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EFFICACY AND SAFETY OF AMOXICILLIN-CLAVULANIC ACID IN THE MANAGEMENT OF BACTERIAL RESPIRATORY TRACT INFECTIONS IN THE REAL-WORLD SETTINGS

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ABSTRACT

Background: Bacterial respiratory tract infections (RTIs), including community-acquired pneumonia (CAP) and acute exacerbations of chronic obstructive pulmonary disease (AECOPD), pose significant health challenges. This study aimed to evaluate the real-world effectiveness and safety of amoxicillin-clavulanic acid in management of bacterial RTIs in the real-world settings. **Methods:** This questionnaire-based study was conducted among health care professionals (HCPs), including pulmonologists, general physicians, and internal medicine specialists. A questionnaire consisting of 17 questions explored HCP preferences regarding the use of amoxicillin-clavulanic acid for bacterial RTIs. The questionnaire focused on last 10 patients with bacterial RTIs. **Results:** A total of 80 HCPs were included in the study. The majority of HCPs (40%) reported that out of 10 patients, >4 had been previously treated with other antibiotics. Inadequate nutrition and low weight (52.50%) were predominantly identified as risk factors for CAP and AECOPD. Streptococcus pneumoniae was reported (62.5%) as the most prevalent pathogen in CAP and AECOPD. Amoxicillin (70.0%) was favored to have the highest drug resistance against Staphylococcus aureus. Amoxicillin-clavulanic acid was preferred (100%) as an effective empiric antibiotic for treating CAP and AECOPD. The majority of HCPs (47.5%) reported symptom resolution of fever and cough by day 2 after treatment with amoxicillin-clavulanic acid. In terms of clinical global impression, 75.00% of HCPs rated amoxicillin-clavulanic acid as excellent. The majority of HCPs (68.75%) considered amoxicillin-clavulanic acid as a first-line agent for outpatient management of CAP and AECOPD. **Conclusion:** Healthcare professionals consider amoxicillin-clavulanic acid as an effective and preferred first-line empiric antibiotic for managing bacterial RTIs.

KEYWORDS : Bacterial respiratory tract infections, community acquired pneumonia, acute exacerbations of chronic obstructive pulmonary disease, healthcare professionals

INTRODUCTION:

Respiratory tract infections (RTIs), caused by various viral and bacterial pathogens, are the second leading cause of global morbidity and mortality. Lower RTIs rank just behind ischemic heart disease in terms of disease burden. European surveillance reports indicate a growing prevalence of antimicrobial-resistant bacteria. The diagnosis and management of community-acquired pneumonia (CAP), hospital-acquired pneumonia, and ventilator-associated pneumonia remain challenging [1].

Community-acquired pneumonia is a major cause of hospitalization, mortality, and healthcare costs. Its severity ranges from mild cases treatable outpatient to severe cases requiring intensive care. Early diagnosis and appropriate care are essential for better outcomes [2, 3].

Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) carry a high mortality, health, and economic burden, with diagnosis and management remaining suboptimal for decades. Recent studies suggest that grouping exacerbations by etiology could help address their heterogeneity in mechanisms and outcomes [4].

Respiratory tract infections are common and potentially severe, with lower RTIs and influenza being the leading infectious causes of death in the U.S. Risk factors include extreme age, smoking, alcoholism, immunosuppression, and comorbidities. The microbial causes of RTIs vary by infection type, setting, and other factors. Streptococcus pneumoniae remains the most common cause of CAP, though newer pathogens like Chlamydia pneumoniae have emerged. Rising antimicrobial resistance, especially in S. pneumoniae, complicates RTI management. Understanding the epidemiology and causative pathogens is essential for effective care [5].

Respiratory diseases are a major global health burden, with antibiotic resistance remaining a challenge. Clavulanic acid, a secondary metabolite produced by Streptomyces clavuligerus and a beta-lactamase inhibitor, was introduced in 1972 and combined with amoxicillin, launching as Augmentin in 1981 [6,7].

Amoxicillin-clavulanate is a widely used antibiotic that combines amoxicillin, which is effective against gram-positive and gram-negative bacteria, with clavulanic acid to counter -lactamase strains. Amoxicillin, due to its good oral absorption and broad-spectrum antimicrobial activity, was chosen as the antibiotic to be co-administered with clavulanic acid. In tablet

formulation, it is used to treat CAP, methicillin-sensitive Staphylococcus aureus (MSSA), and small intestinal bacterial overgrowth (SIBO), with around 50% efficacy for SIBO [6, 8]. Despite new antibiotics in development, amoxicillin-clavulanate remains essential for treating respiratory infections worldwide [6,7].

