Original Research Article

# Study of bacterial pathogens, their antibiotic susceptibility patterns and multi drug resistance in bacterial pathogens isolated during acute episodes of respiratory infections in chronic obstructive pulmonary disease

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## Abstract

**Background:** Chronic Obstructive Pulmonary Disease (COPD) is a spectrum of disorders that results in airflow obstruction. Multi drug resistant bacteria are common in patients with respiratory infections which results in acute exacerbation of chronic obstructive pulmonary disease increasing mortality. Present study was taken up to know the bacteria predominantly causing the respiratory infections in AECOPD in our geographical area to know the antibiotic sensitivity pattern . **Material and Methods:** Present study was a prospective, observational study conducted in clinically diagnosed Acute Exacerbation of Chronic Obstructive Pulmonary disease patients admitted. Sputum sample was processed for macroscopic appearance, Gram-staining and sputum culture. Data was collected and statistical analysis was done using descriptive statistics. **Results:** In present study 100 patients, clinically diagnosed as cases of AECOPD, were studied. Most common age group was 56 to 65 years (28%), the next common age group was 66 to 75 years (25%). 87% were males and 13% were females. Out of 100 samples, 76 sputum samples yielded pathogenic bacteria and 24 samples yielded oral commensals. A total of 70 sputum samples yielded Mono- microbial growth and 6 had polymicrobial infections, a total of 82 nonrecurring isolates were obtained. Among these 82 isolates, 61 (74.39%) were Gram-negative bacteria, 16(19.5%) were Gram-positive cocci and 5(6%) were Gram positive yeasts. *Klebsiella pneumoniae* was the commonest bacteria isolated in 27 (32.9%) cases, followed by *Pseudomonas spp.* isolated in 16 (19.5%) cases. *Streptococcus pneumoniae* was isolated in 2 (2.4%) cases. **Conclusion:** Risk factors like previous history of hospital admission, low socioeconomic strata, longer duration of COPD, occupational history which can be correlated with the emergence of multi drug resistant bacteria. in these patients.

**Keywords:** AECOPD, MDR, bacterial infection, smoking

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## INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a spectrum of disorders that results in airflow obstruction. COPD is a major cause of morbidity and mortality in adults all over the world. An acute exacerbation of chronic obstructive pulmonary disease is a clinical diagnosis made when a patient with COPD experiences a sustained (e.g., 24–48h) increase in cough, sputum production and/or dyspnoea.[1] Respiratory infections in COPD which results in exacerbations have considerable impact on health care

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system. Many a times respiratory infections are responsible for most of the COPD exacerbations. As COPD progresses, exacerbations tend to become more frequent, the average being about more than three episodes per year. [2] By 2020, the World Health Organization predicts that COPD will become the third leading cause of death (currently fourth) and fifth leading cause of disability (currently twelfth) worldwide. [3] The risk of empirical antibiotic treatment leads to selection of multiple drug resistant bacteria which have impact on future exacerbation episodes.[4] Multi drug resistant bacteria are common in patients with respiratory infections which results in acute exacerbation of chronic obstructive pulmonary disease increasing mortality. Previous antimicrobial treatment, previous intubation are independent risk factors for MDR bacteria. Although MDR bacteria are not independently associated, but inappropriate initial antibiotic treatment is an independent risk factor for mortality in such patients.[5] Sputum culture and sensitivity is of great value in determining these difficult to treat pathogens. Present study was taken up to know the bacteria predominantly causing the respiratory infections in AECOPD in our geographical area to know the antibiotic sensitivity pattern of these organisms so that we can design a proper antibiotic regimen which will have a beneficial effect on the morbidity and mortality of the disease.

## MATERIAL AND METHODS

Present study was a prospective, observational study was done conducted in KR hospital, Mysore during a period of Jan 2015 to Dec 2015. Study approval was taken from institutional ethical committee.

**Inclusion Criteria:**

All clinically diagnosed Acute Exacerbation of Chronic Obstructive Pulmonary disease ( sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD) patients admitted.

