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## Introduction

The term COPD encompasses a range of pathophysiologic conditions common to which is a limitation of airflow, predominantly during expiration. The term includes such diverse conditions as chronic bronchitis and emphysema on one hand to chronic asthma and bronchiectasis on the other.<sup>1</sup> From a clinical perspective, this condition is composed of three distinct entities 1) Chronic Bronchitis 2) Emphysema 3) Peripheral airway disease.

The overall brunt of COPD is enormous throughout the world with >16 million adults affected from the disease only in the United States<sup>2</sup> accounting for 110'000 deaths per year and a health care cost of \$18 billion annually.<sup>3,4</sup> According to WHO, COPD kills 2.9 million people in a year throughout the world.<sup>5</sup> Lack of proper statistical data does not allow the exact estimation of the magnitude of problem in Pakistan, but it is considered that industrialization, air pollution, high prevalence of smoking and recent surge for urbanization has not kept this part of the world far behind the developed nations as far as this disease is concerned. It has been observed that the incidence of chronic bronchitis in Pakistan increases with age. In the 15-24 year age group, the prevalence of disease is <2%. Over 65 years of age, it increases to 14% in rural females and 6% in rural males. In the urban regions, the prevalence is 9% for both sexes.<sup>6</sup> The use of wood and charcoal for cooking purposes seems to be responsible for the greater incidence of COPD among rural women where smoking is not so common a practice in this gender. Emerging bacterial resistance and lack of local data regarding the clinical and microbiologic trend of this disease long warranted a large scale clinical study in order to define not only the correct magnitude of the problem but also to formulate clinical guidelines so that exacerbations can effectively be controlled at the primary healthcare level.

The clinical diagnosis of COPD includes cough, expectoration, dyspnea and wheezing. Spirometric testing is done to confirm the diagnosis and stage the severity of disease, which characteristically shows a decrease in FEV<sub>1</sub> and a decrease in FEV<sub>1</sub>/FVC ratio with a partial or incomplete response to bronchodilators. Traditionally, chronic bronchitis shares 85% cases of COPD with emphysema sharing the remaining 15% or so.

The national survey of Pakistan has defined chronic bronchitis as "Having cough with sputum for three or more months in a year for at least three consecutive years."<sup>6</sup>

The European Respiratory Society and the American Thoracic Society system<sup>7</sup> uses FEV<sub>1</sub> to stage the severity of disease whereas the British Thoracic Society takes into consideration, the clinical features of patient's cough, sputum, dyspnea and lung sounds in addition to FEV<sub>1</sub>.

The natural history of chronic bronchitis is punctuated by acute exacerbations in many patients, which are characterized by various combinations of cough, wheezing, dyspnoea, increased sputum production or a change in its' color to green or yellow excluding those situations in which these symptoms arise from a distinct disorder requiring specific therapy like pneumonia, pneumothorax, congestive cardiac failure etc. Anthonisen et al<sup>8</sup> have staged acute exacerbations of chronic bronchitis as type 1 in which there is worsening dyspnoea, increase in sputum purulence and increase in sputum volume. Type II exacerbations are defined as those having any 2 of the above 3 features whereas Type III exacerbations are typified by having any one of the above 3 symptoms. In addition, they should have at least any one of the following clinical criteria.<sup>8</sup>

An upper respiratory tract infection in the past five days or so, fever without any other apparent cause, increased wheezing, increased cough and or increased respiratory rate or heart rate by 20% above baseline.

Air pollutants, changes in weather, microorganisms as well as comorbid conditions are implicated in acute exacerbation of chronic bronchitis. Serological tests and culture studies have shown viral infections in about 20-50% of cases of acute exacerbations.<sup>9</sup> Investigators have reported mycoplasma and chlamydia pneumonia in <1% to upto 20% of cases of acute exacerbations.<sup>10-15</sup> Organisms like *S.pneumonea*, *H.influenzae*, *H. parainfluenzae* and *M.catarrahlis* often colonize both the upper air way as well as the tracheo bronchial tree of many patients of COPD even during periods of disease quiescence<sup>16</sup>, however the specific role that bacterial infection play in all acute exacerbations of COPD is controvertial.<sup>17-25</sup> The usefulness of antibiotics is clearly demonstrated in patients with type I exacerbations as compared to those with less severe disease. Of much concern is the recent emergence of resistant strains of *S. Pneumonea*, *H.influenzae* and *M.cattarahlis* which have shown resistance to many of the first line antibiotics.<sup>26,27</sup> A Meta analysis of clinical studies carried out by Adams et al have showed a very high relapse rate in patients who received amoxicillin and an increasing trend of treatment failure was noted with macrolides and ciprofloxacin<sup>28</sup>, although statistically not significant. It is thus pertinent to understand the regional trend of antimicrobial susceptibilities in order to formulate treatment guidelines and institute empirical treatment till the sensitivity results are received.

