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Original Research Article

Expert perspectives on the clinical use of high-dose amoxicillin with clavulanic acid in pediatric practice in Indian settings

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ABSTRACT

Background: This study was conducted to gather expert opinion regarding the clinical use of a high dose of amoxicillin 600 mg + clavulanic acid 42.9 mg in pediatric practice in Indian settings.
Methods: This cross-sectional study comprised 19 questions and gathered perspectives from pediatricians across India regarding the prescription practices of amoxicillin (600 mg) and clavulanic acid (42.9 mg) for various bacterial infections in pediatric patients. Data were analyzed using descriptive statistics.
Results: Majority (85.65%) of clinicians opined that the high dose of amoxicillin (600 mg) and clavulanic acid (42.9 mg) was very effective in treating bacterial infections in pediatric patients. About 54% of the respondents reported prescribing 600 mg amoxicillin + 42.9 mg clavulanic acid as the high dose for pediatric patients, while 41% of them prescribed 400 mg amoxicillin + 57 mg clavulanic acid as the high dose for pediatric patients. According to 51% of clinicians, the benefits of prescribing the higher-strength formulation of amoxicillin (600 mg) + clavulanic acid (42.9 mg) compared to the standard-strength formulation of amoxicillin (500 mg) + clavulanic acid (125 mg) include increased effectiveness against resistant bacteria, reduced risk of adverse effects, and reduced frequency of dosing.
Conclusions: This study highlighted the clinicians' preference for the high dose of amoxicillin (600 mg) and clavulanic acid (42.9 mg) as an effective treatment for bacterial infections in pediatric patients. The respondents preferred the high dose over other doses of amoxicillin and clavulanic acid due to the lower percentage of adverse effects.

Keywords: Amoxicillin, Clavulanic acid, Bacterial infections, Pediatrics

INTRODUCTION

Bacterial infections represent a significant burden on pediatric health globally, contributing to pediatric hospitalizations and outpatient visits.[1] Infectious diseases pose a greater challenge in low- and lower-middle-income countries (LMICs) compared to upper-middle and high-income countries, with India having the highest burden.[2] Approximately 5.4 million children worldwide succumb to various causes before reaching the age of 5, with infectious diseases accounting for roughly half of these deaths.[3] According to the Global Burden of Disease Study 2019, the estimated mortality linked to 33 bacterial pathogens accounted for 13.6% of all global deaths and 56.2% of all deaths related to sepsis in 2019. Among these, the five primary pathogens namely *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were responsible for 54.9% of the deaths.[4]

Fever often serves as a common clinical manifestation of infectious diseases in children, spanning from mild, self-limiting conditions like upper respiratory tract infections to more severe viral and bacterial illnesses.[5] Antibiotics remain indispensable in managing bacterial infections, and their appropriate use and prescription practices are essential for combating bacterial resistance.[6] Whether for empirical or targeted therapy, several considerations must

be taken into account, including dose, dosing interval, costs, and potential adverse effects. Typically, dosing was weight-based and expressed as milligrams per kilogram of body weight.[7]

Amoxicillin-clavulanate is an essential antibiotic used in emergency departments and primary care settings. Amoxicillin, a derivative of penicillin, is effective against both Gram-positive and Gram-negative bacteria. The combination was first introduced to the market in 1981. The inclusion of clavulanate, a β-lactamase, inhibitor in the formulation is a crucial component in combating antimicrobial resistance.[8] This inclusion broadens the spectrum of activity to include beta-lactamase-producing strains, thereby providing a wider range of coverage across different bacterial species.[9] Amoxicillin and clavulanate are easily absorbed via oral administration with an approximate bioavailability of 60%.[10]

Combination of amoxicillin with clavulanate has proven to be effective for a variety of pediatric infectious diseases, including acute otitis media, sinusitis, pneumonia, urinary tract infections, and infections of the skin and soft tissues.[11] In 2001, a new pediatric formulation of high-dose amoxicillin (600 mg per 5 ml) and clavulanate was approved for use in the United States. This new preparation met the needs of pediatricians by providing higher amounts of amoxicillin while maintaining the same daily dose of clavulanic acid as the regular strength formulation. The high dose formulation provides a 14:1 ratio of amoxicillin to clavulanate.[11] The present survey aimed to gather expert opinion on the preferences and prescribing patterns of high doses of amoxicillin and clavulanic acid in pediatric practice within Indian settings.

