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PRESCRIBING PATTERN OF ANTIBIOTICS IN COPD - A REVIEW

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ABSTRACT

Acute exacerbation of chronic obstructive pulmonary disease (COPD) is a common cause of consultation in general practice across the globe. Antibiotics are widely used in the therapeutic regimen for the chronic obstructive pulmonary disease. The effect of antibiotics in patients with chronic obstructive pulmonary disease is limited and there is no general agreement about the criteria to use them. The benefit of antibiotics in mild to moderate exacerbations of chronic obstructive pulmonary disease remains controversial, and their overuse can contribute to the development of bacterial resistance. This study was carried out to collect relevant demographic information, antibiotic prescribing patterns. For this, various published articles obtained from various sources like google scholar databases, PubMed databases were reviewed. Based on the study conducted, it was found out that, a periodic study on the usage of antibiotics and sensitivity pattern in the hospitals will enable the health care professionals to select the appropriate antibiotic to promote the rational use of antibiotics and to reduce antibiotic resistance.

KEY WORDS: Antibiotics, COPD, Prescribing pattern

INTRODUCTION

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, Chronic Obstructive Pulmonary Disease (COPD) is defined as a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The epidemiological studies show that, COPD is a leading cause of morbidity and mortality worldwide currently being the fourth leading cause of death in the world but is projected to be the 3rd leading cause of death by 2020 that induces an economic and social burden that is both substantial and increasing. COPD prevalence, morbidity and mortality vary across countries and across different groups within countries [1]

Exacerbations of COPD

Exacerbations of chronic obstructive pulmonary disease (COPD) are important events in the management of COPD because they negatively impact health status, rates of hospitalization and readmission, and disease progression. As per Global Initiative for Chronic Obstructive Lung Disease guidelines, COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy.

Exacerbations are mainly triggered by

- Respiratory infections
  - Viral infections
  - Bacterial infections[1]
- Environmental factors
  - Pollution
  - Ambient temperature
  - Short term exposure to fine particulate matter (PM 2.5) [1]
- Non environmental factors
  - Heart failure
  - Noncompliance with medication[2]

Respiratory Infections

Most often, the acute exacerbations of COPD are the result of either a bacterial or viral infection, that the patient may develop due to a possible impairment of the innate immune system.[2]

Viral Infections

Two-thirds of all cases of acute exacerbations of COPD may be due to viral infections.[3] The common viruses that are associated with triggering exacerbations of COPD are *Rhinovirus* (40%–50%), *Parainfluenza* (10%–20%), *Influenza* (10%–20%), *RSV* (10%–20%),

Coronavirus (10%–20%), and *Adenovirus* (5%–10%).[4] The most common virus isolated is the human rhinovirus that causes the common cold and it can be detected for up to a week after an exacerbation onset.[1] Single virus species are frequently detectable in stable COPD patients, whereas detection of more than one virus species is usually associated with exacerbations. In general, viruses are more commonly detectable in patients with more severe airway disease.[4] Viral exacerbations are associated with a higher duration of hospital stay with an average of 9 days than bacterial exacerbations that has an average of 7 days of hospital stay.[5] Optimization of vaccination and antiviral treatment might increase the prognosis of individuals with chronic respiratory disease.[6]

Bacterial Infections

Exacerbations can be associated with increased sputum production and, if purulent, there are studies that demonstrated increased bacteria in the sputum.[1] Bacterial infection is a factor in 70 to 75 percent of exacerbations, which is generally caused by *Streptococcus, pneumoniae* (15%–20%), *Haemophilus influenzae* (30%–50%) or *Moraxella catarrhalis* (15%–20%).[7] The bacteria that are associated with exacerbations in COPD could potentially be a new strains of bacteria from the upper respiratory tract or from chronic colonization of the lower respiratory tract. It is found that the viral infections may down-regulate host defense leading to enhanced bacterial proliferation and inflammation.[8]

Five potential pathways by which bacteria could contribute to the course and pathogenesis of COPD can be identified.