Amoxicillin–clavulanic acid is used more frequently than amoxicillin alone in many countries, though less so in certain regions. For most clinical syndromes, thorough microbiological testing and delayed prescription in mild, likely viral cases is recommended. Amoxicillin alone causes fewer side effects and allows for higher oral doses. When using the combination, a narrow amoxicillin-to-clavulanic acid ratio is preferred for fewer daily doses and better Gram-negative coverage [9].

Amoxicillin-clavulanic acid, a broad-spectrum antibiotic, is widely used for its effectiveness against common pathogens like Streptococcus pneumoniae and Staphylococcus aureus. However, rising antibiotic resistance, including extended-spectrum beta-lactamase (ESBL)-producing pathogens, challenges its efficacy. Therefore, this study aimed to evaluate the real-world effectiveness and safety of amoxicillin-clavulanic acid in management of bacterial RTIs.

MATERIALS AND METHODS:

Study Design

This questionnaire-based study was designed to evaluate the real-world effectiveness and safety of amoxicillin-clavulanic acid in treating CAP and AECOPD. It was conducted among health care professionals (HCPs), including pulmonologists, general physicians, and respiratory specialists. Participation in the study was entirely voluntary, and the study process, along with data analysis, ensured the confidentiality and anonymity of the HCPs. The study protocol was approved by the independent ethics committee (ACEAS-Independent Ethics Committee, Ahmedabad, Date of approval: 26 Dec 2024).

Ethics Committee: Informed consent was obtained from patients before participating in the study.

Study Questionnaire

The study questionnaire was designed based on existing literature, guidelines and expert opinions. It consisted of a total of 17 questions focused on the management of bacterial RTIs, including the use of amoxicillin-clavulanic acid in CAP and AECOPD. The questionnaire also covered prior antibiotic exposure, age group distribution, common risk factors, prevailing pathogens, antibiotic resistance trends, symptom resolution timelines, treatment duration, and the presence of comorbidities such as cardiac disease and uncontrolled diabetes. The questionnaire focused on last 10 patients with CAP and AECOPD.

Inclusion And Exclusion Criteria

The study included pulmonologists, general physicians, and respiratory specialists with at least 5 years of clinical experience in managing bacterial RTIs and who prescribed amoxicillin-clavulanic acid. Participants without a respiratory specialization, no recent amoxicillin-clavulanic acid prescriptions, or unwillingness to participate were excluded.

Data Collection

The HCPs participating in the study were provided with a concise overview of the study's nature and the process for completing the questionnaire.

Data Analysis

The responses of HCPs were entered into Microsoft excel and descriptive statistics, such as frequencies and percentages, were employed to present data.

RESULTS:

A total of 80 HCPs were included in this study. The majority of HCPs (40%) reported that out of 10 patients with CAP or AECOPD, more than four had been previously treated with other antibiotics. The majority of HCPs (51.25%) reported that patients with CAP were 60 years old. Most of the HCPs (57.50%) reported that patients with AECOPD were in the age group of 40 to 60 years. According to 52.50% of HCPs, inadequate nutrition and low weight were the most common risk factor present in patients with CAP or AECOPD. The most prevalent pathogens causing CAP and AECOPD were Streptococcus pneumoniae (62.5%), followed by Staphylococcus aureus (22.5%), Klebsiella pneumoniae (10.0%), and Proteus mirabilis and Moraxella catarrhalis (2.5% each) (Table 1).

According to 70% of HCPs, amoxicillin showed the highest resistance against Staphylococcus aureus, followed by ciprofloxacin (8.75%), levofloxacin (7.50%), azithromycin (7.50%), and cephalexin (6.25%). Approximately 73% of HCPs reported that amoxicillin showed the highest resistance against Streptococcus pneumoniae, followed by ciprofloxacin (10.00%), levofloxacin (8.75%), and azithromycin (8.75%) (Figure 1).

The presence of ESBL-producing pathogens was reported by 77.5% of HCPs. Additionally, all HCPs (100%) considered amoxicillin-clavulanic acid a good empiric antibiotic for patients with CAP and AECOPD. The majority of HCPs (47.5%) reported symptom resolution of fever and cough by day 2 after treatment with amoxicillin-clavulanic acid. Additionally, 36.25% observed improvement by Day 3, while 16.25% noted resolution by day 4. According to 53.75% of HCPs, the treatment duration with amoxicillin-clavulanic acid was 7 days, followed by 5 days (25.00%), 10 days (11.25%), and 14 days (10.00%) (Table 1).

A higher proportion of HCPs (37.5%) reported that cardiac disease was present in 1 out of 10 patients, while 30% observed it in more than 3 out of 10 patients. Additionally, the majority of HCPs (36.25%) reported that uncontrolled diabetes was observed in more than 3 out of 10 patients (Figure 2).