## Patients and Methods

### Study population and design

This was a randomized, parallel, single blind (investigator blind), multicentre study to compare the efficacy and safety of Cefaclor AF vs Clarithromycin in the treatment of acute exacerbation of chronic bronchitis in adult patients. The study was conducted on 300 patients who attended the out patient clinics of ten different hospitals throughout Pakistan.

### Inclusion criteria

Patients were included in the study if they were over 18 years of age, body weight >37 kg, acute exacerbation according to definition, a chest X-ray negative for pneumonia, female patients of child bearing age with a negative pregnancy test willing to take contraceptive measures during the study period and patients who had not received systemic antibiotic therapy within 7 days prior to enrollment.

Patients were excluded from the study if they were pregnant and lactating mothers, had a history of significant hepatic or renal impairment (>3 fold rise in ALT and creatinine levels), those having tuber-

culosis, bronchiectasis on chest X-ray, patients with known hypersensitivity to macrolides or cephalosporins, those who had received systemic corticosteroid treatment within 14 days prior to enrollment and patients who had received an investigational agent as a participant within 30 days prior to enrollment.

Informed consent was signed by all patients which was approved by the Ethical Review Board prior to study initiation.

Chest X-rays of all patients were done to exclude pneumonia or bronchiectasis. Blood samples were taken for the estimation of ALT and serum creatinine levels. The subjects were asked to rinse their mouth with plain water in order to avoid any false positive results for AFB stain due to the presence of food particles in the mouth and sputum was collected for pre therapy culture and sensitivity testing as well as AFB staining using Z. N. stain.

A pre therapy evaluation of all patients was done and recorded on clinical report forms (CRF). The severity of symptoms was recorded and graded on a scale from 0-3 with 0 meaning absent and 3 meaning severe symptoms. The severity of exacerbation was graded according to the scale devised by Anthonisen et al.<sup>8</sup> Peak expiratory flow rates were recorded using Wrights' peak expiratory flow meter on a best of three scale.

Any concomitant illness including its' severity were recorded on the CRF and a record of concomitant medications along with the indications and dosage were also noted.

Patients fulfilling the criteria were grouped and supplied with the study drugs, which consisted of either Clarithromycin 250mg or Cefaclor 375mg in a b.i.d. dose. The drugs were dispensed in sealed envelopes with the investigator blind and at all levels randomization was strictly observed.

All patients were advised to report to the investigator immediately in case of any serious adverse event. A serious adverse event was defined as an event requiring hospitalization or causing severe disability to the patient or resulting in death.

Patients were evaluated at the 3rd - 5th day and then again at 10th - 11th day of treatment. At each of these visits, the severity of the symptoms was recorded and the peak expiratory flow measured. Special attention was given to any emerging side effects or study related adverse event and a separate note of each such event was made along with the remedies used.

A post therapy assessment of clinical response was made on the 10th - 11th day using the same scale (Anthonisen et al grading of disease)<sup>8</sup> and recorded as cured, improved or failure. Cure was defined as elimination of signs and symptoms of infection with no recurrence within the follow up period; improved if there was significant but incomplete resolution of signs and symptoms of infection whereas subjects who did not show any improvement in the signs and symptoms of disease were considered as failure cases. Post therapy culture of the sputum was sent to the same laboratory to assess bacteriological response. The patient was asked to return any left over medicine to assess the compliance, thus were labeled as compliant if they took 80% of the prescribed dose regimen and did not miss two consecutive doses while on therapy.

