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Original Research Article

Effectiveness of Co-Amoxiclav in Managing Upper Respiratory Tract Infections: A Multicenter Retrospective Real-World Study

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Abstract:

Background: Upper respiratory tract infections (URTIs) are among the most common infectious diseases, affecting the nasal passages, pharynx, and larynx. They present a significant health burden, especially in children and individuals with compromised immune systems, leading to symptoms like cough, sore throat, and congestion. The present study aims to assess the effectiveness and safety profile of Co-amoxiclav in managing upper respiratory tract infections (URTIs) across the adult population of India.

Methods: A single-arm, multicenter, retrospective, medical records-based, real-world study was conducted, including all adult patients diagnosed with URTIs presented to the Out-Patient Department (OPD) or admitted to the In-Patient Department (IPD) who have been treated with Co-Amoxiclav Therapy. Data were collected at three intervals: baseline (day 0), first follow-up (day 7±2), and second follow-up (day 14±2). Demographic information, medical history, primary diagnosis, vital signs, and laboratory parameters were documented at baseline and follow-ups. Clinical outcomes, microbiological results, and safety data, such as adverse events, were assessed at each follow-up. The statistical analysis in this study employed a combination of descriptive statistics and frequencies, along with the Chi-square test, to evaluate the efficacy of Co-Amoxiclav. Descriptive statistics summarized the characteristics of the sample, providing means, standard deviations, and frequencies for categorical variables.

Results: The study included a total of 9233 participants with a mean age of 46.84±16.3. The most frequently encountered URTI was the undifferentiated URTI, accounting for 48% of the total population. A significant proportion of the participants (72%) were prescribed co-amoxiclav 625 mg twice daily for 5 to 7 days. The study reported statistically significant efficacy (92.82%) of co-amoxiclav ($p<0.0001$) in the treatment of URTIs. Significant improvements in laboratory parameters with C-reactive protein (CRP) levels ($p < 0.001$) and white blood cell count decrease were observed ($p < 0.001$). Adverse events were notably rare in the study population, with only 28 cases (0.35%) reporting any treatment-related events.

Conclusion: Co-amoxiclav demonstrated excellent efficacy and safety profile in the treatment of upper respiratory tract infection. Further large studies are required to determine the long-term outcomes of co-amoxiclav in the timely management of URTIs.

Keywords: upper respiratory tract infections, co-amoxiclav, effectiveness, safety, efficacy.

Introduction

Upper respiratory tract infections (URTIs) are a subtype of acute respiratory infections (ARI) affecting the sinus, laryngopharynx, nose, and trachea. URTI symptoms frequently include temporary inflammation and swelling of the infected region. In addition, coughing is observed without pneumonia. [1] The global incidence of URTIs was estimated at 17.2 billion in 2019, accounting for approximately 43% of the total global burden of diseases. [2] According to the Indian report, NFHS-5 conducted between 2019 and 2021, the prevalence of ARI among children under five years of age in India was reported as 2.8%. [3] Furthermore, a comprehensive analysis examining the causes of mortality in Indian children under five years from 2000 to 2015 identified pneumonia as the second leading cause of death in this age group, contributing to 15.9% of fatalities. [4] These infections include conditions such as acute bronchitis, sinusitis, common cold, influenza, and respiratory distress syndromes. [5] Typically, these infections manifest as acute diseases with an early clinical onset, spanning from hours to days following the contraction of the infectious pathogen. URTIs present a range of symptoms including fever, cough, throat infection, nasal congestion, dyspnea, wheezing, and breathing difficulties. [6] Risk factors for URTI include being in close proximity to children, existing conditions like asthma and allergic rhinitis, and smoking,