METHODS

We carried out a cross sectional, multiple-response questionnaire based study among specialists in managing bacterial infections in pediatric patients in the major Indian cities from June 2023 to December 2023. The study was conducted after receiving approval from Bangalore ethics, an independent ethics committee which was recognized by the Indian regulatory authority, drug controller general of India.

An invitation was sent to leading clinicians in managing bacterial infections in pediatric patients in the month of March 2023 for participation in this Indian survey. About 216 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. The questionnaire booklet titled PACE (Expert perspectives on high dose of amoxicillin 600 mg in pediatric practice) study was sent to the physicians who were interested to participate. The PACE study questionnaire comprised 19 questions focused on current feedback, clinical observations, and experiences of specialists in managing bacterial infections in pediatric patients. Clinicians had the option to skip any questions they did not wish to answer and were instructed to complete the survey independently without consulting their colleagues. Written informed consent was obtained from all participants before the study began.

Statistical analysis

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to provide clear insight into their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. Graphs were created to visualize the distribution of the categorical variables, utilizing Microsoft excel 2013 (version 16.0.13901.20400).

RESULTS

The survey included 216 experts, with 55% of clinicians reporting that their preferred antibiotic regimen for treating pediatric patients with bacterial infections was a combination of amoxicillin (400 mg) + clavulanic acid (57 mg). Approximately 51% of clinicians indicated that they occasionally prescribe high-dose amoxicillin (600 mg) and clavulanic acid (42.9 mg) for pediatric patients, while 38% reported frequent use of this combination. More than half (53.7%) of respondents reported prescribing high doses of amoxicillin (600 mg) and clavulanic acid (42.9 mg) in pediatric patients for ear infections. Majority (85.65%) of clinicians expressed opinion that high-dose amoxicillin (600 mg) and clavulanic acid (42.9 mg) highly effective in treating bacterial infections in pediatric patients (Figure 1).

Approximately 38% and 33% of clinicians opined that the severity of the infection and the patient's age, respectively, were the factors to be considered while choosing an antibiotic regimen for pediatric patients with bacterial infections. Around 66% of clinicians expressed their preference to prescribe high-dose amoxicillin 600 mg in combination with clavulanic acid 42.9 mg for pediatric patients experiencing recurrent infections, considering its superior effectiveness compared to other antibiotic regimens.

Half (50%) of the respondents reported that the risks associated with prescribing high-dose amoxicillin (600 mg) and clavulanic acid (42.9 mg) in pediatric patients include an increased chance of diarrhea, while 45% of them reported no associated risks. About 54% of the respondents reported prescribing 600 mg of amoxicillin + 42.9 mg of clavulanic acid as the high dose for pediatric patients (Figure 2).

More than half (56.02%) of the clinicians reported occasionally prescribing high-dose amoxicillin (600 mg) and clavulanic acid (42.9 mg) for pediatric patients in the past year. Approximately 33% of the clinicians stated that they consider the efficacy of the 14:1 ratio of high-dose

amoxicillin (600 mg) and clavulanic acid (42.9 mg) compared to other antibiotic regimens (7:1) as most useful in their clinical practice. About 47% of the clinicians indicated that they typically prescribe high-dose amoxicillin (600 mg) and clavulanic acid (42.9 mg) for children aged 6-12 years. Around 44% of clinicians reported that <5% of the patients have reported adverse events or side effects from high doses of amoxicillin (600 mg) and clavulanic acid (42.9 mg) for pediatric patients (Table 1).

According to 44% of the clinicians, the cost of treatment was very important in making the decision regarding the prescription of high-dose amoxicillin (600 mg) and clavulanic acid (42.9 mg) for pediatric patients. The majority (63.89%) of clinicians expressed a preference for prescribing high-dose amoxicillin (600 mg) and clavulanic acid (42.9 mg) for pediatric patients, especially if it was available in a more convenient dosage form, such as once-daily dosing or chewable tablets.