Test of efficacy and post therapy culture of the sputum for those subjects who dropped out for any reason, was done at the time of discontinuation of the drug.

A fourth and optional visit was made between days 20th - 24th to assess the follow up rate of these patients and to judge relapse.

Sputum cultures were applied at standardized local laboratories and susceptibility testing was done according to NCCLS guidelines using standard antibiotic disks for the diffusion test and standard reference powder for MIC dilution. The susceptibility parameters were considered in accordance with table 1. The bacteriological response was recorded as eradicated (causative organism was absent in the post therapy culture), persisted (the post therapy culture remained positive for the causative pathogen) or superinfection (the appearance of new pathogen other than the pathogen isolated from the pretherapy culture with worsening of clinical condition).

Differences between the categorical data for the two treatment groups were compared with the Chi square test. Difference between continuous data for the treatment groups were compared with two sample t-test, assuming equal variances of the two groups. Changes in ordinal data within the groups were analyzed by paired sample t-test. All statistical analysis were performed on SPSS version 10. P-value <.05 was considered statistically significant. All data are presented as means + standard deviations (S.D.) unless stated otherwise.

## Results

A total of 300 patients were enrolled in the study, of which 144 belonged to the cefaclor group and 156 to the clarithromycin group. Eight patients of the cefaclor group and 14 patients of clarithromycin group, did not complete the study protocol and thus the evaluable patients were 136 and 142 in the cefaclor and clarithromycin groups respectively making a total of 278 evaluable patients.

The age of the patients ranged from 17-85 years in the cefaclor group and between 21-94 years in the clarithromycin group (mean 53.17 vs 54.19 resp.  $P=0.552$ ). The average weight of the subjects was 61.72kg in cefaclor and 60.45kg in clarithromycin groups ( $P=0.332$ ).

There were 115 males and 21 females in the cefaclor group and 122 males and 20 females in the clarithromycin group ( $p=0.748$ ). The average height of the patients were 65.6 inches in the cefaclor and 65.7 inches in the clarithromycin group ( $p=0.767$ ).

In the cefaclor group, 108 patients were exposed to smoke (51 to cigarette, 31 to hukka/cigar and 26 to wood/charcoal) where as 106 patients were exposed to smoke in the clarithromycin group (54 to cigarette, 25 to hukka/cigar and 27 to wood/ charcoal). The average number of cigarettes smoked were 5-30 in the cefaclor and 8-40 in the clarithromycin group ( $P=0.234$ ). The disease severity was also comparable between the two groups (Table 2).

The distribution of respiratory symptoms with their severity at baseline and post therapy visit was also comparable amongst the two groups as shown in Tables 3a and 3b.

Among the evaluable patients, the clinical response as judged by the preset standards were, cure in 44 vs 35 subjects, improvement in 78 vs 91 subjects and failure in 16 vs 18 subjects between cefaclor vs clarithromycin groups respectively. The over all clinical efficacy (cure and improved combined) was 88.4% in the cefaclor group and 87.5% in the clarithromycin group. The mean peak flow

rates were 240 lit/min in the cefaclor group and 230 lit/min in the clarithromycin group. The post therapy peak flow measurements showed an increase of 30 lit/min in the cefaclor group and a similar increase of 28 lit/min in the clarithromycin group.

Evaluating the safety profiles of the two drugs, it was found that 115 out of the 136 patients in the cefaclor group and 119 out of 142 patients in the clarithromycin group had no adverse event. Nine patients in the cefaclor group and eleven patients in the clarithromycin group had only one adverse event and twelve patients each in each group had two or more adverse events. Among the adverse events, 9% in the cefaclor group and 8% in the clarithromycin group were not related to the study drug (Table 4). Drug related adverse events were 18% and 19% in the two groups (Table 5). Only one patient developed a serious adverse event and required hospitalization due to atrial fibrillation. This patient was also taking concomitant beta 2 agonist and the event was defined by the investigator as non study drug related event. No death was reported during the study period.