In terms of clinical global impression, 75.00% of HCPs rated amoxicillin-clavulanic acid as excellent, 20.00% as good, and 5.00% as fair for treating CAP and AECOPD. The majority of HCPs (56.25%) preferred the continued sensitivity of pathogens as a key attribute of amoxicillin-clavulanic acid when prescribing it for patients with CAP or AECOPD. The majority of HCPs (68.75%) considered amoxicillin-clavulanic acid as a first-line agent for outpatient management of CAP and AECOPD, followed by severe penicillin allergy (17.50%). According to 51.25% of HCPs, adults with comorbidity were most likely to benefit from amoxicillin clavulanic acid in CAP (Table 1).

DISCUSSION:

The present study provides valuable real-world insights into the effectiveness of amoxicillin-clavulanic acid in the management of CAP and AECOPD.

In the present study, the majority of HCPs reported that the most common age group for CAP patients was 60 years. Previous studies have identified that CAP is a leading cause of hospitalization among the elderly population [10, 11]. Most studies have reported an average patient age of over 60 years for AECOPD. The previous study indicates that younger AECOPD patients may experience poorer clinical outcomes [12, 13]. In the current study, most HCPs reported the 40-60 years age group as the most commonly affected by AECOPD patients. In the present study, the majority of HCPs considered inadequate nutrition and low weight as the primary risk

factors in patient with CAP and AECOPD. This is supported by the evidences indicating that inadequate dietary intake, its-induced malnutrition and weight loss were prevalent in patients with COPD [14]. Most of the HCPs identified Streptococcus pneumoniae as the most prevalent pathogen causing CAP and AECOPD. This finding aligns with real-world study which indicate that Streptococcus pneumoniae is the most common cause of pneumonia and one of the most frequently isolated pathogens in AECOPD cases [15, 16].

In the present study, the majority of HCPs identified that amoxicillin showed the highest resistance against Staphylococcus aureus and Streptococcus pneumoniae. Previous study has reported that amoxicillin is one of the most active drugs against Streptococcus pneumoniae [17].

The proliferation of ESBL-producing organisms poses a significant public health threat, as infections caused by these resistant strains have been linked to unfavorable clinical outcomes [18]. In the present study, majority of HCPs reported the presence of ESBL-producing pathogens, highlighting the widespread nature of this issue. Additionally, all of the HCPs considered amoxicillin-clavulanic acid as a good empiric antibiotic for patients with CAP and AECOPD. Previous studies have reported that amoxicillin-clavulanic acid is frequently prescribed as empiric therapy for several priority infectious syndromes identified by the World Health Organization in both adults and children [9, 19]. Findings from previous studies provide valuable insights into the antibiotic choices made by clinicians when treating RTIs. In particular, they highlight the potential benefits of prescribing the amoxicillin-clavulanic acid combination for effective symptom management [20]. In the present study, the majority of HCPs reported symptom resolution of fever and cough by day 2 after treatment with amoxicillin-clavulanic acid, reinforcing its role as a preferred therapeutic option for RTIs. In the present study, the majority of HCPs reported a treatment duration of 7 days with amoxicillin-clavulanic. Consistently, previous study has shown that standard amoxicillin-clavulanate therapy typically involves a 7-day treatment regimen [21, 22].

Lung disease is recognized as an independent risk factor for cardiovascular conditions, particularly ischemic heart disease and heart failure, both of which significantly contribute to overall mortality [23]. Additionally, observational studies have shown that acute RTIs increase the risk of myocardial infarction and stroke [24]. Consistent with previous research, the present study found that a considerable proportion of HCPs reported the presence of cardiac disease in their patients. Lower RTIs are a common clinical concern among diabetic patients. The risk of developing lower RTIs and other diabetes-related complications is particularly high in individuals over 50 years of age, those with diabetes for more than four years, and those with poor glycemic control. In line with these findings, the present study revealed that a significant proportion of HCPs (36.25%) reported uncontrolled diabetes in more than 3 out of 10 patients [25].

In the present study, majority of HCPs rated amoxicillin-clavulanic acid as excellent for treating CAP and AECOPD. Previous studies have reported high-dose amoxicillin-clavulanate demonstrated the highest predicted clinical efficacy in the treatment of both mild-to-moderate and severe AECOPD [26]. The majority of HCPs preferred the continued sensitivity of pathogens as a key attribute of amoxicillin-clavulanic acid when prescribing it for patients with CAP or AECOPD. This is supported by the evidence that pathogens responsible for CAP and AECOPD that are sensitive to amoxicillin-clavulanate are also sensitive to amoxicillin [27, 28]. Amoxicillin-clavulanic acid is widely recognized as a preferred first-line treatment for community-acquired lower RTIs [29]. Consistently, the majority of HCPs in the present study considered amoxicillin-clavulanic acid as the first-line agent for outpatient management of CAP and AECOPD, reinforcing its clinical significance in respiratory infections. In the present study, adults with comorbidities were considered most likely to benefit from amoxicillin clavulanic acid in CAP. Previous studies have reported amoxicillin-clavulanate is the standard regimen for outpatients with CAP who have comorbidities [30-32].