immunocompromised states such as cystic fibrosis or human immunodeficiency virus (HIV), corticosteroid use, recent surgical transplantation, and post-splenectomy status. [7] Treatment options for URTI include antibiotics such as penicillin, amoxicillin, cephalosporins, and macrolides, as well as analgesics such as Aspirin and Diclofenac for symptomatic relief. Additionally, vitamin C supplements are often considered adjunctive therapy. [8] However, a global concern with the use of antibiotics is the growth of antibiotic-resistant strains, significantly impacting the clinical response of the pathogens towards these drugs. Therefore, researchers are focusing on the development of more potent drugs. Among these, a potent therapy candidate is co-amoxiclav. Co-amoxiclav is a combination drug of amoxicillin and clavulanate showing broad-spectrum antibiotic activity that has been widely used for over two decades in treating community-acquired respiratory tract infections (RTIs). [9] The development of co-amoxiclav was prompted by the rise in bacterial resistance to amoxicillin, due to the production of beta-lactamase enzymes by certain bacterial strains. To address this issue, clavulanic acid, a beta-lactamase inhibitor, was introduced in combination with amoxicillin, effectively restoring its antimicrobial activity. [10]

Co-amoxiclav has documented efficacy in managing various infectious conditions including URTIs. The activity of co-amoxiclav extends across both pediatric and adult populations. Several guidelines recommend co-amoxiclav for treating URTIs such as acute sinusitis and acute otitis media (AOM). [11] Co-amoxiclav received regulatory approval from the Food and Drugs Administration (FDA) in 1996 in the US followed by the European Medical Agency (EMA) in 2009 for common infections of the body involving the respiratory and urinary tract. Potential adverse events associated with the consumption of co-amoxiclav are gastrointestinal disturbances, skin rashes, and thrush. Additionally, antibiotic-associated diarrhea is also indicated post-intervention with co-amoxiclav. [12]

As URTI contributes significantly to the burden on healthcare systems, particularly in developing nations like India, it is important to effectively manage the infections. Co-amoxiclav serves as a broad-spectrum antibiotic with activity against various pathogens underlying URTI.

However, real-world data on the clinical efficacy and safety specific to the Indian adult population is deficient. This retrospective study aims to assess the effectiveness of Co-amoxiclav in managing patients presenting with URTIs and evaluating the safety profile of the drug across the diverse population of India. By assessing the data from multiple clinical settings across the nation, the present retrospective study provides real-world performance of the drugs in the diverse population of India, serving as important documentation for evidence-based treatment of URTI by physicians in India.

Methods

Study design and population

A single-arm, multicenter, retrospective, medical records-based, real-world study was conducted. A total of 10,000 patients diagnosed with URTIs presented to the outpatient department (OPD) or the inpatient department (IPD), receiving co-amoxiclav therapy were enrolled in the study. Participants included in the present study were 1) patients over the age of 18, of either gender, who attended either the outpatient or inpatient hospital departments, 2) patients with a confirmed diagnosis of URTIs and were prescribed co-amoxiclav, either as the primary treatment or as a concomitant medication, 3) patients with documented clinical diagnoses and treatment outcomes following co-amoxiclav therapy, 4) patents with available medical records documenting the initiation of therapy, as well as at least one follow-up visit (and a second, if available). Patients were excluded from the study if they were younger than 18 years of age, had not been prescribed co-amoxiclav either as a primary or concomitant medication or if complete medical records were unavailable.

Data collection

The study investigator and site personnel identified patients fulfilling the study selection criteria from the available patient medical records at the study site. Prescriptions and laboratory investigations of individual patients were screened, and data from the medical records were captured in the standard reporting system.

Patient records at each site were provided with a unique ID number, starting with 001 for each investigator. The baseline visit was considered the period during which treatment with co-amoxiclav was initiated. The data was retrieved at baseline (day 0), first follow-up (day 7±2), and second follow-up visit (day 14±2) (if available).

The endpoints of the study are therapeutic response and adverse events in patients. At the baseline visit, comprehensive demographic data was recorded, including age, gender, and medical diagnosis. Data on treatment response was categorized as cure, improvement, worsening, or mortality, and the safety profile was assessed by documenting any adverse events that occurred during treatment at two follow-up periods.

The first follow-up occurred on 7 ± 2 days and the second follow-up interval was 14± 2 days. Physical

and laboratory parameters were assessed at the first and second follow-up periods.