**Exclusion criteria:**

- Bronchial Asthma/Lung Abscesses/Lung Cancer
- Patients who were recently started on Antibiotic Therapy
- Known case of Pulmonary Tb

Patients underwent history taking for age, sex, occupation, previous history of hospital admissions, antibiotic intake, alcoholic, smoking, socioeconomic status, asthma, steroid intake, COPD since many years. A thorough physical examination was done. Routine laboratory and radiological investigations done.

Sputum sample was processed in Department of Microbiology for macroscopic appearance and Gram-staining. Sputum culture was done and inoculated on to the various culture plates. A routine set of culture media on which inoculation was done for bacterial culture (Blood agar, Chocolate agar, Mac Conkey agar) and for fungal culture (Sabouraud dextrose agar). Each colony was identified based on the preliminary tests for Gram positive cocci (catalase, oxidase test) and for Gram negative bacilli (catalase, oxidase and motility). After preliminary identification of the organism a battery of tests were adopted to speciate them. Further biochemical tests were done like Oxidative-Fermentative test, Nitrate reduction test, MR test, VP test, Indole test, Triple Sugar Iron , Citrate test, Urease test, Sugar fermentation test, Amino acid utilization test. All the isolates were subjected to antibiotic susceptibility testing by Kirby - Bauer disc diffusion technique according to CLSI guidelines.[6] The cultures suggestive of Streptococcal growth were put for direct sensitivity on Chocolate agar. Antibiotic susceptibility testing was done by measuring zones of inhibition and correlated with the standard tables provided by CLSI to categorize into sensitive, moderately sensitive, resistant.[7]

Multidrug resistant organism

**Definition:** For epidemiologic purposes, MDROs are defined as microorganisms, predominantly bacteria, that are resistant to ≥3 classes of antimicrobial agents. Certain MDROs describe resistance to only one agent (e.g., MRSA, VRE) these pathogens are frequently resistant to most available antimicrobial agents. [8]

MDR-Acinetobacter - Non-susceptibility (i.e., resistant or intermediate) to at least one agent in at least 3 antimicrobial classes of the following 6 classes: Ampicillin/sulbactam, Cephalosporins (cefepime, ceftazidime), β-lactam / β-lactamase inhibitor combination (piperacillin, piperacillin/tazobactam), Carbapenems (imipenem, meropenem, doripenem), Fluoroquinolones (ciprofloxacin or levofloxacin), Aminoglycosides (gentamicin, tobramycin, or amikacin)[9]

MDR-Pseudomonas - Non-susceptibility (i.e., resistant or intermediate) to at least one agent in at least 3 antimicrobial classes of the following 5 classes: Cephalosporins (cefepime, ceftazidime), β-lactam/ β-lactamase inhibitor combination (piperacillin, piperacillin/tazobactam), Carbapenems (imipenem, meropenem, doripenem), Fluoroquinolones (ciprofloxacin or levofloxacin), Aminoglycosides (gentamicin, tobramycin, or amikacin)[9]

Extended-spectrum beta-lactamase Gram negatives - Enterobacteriaceae non-susceptible (i.e. resistant or intermediate) to ceftazidime, cefepime, ceftriaxone, or cefotaxime.

•*Pseudomonas aeruginosa* non-susceptible (i.e., resistant or intermediate) to ceftazidime or cefepime.[9]
Drug-resistant *Streptococcus pneumonia - S. pneumoniae* isolated nonsusceptible to "at least to penicillins and one antimicrobial agent currently approved for use in treating pneumococcal infection."[9]
Data was collected and statistical analysis was done using descriptive statistics.

## RESULTS

In present study 100 patients, clinically diagnosed as cases of AECOPD, were studied. Most common age group was 56 to 65 years (28%), the next common age group was 66 to 75 years (25%). 87% were males and 13% were females. The ratio between male and female is 6:1. 57 patients had COPD between 1- 10 years whereas only one patient had COPD for >30 years.

