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Open Access Journal of Pulmonary & Respiratory Sciences
ISSN: 2642-1143

Patterns of Recurrence and Antimicrobial Management in Respiratory Infections: A Real-World Retrospective Study

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Research Article

Volume 6 Issue 1

Received Date: September 07, 2021

Published Date: October 20, 2021

DOI: 10.23880/oajprs-16000148

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Abstract

Objectives: Respiratory tract infections (RTIs) significantly contribute to morbidity and mortality. Management of RTIs is complex with several etiological agents, development of resistance to antimicrobials, and multiple risk factors which may result in recurrence of infections. Therefore, choice of antibiotic therapy needs to be evidence-based for appropriate treatment and prevention of recurrence. This study aimed to explore the pattern of recurrence in RTIs and the type of antimicrobials used in real-world clinical settings.

Methods: This study was a retrospective, cross-sectional, observational, multicenter study. Electronic medical records of patients with upper RTIs (URTIs) and lower RTIs (LRTIs) visiting three centers from 2014 to 2020 were considered for the analysis.

Results: A total of 236 patients had an overall 531 episodes of RTIs with a mean age of 41.75 years. There were 391 LRTIs and 140 URTIs. Majority of the patients were adults (64.83%), and males were predominant (65.68%). In LRTI episodes, the most frequently prescribed antimicrobial monotherapy/fixed dose combination was macrolide (clarithromycin) (12.53%), followed by cefpodoxime-clavulanic acid (9.97%). Majority of the URTIs were managed with clarithromycin (49.28%) and azithromycin (16.43%). Recurrence of LRTI was observed in 23 patients with gram stain positive cocci. Additionally, out of 27 patients with culture-positive pseudomonas infections, 10 had recurrent LRTI episodes. Macrolides and cephalosporins were mostly prescribed in these episodes.

Conclusion: This study highlights that one of the major causes of recurrence could be incomplete eradication of pathogens. In the real-world scenario, recurrent URTI and LRTI episodes can be managed by macrolides and cephalosporins.

Keywords: Respiratory Infections; Recurrent Respiratory Tract Infections; Antimicrobial Management; Real-world

Abbreviations: RTIs: Respiratory Tract Infections; COPD: Chronic Obstructive Pulmonary Disease; ABPA: Allergic Bronchopulmonary Aspergillosis; GERD: Gastroesophageal Reflux Disease; EMRs: Electronic Medical Records; LRTI: Lower Respiratory Tract Infections; URTI: Upper Respiratory

Tract Infections; FDC: Fixed Dose Combination; ICMR: Indian Council of Medical Research; ATS: American Thoracic Society; NICE: National Institute for Clinical Excellence.

Introduction

Respiratory tract infections (RTIs) are common and significantly contribute to morbidity and mortality [1]. It is a common observation that respiratory infections are not only frequent in children but also found frequently among adults and the elderly with respiratory comorbidities such as chronic obstructive pulmonary disease (COPD) and bronchiectasis. Though many research studies have highlighted the epidemiology of respiratory infections, only a few have tried to explore the phenomenon of recurrence. Recurrence was found to be common in a cohort (0-2 years of age) of children, and the top 10 percentile had a median of 9.6 episodes per year. Early nasopharyngeal colonization with *Streptococcus pneumoniae* was common in children, who later developed recurrent infections. This study also highlighted the extent of morbidity because of recurrence as children with recurrent respiratory infections documented a median of 113 days with symptoms and six physician visits per child per year for respiratory infections [2]. The substantial burden of respiratory diseases in adults is associated with respiratory pathogens and their colonization [3]. Recurrent respiratory infections are caused by a wide variety of organisms, including bacteria and viruses. Important implicated bacteria includes *S. pneumoniae*, *S. pyogenes*, *Haemophilus influenzae* (type b and other strains), *Staphylococcus aureus*, and *Moraxella catarrhalis*. The viruses primarily include adenovirus, respiratory syncytial virus, influenza, and parainfluenza viruses [4]. The augmentation caused by the outgrowth of opportunistic pathogens within the microbiome of respiratory areas leads to the bacterial superinfection especially promoted by respiratory viruses. Therefore, there is increased morbidity and mortality, which are associated with bacterial superinfection in adults and children [5].