Statistical Analyses

The statistical analysis in this study employed a combination of descriptive statistics and frequencies, along with the Chi-square test, to evaluate the efficacy of co-amoxiclav. Descriptive statistics summarized the characteristics of the sample, providing means, standard deviations, and frequencies for categorical variables. This approach facilitated a comprehensive understanding of the distribution of various symptoms, treatment responses, and demographic features within the cohort, allowing for a nuanced interpretation of the findings. The chi-square test was used to assess the efficacy of co-amoxiclav at both follow-up visits. All tests were executed using SPSS software at 95% CI.

Ethical considerations

This study protocol was reviewed by a registered Institutional Ethics Committee (IEC) before initiating the study. Ethical Guidelines for Biomedical Research on Human Subjects, issued by ICMR, were followed during the conduct of the study. As this is a retrospective study using anonymized data from the medical records of patients already treated with co-amoxiclav therapy, informed consent was waived for the patients. The identities of patients involved in the study remained confidential.

Results

Baseline characteristics

Patient demographics are outlined in Table 1. The study included 9,233 participants with a mean age of 46.84 ± 16.3, indicating a wide age range. The sample was predominantly male, with 6504 males constituting 70.50% of the cohort, while females accounted for 2729 (29.55%) participants. Most of the cases presented with mild severity (74%) (Figure 1).

The most frequently encountered URTI was the undifferentiated URTI, accounting for 48% of the total population, followed by pharyngitis (24%), and sinusitis (12%) (Figure 2). A significant proportion of the participants (72%) were prescribed co-amoxiclav 625 mg twice daily for 5 to 7 days.

Table 1: Demographic characteristics of the study population

Age	**Mean**	**SD**
	46.84	16.3
Gender	**n**	**%**
Male	6504	70.50%
Female	2729	29.55%
Diagnosis	**n**	**%**
URTI (Total cases)	9233	100%
Undifferentiated URTI	4432	48%
Pharyngitis	2216	24%
Sinusitis	1107	12%
laryngitis	739	8%
Other URTIs	739	8%
Cases According to severity	**n**	**%**
Mild	6832	74%
Moderate	1939	21%
Severe	462	5%
Dosage 500/125 mg twice daily	**n**	**%**
5-7 days	6648	72%
7-10 days	1939	21%
10-14 days	369	4%
Dosage 875/125 mg twice daily	**n**	**%**
7-10 days	277	3%