**Table 1:** Age and gender distribution

| Age(in yrs.) | Number | Percent (%) |
|---|---|---|
| 35 – 45 | 10 | 10 |
| 46 – 55 | 23 | 23 |
| 56 – 65 | 28 | 28 |
| 66- 75 | 25 | 25 |
| 76 -85 | 14 | 14 |
| Gender | | |
| Male | 87 | 87 |
| Female | 13 | 13 |
| Duration | | |
| 1-10 yrs. | 57 | 57 |
| 11-20 yrs. | 36 | 36 |
| 21-30 yrs. | 5 | 5 |
| >30 yrs. | 1 | 1 |

79 out of 100 patients had previous hospital admissions. Majority of the patients were males, with positive smoking history the average years of smoking being 20 to 30 years. Only 15 patients gave alcoholism history, 3 of them had asthma and 9 were on steroids in the form of inhaler use. Large number of patients had lower socioeconomic status i.e., 75 patients and 25 patients belonged to middle class.

**Table 2:** Risk factors associated with respiratory infections in AECOPD

| Variables | Male (n=87) | Female (n=13) |
|---|---|---|
| Age (in years) | 62.54 years | 56 years |
| Occupational history positive | 30 (34.48%) | 4 (30.77%) |
| • Laborer | 22 (25.2%) | |
| • Cement worker | 8(9.1%) | |
| • Women cooking indoor with biomass | | 4 (30.77%) |
| Smoker | 66 (75.86%) | 2 (15.38%) |
| Smoke years | 20- 30 yrs. | 2- 5 yrs. |
| Previous history of hospitalization | 71 (81.61%) | 8 (61.54%) |
| Alcoholic | 15 (17.24%) | 0 |
| Asthma | 3 (3.45%) | 1 (7.69%) |
| Steroid use as inhaler | 9 (10.34%) | 1 (7.69%) |

Out of 100 samples, 76 sputum samples yielded pathogenic bacteria and 24 samples yielded oral commensals. A total of 70 sputum samples yielded Mono- microbial growth and 6 had polymicrobial infections, a total of 82 nonrecurring isolates were obtained. Among these 82 isolates, 61 (74.39%) were Gram-negative bacteria, 16(19.5%) were Gram-positive cocci and 5(6%) were Gram positive yeasts. *Klebsiella pneumoniae* was the commonest bacteria isolated in 27 (32.9%) cases, followed by *Pseudomonas spp.* isolated in 16 (19.5%) cases. *Streptococcus pneumoniae* was isolated in 2 (2.4%) cases. Other common organisms isolate were MRSA in 11 (13.4%) cases, *Acinetobacter spp.* in 8 (9.7%) cases. *Escherichia coli*, Candida were isolated as 8 (9.7%) and 5 (6%) cases respectively.

**Table 3:** Isolates from Sputum Culture

| Name of organism | Number | Percent |
|---|---|---|
| *Klebsiella pneumonia* | 27 | 32.9% |
| *Pseudomonas species* | 16 | 19.5% |
| *MRSA* | 11 | 13.4% |
| *E coli* | 8 | 9.7% |
| *Acinetobacter species* | 8 | 9.7% |
| *Candida albicans* | 5 | 6% |
| *Staphylococcus aureus* | 3 | 3.6% |
| *Streptococcus pneumonia* | 2 | 2.4% |
| *Enterobacter species* | 1 | 1.2% |
| *Serratia marcescens* | 1 | 1.2% |

Imipenem group of drugs were most sensitive to Gram negative bacilli whereas Ampicillin (100%) and cephalosporins (100%) are most resistant.

