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# Microbiological Profile and Antibiotic Resistance Pattern in Acuteexacerbations of COPD: A Study from Northern India

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## ABSTRACT

### Background

Chronic Obstructive Pulmonary Disorder (COPD) is a major cause of morbidity and one of the principal causes of death worldwide. The objective of this study is to identify the bacterial etiological agents in patients with acute exacerbations of COPDs by sputum culture and their antibiogram.

### Methods

This is a prospective study comprising 100 diagnosed patients of COPD taken as GOLD Grade 4who were admitted in the Department of Pulmonary Medicine, TB and Chest Hospital which comes under King George Hospital, Visakhapatnam.

### Results

Out of 100 patients, 83 were males of which 87% were smokers. The most common organisms isolated were Gram negative bacilli in 51 patients and only 26 were Gram positive cocci. The mostcommon Gram-negative isolate was *Klebsiella pneumoniae* 27 cases followed by *Pseudomonas aeruginosa* in 19 cases. The most common Gram-positive isolate was *Streptococcus pneumoniae* in 16 cases followed by *Streptococcus pyogenes* in 6 cases and *Staphylococcus aureus* in 2 cases.

### Conclusions

Frequent exacerbations appear to be associated with worsening healthoutcomes and effort should focus on prompt and effective treatment of eachepisode. Bacterial pathogens, mostly Gram negative bacilli are found to be the chief etiological agents in AECOPD. Antibiotic therapy shouldbe initiated early depending on the culture. Susceptibility patterns of that particular region should be determined to prevent antibiotic resistance and to decrease health costs.

**Keywords:** COPD; bacterial aetiology; acute exacerbation; smokers; antibiogram.

## INTRODUCTION

Chronic Obstructive Pulmonary Disorder (COPD), is characterized by persistent airflow limitation that is progressive and associated with an enhanced chronic inflammatory response to noxious particles or gases.[1] This leads to excessive mucus production, during at least 3 consecutive months for more than two successive years associated with functional disability.[2] Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is defined as an acute change in a patient's baseline dyspnea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in therapy.[3] A strong association exists between tobacco smoking and the occurrence of COPD. Chronic colonization of the lower respiratory tract by bacterial pathogens amplifies the inflammatory response present and results in progressive airway obstruction (vicious circle hypothesis)[4] leading to symptoms that are termed "acute exacerbations".[5] Furthermore, the local inflammatory response of the host increases with increasing airway bacterial load.[6]

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## METHODS

All procedures performed in the study were by the ethical standards of the institutional and or national research committee and with the 1964 Helsinki Declaration and its later amendments. In this cross-sectional study, a total of 100 patients diagnosed with COPD Grade 4 as per GOLD guidelines were included in the study. The study was carried out at the Department of Microbiology with the help of the Department of Pulmonary Medicine under the TB and Chest Hospital, King George Hospital, Visakhapatnam, during the period from May 2015 to May 2016. The study comprises all gender with age groups ranging from 45 to 80 years. For all the 100 patients admitted, detailed history was taken, those patients with increased cough, increased severity of dyspnoea, excessive sputum production and sputum sample collected prior to the administration of antibiotics were included in the study. Patients diagnosed with tuberculosis, bronchial asthma, lung abscess, lung carcinoma, and ischemic heart disease and who were already on antibiotic treatment were excluded from the study. Classification of severity of airflow limitation in COPD In pulmonary function testing, a postbronchodilator FEV1/FVC ratio of <0.70 is commonly considered diagnostic of COPD. In patients with this ratio:

- GOLD 1 – mild: FEV1 ≥ 80% predicted
- GOLD 2 – moderate: 50% ≤ FEV1 < 80% predicted
- GOLD 3 – severe: 30% ≤ FEV1 < 50% predicted
- GOLD 4 – very severe: FEV1 < 30% predicted

The GOLD guideline uses a combined COPD assessment approach based on patient's symptoms and previous history of exacerbations into 4 groups:

- Group A: low risk (0-1 exacerbation / year, not requiring hospitalization) and fewer symptoms.
- Group B: low risk (0-1 exacerbation / year, not requiring hospitalization) and more symptoms.
- Group C: high risk (≥ 2 exacerbations / year or one or more requiring hospitalization) and fewer symptoms.
- Group D: high risk (≥ 2 exacerbations / year or one or more requiring hospitalization) and more symptoms.