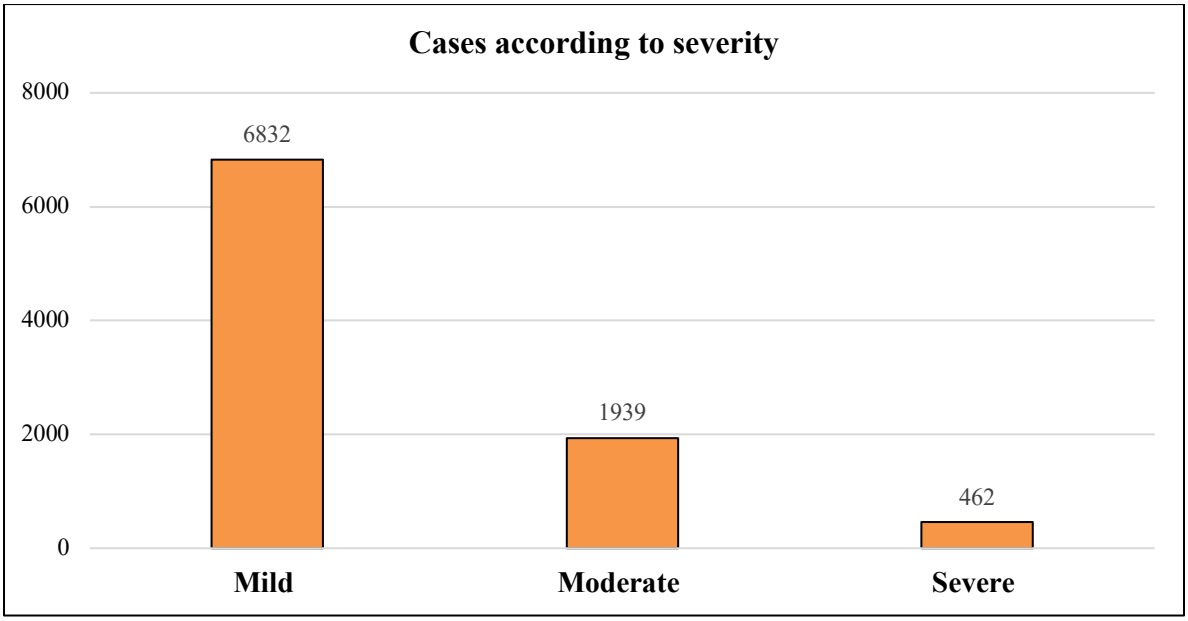

Figure 1: URTI cases according to disease severity

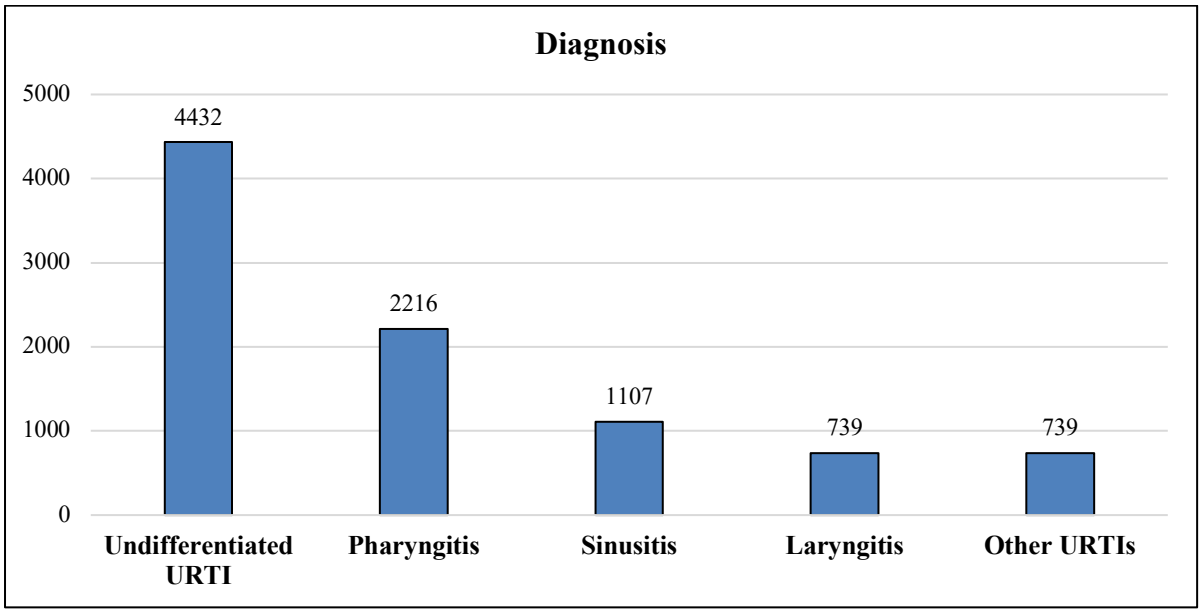

Figure 2: A Subpopulation Analysis of URTIs in the Study Population

Treatment Response

A key focus of the study was the efficacy of the co-amoxiclav response in participants with URTI (Table 2). Most of the patients (84.37%) reported improvement of the symptoms after the first follow-up period (7 ± 2 days), accounting for an overall efficacy of co-amoxiclav to be 92.82% during the second follow-up visit. However, 3.68% of the population did not experience any improvement in their symptoms following the drug administration. The percentage of patients who experienced worsening or no response was low, suggesting the treatment was generally effective in managing the URTI patients.