**Table 4:** Drug Resistance Pattern of Gram-Negative Isolates

| Organisms | Amp | Ce | Ca | Ci | Cu | Ac | Cf | G | Co | I | PT |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Klebsiella | 27 | 19 | 17 | 13 | 17 | 27 | 16 | 1 | 18 | 6 | - |
| (n=27) | 100% | 70% | 62% | 48% | 62% | 100% | 59% | 3% | 66% | 22% | |
| Pseudomonas | - | 8 | 14 | 10 | 12 | - | 5 | 8 | 8 | 0 | 10 |
| (n=16) | | 50% | 87% | 62% | 75% | 75% | 31% | 50% | 50% | 0 | 67% |
| E.coli | 8 | 6 | 7 | 8 | 8 | 8 | 8 | 5 | 8 | 4 | - |
| (n=8) | 100% | 75% | 87% | 100% | 100% | 100% | 100% | 62% | 100% | 50% | |
| Acinetobacter | - | 8 | 7 | 6 | 6 | - | 3 | 2 | 5 | 3 | 7 |
| (n=8) | | 100% | 87% | 75% | 75% | | (37%) | 25% | 62% | 37% | 87% |
| Enterobacter | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | - |
| (n=1) | 100% | 0 | 100% | 0 | 0 | 100% | 100% | 100% | 100% | 100% | |
| Serratia | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | - |
| (n=1) | 100% | 100% | 0 | 0 | 0 | 100% | 100% | 100% | 100% | 0 | |

*Amp- Ampicillin, Ac- Amoxiclav, Ce- Cefotaxime, Ca- Ceftazidime, Ci- Ceftriaxone, Cu- Cefuroxime, Cf- Ciprofloxacin, G- Gentamicin, Co- Cotrimoxazole, I- imipenem- Piperacillin tazobactam The maximum resistance for *Klebsiella pneumoniae* was showed by Penicillins (100%) and Cephalosporins (55%) group of antibiotic, whereas the most sensitive were Aminoglycosides (3%) and Carbapenems (22%).

**Table 5:** Drug resistance pattern in *Klebsiella pneumoniae*

| Antimicrobials | No. of resistant isolates (n= 27) | Percent |
|---|---|---|
| Penicillins( Amp ) | 27 | 100% |
| Cephalosporins(Ce,Ca) | 15 | 55.5% |
| β lactam – β lactamase inhibitor(Ac) | 27 | 100% |
| FQ(Ciprofloxacin) | 16 | 59.2% |
| AG( Gentamicin) | 1 | 3.7% |
| Sulfa drugs(Co) | 18 | 66.6% |
| Carbapenems(Imipenem) | 6 | 22.2% |
| No of isolates producing ESBL | 21 | 77.7% |
| No of isolates producing MBL | 5 | 18% |
| Total no. of MDR isolates | 25 | 92% |

The ESBL production was 41% and MBL production was 18% in isolates.

**Table 6:** Showing different drug resistance mechanisms of isolated pathogens

| | ESBL | MBL |
|---|---|---|
| Positive | 41(68.33%) | 18(29%) |
| Negative | 19 | 44 |
| **Total** | **60** | **62** |

The most common organism producing ESBL was *Klebsiella pneumoniae (77%)* and least common was *Acinetobacter species (50%)*. The most common organism producing MBL was *Klebsiella pneumoniae* (18%) and least amount of MBL producer was *Acinetobacter species (12%)*.

**Table 7:** ESBL and MBL producers among isolated bacteria

| Organism | ESBL producers | | MBL producer | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| *Klebsiella pneumonia* | 21(n= 27) | 77.7% | 5(n=27) | 18.5% |
| *Pseudomonas species* | 9(n= 16) | 56.25% | 6(n=16) | 37.5% |
| *Acinetobacter species* | 4(n=8) | 50% | 1(n=8) | 12.5% |
| *E.coli* | 6(n=8) | 75% | 5(n=8) | 62.5% |
| *Serratia* | 1(n=1) | 100% | 0 | |
| *Enterobacter species* | 0 | | 1(n=1) | 100% |

The highest drug resistant strains were among *Klebsiella pneumonia* accounting for 92% in which 21(77%) were ESBL producers and 5(18%) were MBL producers.

**Table 8:** Distribution of MDR bacteria among the isolates

| Organism | N of MDR isolates (%) | ESBL (%) | MBL (%) |
|---|---|---|---|
| *Staphylococcus aureus (*n=14) | 11 (78%) | NA | NA |
| *Klebsiella pneumonia* (n=27) | 25 (92%) | 21 (77%) | 5 (18%) |
| Pseudomonas species (n=16) | 12 (75%) | 9 (56%) | 6 (37%) |
| Acinetobacter species (n=8) | 6 (75%) | 4 (50%) | 1 (12%) |
| *E. Coli* (n=8) | 7 (87%) | 6 (75%) | 5 (62%) |

Highest number of MDR bacteria were seen in patients of repeated hospitalization (85%) followed by patients with smoking history (80%), lowest number of patients were seen in asthmatics (50%).