Identification of factors associated with recurrence can be challenging but essential for the management of these infections in children. There are several conditions associated with recurrence of respiratory infections in children viz. chronic suppurative lung diseases, primary and secondary immunodeficiency disorders, ciliary function disorders (cystic fibrosis), congenital abnormalities of the lung (lobar sequestration, bronchomalacia), and environmental factors (overcrowded homes, parental smoking) [6]. Recurrent respiratory infections are common in adults and have multiple potential causes [7]. These potential causes can be broadly classified into three categories viz. anatomical defects, primary and secondary immunodeficiencies. Major anatomical defects include structural abnormalities of the upper airway (deviated nasal septum, nasal polyps) or bronchi (congenital hypoplasia), which predisposes the patients to recurrent LRTIs. Lung diseases like bronchiectasis, allergic bronchopulmonary aspergillosis (ABPA) are few important risk factors for recurrent respiratory infections. Lung cancer, foreign bodies, and aspiration (seizure, alcohol) frequently show clinical presentations of recurrent respiratory infections. Among other conditions, cystic fibrosis, gastroesophageal reflux disease (GERD), and alfa-1 antitrypsin deficiency frequently present with recurrent respiratory infections. Immunodeficiencies, primary (selective IgA deficiency) and secondary (HIV, chemotherapy, nephrotic syndrome, immunosuppressive therapies) immunodeficiency disorders can also be implicated in the recurrence of these infections, though not as common as anatomical defects. Specific respiratory infections can be associated with a specific structural or other type of abnormality. Recurrent sinusitis more likely reflects allergic rhinitis, inadequate antibiotic therapy, or a local anatomic defect (nasal polyposis, deviated nasal septum). Recurrent streptococcal pharyngitis often reflects the inadequacy of antimicrobial therapy to eradicate pharyngeal carriage of group A beta-hemolytic Streptococci [8]. Recurrent pneumonia may be limited to an anatomical region (right middle lobe) because of a local anatomical defect (foreign body, mediastinal adenopathy) or can involve various lung regions, where a systemic abnormality can be an underlying reason [9,10].

Management of these infections is complex as there are multiple risk factors and various etiological agents that require detailed diagnostic workup. Several guidelines have been proposed by different academic bodies. Antimicrobial agents have a special role in both empirical as well as confirmatory treatment, though because of local variations in antimicrobial resistance patterns and involvement of many different bacteria, virus and atypical organisms, the choice of an appropriate antimicrobial agent is not easy. The current study explores the pattern of recurrence in respiratory infections and the type of antimicrobials used in real-world clinical settings.

Methods

This study was a retrospective, observational, cross-sectional, multicenter study based on the electronic medical records (EMRs) from one hospital and two clinic settings in India. Anonymized and de-identified data was used for analysis. Electronic medical records of patients who visited these centres from 2014 to 2020 and who had a diagnosis of RTI as per physician's discretion were included in the study. The study was conducted to explore the factors associated with the recurrence of respiratory infections in real-world clinical settings. Furthermore, associated conditions with

recurrence and type of microorganism implicated in these infections were assessed. This study tries to highlight the patterns of antimicrobial agents used empirically and as definitive treatment in different types of respiratory infections. Patients who had at least two RTIs in a year with at least two symptom free weeks between two episodes were included while pregnant or lactating women and tuberculosis patients were excluded from the study. Information on the patient profiles, significant medical history, distribution of complaints pattern across patients, comorbidities, diagnosis, antimicrobial prescription patterns, and status of the patients at the end of the episode was collected and analysed.

Statistical Analysis

Data analysis was done using Microsoft Excel (2016) and R Studio 3.6.2. Descriptive statistics were presented in the form of categorical and continuous variables. Categorical variables (like gender, status at the end of the episode) were expressed as percentages and compared using exact tests (Chi-square/Fisher's exact test). Continuous variables (like age) were expressed as means and compared by using t-statistics. Statistical significance was considered at $p<0.05$.