Bacterial infections are one of the most common causes of acute exacerbation of COPD. They account for 25% of exacerbations alone.[6] Patients were instructed, and a deep coughed sputum sample was collected into a sterile wide-mouth container with a screw cap. Smears were prepared and were stained by the Gram staining technique (Figure 2 & 6). The smears were then examined, and the quality of the sputum was assessed by Bartlett's grading (Table 1) and having a score of 1 or more was processed further.[8] A final score of 0 or less indicates either lack of inflammatory response or the presence of significant salivary contamination, thus invalidating the specimen. Selected sputa were processed microbiologically by using a calibrated loop, 0.01 ml onto the following culture media: blood agar, MacConkey agar and chocolate agar. Incubated at 35 ± 2°C under aerobic conditions. Chocolate agar was incubated in a candle jar. A first reading was taken after 24 hrs, and a second final one was taken after 48 hrs of culture.

**Table 1. Bartletts grading of sputum.**

| No. of neutrophils per 10x low power field | Grade |
|---|---|
| <10 | 0 |
| 10-25 | 1 |
| >25 | 2 |
| Presence of mucus | 1 |
| **No. of epithelial cells per 10x low power field** | **Grade** |
| 10-25 | -1 |

## RESULTS

A Total of 100 patients clinically diagnosed and admitted with AECOPD were studied. Bacterial infections of AECOPD were analyzed. Organisms grown were identified based on their morphology, cultural characteristics and biochemical reactions their culture & sensitivity patterns to various antibiotics were also recorded.

In 100 patients 83(83%) were males and 17(17%) were females. Male:female ratio was 4.8:1. As shown in (Table 2), among the 83 males 73( 88%) were smokers, out of 17 females 9 (53 %) were smokers. 12 % were nons mokers. Majority of the patients in the study population were smokers.

**Table 2. Incidence of smoking.**

| Smoking status | Male | Female | Total (%) |
|---|---|---|---|
| Smoker | 73 | 9 | 82% |
| Non-Smoker | 10 | 8 | 18% |

Out of the 100 specimens processed, 14 samples

showed polymicrobial growth, 77 samples showed monomicrobial growth and the remaining ones were sterile. 77 samples that showed monomicrobial growth had *Klebsiella pneumonia* (Figure1) the most common isolate, followed by *Pseudomonas aeruginosa* (Figure 5) and *Streptococcus pneumonia* (Figure 6).

The antibiotic discs which were tested for antimicrobial susceptibility upon Mueller Hinton agar by Kirby Bauer disc diffusion method.With the help of antibiotic scale from HIMEDIA, the following sensitivity patterns were noted. The antibiotic susceptibility patterns of isolates of Gram negative baccilli are depicted in (Table 3).

**Table 3. Isolates of Gram-negative bacilli growth.**

| Different species of Gram-negative bacilli isolated | Number of bacterial isolates |
|---|---|
| *Klebsiella pneumoniae* | 27 |
| *Pseudomonas aeruginosa* | 19 |
| *Acinetobacter baumanii* | 5 |

A total of 26 number of Gram positive cocci were isolated (Table 4).

**Table 4. Showing Gram positive cocci in isolates.**

| Gram positive cocci isolated | Number of isolates |
|---|---|
| *Streptococcus pneumoniae* | 18 |
| *Streptococcus pyogenes* | 6 |
| *Staphylococcus aureus* | 2 |

**Table 5. Antimicrobial susceptibility patterns in isolates of Gram-negative bacilli (S=Sensitive, R= Resistant).**

| Antibiotic discs | *Klebsiella pneumoniae* | | *Pseudomonas aeruginosa* | | *Acinetobacter baumanii* | | Drug total sensitivity % |
|---|---|---|---|---|---|---|---|
| | S | R | S | R | S | R | |
| Meropenem | 27 | 0 | 19 | 0 | 5 | 0 | 100% |
| Ceftriaxone | 17 | 10 | 15 | 4 | 3 | 2 | 68.60% |
| Levofloxacin | 26 | 1 | 17 | 2 | 4 | 1 | 92.15% |
| Piperacillin tazobactam | 25 | 2 | 16 | 3 | 2 | 3 | 84.31% |
| Azithromycin | 20 | 7 | 15 | 4 | 3 | 2 | 74.50% |
| Gentamycin | 26 | 1 | 15 | 4 | 3 | 2 | 86.27% |
| Amoxyclav | 5 | 22 | 2 | 17 | 2 | 3 | 17.60% |