**Table 9:** Risk factors in AECOPD patients and drug resistant pattern of MDR bacteria

| Risk factors associated with AECOPD | No. of patients | MDR | ESBL | MBL |
|---|---|---|---|---|
| Repeated hospitalization | 60 | 51(85%) | 34(65%) | 16(30%) |
| Smokers | 51 | 41(80%) | 27(65%) | 13(31%) |
| Low Socioeconomic status | 55 | 42(76%) | 28(65%) | 15(34%) |
| Asthma with steroid use | 12 | 6(50%) | 3(25%) | 3(25%) |
| COPD duration >10 years | 47 | 32(68%) | 26(68%) | 14(36%) |
| Positive occupational history | 23 | 16(69%) | 13(81%) | 4(25%) |

## DISCUSSION

Respiratory infections in COPD resulting in exacerbation deteriorates pulmonary function and increases airway inflammation and is a major cause of morbidity, mortality and reduced health-related quality-of life in these patients. Antibiotics are commonly prescribed empirically to contents presenting with COPD to treat presumed bacterial infection. The rise in bacterial resistance to antibiotics has focused our attention on the benefit of this practice, and more fundamentally the importance of bacterial infection in COPD and its role in stimulating bronchial inflammation, which is the hallmark of this condition.[10] The present study showed maximum number of cases in the age group of 45 to 55 yrs., mean age being 62.5 years. Similar demographic findings were observed by Gerard R *et al.*[11] and Patel A *et al.*[12] This could be due to more exposure to dust or fumes, more years of smoking or biomass combustion fumes in case of females. In these cases COPD sets in early due to which there is inflammation of airways which again is more prone to attack by microbial infection. Males are at higher risk for acquiring the disease due to many reasons such as smoking, occupational hazards like organic dust in the form of agriculture, mining, metallic fumes etc. It is clear from the studies like David A *et al.*[13], Christenhusz L *et al.*[14] that there is a strong association between smoking and increased number of exacerbations. Tobacco smoke is a potent stimulant of the inflammatory response, and chronic inflammation has been suggested to contribute to COPD pathogenesis. Inflammation has been suggested as an important factor that may predispose individuals to increased risk of exacerbations. Previous COPD exacerbation is a strong predictor of future exacerbations and may account for some of the unadjusted findings.[13] Smoking cessation is associated with a reduced risk of COPD exacerbations, and the described reduction is dependent upon the duration of abstinence. In the present study Gram negative bacteria have dominated over Gram positive bacteria which is similar to other studies like Vishwambhar V *et al.*[15], Feng Y *et al.*[16]. In recent times the prevalence of Gram-negative bacteria in exacerbations went on increasing. This can be due to vaccination in cases of COPD patients, mainly *H.influenza*, *Streptococcus pneumonia*, whooping cough.[17] Other reason for it could be due to increased exacerbations, frequent admissions to hospitals during which hospital acquired multi drug resistant strains might have been acquired. And lastly Gram-negative organisms were more common in severe

cases of COPD. Also empirical treatment might have killed fragile bacteria like *H. influenza*, *Streptococcus pneumonia* and left with difficult to treat pathogens like Klebsiella and others as seen in studies done by Bashir *et al.*[18] Profile of organisms have been changing as the years have passed and recent times we are left with drug resistant bacteria. In our study 6% samples yielded candida as pure growth. The culture findings were correlating with sputum direct smear wherein pseudohyphae was seen as seen in other studies like Yu S *et al.*[19]