Results

A total of 236 patients reported 531 episodes of respiratory infections. The average age of the patients was 41.75 years. The total number of lower RTI (LRTI) and upper RTI (URTI) episodes were 391 and 140, respectively. Majority of the patients were adults (64.83%) and males (65.68%) (Table 1). In LRTI episodes, the most frequently prescribed antimicrobial monotherapy/fixed dose combination (FDC) was clarithromycin (12.53%), a macrolide, followed by cefpodoxime-clavulanic acid (9.97%). The most common combination for the management of LRTI included cefpodoxime-clavulanic acid with clarithromycin (26.60%) (Table 2). Further, majority of the URTIs were managed mainly with a single antimicrobial agent, clarithromycin (49.28%) which was followed by azithromycin (16.43%). Gram staining was done in 75 episodes of LRTI with gram-positive cocci in 57 (76.00%) episodes. Culture and sensitivity testing were done in 102 LRTI episodes and showed a positive growth in 57 (55.88%) episodes. *Pseudomonas aeruginosa* was found to be the most common isolate (26.47%) followed by *Klebsiella pneumoniae* (17.64%) and *Escherichia coli* (4.90%). Other important isolates included *S. pneumoniae, Acinetobacter baumanii, S. aureus* and *Serratia marcescens* (Table 3). Gram-positive cocci (gram staining) were associated with structural lung diseases as 77.19% episodes had a diagnosis of COPD, 26.31% of pneumonia, and 14.03% of bronchiectasis. *P. aeruginosa* was commonly isolated in patients with COPD (59.26%) and bronchiectasis (33.33%). *K. pneumoniae* was also isolated in patients with COPD (88.89%) and pneumonia (50.00%). There are instances in data where gram-positive cocci were reported in two episodes in the same patient, which showed colonization with these organisms. Common diagnoses with gram-positive cocci colonization were COPD and bronchiectasis. Similarly, *P. aeruginosa* isolation was more commonly found with COPD and bronchiectasis (Table 4).

Descriptive characteristics	N (%)
Total number of patients	236
Average age of the patients (mean, years)	41.75
Total number of episodes	531
Total number of episodes in LRTI	391 (73.63%)
Total number of episodes in URTI	140 (26.37%)
Age	
0-18 years	82 (34.75%)
19-55 years	44 (18.64%)
>55 years	110 (46.61%)
Gender	
Male	155 (65.68%)
Female	81 (34.32%)

LRTI, Lower Respiratory Tract Infection; N, Number of Patients; URTI, Upper Respiratory Tract Infection.

Table 1: Demographic characteristics of the patients.

Major combinations of antimicrobial agents	Class of antibiotics	N (%)
Antimicrobial agents/FDC in URTI (Top 5)		
Clarithromycin	Macrolide	69 (49.28%)
Azithromycin	Macrolide	23 (16.43%)
Amoxycillin-clavulanic acid	Penicillin-β lactamase inhibitor	9 (6.43%)
Cefdinir	Cephalosporin	7 (5.00%)
Amoxicillin	Penicillin	5 (3.57%)
Single antimicrobial agent/FDC in LRTI (Top 5)		

Clarithromycin	Macrolide	49 (12.53%)
Cefpodoxime-clavulanic acid	Cephalosporin-β lactamase inhibitor	39 (9.97%)
Amoxycillin-sulbactam	Penicillin-β lactamase inhibitor	20 (5.12%)
Azithromycin	Macrolide	15 (3.83%)
Amoxicillin-clavulanic acid	Penicillin-β lactamase inhibitor	14 (3.58%)
Two antimicrobial agents/FDC in LRTI (Top 6)		
Cefpodoxime-clavulanic acid + clarithromycin	Cephalosporin-β lactamase inhibitor + macrolide	104 (26.60%)
Cefpodoxime + clarithromycin	Cephalosporin + macrolide	9 (2.30%)
Meropenem + ciprofloxacin	Carbapenem + fluoroquinolone	9 (2.30%)
Meropenem + clarithromycin	Carbapenem + macrolide	9 (2.30%)
Cefpodoxime-clavulanic acid + azithromycin	Cephalosporin-β lactamase inhibitor + macrolide	4 (1.02%)
Cefpodoxime-clavulanic acid + ciprofloxacin	Cephalosporin-β lactamase inhibitor + fluoroquinolone	4 (1.02%)

FDC, Fixed-dose Combination; LRTI, Lower Respiratory Tract Infection; N, Number of Patients; URTI, Upper Respiratory Tract Infection.

Table 2: Antimicrobial patterns in the management of URTI and LRTI.