The pretherapy culture and sensitivity results of the sputa of 278 evaluable patients showed *S. pneumoniae* to be the most common isolate (27%) followed by *S. aureus* (16%), *K. pneumoniae* (15%), *H. influenzae* (13%), *M. catarrhalis* (13%), *E. coli* (8%), *H. parainfluenzae* (2%) and *S. viridans* and other species growing in 12% of the cultures collectively. The growth of double isolates was noted in 6% of cultures.

The post therapy culture and sensitivity showed eradication of the primary pathogen in 76% of cases in the cefaclor group and in 70% of cases in the clarithromycin group. In the cefaclor group, the eradication rate was 100% for streptococcus species, *H. parainfluenzae* and *E. coli*, 83% each for *H. influenzae* and *S. Aureus*, 75% for *M. catarrhalis* and 73% for *S. Pneumonia* whereas in the clarithromycin group, the eradication rates were, 67% streptococcus species, 83% for *E. coli*, 64% for *H. influenzae*, 88% for *S. Aureus*, 64% for *M. catarrhalis* and 60% *S. Pneumonia*. *H. parainfluenzae* were totally resistant to this drug in vivo. Seventeen percent subjects showed superinfection as evidenced by the growth of a new organism in the post therapy culture in the cefaclor group as compared to 18% of the cultures belonging to the clarithromycin group. Super infection agent was *S. Pneumonia* (15 cases) followed by *H. influenzae* (8 cases), *K. pneumoniae* (7 cases) and *M. catarrhalis* (6 cases). *H. parainfluenzae* and other organisms grew in minority of cultures.

The susceptibility pattern of the bacterial isolates for the two study drugs is depicted in tables 6 and 7.

## Discussion

Despite the enormous economic and social burden of this disease, there are few studies in literature and even fewer in Pakistan that give us results to formulate clinical guidelines to treat COPD on cost effective basis. Trials regarding the use of antibiotics are mostly retrospective data analysis. Those, which are prospective, have a small sample size and are thus not truly representative of the study population.<sup>16</sup> Our study was conducted at ten different sites throughout Pakistan, with a sample size of 300 patients belonging to all socioeconomic classes and thus is truly representative of the study population. Previously, the most extensive study, which supported the use of antibiotics, was done in Canada by Anthonisen et al<sup>8</sup> in 1987 which enrolled 173 patients showed a statistically significant difference among those subjects who received antibiotics as compared to those who did not. As done by Anthonisen et al, we have also included radiography as well as microbiological support in addition to the clinical parameters. The American college of physicians- American society of internal medicine (ACP-ASIM) and the American college of chest physicians (ACCP) have developed evidence based clinical practice guidelines for the management of acute exacerbation of chronic obstructive pulmonary disease (AE COPD) on the basis of a research report prepared by The Evidence Based Practice Center at Dukes University.<sup>1</sup> In their analysis, they found 11 randomized, placebo controlled trials, which showed a beneficial effect of antibiotics in selected patients of AE

COPD. Although these trials were done before the emergence of drug resistant strains, evidence showed only a minimal benefit to antibiotic therapy in the more severe exacerbations when first line antibiotics like Amoxicillin, Tetracycline and Trimethoprim-Sulphamethaxazole were used. With the emergence of drug resistant strains of bacteria particularly *S.pneumonia*, *H. influenzae* and *M. catarrhalis*, it seems mandatory that clinical studies are done using broader spectrum antibiotics to prove their efficacy in this disease as well. The ACP-ASIM group have, in their clinical practice guidelines, recommended and emphasized the need for randomized, placebo controlled trials of the newer antibiotics. The present study was done in a scenario where, it has become a trend to prescribe the newer broad spectrum antibiotics with out any evidence of their superiority over the older first line agents.

