branhamella catarrhalis* and *Haemophilus influenzae*. J Antimicrob Chemother. 1990;26(3):371-380. https://doi.org/10.1093/jac/26.3.371
69. Gould IM, Harvey G, Golder D, Reid TM, Watt SJ, Friend JA, Legge JS, et al. Penetration of amoxycillin/clavulanic acid into bronchial mucosa with different dosing regimens. Thorax. 1994;49(10):999-1001. https://doi.org/10.1136/thx.49.10.999
70. Jacobs MR. Building in efficacy: Developing solutions to combat drug-resistant *S. pneumoniae*. Clin Microbiol Infect. 2004;10(Suppl 2):18-27. https://doi.org/10.1111/j.1470-9465.2004.00862.x
71. Sethi S, Breton J and Wynne B. Efficacy and safety of pharmacokinetically enhanced amoxicillin-clavulanic acid at 2,000/125 milligrams twice daily for 5 days versus amoxicillin-clavulanic acid at 875/125 milligrams twice daily for 7 days in the treatment of acute exacerbations of chronic bronchitis. Antimicrob Agents Chemother. 2005;49(1):153-160. https://doi.org/10.1128/AAC.49.1.153-160.2005
72. File TM Jr., Lode H, Kurz H, Kozak R, Xie H, Berkowitz E, et al. Double-blind, randomized study of the efficacy and safety of oral pharmacokinetically enhanced amoxicillin-clavulanic acid (2,000/125 milligrams) versus those of amoxicillin-clavulanic acid (875/125 milligrams), both given twice daily for 7 days, in treatment of bacterial community-acquired pneumonia in adults. Antimicrob Agents Chemother. 2004;48(9):3323-3331. https://doi.org/10.1128/AAC.48.9.3323-3331.2004
73. Prabhudesai PP, Jain S, Keshvani A and Kulkarni KP. The

efficacy and safety of amoxicillin-clavulanic acid 1000/125 mg twice daily extended release (XR) tablet for the treatment of bacterial community-acquired pneumonia in adults. J Indian Med Assoc. 2011;109(2):124-127.

74. Chambers HF, Kocagöz T, Sipit T, Turner J and Hopewell PC. Activity of amoxicillin/clavulanate in patients with tuberculosis. Clin Infect Dis. 1998;26(4):874-877.
https://doi.org/10.1086/513945

75. Prasad R. IISc Works to Make a Common Antibiotic more Effective against TB; 2017.

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