BACTERIOLOGICAL PROFILE AND ANTIBIOTIC SENSITIVITY PATTERN IN ACUTE EXACERBATION OF ADVANCED CASES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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ABSTRACT

Acute exacerbations are significant and frequent events in the natural history of chronic obstructive pulmonary disease. Majority of these exacerbations are of infectious aetiology, bacteria being responsible for 30-50% of these cases. With not many studies of similar type being conducted in the Indian context, this study was undertaken with the purpose of determining the bacteriology of acute exacerbations of chronic obstructive pulmonary disease in hospitalized patients with advanced disease and their antibiotic susceptibility pattern to formulate a cost effective algorithm for antibiotic usage while at the same time reducing the chances of emergence of drug resistance. Sputum sample from a total of 338 patients were send for Gram's stain and culture sensitivity testing using an array of the commonly used antibiotics. Pathogenic bacteria were isolated from 203 (60.1%) samples. Gram negative bacteria were isolated from 79.8 percent (162/203) cases while the rest were Gram positive. Klebsiella species were the commonest (49.2%; 100/203) Gram negative isolates 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. 5.0 percent of the Klebsiella infections were multi drug resistant. It was thereby concluded that either Amikacin, Ciprofloxacin or Piperacillin-Tazobactam for be considered for Gram negative organisms and Linezolid be considered for Gram positive organisms as first line antibiotics in empirical therapy while Carbapenems may be kept as reserve drugs should the first line drugs fail.

KEYWORDS
COPD, GOLD Criteria, Acute exacerbations, Bacterial aetiology.

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INTRODUCTION: Chronic obstructive pulmonary disease (COPD) has been defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a disease state characterized by airflow limitation that is not fully reversible.[1] COPD includes emphysema, an anatomically defined condition characterized by destruction and enlargement of the lung alveoli; chronic bronchitis, a clinically defined condition with chronic cough and phlegm; and small airways disease, a condition in which small bronchioles are narrowed. Persistent reduction in forced expiratory flow rates is the most typical finding in COPD.

Increases in the residual volume and the residual volume/total lung capacity ratio, non-uniform distribution of ventilation, and ventilation-perfusion mismatching also occur. GOLD estimates suggest that COPD will rise from the sixth to the third most common cause of death worldwide by 2020. Chronic obstructive pulmonary disease (COPD) is a leading cause of death in developed countries.[2,3,4] Spirometry is required to make a clinical diagnosis of COPD; the presence of a post bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and thus of COPD[3]. According to GOLD criteria, Stage III COPD Patient denotes Severe cases with Spirometry findings FEV1/FVC <0.7 and FEV1 ≥30% but <50% predicted. Stage IV COPD Patient denotes Very severe cases with Spirometry findings FEV1/FVC <0.7 and FEV1 <30% predicted.[1]

An exacerbation of COPD (AECOPD) is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day to day variations and leads to a change in medication. An exacerbation can contribute to irreversible progression of disease.[5] It is estimated that bacterial infections are responsible for more than 40% all acute exacerbation of COPD in India.[6] Bacterial flora of AECOPD is changing from usual pathogen.[7] The study was done to find out the local prevalence of bacterial exacerbation of advanced COPD (GOLD stage 3 and stage 4) admitted at TMC& DR. BRAM Teaching Hospital, Agartala,

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Tripura, and also to find out the type of bacteria and sensitivity pattern in these group of patients.

MATERIALS AND METHODS: This study is a retrospective observational cohort study of advanced COPD (GOLD stage 3 & stage 4) patients admitted in the Medicine ward with acute exacerbation at the Tripura Medical College and Dr. B. R. Ambedkar Teaching Hospital.

Inclusion Criteria:

1. COPD patients who had previous record of spirometry levelled as GOLD stage 3 and stage 4.
2. Able to produce appropriate sputum sample containing <10 squamous epithelial cells and >25 pus cell.
3. Acute exacerbation of COPD defined as-
   - Increased dyspnoea.
   - Increased sputum volume.
   - Increased prevalence.