Although a few studies available in the literature have used FEV1 to diagnose COPD and to assess its severity, we, in our study, have emphasized more on the clinical parameters devised by Anthonisen et al.<sup>8</sup> The ACP-ASIM and ACCP group have formulated clinical practice guidelines for the treatment of acute exacerbations of COPD, in which they have recommended that in patients hospitalized with acute exacerbation of COPD, spirometry should not be used to diagnose an exacerbation nor to assess its severity.<sup>29</sup> PEFr was however used to support the clinical parameters and to judge the percent improvement in the flow rates after therapy in place of FEV1. Similarly most studies available in literature do not standardize the concomitant treatment taken by the patients. Diuretics, steroids, and other similar medications are known to alter the disease course in relevant clinical settings. Similarly, steroids alter the bacterial flora and thus may influence the study results.<sup>30-32</sup> We had excluded all patients who were on systemic corticosteroid therapy within past 14 days of enrollment and the top seven concomitant medications used by the subjects did not include corticosteroids thus avoiding the bias. The Canadian study of Anthonisen et al on the other hand, had an incidence of systemic corticosteroid therapy in as much as 40% of patients. Another problem with the antibiotic related studies is that many of the investigators have not included sputum microbiology to assess the results.<sup>16</sup> Hirschman et al in their Meta analysis, have found several discrepancies in various trials which, according to them, make the results uninterpretable.<sup>33-35</sup> The discrepancies observed are:

- Lack of standard criteria for a pathogen to be responsible for an acute exacerbation.
- Not allowing for a longer window period for antibiotics taken prior to enrollment which may simply mean that the resultant culture may be representative of colonizing, non pathogenic bacteria recently acquired because of earlier antibiotic therapy.
- The subjects were often evaluated late after several weeks of therapy thus resulting in a biased, high clinical response to all interventions.

We maintained stringent criteria to avoid such bias. The application of sputum culture both at the pretherapy and post therapy visit, frequent evaluation of patient during the study period, the test of cure or evaluation of clinical response within 3 days of completing the study drug, and the application of post therapy culture within 3 days of stopping the drug, definitely make the results more reliable. The fourth visit help us to evaluate the relapse rate. Furthermore, our study includes both clinical as well as bacteriological criteria to assess the efficacy of the drugs involved.

The bacterial isolates reported in our study, more or less follow the trend of the disease. Although the significance of isolation of *S. pneumonia* in acute exacerbations is debated as the organism is found to colonize the upper respiratory tract, protected brush specimen obtained during bronchoscopy from patients of COPD have yielded this organism in 30-40% of cases.<sup>16</sup> Although gram negative bacteria have usually not been implicated in acute bronchitis, several investigators have

reported these organisms to be isolated from patients who had severe exacerbation of chronic bronchitis and from those patients whose exacerbations required mechanical ventilation. Mobs et al<sup>36</sup> have reported a study of 40 patients with stable chronic bronchitis of various severities in which they have concluded that the oropharyngeal carrier rate for gram negative organisms increases with disease severity being nil in mild disease and upto 29.4% in patients with severe disease. Our study has yielded E.coli in 8% of cases, most of these patients had moderate to severe disease at baseline. Two patients had Pseudomonas infection and were excluded from the study. The antibiotic susceptibility pattern in our study has shown a significant figure of 29% and 33% resistance of S.pneumonia to cefaclor and clarithromycin respectively whereas strains of S.aureus were found to be resistant to the two drugs in 21% and 34% of cases respectively. Resistance of S. pneumonia to different first line antibiotics is being observed globally during the past decade, however a figure of 29% and 33% resistance against cefaclor and clarithromycin respectively is alarming and indicates a need to strictly adhere to the local treatment guidelines so that the efficacy of these agents against this not so uncommon bacteria is maintained.

The clinical efficacy of both the drugs was comparable and the bacteriological response was comparable to the clinical response with an eradication rate of 76% for cefaclor and 70% for the clarithromycin group although the bacteriological response was observed to be slightly less as compared to the clinical response. Fisher et al<sup>17</sup> have followed a cohort of 23 patients of chronic bronchitis for a period of two years. Sputum c/s were done routinely every two months and also during exacerbations. They found S. pneumonia and/or H.influenzae in 9% of 233 samples during remission and in 40% of 56 samples during exacerbations. This observation may imply the need for antibiotics for a longer duration so that the organisms may be completely eradicated from the respiratory tract resulting in a lower relapse/ recurrence of infection. The isolation of these pathogens from the respiratory tract of COPD patients during periods of remission may also indicate a change in the bacterial flora of these chronically affected patients. What ever the reason be, the low rate of eradication observed in the present study is an alarming trend which warrants a serious effort to formulate the local treatment guidelines and to strictly follow these guidelines so that the efficacy of these relatively newer antibiotics is maintained.

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