Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction that is not fully reversible. The airflow obstruction does not change markedly over several months and is usually progressive in the long-term. Exacerbations are key events in COPD, defined by the presence of worsening symptoms, but also often associated with concurrent deteriorations in pulmonary function and increases in both local and systemic inflammation. COPD is a leading cause of morbidity and mortality worldwide, and results in economic and social burdens that is both substantial and increasing. COPD is the fourth leading cause of death worldwide and is estimated to be the third leading cause of death by 2020. The role of antibiotics in treating mild or moderate exacerbations in patients with acute COPD is unclear. The enormous clinical and economic impact of COPD has prompted the development of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD. This committee has adequately outlined the goals of COPD management that include reduction of disease progression and mortality, relief of symptoms, improvement in exercise tolerance and health status, and prevention of exacerbations and complications. Acute exacerbations of COPD are treated with oxygen (in hypoxemic patients), inhaled β-agonists, inhaled anticholinergics, antibiotics and systemic corticosteroids. Methylxanthine therapy may be considered in patients who do not respond to other bronchodilators. Antibiotic therapy is directed at the most common pathogens, including Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis. Mild to moderate exacerbations of COPD are usually treated with older broad-spectrum antibiotics.
such as doxycycline, trimethoprim-sulfamethoxazole and amoxicillin-clavulanate potassium. Treatment with augmented penicillins, fluoroquinolones, third-generation cephalosporins or aminoglycosides may be considered in patients with more severe exacerbations.[6] International guidelines advocate a 7- to 14-day course of systemic glucocorticoid therapy in acute exacerbations of COPD. However, the optimal dose and duration are unknown.[7] Drug utilization studies are powerful exploratory tools to ascertain the role of drugs in society. These studies create a sound sociomedical and health economic basis for healthcare decision making. COPD is underdiagnosed and repeatedly misdiagnosed, which possibly underwrites to the ongoing upsurges in the occurrence, sickness and death-related with this disease. This is unlucky since COPD cannot be healed, it can be cured efficiently, chiefly through the previous stages of the disease. Evidence-based guidelines (GOLD) established to contribute in the inhibition, diagnosis and controlling of COPD, are offered to health care professionals concerned in learning more about COPD. These guidelines are efficient and reviewed on a consistent basis to replicate recent developments in our understanding of the pathophysiology of and managements available for COPD. However, primary-care physicians have stated a lack of awareness of the essential ideas behind the best management of COPD obtainable in the guidelines.

**Methods**

The study was conducted during the period of year 2008 from January to June at Trivandrum Medical College and Hospital in Kerala, India which is a tertiary care hospital. This was a prospective observational study aimed at recognizing the drug utilization pattern for the treatment of acute exacerbation of COPD for 7-day under nonexperimental settings. All information significant to the study was collected from the case records and discussions conducted with the inpatients and bystanders during ward rounds, with the support of a physician. Moreover, daily follow-ups were conducted to assemble data on amendment in therapy, add-on therapy, and clinical improvement until the patient was discharged from the hospital or to a upper limit of 7-day, whichever is earlier.[8,9] The adverse drug reactions related to the drugs were monitored and documented in a suitably designed adverse drug reaction documentation form through an interview with the patients. The study was approved by the Human Ethical Committee of the concerned hospital in India. An informed consent form, approved by the Human Ethical Committee, was signed by all patients and this process was in accordance with good clinical practices.

**Study sample**

A total number of 120 eligible consenting patients were randomly selected by convenience sampling technique for the study. Patients with diagnosis of acute exacerbation of COPD continued treatment as defined by GOLD were randomly selected.[8,9] Exclusion criteria were as follows: Diagnosis of cystic fibrosis, asthma, or severe bronchiectasis, evidence of pneumonia either at presentation or during follow-up.

**Statistical analysis**

Data were analyzed using computer software, Statistical Package for Social Sciences (SPSS) version 17 by IBM Corporation. Data are expressed in its frequency and percentage. To elucidate the associations and comparison between different parameters, Chi-square test, t-test, paired t-test, were used.

**Results**

A total of 120 patients were initially identified and included in the analysis. Demographic and clinical characteristics of the study patients at the time of identification are summarized [Table 1]. Majority of the patients were of a low socioeconomic status according to the modified Kuppuswamy scale.[10] Most of the patients came under Types I and II grade of exacerbation (52.5% and 37.5%, respectively) as per the grading scale for exacerbation of COPD.[3,11]

