Introduction

Chronic obstructive pulmonary disease (COPD) has a high rate of morbidity and mortality worldwide [1]. Exacerbations are thought to be caused by complex interactions between the host, respiratory viruses, airway bacteria and environmental pollution. Recent studies have shown that bacteria play an important role in the exacerbation of COPD, and up to 50% of exacerbations are caused by bacterial infections. C-reactive protein (CRP) levels are useful in evaluating COPD exacerbation [2-3]. High serum levels of CRP are found in purulent bronchitis and COPD exacerbation with potential pathogenic microorganisms (PPMs) in the sputum. CRP levels when compared to baseline levels are significantly higher during acute exacerbations of COPD compared, especially if a bacterial origin is likely [4]. A previous study has shown that patients with an acute exacerbations of COPD admitted to hospital with a CRP level of ≥50 mg·L⁻¹ showed a trend to benefit more from antibiotics than patients with low CRP values [5].

Methods

Patients

Ninety three patients with acute exacerbations of COPD (AECOPD) were recruited from south Indian hospital. COPD was defined as forced expiratory volume in 1 second (FEV1) of < 80% predicted for age and height, and a ratio of FEV1-to-forced-vital-capacity of <70%. Exacerbation was considered if the patient had a background COPD with a combination of worsening respiratory symptoms including shortness of breath, a change in volume and color of sputum, cough, wheeze or systemic symptoms.
Inclusion criteria
- Age >18 years of age
- Patient with bacterial exacerbation of COPD. Bacterial exacerbation was defined by van der Valk et al. as follows:
  1. The abundance of >= 1 PPMs in excess (>= log) of the normal microbiological flora in sputum
  2. PPMs reaching a level of absolute growth of >10^6 colony-forming units per milliliter, except for Streptococcus Pneumoniae, for which a level of growth of >10^5 colony-forming units per milliliter was sufficient

Exclusion criteria
- History of asthma
- Bronchiectasis, tuberculosis, malignancies
- Any other inflammatory diseases arthritis, connective tissue disorders or inflammatory bowel disease.
- Infiltrates on chest x-ray examination were diagnosed as having pneumonia and Patients with pneumonia were also excluded.

Sputum sample
Sputum was examined by Gram stain microscopy according to local protocols and reported semi-quantitatively. Sputum was cultured on sheep blood agar and chocolate agar plates according to local protocols. The plates were then incubated for 18 hours in 5% CO2 at 37°C with, and bacterial colonies were counted and sub cultured for identification using standard morphological and biochemical assessments. Bacterial agents were classified as PPMs or non-PPMs as described by Cabello et al.

CRP Assay
Blood samples were obtained and CRP levels measured using an automated latex-enhanced turbidimetric assay (Beckman Image 800, Beckman Coulter Inc, Fullerton, CA) with an analyzer according to the manufacturer’s instructions.

Statistical analysis
The data were analyzed using SPSS 11.5 software (SPSS Inc, Chicago, IL). Categorical variables were compared using the univariate analysis, and continuous variables using the Student’s t test or the Mann-Whitney’s U test.

Results
Of the 93 hospitalized patients with COPD, 90 were selected for evaluation. The remaining 3 patients were excluded because of the absence of CRP measurements on the day of admission and sputum culture contamination. Baseline characteristics of patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) in table 1. Among all identifiable pathogens Klebsiella pneumonia and staphylococcus species were most common isolated gram negative and gram positive organism respectively (table 2). Median CRP levels for gram positive and gram negative organism were 62.84mg/dl and 40.86mg/dl respectively. There was statistically significant differences in median CRP levels for gram positive and gram negative pathogens, with median CRP levels higher in gram positive pathogens and p value was <0.5. Patient with high CRP level were noted in older age group (age >65 years), duration of COPD more than 5 years, male gender, Univariate and multivariate logistic regression analysis was applied and showed it to be statically significant. Patient with high CRP levels had longer duration of stay in the hospital when compared to patient with low CRP levels and statically significant.

Discussion
In this study, our results suggest that High CRP level is a good potential biomarker for the diagnosis of bacterial infections- caused by gram positive organism, especially in patients with AECOPD. Klebsiella pneumonia, the most common causative agent in our geographic area, played a major role in 30% of exacerbations, whereas staphylococcus species occurred in 15.5% of exacerbations in our study, which was different from other studies. This discrepancy may be because of distinct antibiotic pressure in different geographic areas and the exclusion of patients with pneumonia. There was significant difference in the CRP values among the different pathogens in patients with AECOPD was observed in these studies. Gram positive pathogens had high CRP levels when compared to gram negative organisms. And patient with high CRP levels at presentation had long duration of hospital stay when compared with the rest.