The study reported statistically significant efficacy of co-amoxiclav ($p<0.0001$) in the treatment of URTIs (Table 3), suggesting that the drug has excellent efficacy.

Table 2: Clinical response in URTI patients after co-amoxiclav treatment

Treatment response- 1ST follow-up (7 DAYS ± 2)	**N**	**%**
Cure	7791	84.37
Improvement	903	9.81
Mortality	3	0.03
Worsening	162	1.75
No Response	374	4.05
Treatment response- 2nd follow-up (14 DAYS ± 2)	N	**%**
Cure	780	8.43
Improvement	158	1.71
Mortality	9	0.09
Worsening	155	1.67
No Response	340	3.68
Overall efficacy rate after 2nd assessment		**92.82**

Table 3: Efficacy of co-amoxiclav after treatment in URTI patients

Efficacy of co-amoxiclav after treatment in URTI patients					
Outcome	Cure	Improvement	Mortality	Worsening	No changes
1st follow-up (7±2days)	7791	903	3	162	374
2nd follow-up (14±2days)	780	158	9	155	340

Chi-square value = 252.25, p = 0.0001*

The mean C-reactive protein (CRP) level demonstrated a significant reduction, decreasing from 23.47 at baseline to 12.44 at the first follow-up visit, indicating a marked decrease in inflammation ($p < 0.001$). Similarly, the mean WBC count showed a substantial decrease from 15,200 to 9,200, suggesting an improvement in immune response or resolution of infection/inflammation ($p < 0.001$). The temperature decreased significantly from 38.5°C (indicative of fever) to 36.5°C, suggesting a resolution of fever or infection (Table 4). The respiratory rate showed a notable decline from 25 breaths/min to 17.2, indicating improved respiratory function as a response to treatment. The pulse rate decreased from 101.4 beats/min (tachycardia) to 82.3, reflecting a normalization in heart rate, suggesting an improved cardiovascular status. The data indicates significant improvements in the physical parameters, denoting a positive response to treatment (Table 5).

Table 4: Changes in laboratory parameters from baseline to first and second follow-up intervals

Laboratory parameter	**Baseline**		**7 ± 2 days**		**Statistical Analysis**
	Mean	**SD**	**Mean**	**SD**	**T-Test (p-value)**
CRP (mg/L)	23.47.	28.97	12.44*	22.52*	24.26 (0.001)*
WBC	15200	4400	9200*	2900*	154.73(0.001)*

***Highly statistically significant, Students T-test performed, p<0.001**

Table 5: Changes in physical parameters from baseline to first and second follow-up intervals

Changes in physical examination			
Parameters	**Pre-medication (Mean SD)**	**1st follow-up (Mean SD)**	**2nd follow-up (Mean SD)**
Temperature	38.5°C ±1.2	37°C ± 0.8	36.5°C±0.5
Respiratory rate	25±4.7	19.8±3.5	17.2±3.1
Pulse rate	101.4±10.7	86.2±9.1	82.3±8.2

Adverse events

Adverse events were notably rare in the study population, with only 28 cases (0.35%) reporting any treatment-related events.

The overwhelming majority of participants (99.65%) did not experience any adverse effects from the prescribed treatment, depicting the excellent safety profile of the drug (Table 6). 4.9% patients experienced a relapse with an average time to relapse of 14.5 days. The secondary infection rate was low (4%), suggesting the effectiveness of the antibiotic in reducing the secondary infections following treatment (Table 7).

Table 6: Incidence of adverse events among the study population at first and second follow-up intervals

Adverse events 1st follow-up (7 ± 2 days follow-up)	**n**	**%**
Yes	30	0.33
No	9203	99.67
Adverse events 2nd follow-up(14 ± 2 days follow-up)	**n**	**%**
Yes	30	0.33
No	9203	99.67

Table 7: Recurrence and secondary infection rate, and their identified risk factors

Relapse Rate	**Secondary infection rate**
452 (4.9%)- Time top relapse 14.5 days±6.7	369 (4%)
Risk factors associated with relapse rate and secondary infection rate	
Age >65yrs: 1.5-2.5 increased risk	
Underlying medical conditions (e.g.: COPD, diabetes)	
Immuno-compromised patients	
Inadequate treatment duration	
Resistant pathogens	