All the patients in this study were receiving combination therapy [Table 2]. Among the inhalational β-agonists, salbutamol accounted for 74%, followed by formoterol. Among the oral β-agonist, all of them received salbutamol. Parenteral steroids were used in 72.5% of the patients and all of them received hydrocortisone. Steroid inhalers were used in 25% of patients with all of them receiving budesonide. Methylxanthine was taken by all the patients (100%), in which the most common was deriphylline (hydroxyethyl theophylline), which accounted for about 96% use, followed by aminophylline. Anticholinergics

| Table 1: Characteristics of the study population (n=120) |
|---------------------------------|-----------------|
| Variables                       | Mean (SD) or percentage |
| Demographic                     |                  |
| Male sex                        | 87.5             |
| Age (in years)                  | 66 (11)          |
| Socioeconomic status            |                  |
| Upper middle                    | 7.5              |
| Lower middle                    | 42.5             |
| Upper lower                     | 50               |
| Active smokers                  | 42.5             |
| Smoking index >300 pack-year    | 94.4             |
| Co-morbid conditions            |                  |
| Hypertension                    | 30               |
| Diabetes                        | 30               |
| Alcoholism                      | 55.8             |
| Coronary artery disease         | 10               |
| Tuberculosis                    | 10               |
| Renal disease                   | 5                |
| Hyperlipidemia                  | 2.5              |
| Severity index of lung function test |                |
| FEV<sub>1</sub>, percentage of predicted | 44.1 (6.2) |
| FEV<sub>1</sub>,<40             | 38.9             |
| FEV<sub>1</sub>,>40             | 61.1             |
| Grade of exacerbation           |                  |
| I                               | 52.5             |
| II                              | 37.5             |
| III                             | 10               |

FEV<sub>1</sub>: Forced expiratory volume in 1 s; SD: Standard deviation
were used in 77.5% of patients in which 90% were ipratropium, followed by tiotropium. Oxygen therapy was used in 82% patients.

Antibiotics were used in 86.7% patients. According to the antibiotic groups, most of the patients came under Group B (62.5%), followed by Group A (17.5%) and Group C (7.5%) where group A indicates mild exacerbation: No risk factors for poor outcome, Group B indicates moderate exacerbation with risk factor (s) for poor outcome and Group C indicates severe exacerbation with risk factors for *Pseudomonas aeruginosa* infection.[12] Drug utilization pattern of antibiotics in this study is given in Tables 3 and 4. Number of drugs including antibiotics used during the study period has been shown in these tables. The adverse effects noted were dry mouth (15%), had taste (10%), tremor (10%), nausea/vomiting (7.5%), and diarrhea (7.5%). The main adverse effects noted were highly correlated with use of anticholinergics (*P* < 0.05).

### Discussion

The age distribution added support to the evidence of the previous studies that only those above 40 years of age were admitted during the period of the study. According to the sex wise distribution, majority of the patients were of the male sex which was as high as 87.5%. The females accounted for around 12%. Male to Female ratio was 7:1. This only confirmed the finding of the previous study conducted that males accounted for the majority of the disease burden.[13]

Demographic profile of patients who came under this study revealed that most of them were of a low socioeconomic status according to the modified Kuppuswamy scale.[10] This may be because the hospital in which the study was undertaken was a Government hospital offering free treatment. Another explanation may be that according to the GOLD guideline, people of low socioeconomic status tend to have increased incidence of COPD.[5,14]

Majority of the patients in the present study had co-morbid conditions (*n* = 93; 77.5%). The most commonly observed co-morbid conditions were alcoholism (55.8%), Type II diabetes mellitus (30%), and hypertension (30%). These findings were almost similar to the result of previous study in which 69.8% patients had co-morbid conditions.[10]

All the patients in this study were receiving combination therapy.[13] All of the patients were receiving methyloxanthines out of which 96% were receiving hydroxyethyl theophylline (deriphylline) and the remaining aminophylline. However in the previous studies,[5,14] the use of methyloxanthines was minimal. This may be because methyloxanthines were one of the most freely available drugs in the hospital in which the study was under taken.

Similarly, all of the patients were receiving either oral or inhalational *β*-agonists. Among the inhalational *β*-agonists, salbutamol accounted for 74%, followed by formeterol. Parenteral steroids were used in 72.5% of the patients and all of them received hydrocortisone. Steroid inhalers were used in 25% of patients with all of them receiving budesonide. Anticholinergics were used in 77.5% of patients in which 90% were ipratropium.[13]

Antibiotics were used in 86.7% of patients in this study. This finding was not in accordance with the previous studies,[15,16] which revealed 52% and 99% use, respectively. This may be an indicator of the prevalence of infections among the patients admitted with acute exacerbation of COPD in different demographic areas.

According to the GOLD criteria and Cochrane reviews,[17-20] patients presenting with acute exacerbation of COPD is to be initially managed with *β*-agonists following which if there is no

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#### Table 2: Drug utilization pattern (*n*=120)

| Pattern                          | Drugs utilized | Number of times prescribed | Percentage |
|----------------------------------|----------------|-----------------------------|------------|
| Prescription                     | β-agonist (inhaled) | 117                     | 97.5       |
| pattern                          | β-agonist (oral)   | 67                        | 55.8       |
|                                  | Anticholinergic    | 93                        | 77.5       |
|                                  | Methylxanthine     | 120                      | 100.0      |
|                                  | Steroid (parenteral) | 87                        | 72.5       |
|                                  | Steroid (inhaled)  | 30                        | 25.0       |
|                                  | Antibiotics        | 104                      | 86.7       |

| Number of drugs per prescription | 3-4 | 5-6 | 7   |
|----------------------------------|-----|-----|-----|
|                                  | 33  | 76  | 11  |
|                                  | 27.5| 63.3| 9.2 |