(i) Childhood lower respiratory tract infection impairs lung growth, reflected in smaller lung volumes in adulthood.
(ii) Bacteria cause a substantial proportion of acute exacerbations of chronic bronchitis which cause considerable morbidity and mortality.
(iii) Chronic colonization of the lower respiratory tract by bacterial pathogens amplifies the chronic inflammatory response present in COPD and leads to progressive airway obstruction (vicious circle hypothesis).
(iv) Bacterial pathogens invade and persist in respiratory tissues, alter the host response to cigarette smoke, or induce a chronic inflammatory response and thus contribute to the pathogenesis of COPD.
(v) Bacterial antigens in the lower airway induce hypersensitivity that enhances airway hyperreactivity and induces eosinophilic inflammation.[9]

Environmental Factors

Environmental factors such as pollution and ambient temperature may also initiate and/or amplify these events. Short-term exposure to fine particulate matter (PM2.5) is associated with increased hospitalizations for acute exacerbations and increased mortality of COPD.[1]

Non-Environmental Factors

Exacerbations of COPD can be caused by non-environmental factors or patient specific factors like heart failure or noncompliance with medication use.[1]

The Role of Antibiotics in The Treatment of Exacerbations

Although as many as two-thirds of all cases of AECOPD may be due to viral infections, COPD treatment guidelines nevertheless recommend antibiotic treatment for patients qualifying the Anthonisen criteria, which is characterised by increased dyspnoea, increased sputum volume and increased sputum purulence.[10] The role and choice of antibiotics in the treatment of exacerbations has been a matter of controversy.[7] Antibiotic therapy has been shown to have a small but important effect on clinical recovery and outcome in patients with acute exacerbations of chronic bronchitis and emphysema.[11] Therefore, antibiotic administration should be considered at the beginning of treatment for exacerbations of COPD.[12]

Most adult patients are experiencing an exacerbation of chronic lung disease, particularly chronic obstructive pulmonary disease, when neutrophilic inflammation in response to bacterial infection leads to increased sputum volume and viscosity, and breathlessness due to airflow obstruction. In these circumstances, bacteria are cultured from sputum in about half of the cases which means that, in some of the others, accepting that sputum culture is not a sensitive investigation, antibiotics are given unnecessarily.

Antibiotics are essential when a patient with severe COPD presents with purulent sputum and systemic symptoms of infection, but they are often given either to speed up recovery from a bacterial infection that might be expected to resolve spontaneously following a successful host inflammatory response, or in a defensive manner to avoid the risk of airway infection progressing to pneumonia and causing deterioration in a more compromised patient whose host defenses are more seriously impaired.[13]

Choice of Antibiotics in The Treatment of Exacerbations

Antimicrobial choices can be based upon the local patterns of antibiotic sensitivity among the most common responsible pathogens.[14] According to Sethi, rather than using the same antibiotic for all exacerbations as initial empiric therapy, a stratification approach to choosing an antibiotic that takes into consideration, the risk factors for poor outcome and the probability of infection with an antimicrobial-resistant pathogen should be advocated.

Patients with exacerbations can be stratified into:

- Complicated (those with one or more of the following risk factors: advanced age, severe airflow obstruction, frequent exacerbations, comorbid cardiac disease)
- Uncomplicated (none of those risk factors).

Complicated patients should be treated with a fluoroquinolone or amoxicillin/clavulanate, whereas the uncomplicated patients with a macrolide, cephalosporin, tetracycline or trimethoprim/sulfamethoxazoleis appropriate. It also suggests that in all patients, a class of antibiotics that differs to those received in the previous 3 months for any reason should be used, in order to minimise ineffective therapy because of antibiotic resistance. The response to therapy should be evaluated after 48–72 hours.[15]

Antibiotics Prescribed in COPD

1. Penicillins

Penicillin antibiotics were among the first medications to be effective against many bacterial infections caused by staphylococci and streptococci.[16]

The analysis of prescriptions for class of antibiotics in respiratory tract infections in COPD exacerbations by Errabelly *et al*, showed that penicillins + beta lactams constituted 38.31% of the prescriptions. Among this penicillin +beta lactam class of antibiotic the most preferred antibiotic was piperacillin + tazobactam which constituted 92.68% and was followed by amoxicillin + clavulanic acid in 7.31% of the prescriptions.[17]