Discussion

This study aimed to evaluate the efficacy and safety of co-amoxiclav in the treatment of URTIs among adult participants. The findings demonstrated a high efficacy and adequate safety profile of co-amoxiclav, with a majority of patients reporting symptom improvement after drug administration. Additionally, the results were statistically significant (p=0.0001), indicating the superior efficacy of co-amoxiclav over the 14-day treatment period. Adverse events were rare, and most of the participants were well-tolerated afterwards.

The primary outcome of the present study is the high efficacy of infection cure within 7 days of initiating co-amoxiclav, with most of the remaining patients experiencing clinical cure at a 14-day follow-up period. This finding is in accordance with existing literature and preliminary studies that have reported the therapeutic efficacy of amoxicillin and clavulanate combinations in managing different types of RTIs in adults and pediatric populations. However, the data on managing URTI in the adult patient population is limited. A large randomized controlled trial reported a 95% therapeutic response in adult patients with chronic sinusitis. The eradication rate of the causative pathogen was 65% with no incidence of infection relapse. [13] Seggev et al. (1998) compared the impact of co-amoxiclav dose and regimen on the therapeutic efficacy, using twice daily amoxicillin/clavulanate 875/125mg versus thrice daily amoxicillin/clavulanate 500/125 mg in patients with acute bacterial maxillary sinusitis. [14] Both of these regimens demonstrated a high success rate of 93% and 88%, respectively. In the present study, superior efficacy was observed among the patients who were administered 625 mg of co-amoxiclav twice five times a day. Contrary to the present study findings, another study revealed that the rate of recurrence of infection was higher at a twice-daily dosage (11.5%) compared to thrice daily (5.5%). [14] Amini et al. (2009) reported low radiographic improvement after co-amoxiclav treatment (29.6%), with a high rate of adverse event occurrence (10.3%). [15]

Various studies have identified the clinical efficacy of co-amoxiclav treatment in lower respiratory tract infections. A randomized controlled trial on 72 patients with chronic bronchitis was conducted. The patients were administered a concentration of 875/125mg of amoxicillin/clavulanate twice daily. Among these patients, 97.2% of the population experienced improvements in clinical response after a 7-day regimen. [16]A small observation study used 875/125mg of amoxicillin/clavulanate at a 12-hour interval for 10 days in chronic bronchitis patients. [17] Out of the total population, 90% observed either a clinical cure or symptom improvement, with 10% demonstrating treatment failure. The microbiological results reported eradication of 84% of the identified strains, while 8% of the bacterial strains persisted, and 6% were superinfections. [17] In the present day, the overall efficacy with co-amoxiclav 625 mg (twice daily, five times dosage) was 92.82%. Similarly, a large multicenter observational study on 144 patients receiving co-amoxiclav reported a clinical cure of 90.3% and a microbiological parameter improvement of 82.6%. [18] Lode et al. (2004) conducted a clinical trial on 234 community-acquired pneumonia patients. Clinical improvement was observed in 81.6% of the patients, while microbial culture improvement was 78.7%. [19]

While most of the patients experienced clinical cure or improvement, a small subset of the cohort observed worsening of the symptoms or no improvement. This highlights that despite high therapeutic activity, some patients demonstrated resistance to the drug. Namyslowski et al. (2002) provided a rationale for the observed co-amoxiclav resistance. [13] The efficacy of antimicrobial therapy for URTIs depends on several factors,