#### Table 3: Drug utilization pattern of antibiotics (*n*=120)

| Type of antibiotics | Number of times prescribed | Percentage |
|---------------------|----------------------------|------------|
| Amoxicillin         | 48                         | 40.0       |
| Amoxicillin         | 6                          | 5.0        |
| Azithromycin        | 54                         | 45.0       |
| Benzyl penicillin   | 27                         | 22.5       |
| Cefotaxime          | 27                         | 22.5       |
| Gentamicin          | 36                         | 30.0       |
| Ciprofloxacin       | 9                          | 7.5        |

| Number of antibiotics | Percentage |
|-----------------------|------------|
| 0                     | 12.5       |
| 1                     | 25.0       |
| 2                     | 40.0       |
| 3                     | 22.5       |

#### Table 4: Drug utilization pattern of antibiotics according to the antibiotic groups (GOLD committee)

| Antibiotic used       | Group A % | Group B % | Group C % |
|-----------------------|-----------|-----------|-----------|
| Ampicillin            | 0.0       | 64.0      | 0.0       |
| Amoxicillin           | 28.6      | 0.0       | 0.0       |
| Azithromycin          | 71.4      | 52.0      | 0.0       |
| Benzyl penicillin     | 0.0       | 36.0      | 0.0       |
| Cefotaxime            | 0.0       | 28.0      | 66.7      |
| Gentamicin            | 0.0       | 40.0      | 66.7      |
| Ciprofloxacin         | 0.0       | 0.0       | 100.0     |

GOLD: Global initiative for chronic obstructive lung disease
response, then has to be initiated with anticholinergics. The role of methylxanthines is controversial due to the alleged adverse effects. In this study, the use of methylxanthines was found to be high and the usage of anticholinergics was on the lower side. This may be due to the apparent free availability of the methylxanthines and nonavailability of anticholinergics in the hospital of study.

Despite the use of antibiotics according to the availability and physician’s preference, it was found in the analysis that majority were in accordance with GOLD criteria recommendations.[5] The GOLD committee had recommended the stratification of patients with acute exacerbation of COPD into three groups, Group A, Group B and Group C for prescribing the antibiotic use. Group A were to be prescribed oral antibiotics of the beta lactams, tetracyclines, macrolides; Group B to receive parenteral or oral antibiotics. Group C were to receive antipseudomonas treatment. It was found in the study that out of the patients coming under Group A, who received oral antibiotics, 71.4% received macrolides and 28.6% received beta lactam, which was in concordance with the GOLD guidelines. Group B received treatment, which was almost similar to the GOLD guidelines. However, the use of gentamicin by 40% of the patients was not in accordance with the guidelines. All of the patients in the Group C were treated with fluoroquinolones in high dose. But they also received cefotaxime (67%) and gentamicin (67%) which was probably for the coverage of other gram positive and Gram-negative organisms.

Despite the rampant use of methylxanthines, the predicted adverse effects of these drugs did not occur in the institution of our study. The main adverse effects noted were dry mouth in approximately 15% of individuals and bad taste (10%). However, these individuals were also receiving anticholinergics, which was a confounding factor. The subsequent main adverse effects were tremor (10%) and nausea/vomiting (7.5%), and their incidence were lower than the previous studies.[18] Tremor might have been due to the use of β-agonists in all these patients. So the predicted adverse effects of methylxanthines according to the Cochrane review and GOLD expert committee did not occur in the population of the study. Diarrhea which was reported by 7.5% patients may be associated with the use of antibiotics, and this was almost similar to the previous study.[20] However, awareness and understanding of COPD need to increase, especially in primary-care settings where the majority of undiagnosed patients with COPD will initially be seen and most of the patient care administered. Health care providers must therefore be committed to disseminating and implementing evidence-based guidelines into their everyday clinical practices if the current trends of increased morbidity and mortality associated with COPD are to be reversed.[21]

**Conclusions**

Despite the use of drugs according to the availability and physician’s preference, it was found in the analysis that majority were in accordance with GOLD criteria recommendations. Even though the treatment prescribed by the physicians was in accordance with the standard treatment guidelines, majority of the patients were not adhering to it. This was because of their financial constraints. Most of the patients were only taking the free medications offered at the hospital, and not buying the drugs, which were unavailable in the hospital. By including these drugs in the central purchase committee list of government, the treatment can be more effective and economy.

**Recommendations**

The guidelines set forth suggested both viral and bacterial involvement of which the main bacteria were *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* and other atypical organisms. Studies for the identification of main causative organisms in exacerbation of COPD have not been done in India. Hence, it is a requisite in our institution to send culture and plan treatment according to sensitivity pattern. It’s also advisable to find out the microbiological spectrum of COPD exacerbation by various investigational studies, so as to define antibiotic treatment protocols.

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