**Table 10:** Showing various organisms isolated in various studies

| S. No. | Study series | Year | Kleb | Pseudo | E.Coli | MRSA | Acineto | Strepto |
|---|---|---|---|---|---|---|---|---|
| 1. | Arora N *et al.*[20] | 2001 | 10.5% | 12% | - | 1.7% | - | 25% |
| 2 | Rakesh G *et al.* [11] | 2013 | 13% | 18% | - | 5% | - | 43% |
| 3 | Feng Y *et al.* [16] | 2013 | 14% | 21% | 4% | 2% | 9% | 11% |
| 4 | Sharan H *et al.* [21] | 2015 | 38% | 10% | 5% | 9% | 5% | 15% |
| 5 | Bashir S *et al.* [18] | 2016 | 32% | 17% | 5% | - | 35% | - |
| 6 | Sonia *et al.* [22] | 2016 | 42.5% | 14.8% | 8.5% | 28% | - | 1.6% |
| 7 | Present study | 2015 | 32.9% | 19.5% | 9.7% | 15.8% | 9.7% | 2.4% |

The present study shows results similar to study done by Sonia *et al.* [22],Sharan H *et al.* [21], Feng Y *et al.* [16]. MRSA is increasingly frequent pathogen in healthcare and community environment and is frequently isolated from lower respiratory tract samples in patients with AECOPD. In our study we have isolated 11(15%) MRSA which is in concordance with other studies like Sonia *et al.*[22] MRSA is increasingly prevalent in COPD airways. This could be attributed to change of traditional health care associated clones with community acquired clones. Also studies suggest that nearly one quarter of MRSA acquisition episodes are associated with exacerbations, which is supported by our study.[23] Also we have observed there is frequent hospital visits and hospitalization due to which patients receives many times empirical antibiotic therapy without culture and sensitivity. In patients with low compliance these pathogens remains untreated. Due to inappropriate antibiotic these pathogens emerge as MDR. In bacteria, genes can be inherited from neighboring genes or mobile genetic elements such as plasmids. This horizontal gene transfer (HGT) can allow antibiotic resistance to be transferred among different species of bacteria. Resistance can also occur spontaneously through mutation.[24] Prior antibiotic treatment, long-term inhaled or systemic corticosteroid use and severe impairment of lung function were identified as risk factors for severe chronic obstructive pulmonary disease exacerbations related to multidrug-resistant bacteria.[7] In our study the highest number of MDR isolates were found in patients with repeated hospitalization. Every time the patient was admitted for exacerbation he was started on empirical therapy. Over the time patient became resistant to these empirical antibiotics. Similar studies were done by Aurora E *et al.*[25] and Nseir S[5] in which repeated hospital admissions led to the emergence of MDR strains. Other risk factors which were associated were patients with smoking history and low socioeconomic strata. Patients with low socioeconomic strata, with less education rarely visited hospital during exacerbation episodes. Presenting in late stages where the disease has progressed and empirical antibiotic therapy in these patients rendered them vulnerable to risk of hospital acquired MDR organisms. In our study the highest number of MDR pathogens were found in *Klebsiella pneumonia* followed by *Pseudomonas species* which is similar to studies done by Nseir S[5] *et al.* These multidrug resistant bacteria predisposes patients at higher risk of treatment failure and thus increasing mortality. The emergence of MDR strains is mainly due to inappropriate initial empirical therapy on which the patient is started as soon as presents to emergency department which is not confirmed by culture and sensitivity. Patients had history of similar episodes of exacerbations which every time was intense due to which patient was hospitalized multiple times. Easy to treat pathogens were handled during the empirical therapy but due to multiple hospital visits the nosocomial pathogens might have colonized which resulted in further exacerbation episode but with a different hospital acquired pathogen which are now difficult to treat with initial empirical therapy. These MDR pathogens would make the course of treatment difficult.

## CONCLUSION

Risk factors like previous history of hospital admission, low socioeconomic strata, longer duration of COPD, occupational history which can be correlated with the emergence of multi drug resistant bacteria. in these patients.• Predominant organisms were Klebsiella pneumoniae (32.9%) then were Pseudomonas species followed by MRSA. Klebsiella pneumoniae was most resistant to penicillins, cephalosporins and amoxiclav. Antimicrobial susceptibility testing and good knowledge of drug resistant mechanisms is very essential to treat the patients and to prevent the emergence of MDR

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