**Table 6. Antimicrobial susceptibility patterns in isolates of in Gram positive cocci (S=Sensitive, R=Resistant).**

| Antibiotic discs | Streptococcus pneumonia | | Streptococcus pyogenes | | Staphylococcus aureus | | Drug total sensitivity (%) |
|---|---|---|---|---|---|---|---|
| | S | R | S | R | S | R | |
| Meropenem | 16 | 0 | 8 | 0 | 2 | 0 | 100% |
| Ceftriaxone | 12 | 4 | 4 | 4 | 2 | 0 | 69.20% |
| Levofloxacin | 15 | 1 | 6 | 2 | 2 | 0 | 88.46% |
| Azithromycin | 14 | 2 | 6 | 2 | 1 | 1 | 80.76% |
| Tigecycline | 15 | 1 | 7 | 1 | 2 | 0 | 92.30% |
| Teicoplanin | 13 | 3 | 6 | 2 | 2 | 0 | 80.70% |
| Amoxyclav | 11 | 5 | 3 | 5 | 0 | 2 | 53.80% |

**Table 7. Shows total drug sensitivity percentage.**

| Antibiotic | Gram negative bacilli sensitivity | Gram positive cocci sensitivity | Total sensitivity of the drug |
|---|---|---|---|
| Meropenem | 100% | 100% | 100% |
| Ceftriaxone | 68.60% | 69.20% | 68.90% |
| Levofloxacin | 92.15% | 88.46% | 90.48% |
| Piperacillin tazobactum | 84.31% | - | 84.31% |
| Azithromycin | 74.50% | 80.76% | 77.63% |
| Gentamycin | 86.27% | - | 86.27% |
| Amoxyclav | 17.60% | 53.80% | 35.70% |
| Tigecyclin | - | 92.30% | 92.30% |
| Teicoplanin | - | 80.70% | 80.70% |

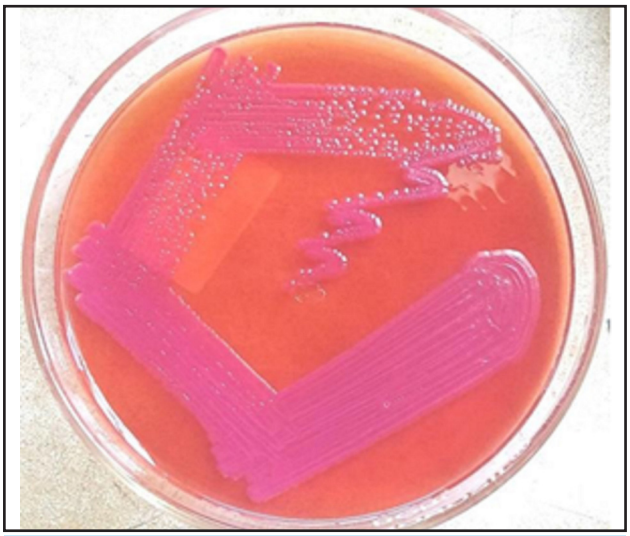

**Figure 1. Pink coloured mucoid lactose fermenting colonies on Mac Conkey agar resemble *Klebsiella* species.**

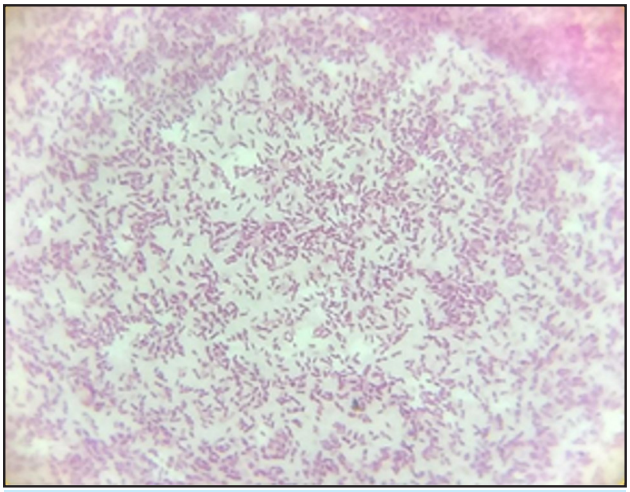

**Figure 2. Gram negative bacilli seen in smear from Mac Conkey agarshowing short and stout bacilli resemble *Klebsiella* species showing short and stout bacilli resemble *Klebsiella* species.**