Approximately 45% of clinicians reported prescribing high-dose amoxicillin (600 mg) + clavulanic acid (42.9 mg) for 7 days in cases of recurrent otitis media. As reported by 43% of clinicians, less than 10 to 25% of patients were prescribed with high-dose amoxicillin (600 mg) + clavulanic acid (42.9 mg) for recurrent otitis media. According to 51% of clinicians, the benefits of prescribing the higher-strength formulation of amoxicillin (600 mg) + clavulanic acid (42.9 mg) compared to the standard-strength formulation of amoxicillin (500 mg) + clavulanic acid (125 mg) include increased effectiveness against resistant bacteria, reduced risk of adverse effects, and reduced frequency of dosing (Table 2).

Approximately 48% of clinicians responded that pediatric patients may benefit more from the higher-strength formulation of amoxicillin (600 mg) + clavulanic acid (42.9 mg). According to 44% of clinicians, they prescribe high dose amoxicillin (600 mg) + clavulanic acid (42.9 mg) in tonsillar pharyngitis in <25% of the patients.

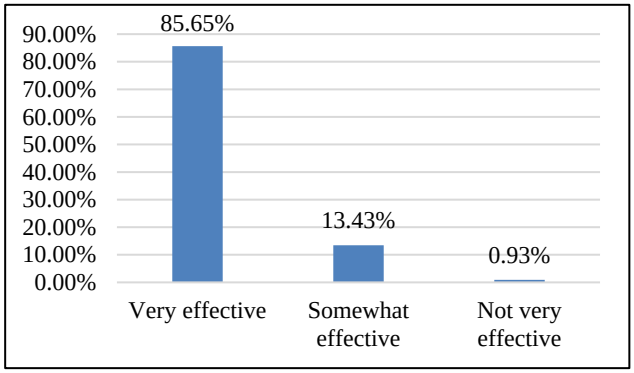

Figure 1: Distribution of responses on the effectiveness of high-dose amoxicillin 600 mg and clavulanic acid 42.9 mg in treating bacterial infections in pediatric patients.

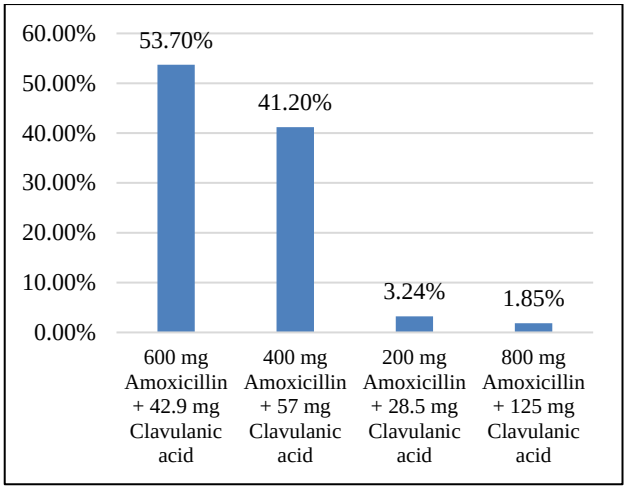

Figure 2: Distribution of response to the dosage of high-dose amoxicillin and clavulanic acid typically prescribed for pediatric patients.

Table 1: Distribution of response on the percentage of patients, adverse/side effects reported from high-dose amoxicillin 600 mg and clavulanic acid 42.9 mg.

Percentage of adverse effects	Response rate, (n=216)
<1%	25.46%
<5%	44.44%
<10%	23.61%
<15%	6.48%

Table 2: Distribution of responses on the benefits of prescribing the higher-strength formulation of amoxicillin compared to the standard-strength formulation.