Gram staining and culture isolates in LRTI	N (%)
Gram-positive cocci (Gram staining done in 75 episodes)	Showed gram-positive cocci in 57 (76.00%)
Total culture done in 102 episodes	Positive culture: 57 (55.88%)
Pseudomonas aeruginosa	27 (26.47%)
Klebsiella pneumoniae	18 (17.64%)
Escherichia coli	5 (4.90%)
Streptococcus pneumoniae	3 (2.94%)
Acinetobacter baumannii	2 (1.96%)
Staphylococcus aureus	1 (0.98%)
Serratia marcescens	1 (0.98%)
No growth	45 (44.12%)

LRTI, Lower Respiratory Tract Infection; N, Number of Patients.

Table 3: Culture testing and gram staining results in LRTI episode.

Culture isolates/ gram staining results (N)	Mean age (years)	Respiratory diseases							
		Gender N (%)	COPD N (%)	Pneumonia N (%)	Bronchiectasis N (%)	ACO N (%)	ABPA N (%)	Bronchiolitis N (%)	Asthma N (%)
Gram staining									
Gram-positive cocci (57)	62.50	M 34 F 11	44 (77.19%)	15 (26.31%)	8 (14.03%)	3 (5.26%)	2 (3.51%)	4 (7.01%)	3 (5.26%)
Sputum culture results									
Pseudomonas aeruginosa (27)	60.40	M 19 F 3	16 (59.26%)	8 (29.62%)	9 (33.33%)	2 (7.41%)	5 (18.52%)	3 (11.11%)	2 (7.41%)

Klebsiella pneumoniae (18)	69.40	M 13 F 1	16 (88.89%)	9 (50.00%)	5 (27.78%)	-	1 (5.56%)	-	-
Culture microorganisms and gram-positive cocci isolated in recurrent episodes									
Gram positive cocci (23)	65.00	M 10 F 1	9	8	1	1	2	-	2
Pseudomonas aeruginosa (10)	54.20	M 3 F 2	4	2	3	1	2	1	2

ABPA, Allergic Bronchopulmonary Aspergillosis; ACO, Asthma-COPD Overlap; COPD, Chronic Obstructive Pulmonary Disease; FDC, Fixed-dose Combination; N, Number of Patients

Table 4: Summary of diagnosis of LRTI episodes and recurrent LRTI episodes amongst isolated microorganisms and gram-positive cocci.

Antimicrobial Prescription Patterns

Nearly half of the LRTI episodes (47.36%) in which gram-positive cocci were present, were managed with a combination of cefpodoxime-clavulanic acid and clarithromycin. In LRTI episodes with *P. aeruginosa* positive cultures, cefpodoxime-clavulanic acid and clarithromycin (25.92%) and a combination of meropenem and ciprofloxacin (18.51%) were prescribed more frequently. Recurrence of LRTI was observed in 23 patients with gram stain positive cocci. Additionally, out of 27 patients with culture-positive pseudomonas infections, 10 had recurrent LRTI episodes. A combination of two antimicrobial agents/FDC was prescribed more often in the recurrent LRTI episodes with *P. aeruginosa* in their sputum culture. A combination of macrolide and cephalosporin (clarithromycin and cefpodoxime-clavulanic acid) was mostly prescribed in these cases (Table 5). The most common adverse events noticed were diarrhea, abdominal discomfort, urticaria, phlebitis, and nausea. Of these, two patients were switched to clarithromycin (Table 6).

Antimicrobial therapy	N (%)
Gram-positive cocci (57)	
Cefpodoxime-clavulanic acid + clarithromycin	**27 (47.36%)**
Cefpodoxime-clavulanic acid	7 (12.28%)
Meropenem + clarithromycin	3 (5.26%)
Amoxycillin-sulbactam	2 (3.50%)
Clarithromycin	2 (3.50%)
***Pseudomonas aeruginosa* (n=27)**	
Cefpodoxime-clavulanic acid + clarithromycin	**7 (25.92%)**
Meropenem + ciprofloxacin	**5 (18.51%)**
Cefpodoxime + ciprofloxacin	1 (3.70%)
Cefepime + clarithromycin	1 (3.70%)
Cefoperazone-tazobactam + ciprofloxacin	1 (3.70%)
Clarithromycin	1 (3.70%)
Clarithromycin + meropenem	1 (3.70%)
Polymyxin B + aztreonam	1 (3.70%)
Ciprofloxacin	1 (3.70%)
Note: Clarithromycin was used in 13 out of 27 episodes, ciprofloxacin in 10 episodes and cefpodoxime-clavulanic acid in 7 episodes	
***Klebsiella pneumoniae* (18)**	