On a study conducted in antibiotic prescribing pattern, with reference to antibiotic sensitivity test in the acute exacerbations of COPD done by Shrestha *et al*, showed that 23% of the prescribed drugs came from the penicillin group.[18]

Penicillin antibiotics that were prescribed at the time of discharge of patients in the study conducted by Ravi *et al* were with amoxicillin being most commonly prescribed consisting of 38.7%, followed by Ampicillin (24.8%), amoxicillin (16.7%), crystalline penicillin (8.1%) among the predominant antibiotics, that were prescribed.[19]

In the study performed by Lakshmi *et al* on the antibiotic prescribing pattern in obstructive lung disease inpatients showed that penicillins were prescribed only in 14% of the cases.[20]

Faheemuddin *et al* found out that Penicillins were used in 20% of their patients.[21]

Kothai *et al* in their study determined that amoxicillin was prescribed in 11.11% cases in COPD patients.[22]

Gupta *et al* found out in their study that out of the total prescription of co-amoxiclav, 37.5% were prescribed to COPD patients.[23]

Amoxicillin &Clavulanic acid constituted 21.63% of the prescription in the study conducted by Maqusood *et al*.[24]

Adil *et al* in their study were able to identify that, of the antibiotics prescribed to the COPD patients, 42.2% constituted penicillin class of antibiotics.[25]

Mahmoodan *et al* found that Piperacillin–Tazobactam were used in 14.5% of the cases and Amoxicillin-Clavulanate in 7.2% of the cases.[26]

2. Cephalosporins

Cephalosporins are broad spectrum antibiotics similar to penicillin. They have a beta-lactam ring which interferes with bacterial cell wall synthesis by binding to penicillin-binding proteins, eventually leading to cell lysis and death.[27]

Errabelly *et al* in their study found that cephalosporins 30.84% constituted the prescriptions, also cephalosporins + beta lactams combination was used in 7.47% cases. Among the prescribed cephalosporins, the most widely prescribed cephalosporin was cefuroxime (73%), followed by ceftriaxone (12%), cefotaxime (9%), cefoperazone (3%) and cefixime (3%). In the cephalosporins + beta lactams class, the preferred antibiotic was ceftriaxone + sulbactam (50%) followed by ceftriaxone+ tazobactam (25%), and cefoperazone+ sulbactam (25%) in the prescriptions.[17]

Cephalosporin group of drugs constituted 68% of prescription in the study conducted by Shrestha *et al*. In this study, the widely prescribed antibiotic combination was one group from Cephalosporin group plus Azithromycin, which consisted of 22% of the prescription and about 3% of the treated patients were also prescribed with one group from Cephalosporin plus Amoxicillin + Clavulanate.[18]

Cephalosporins are the most frequently prescribed antibiotic in the study conducted by Lakshmi *et al* which covered 88% of the prescription.[20]

Cephalosporin's consisted of 25.2% of prescriptions in the study by Faheemuddin *et al* and Cephalosporins + β-lactamase inhibitors consisted of 8.6%.[21]

In the study by Kothai *et al* 77% of the total prescription consisted of cephalosporins class of antibiotics, of which, 54.97% were Ceftriaxone and 16.69% was Cefotaxime.[22]

Gupta *et al* in their study found out that cephalosporins were prescribed in 13.75% of cases.[23]

In the study conducted by Adil *et al*, Cephalosporin were used in 30.1% of the prescriptions of antibiotics.[25]

Mahmoodan *et al* found out that Cefotaxime and Ceftriaxone, under the cephalosporin class of antibiotics were used in 16.9% and 13.2% of the prescriptions respectively.[26]

3. Macrolides

Macrolides interfere with bacterial protein synthesis and, depending on concentration and bacterial species, are either bactericidal (kill bacteria), or bacteriostatic (inhibit growth of bacteria). Macrolides also have immunomodulatory and anti-inflammatory effects.[28]