## DISCUSSION

Inspite of the multifactorial etiopathogenic nature of AECOPD, infection plays a very important and

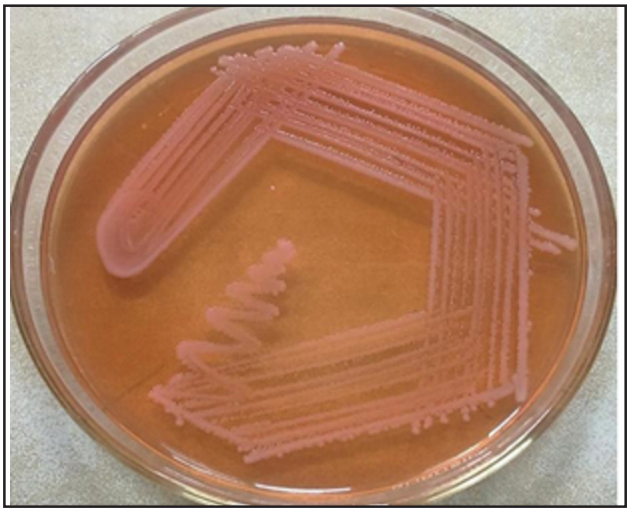

**Figure 3. Late lactose fermenting colonies on Mac Conkey agarresembling *Acinetobacter* species.**

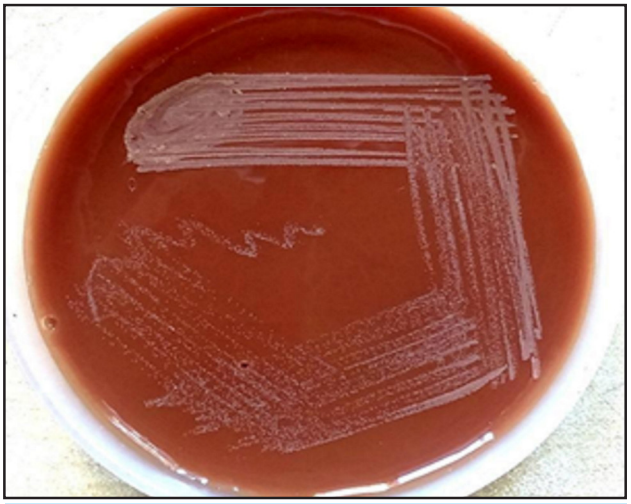

**Figure 4. Tiny greyish colonies on chocolate agar resemble *Streptococcus* species.**

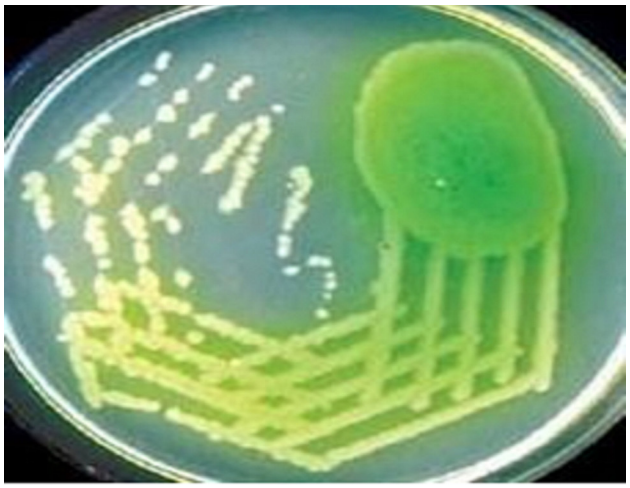

**Figure 5. Green pigmented colonies on nutrient agar resemble *Pseudomonas* species.**

unique role, impairing not only ventilator function of the lung but also restricting patient daily routine