Conclusion
CRP levels were higher in gram positive infections when compared to gram negative infections. High CRP levels can be used as biomarker for prediction of bacterial exacerbation and prolonged hospital stay.

Table 1: Baseline characteristics of patients with acute exacerbations of chronic obstructive pulmonary disease with comparison CRP levels

| Parameters       | N (%) | CRP       | Univariate analysis | P value |
|------------------|-------|-----------|---------------------|---------|
| Age group        |       |           |                     |         |
| <65 years        | 39    | 25        | 14                  | 0.007   |
| >65 years        | 53    | 44        | 9                   |         |
| Gender           |       |           |                     |         |
| Male             | 65 () | 53        | 12                  | 0.032   |
| Female           | 27 () | 16        | 11                  |         |
| Duration of COPD |       |           |                     |         |
| <5 years         | 40    | 32        | 8                   | 0.006   |
| >5 years         | 52    | 37        | 15                  |         |
| Diabetes mellitus|       |           |                     |         |
| Yes              | 25    | 19        | 6                   | 0.431   |
| No               | 67    | 17        | 50                  |         |
| Hypertension     |       |           |                     |         |
| Yes              | 28    | 21        | 7                   | 0.381   |
| No               | 64    | 48        | 16                  |         |
|                | Yes | No | P value |
|----------------|-----|----|---------|
| Smoking        |     |    | 0.165   |
| Yes            | 47  | 36 |         |
| No             | 45  | 33 |         |
| Cough with expectoration |     |    | 0.678   |
| Yes            | 80  | 60 |         |
| No             | 12  | 9  |         |
| Fever          |     |    | 0.229   |
| Yes            | 34  | 28 |         |
| NO             | 58  | 41 |         |
| High TLC count |     |    | 0.137   |
| Yes            | 53  | 41 |         |
| No             | 39  | 28 |         |
| Gram Stain     |     |    | 0.046   |
| Positive       | 22  | 20 |         |
| Negative       | 69  | 49 |         |
| Duration of Hospital stay |     |    | 0.008   |
| >7 days        | 28  | 17 |         |
| <7 days        | 64  | 52 |         |

Table 2: Serum C-reactive protein values in patients with bacterial acute exacerbations of chronic obstructive pulmonary disease according to the causative pathogen

| Pathogen                  | No. case | Median CRP(mg/dl) |
|---------------------------|----------|------------------|
| Klebsiella pneumoniae     | 27       | 40               |
| Pseudomonas aeruginosa    | 10       | 43.75            |
| Acinetobacter species     | 10       | 26.6             |
| Staphylococcus aureus     | 14       | 94.38            |
| E.coli                    | 8        | 35.18            |
| Enterobacter species      | 5        | 56               |
| Non fermenting GNB        | 5        | 53.26            |
| Moraxella species         | 5        | 41               |

Table 3: Shows the Variables N (%) CRP N (%) Unadjusted OR (95%CI) P value Adjusted OR (95% CI) P value

| Variables                  | N (%) | CRP N (%) | Unadjusted OR (95% CI) | P value | Adjusted OR (95% CI) | P value |
|---------------------------|-------|-----------|------------------------|---------|----------------------|---------|
|                            | High  | Low       |                        |         |                      |         |
| Age                       |       |           |                        |         |                      |         |
| >65 years                 | 53    | 44        | 4.57 (1.33-15.68)      | 0.016   | 4.57 (1.33-15.68)    | 0.016   |
| <65 years                 | 39    | 25        | 9                      |         |                      |         |
| Duration of COPD          |       |           |                        |         |                      |         |
| <5 years                  | 40    | 32        | 8                      |         |                      |         |
| >5 years                  | 52    | 37        | 4.34 (1.34-13.19)      | 0.014   | 3.51 (1.08-11.36)    | 0.035   |
| Gender                    |       |           |                        |         |                      |         |
| Male                      | 65    | 53        | 12                     | 0.035   | 3.51 (1.08-17.9)     | 0.017   |
| Female                    | 27    | 16        | 11                     |         |                      |         |
| Duration of hospital stay |       |           |                        |         |                      |         |
| <7 days                   | 28    | 17        | 11                     |         |                      |         |
| >7 days                   | 64    | 52        | 12                     | 0.017   | 4.21 (1.34-13.19)    | 0.014   |

References
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