Cefpodoxime-clavulanic acid + clarithromycin	**7 (38.88%)**
Meropenem + clarithromycin	2 (11.11%)
Cefoperazone-tazobactam + cefpodoxime + clarithromycin	1 (5.55%)
Cefpodoxime + clarithromycin + phenazopyridine	1 (5.55%)
Cefpodoxime + clarithromycin + phenazopyridine + cefpodoxime-clavulanic acid	1 (5.55%)
Antibiotic therapy for recurrent episodes with positive cocci on gram staining	
Gram positive cocci (23)	
Cefpodoxime-clavulanic acid	**2 (8.69%)**
Cefoperazone-tazobactam + ciprofloxacin	1 (4.35%)
Cefpodoxime + ciprofloxacin	1 (4.35%)
Cefpodoxime-clavulanic acid + ciprofloxacin	1 (4.35%)
Cefpodoxime-clavulanic acid + clarithromycin	1 (4.35%)
***Pseudomonas aeruginosa* (10)**	
Cefpodoxime-clavulanic acid + clarithromycin	**3 (30.00%)**
Meropenem + ciprofloxacin	**2 (20.00%)**
Cefoperazone-tazobactam + ciprofloxacin	1 (10.00%)
Cefpodoxime + ciprofloxacin	1 (10.00%)
Cefpodoxime-clavulanic acid	1 (10.00%)

Table 5: Common antibiotic therapy prescribed for culture isolates and gram-positive cocci in LRTI episodes.

Antimicrobial agents	Total no. of antimicrobial agents (Prescription)	Adverse events (n)	Switch to antimicrobial agents
Amoxicillin-clavulanic acid	24	Diarrhoea (2)	-
Clarithromycin	280	Abdominal discomfort (1)	-
Amoxicillin	10	Urticaria (1)	Clarithromycin (1)
Ceftriaxone-sulbactam	1	Phlebitis (1)	Clarithromycin (1)
Doxycycline	3	Nausea (1)	-

Table 6: Adverse event profile of antimicrobial agents and switch over patterns.

Discussion

The current study was designed to understand the management of recurrent respiratory infections in real-world clinical settings along with the clinical factors associated with the recurrence of these infections. According to the treatment guidelines for antimicrobial use in common syndromes, 2019, by the Indian Council of Medical Research (ICMR), important non-viral causes of URTIs include *S. pyogenes, M. catarrhalis, Pneumococci, S. aureus, H. influenzae, Mycoplasma, Bordetella pertussis,* etc. These guidelines recommend penicillin V and amoxicillin for streptococcal pharyngitis and amoxicillin-clavulanic acid for bacterial sinusitis and acute otitis media, and cephalosporins (ceftriaxone, cefpodoxime, cefuroxime, cefdinir) as an alternative to the primary antimicrobial agent. Macrolides and respiratory quinolones are recommended for patients with an allergic history of penicillin [11]. The current study also explored factors associated with the recurrence of respiratory infections. It was ascertained that most of the respiratory episodes have been managed as an isolated case on an outpatient basis in which culture and sensitivity testing was done in only a few episodes of infection and the majority were treated empirically.

For the management of community-acquired pneumonia, ICMR guidelines [11] recommend amoxycillin-clavulanic acid as the first-line drug for outpatients without comorbidity and macrolides as alternatives, while for inpatients ceftriaxone with macrolides/doxycycline. For inpatients with risk factors for *P. aeruginosa* and other gram-negative bacteria, a combination of piperacillin-tazobactam/

macrolides/doxycycline is the preferred choice and cefotaxime/amoxiclav with a macrolides/doxycycline as the alternative. Our analysis showed that similar combinations were used among inpatients with LRTI. Cefpodoxime-clavulanic acid with clarithromycin was commonly used as a combination therapy in LRTI. Major single agents/FDC in LRTI included cefpodoxime-clavulanic acid, clarithromycin, azithromycin, amoxicillin-sulbactam and amoxicillin-clavulanic acid. As majority of the patients either recovered or improved, it is difficult to compare the efficacy of these antimicrobial regimens. But these combinations were found to be effective in LRTIs with or without comorbidities. Further, the frequently used antimicrobials in URTI included clarithromycin, azithromycin and amoxicillin-clavulanic acid.