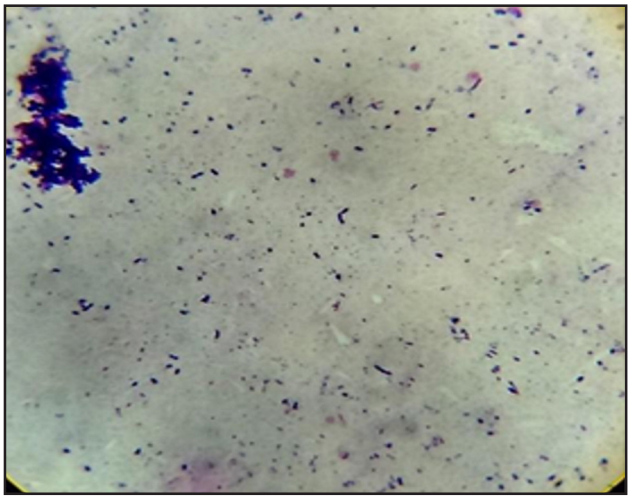

**Figure 6. Gram's staining smear from chocolate agar showing *S. pneumoniae.***

activities.The present study confirms previous data reporting a role of bacterial infection in AECOPD during hospital admissions for acute exacerbations. Presence of bacterial pathogens was found in 91 % of all admitted patients.Remarkably, the incidence of positive sputum cultures in 91% of our patient population was quite similar to previous studies.[9,10,11] The present study also showed a signifigant number of higher males 88% which were chain smokers had COPD infection as compared to females which was 53% were non smokers. This finding was in conformity with other co-workers who reported similar findings.[12] The male predominance in the current study can be attributed to smoking and COPD being common among females can be due to indoor air pollution while domestic work. Aleemullah et al obtained pathogenic organisms from 109 (73.65%) sputum samples. Out of 148 samples processed Gram negative organisms were isolated predominantly 68(62.39%). While Gram positive organisms accounted for 41(37.61%).[13] Saikat basu et al showed 21 positive sputum cultures. Among them, 76.20% were males and 23.80% were females. The prevalence of Gram negative bacteria was 71.42% and Gram positive bacteria was 28.58%. *Klebsiella pneumoniae* was the commonest isolated (33.33%) followed by P. aeruginosa (19.05%) and Staphylococcus aureus (14.30%).[14] Chakraborty et al isolated pathogenic bacteria from 203 (60.1%) samples. Gram negative bacteria were isolated from 79.8 percent (162/203)

while the rest were Gram positive. *Klebsiella* species was the commonest (49.2%; 100/203) Gram negative isolate from the sputum samples. Among the Gram negative organisms, carbapenem had the highest sensitivity (90.2%) followed by amikacin, ciprofloxacin and piperacillin tazobactam. Linezolid was found to be 100 percent sensitive amongst the Gram positive organisms while both amoxicillin clavulanate and azithromycin showed a rather low sensitivity profile overall.[15] Pradhan K.C. et al, conducted a study on the sputum samples of 100 cases, suffering from chronic obstructive pulmonary disease among them 16 cases had chronic bronchitis. The isolates obtained were *Klebsiella* spp - 40%, Staphylococcus aureus - 26%, *Pseudomonas aeruginosa* - 8%, Escherichia coli - 2%, Proteus species - 1%.[16] In the current study Gram negative bacilli 51 out of 77 isolates (66.23%) outnumbered the Gram positive cocci 26 out of 77 isolates (33.76%) in monomicrobial isolates. In the study by Aleemullah et al, Saikat basu et al, Chakraborty et al, the isolates of Gram negative bacilli (62.39%) were more than the Gram positive cocci (37.61%) which is comparable to the present study.[17,18,19]

In the studies like Pradhan et al, Chawla et al, Soler et al, Hariom Sharan et al, Chakraborty et al, Alemullah et al, Narayangowda et al, Jayasimha et al and Rakhee et al had similar findings.[13,16-22] Another study done by Mahmoud Ahmed et al showed a difference in bacteriological profile showing that there was a predominance of Gram positive cocci than Gram negative bacilli.[31] In this study, 3 commonest organisms isolated were *Klebsiella pneumoniae* in 27 cases (35.06%), *Pseudomonas aeruginosa* in 19 cases (24.67%) and *Streptococcus pneumoniae* in 18 cases (23.37%).