Benefits	Response rate, (n=216)
Increased effectiveness against resistant bacteria	38.43%
Reduced risk of adverse effects	6.48%
Reduced frequency of dosing	4.17%
All of the above	50.93%

DISCUSSION

The survey findings indicated a strong consensus among clinicians regarding the effectiveness of the high dose of amoxicillin (600 mg) and clavulanic acid (42.9 mg) in treating bacterial infections in pediatric patients. In line with this finding, White et al concluded that a high dose of amoxicillin/clavulanate can effectively treat bacterial infections caused by pathogens with reduced susceptibility to other antimicrobials while minimizing the emergence of resistant strains.[12] Chu et al also concluded that treating bacterial infections like acute otitis media in children with high-dose amoxicillin with clavulanate was superior to conventional doses only in children.[13] According to Dagan et al high-dose

amoxicillin and clavulanate were highly effective in treating AOM in children. The treatment proved to be effective in children who were less than 24 months old and those with bacterial infections, even in cases where they were likely to fail treatment. Both bacteriologic and clinical efficacy were observed during the study.[14]

In the current survey, it was observed that clinicians routinely prescribe 600 mg of amoxicillin + 42.9 mg of clavulanic acid as a high dose for pediatric patients. Amparo Sanchez Navarro, in a review study, stated that amoxicillin (600 mg) and clavulanic acid (42.9 mg) appear appropriate for favorable tolerability and efficacy in bacterial infections among children.[15] Lahiry et al reported that a high dose of 600 mg amoxicillin + 42.9 mg clavulanic acid was effective in treating bacterial infections in children.[16] In another comparative study, Marchant et al reported the effectiveness of high-dose amoxicillin-clavulanate for the treatment of acute otitis media.[17] Klein also recommended high-dose amoxicillin 600 mg and clavulanic acid 42.9 mg for children weighing 40 kg or above.[11]

The current survey showed that <5% of the patients have adverse events or side effects from prescribing high doses of amoxicillin 600 mg and clavulanic acid 42.9 mg for pediatric patients. According to Evans et al the combination of amoxicillin and clavulanate was generally safe and well-tolerated. Most adverse effects are mild and related to the gastrointestinal tract. The most common complaint was diarrhea, but patients may also experience nausea, vomiting, loose stools, and abdominal discomfort.[9] White et al also reported that amoxicillin and clavulanate were generally well tolerated, with the incidence of upper gastrointestinal symptoms such as nausea being the most common adverse effect noticed.[12]

A randomized controlled trial by Wald et al compared the efficacy of high-strength amoxicillin-clavulanate (600 mg amoxicillin + 42.9 mg clavulanic acid) versus standard-strength formulation (500 mg amoxicillin + 125 mg clavulanic acid) in pediatric patients with acute bacterial sinusitis. The study demonstrated superior clinical cure rates and microbiological eradication of resistant pathogens, including beta-lactamase-producing strains, in patients receiving the higher-strength formulation.[18] Hoberman et al reported a significantly lower frequency of dosing and improved adherence to therapy in patients with acute otitis media receiving the higher-strength formulation, thereby enhancing treatment outcomes.[19]

The current survey results can aid clinicians in enhancing treatment strategies and patient care by considering the preferences and prescription practices of amoxicillin (600 mg) + clavulanic acid (42.9 mg) in Indian settings. Additionally, insights from this survey can inform clinicians about the high efficacy and tolerability of this regimen, as well as its potential benefits in managing bacterial infections in pediatric patients. The major strength of the current survey was the utilization of a well-designed and validated questionnaire to collect data from clinicians. However, it was important to acknowledge certain limitations of the survey. The results may be subject to bias due to reliance on expert opinion, which can be influenced by diverse perspectives and preferences among clinicians. It was essential to keep these limitations in mind when interpreting the findings. Additionally, the survey may not fully account for emerging evidence or evolving trends in infection management. To address these limitations, it was recommended to conduct prospective trials or real-world observational studies to validate the survey results and provide a more comprehensive understanding of optimal treatment approaches.

CONCLUSION

A significant proportion of respondents favored prescribing the higher-strength formulation of amoxicillin (600 mg) + clavulanic acid (42.9 mg) over alternative doses, citing its enhanced effectiveness against resistant bacteria, reduced risk of adverse effects, and less frequent dosing as key advantages.

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