In our study, gram stain results showed that out of 57 patients, 23 patients with gram stain positive cocci showed recurrence (2 or 3 episodes). These patients had a higher proportion of comorbidities like COPD (9 patients), pneumonia (8 patients), ABPA (2 patients), and asthma (2 patients). D Bogaert [12] in his study, concluded that pneumococcal colonization is the first step of invasive disease. Another study reported colonization by bacterial pathogens (*H. influenzae, Pneumococci, P. aeruginosa*, and *M. catarrhalis*) in COPD patients was associated with a significant increase in daily clinical symptoms [13]. An analysis of pooled data from six studies by Russel et al. [14], estimated that 25% of COPD patients are colonized with potentially pathogenic microorganisms and a higher load of these microorganisms were reported in stable COPD (*H. influenzae, Pneumococci*) and during acute exacerbations of COPD (*H. influenzae* and *P. aeruginosa*). Higher contribution of bacterial infections in acute exacerbations of COPD rationalizes the use of antimicrobial therapy as our study found a high association of bacterial isolation with COPD. Patients with culture-positive pseudomonal infections had conditions such as COPD (~60.00%) and bronchiectasis (33.33%). Out of 27 patients with culture-positive pseudomonas infections, 10 had recurrent culture-positive episodes. Pseudomonas was more commonly found with COPD and bronchiectasis. Studies have also explored the role of antimicrobial agents in reducing the rate of exacerbations in COPD, especially macrolides because of their immunomodulatory and anti-inflammatory properties other than high activity against microorganisms implicated in COPD exacerbations [15].

Overall, outcomes were recorded in 517 episodes, and all episodes were either resolved or improved. Because of the good universal outcomes, it is not possible to compare different regimens in terms of efficacy. Macrolides (clarithromycin, azithromycin), cephalosporins (cefpodoxime, cefoperazone), fluoroquinolones (ciprofloxacin), carbapenems (meropenem), beta-lactamase inhibitors (amoxicillin-clavulanic acid, piperacillin-sulbactam), and penicillin (amoxicillin) were among the major antimicrobials used to treat respiratory infections as a single agent or in combinations. A retrospective cohort study compared the effectiveness of macrolides and quinolones for patients hospitalized with acute exacerbations of COPD and found a similar rate of treatment failure (6.8% for macrolides and 7.7% for fluoroquinolones), though macrolides were less frequently associated with diarrhea (0.6% vs 1.2%) [16]. There was only one episode (0.36%) of abdominal discomfort reported with clarithromycin, while there were two episodes (8.33%) of diarrhea in 24 prescriptions of amoxycillin-clavulanic acid. A review of clinical trials reported incidence of antibiotic-associated diarrhea as 19.8% for amoxycillin-clavulanic acid and 8.1% for amoxicillin in children [17]. Prescription patterns of antimicrobial agents vary across hospitals and also at the same centers which might be because of slightly conflicting recommendations by different guidelines. For example, the American Thoracic Society (ATS) recommends a fluoroquinolone or amoxicillin-clavulanic acid, while the National Institute for Clinical Excellence (NICE) guidelines recommends empirical treatment with aminopenicillin, a macrolide or a tetracycline in acute exacerbations of COPD [18,19]. It is difficult to ascertain the effectiveness of these agents as multiple medications are co-prescribed; for example, macrolides are commonly prescribed along with cephalosporins.

Conclusion

Our study is an effort to understand the phenomenon of recurrence of respiratory infections in real-world clinical settings. Though it is difficult to ascertain factors associated with recurrence without understanding several epidemiological, demographic, socioeconomic, and environmental factors, however, we have tried to highlight certain factors such as structural lung diseases (COPD, bronchiectasis) are associated with colonization of pseudomonas and gram-positive cocci. In the real-world scenario, recurrent URTI and LRTI episodes can be managed by macrolides and cephalosporins. There are variations in antimicrobial regimens and most of the patients receive empirical treatment, though judicious use of antimicrobials results in improved outcomes in most cases. This study highlights that recurrence could be because of incomplete eradication of pathogens, and risk factors for colonization need to be explored in detail and their contribution in recurrences should be investigated in prospective studies.

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