Studies by Chawla et al, Basu et al, Chakraborty et al, showed that *Klebsiella pneumonia* (33.33%) was predominantly isolated followed by Pseudomonas aeruginosa (25.9%).[14,15,17] Similarly other studies done by Pradhan et al, Hariom et al, Saxena et al and Narayanagowda et al also suggested the higher isolation of K. pneumoniae as the predominant organism.[16,19,20,23] As the time has passed over, Enterobacteriaceae family organisms and Pseudomonas species have dominated the bacterial flora during acute exacerbations leading to increased severity of the disease. Multidrug resistance and biofilm formation by these organisms have further worsen the situation limiting the therapeutic option.[31] In the studies conducted by N. Arora et al (25.8%), Patel et al (32%), Rakesh et al(38.1%), Suseela et al (22%), Shashibhushan et al (42%) and Vishwamber et al (45%), the predominant pathogen isolated was *Streptococcus pneumoniae*.[24-29] Other pathogens isolated were A. baumanii 05 cases (6.49%), Streptococcus pyogenes 06 cases (7.79%) and S. aureus in 02 cases (2.59%). In the study conducted by Hariom Sharan et al of (5.13%), Suseela et al, 3% is the rate of isolation for A.baumanii comparable to the present study.[19,27] Investigation for diagnosis of AECOPD sputum culture is a very simple and useful technique. It offers easy detection, aetiology & complications due to bacteria causing the severe infection. If followed in a well-disciplined way, it can replace the costlier diagnostic methods like immunodiffusion. Management of AECOPD can be achieved by the study of antibiogram which helps in creating a correct treatment protocol and hence antibiotics can be started empirically to treat the presumed bacterial infection. The mortality and morbidity can be reduced by finding out resistant pathogens and hence the treatment can be planned according to the organisms. Aminopenicillins like ampicillin and amoxicillin were formerly the standard treatment in AECOPD. Due to emergence of resistance among respiratory pathogens, their utility had been limited. Beta lactams, amoxyclav has been used in the study to know about the resistance patterns. Aminopenicillins with beta lactamase inhibitor is a better choice. Cephalosporins demonstrated clinical efficacy and tolerability that can surpass the standard aminopenicillins. A third generation cephalosporin has been used to test it's efficacy against pathogens. Quinolones like levofloxacin exhibit a broad spectrum of activity that includes both Gram positive and Gram negative organisms causing AECOPD. It was proven to be better than the other quinolones in treating Pseudomonas infection. Macrolides are the most potent drugs used for

treating sputum related infections Azithromycin has been used to see it's efficacy. The newer and powerful drugs available are carbapenems and the drug used is meropenem. The antibiotic meropenem, had 100% sensitivity to all the isolates tested was this was comparable to the study done by Chakraborty et al were carbapenems show 90.2% sensitivity.[51] In the study conducted by Rakhee et al imipenem had 85% sensitivity.[22] In our study 3rd generation cephalosporin used was ceftriaxone which showed a sensitivity of 68.9%. In his study, Shashibhushan et al stated that ceftriaxone is the most effective drug.[28] In his study, Vishwambhar et al isolated Streptococcus pneumonia which was 100% sensitive to cephalosporins, a little higher than the present study.[29]

In his study Chakraborty et al had 37% of sensitivity rate for ceftriaxone which is much less compared to the present study.[15] In the present study quinolones used were levofloxacin which showed a sensitivity of 90.48%., comparable to study by Vishwambhar et al which showed 89% efficacy with levofloxacin and 80% sensitivity to ciprofloxacin.[29] Studies by Chakraborty et al and Kumar et al have efficacy of 62% and 76.9% for ciprofloxacin which are too low.[15,30] Much lower rates of sensitivity to seen with Narayanagowda et al with 54.55% and Saxena et al with 25.53% for ciprofloxacin and 22.34% for levofloxacin.[20,23] Periodic isolation, identification and resistant status of pathogens responsible for AECOPD will help us formulate appropriate treatment protocol and this will be of immense use in reducing mortality and morbidity besides reducing the volume of antibiotics and development of resistance to antibiotics. The protective host immune responses that develop after exacerbation needs to be characterized to facilitate vaccine development. Further, the interaction among different etiologic factors such as environment, bacteria, viruses and atypical pathogens needs to be better understood to treat exacerbations and develop novel as well as cost effective preventive and therapeutic strategies.

## CONCLUSIONS

There have been significant advances in our understanding of aetiology of acute exacerbations of COPD (AECOPD). Frequent exacerbations appear to be associated with worsening health outcomes and effort should focus on prompt and effective treatment of each episode. Bacterial pathogens, mostly Gram negative bacilli are found to be the chief etiological agents in AECOPD. Antibiotic therapy should be initiated early depending on the culture. Susceptibility patterns of that particular region should be determined to prevent antibiotic resistance and to decrease health costs. However treatment options are limited and further research is needed to clarify the mechanisms that commence and sustain exacerbations and to identify new therapeutic agents. Better and more specific approaches to boost immune competence are currently under study.

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