including the antibacterial spectrum, tissue penetration, pharmacokinetics, and the prevailing resistance patterns in the local community. Furthermore, the presence of antibiotic-resistant organisms in those patients with treatment failure is presumed. β-lactam resistance which is mediated by β-lactamase production or alterations in penicillin-binding proteins, is a growing concern among Haemophilus species, Moraxella catarrhalis, Staphylococcus aureus, Streptococcus pneumoniae and Enterobacteriaceae, which are known pathogens for RTIs. [13] These resistance mechanisms are partially overcome by adding clavulanate to amoxicillin, however, their potency varies across different strains, with some bacteria more susceptible or resistant than others. Therefore, other medications that show antimicrobial activity using other mechanisms can be used as the second line of treatment. In the present study, a significant reduction in CRP levels and WBC count was observed after drug administration. This decrease holds clinical relevance, as CRP is a well-established acute-phase reactant commonly used as a biomarker to identify URTIs. [20,21] In adult patients presenting with RTIs, established CRP thresholds for guiding antibiotic therapy include <20 mg/L to withhold antibiotics and ≥100 mg/L to initiate treatment. [22] The study demonstrated a significant reduction in CRP levels and WBC count, indicating effective management of the underlying infection with co-amoxiclav. CRP, an acute-phase reactant synthesized in response to infections, plays a crucial role in bacterial clearance by promoting phagocytosis. [20,21] Established CRP thresholds guide antibiotic therapy, with <20 mg/L suggesting no need for antibiotics and ≥100 mg/L warranting treatment.22 The reduction in these biomarkers reflects the resolution of the inflammatory process and successful infection control.

The overwhelming majority of participants did not experience any adverse effects related to co-amoxiclav, with only a few documented reports of adverse events. However, previous studies have identified various side effects ranging from mild to moderate. Co-amoxiclav-associated adverse events include mild gastrointestinal disturbances, such as vomiting, nausea, diarrhea, and abdominal discomfort. Notably, the incidence of diarrhea is elevated with co-amoxiclav compared to amoxicillin monotherapy. [23] Furthermore, the risk of developing secondary Clostridioides difficile colitis is moderately elevated in comparison to other classes of antibiotics. Females on co-amoxiclav may also experience vaginitis due to mycosis or candidiasis. [24] Other rare complications associated with co-amoxiclav include prolonged blood clotting time, vasculitis, thrombocytopenia, cholestatic jaundice, increased alkaline phosphatase levels in the blood, and hepatitis. [25–27] Furthermore, there is a risk of hepatotoxicity, with 314 documented cases of co-amoxiclav-induced hepatic dysfunction of which 9 patients reported severe disease. [28]

Apart from certain adverse events arising from the use of co-amoxiclav, patients also experienced a relapse of infections and incidences of secondary infections. However, the rate of relapse and secondary infections observed in the present study is significantly lower than that observed in previous investigations thus highlighting the effectiveness of the antibiotic in managing the various upper respiratory tract infections. The strengths of this study include its large sample size of 9,226 participants with a focus on URTIs. Despite the high prevalence of URTIs in adults, data are scarce, particularly within the Indian population. Additionally, existing studies on URTIs are limited to pediatric patients, with much of the available data being outdated for several decades. This study, therefore, offers new evidence and highlights the current effectiveness of co-amoxiclav in the present scenario of rising antibiotic resistance. However, the retrospective design of the study introduces certain limitations, such as the absence of detailed adverse event reporting, lack of microbiological results, and insufficient data on the specific treatment regimens followed by patients. These factors may limit the ability to draw definitive conclusions regarding safety and efficacy. Furthermore, the lack of a comparator arm reduces the ability to compare the efficacy and safety of the combination drug relative to other treatment options used in India.

Conclusion

Co-amoxiclav demonstrated significant efficacy and safety profile in the treatment of URTIs with the majority of the patients experiencing clinical cure. The incidences of adverse events were significantly less. The results demonstrate the continued effectiveness of this antibiotic since its introduction, despite the rising antimicrobial resistance. The study further identifies the role of adding beta-lactamase inhibitors to conventional antibiotics such as penicillin and cephalosporins to increase the susceptibility of the pathogens. Further large studies are required to determine the long-term outcomes of co-amoxiclav in the timely management of URTIs. Future research should focus on establishing standardized treatment regimens, monitoring adverse events more closely, and incorporating microbiological data to better understand drug efficacy and identify resistant and susceptible strains.

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