Errabelly *et al* in their study found out the use of macrolides to be 13.08%. Among the prescribed macrolides the most prescribed regimen was azithromycin (71.42%) followed by clarithromycin (28.57%).[17]

In the study of Shrestha *et al*, the macrolide Azithromycin constituted 32% of the prescription.[18]

Lakshmi *et al* in their study found out the use of macrolides in 39% of their study cases.[20]

In their study, Faheemuddin *et al* found the usage of Macrolides in the prescription to be 19.3%.[21]

According to Aleksandr *et al*, 40.67% of their study prescription consisted of macrolides.[29]

Gupta *et al*, in their study found that the macrolides, Azithromycin and clarithromycin were prescribed in 17.5% and 12.55% of the COPD cases respectively.[23]

Macrolides consisted of 5.4% of the prescriptions in the study by Adil *et al*. [25]

The use of azithromycin in the prescription for COPD patients were found to be 10.8% and 10.82% in the studies conducted by Mahmoodan *et al* [26] and Maqusood *et al*, respectively.[24]

4. Aminoglycosides

Aminoglycosides are highly potent, broad-spectrum antibiotics with many desirable properties for the treatment of life-threatening infections. Aminoglycosides act primarily by impairing bacterial protein synthesis through binding to prokaryotic ribosomes.[30]

In the study conducted by Errabelly *et al*, the use of aminoglycosides was found to be the least consisting of 0.93% of the prescriptions only.[17]

Aminoglycosides constituted 12.5% of the total prescriptions in the study conducted by Lakshmi *et al*. [20]

Faheemuddin *et al* in their study found out that aminoglycosides were utilized in 8.6% of cases in their study.[21]

The prescribed aminoglycosides constituted, 6.25% of the total antibiotic prescription in the study conducted by Gupta *et al*. [23]

Adil *et al* during their study found out that aminoglycosides were used only in 0.8% of the cases.[25]

5. Tetracyclines

The tetracyclines, are a family of antibiotics that inhibit protein synthesis by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor (A) site. Tetracyclines are broad-spectrum agents, exhibiting activity against a wide range of gram-positive and gram-negative bacteria, atypical organisms such as chlamydiae, mycoplasmas, and rickettsiae, and protozoan parasites.[31]

The use of tetracyclines were found to be 6.5% in the study by Lakshmi *et al*. [20]

6. Quinolones and Fluroquinolones

Quinolones are one of the most commonly prescribed classes of antibacterial in the world and are used to treat a variety of bacterial infections in humans. Quinolones act by converting their targets, gyrase and topoisomerase IV, into toxic enzymes that fragment the bacterial chromosome.[32]

In their study, Errabelly *et al* quinolones were used in 2.80% of the total antibiotic prescription.[17]

Ravi *et al* in their study determined the use of ciprofloxacin to be 11.5%.[19]

The use of quinolones was found to be 48% and 34.89% in the studies conducted by Lakshmi *et al*[20] and Aleksandr *et al*[29] respectively.

Faheemuddin *et al* during their study found that 5.2% were Fluroquinolones.[21]

In their study, Gupta *et al* found the use of fluoroquinolones like moxifloxacin used in 12.5% of the prescriptions.[23]

Adil *et al* found that fluroquinolones were prescribed in 14.6% of the prescriptions.[25]

Mahmoodan *et al* found during their study that, ciprofloxacin constituted 22.9% and levofloxacin constituted 14.5% of the total prescriptions.[26]

Conclusion

The prescribing pattern and the choice of antibiotics differ to a greater extend among different prescribers across the globe. The need for the antibiotic therapy should be justified based on the signs and symptoms presented by the patient. The choice of antibiotics should be based on the local patterns of antibiotic sensitivity among the most common responsible pathogenic

organisms. The complications associated with the patients should also be taken into consideration while prescribing antibiotics in COPD patients presenting acute exacerbations. The use of antibiotics should be rational way in such a way that it does not lead to antibiotic resistance as well as reduce or prevent the occurrence of adverse events associated with antibiotic use in patients.

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