Limitations:

This study has few limitations. A small sample size may limit the generalizability of findings, as the responses may not adequately represent the larger population of HCPs. The use of a self-reported questionnaire introduces the potential for response bias. The questionnaire may not cover all relevant aspects of the subject matter.

CONCLUSION:

Healthcare professionals consider amoxicillin-clavulanic acid as an effective and preferred first-line empiric antibiotic for managing bacterial RTIs, including CAP and AECOPD, with rapid symptom resolution and high clinical satisfaction.

Conflict Of Interest: All authors have no conflict of interest to declare.

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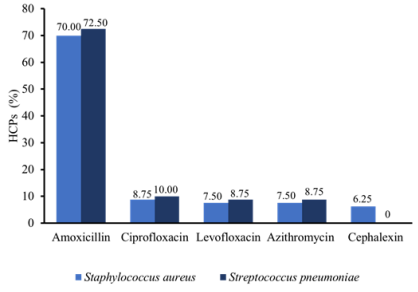
Table 1: Responses of HCPs on amoxicillin-clavulanic acid use in patients with CAP and AECOPD

Options	Response of HCPs (N=80)
Patients previously treated with other antibiotics	
2/10	15 (18.75)
3/10	14 (17.50)
4/10	19 (23.75)
>4/10	32 (40.00)
Age group of CAP patients	
<25 years	18 (22.50)
25-30 years	6 (7.50)
30-40 years	5 (6.25)
40-60 years	10 (12.50)
60 Years	41 (51.25)
Age group of AECOPD patients	
25 years	9 (11.25)
25-40 years	13 (16.25)
40-60 years	46 (57.50)
60 Years	12 (15.00)
Risk factors in CAP and AECOPD	
Inadequate nutrition & low weight	42 (52.50)
Recent history respiratory infection	21 (26.25)
Uncontrolled diabetes	10 (12.50)
Living in damp regions	7 (8.75)
Pathogens causing CAP and AECOPD	
Streptococcus pneumoniae	50 (62.50)
Staphylococcus aureus	18 (22.50)
Klebsiella pneumonia	8 (10.00)
Proteus mirabilis	2 (2.50)
Moraxella catarrhalis	2 (2.50)
ESBL-producing pathogens	62 (77.50)
Amoxicillin-clavulanic acid as empiric antibiotic	80 (100)
Fever and cough resolution after amoxicillin + clavulanic acid	

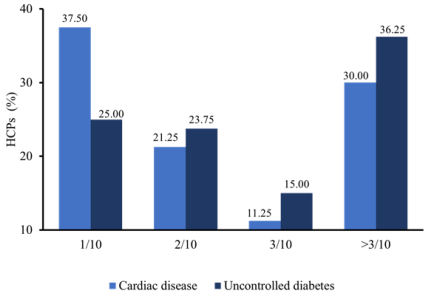
Day 2	38 (47.50)
Day 3	29 (36.25)
Day 4	13 (16.25)
Amoxicillin-clavulanic acid treatment duration in CAP or AECOPD	
5 days	20 (25.00)
7 days	43 (53.75)
10 days	9 (11.25)
14 days	8 (10.00)
Clinical global impression of amoxicillin-clavulanic acid in CAP (efficacy and safety)	
Excellent	60 (75.0)
Good	16 (20.0)
Fair	4 (5.0)
Key attributes for preferring amoxicillin-clavulanic acid in CAP or AECOPD	
Continued sensitivity of pathogens	45 (56.25)
Safety in cardiac patients	17 (21.25)
High clinical cure rates	5 (16.25)
No adverse effects on blood glucose	13 (6.25)
Appropriate treatment option for amoxicillin-clavulanic acid	
First-line agent for outpatient management	55 (68.75)
Severe penicillin allergy	14 (17.50)
When Legionella spp. is suspected	9 (11.25)
Elderly patients without comorbidities	2 (2.50)
Patient population benefiting from amoxicillin-clavulanic acid in CAP	
Adults with comorbidities	41 (51.25)
Adults with no comorbidities	16 (20.00)
Patients with severe pneumonia (ICU admission)	15 (18.75)
Immunocompromised patients	6 (7.50)
Children under 5 years	2 (2.50)

Data presented as n (%).
AECOPD, acute exacerbations of chronic obstructive pulmonary disease; CAP, community-acquired pneumonia; ESBL, extended-spectrum beta-lactamase; HCP, health care professional; ICU, intensive care unit.



HCP, health care professional.

Figure 1. Rising drug resistance in Staphylococcus aureus and Streptococcus pneumoniae based on local lab reports (N=80)



HCP, health care professional.

Figure 2: Patients with cardiac disease and uncontrolled diabetes (N=80)

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