Exclusion Criteria:

1. Patients having interstitial lung disease (ILD), bronchial asthma, bronchiectasis, tuberculosis, pneumonia, malignancy or other evident diseases on chest X-ray.
2. Patients previously admitted within 21 days.
3. Patients who have already received antibiotics.

All hospital case records of COPD patients admitted from Jan 2015 till Nov 2015 were screened. Patients fulfilling inclusion criteria were selected in the study. Physical examination of all the patients documented was done. Spontaneous and induced sputum with 3% Sodium Chloride nebulization after proper mouth rinsing with 0.2% Chlorhexidine solutions as per protocol in IPD patients were taken. Record of sputum for physical appearance, Gram stain, AFB smear, and culture and drug sensitivity for bacteria were taken from Microbiology Department data base.

RESULTS: A total of 338 cases were included in the present study. Of them 281(83.1%) were males and 57 (16.9%) were females (M: F ratio 4.92:1). All the 338 patients screened were between 50 to 80 years of age with maximum number (18.05%) being in the age group of 76 to 80 years. Of 338 analyzed appropriate sputum samples, 203 (60.1%) showed growth for pathogenic bacteria. Gram stain was positive in 185 (91.2%) cases. Gram negative bacteria comprising of Klebsiella species, Pseudomonas aeruginosa, Acinetobacter and Escherichia coli were the predominant (162/203, 79.8%) amongst the pathogenic flora. Gram positive bacteria comprising of Staphylococcus aureus and Streptococcus pneumonia formed the rest (21.2%). Klebsiella species were the commonest (49.2%) organisms (3 out of 100 cases of Klebsiella species being Klebsiella oxytoca and the rest being Klebsiella pneumoniae) followed by Staphylococcus aureus (18.7%) and Pseudomonas aeruginosa (12.8%). Acinetobacter comprised of 9.36 percent cases while only 3 cases grew Streptococcus pneumonia in culture. Among the gram negative organisms, Carbapenem had the highest sensitivity (90.2%) followed by Amikacin (70.4%), Ciprofloxacin (68.0%), Piperacillin-Tazobactam (64.0%) and Ceftriaxone (37.0%). Among the gram positive organisms, Linezolid was found to be sensitive in all the cases. Vancomycin was sensitive in 68% cases. Vancomycin resistant Staphylococcus aureus was detected in 34.2% cases. Amoxicillin Clavulanate was sensitive in only 5.24 percent gram negative cases and 36.0% gram positive cases. Azithromycin was found to be sensitive in 23.0 percent gram negative cases while 41.0 percent gram positive cases showed sensitivity to the same. 5.0 percent (5/100) Klebsiella cases turned out to be multi drug resistant.

DISCUSSION: Bacterial infections are considered to be the most important cause AECOPD. It is estimated that roughly 50 percent cases of AECOPD are of bacterial origin. [Chawla] A proper algorithm for antibiotic usage is therefore needed in such cases to avoid over usage of antibiotics with low sensitivity profile and ensure an adequate usage of those which show a satisfactory sensitivity pattern.

As comparable with similar studies on AECOPD, the age group of our study population effected with AECOPD was found to be above 50 years with more than 80 percent of the study population being males. A probable cause for this could be the much higher prevalence of chronic active smoking in males as well as a much prolonged exposure to smoking in the same. More than 95 percent cases had smoking history of more than 40 pack years. Females on the contrary are much less exposed to active cigarette smoking although passive smoking was found to be a possible cause for COPD in this population. Besides household smoke such as those from biomass fuel was associated with many of the female cases.

Of all the 338 cases whose sputum was sent for culture, 203(60.1%) cases grew a pathogenic organism, a figure that closely matches with similar studies by Chawla et al (56.0%)[6] and Madhabi et al (55%)[8] but higher than a study conducted by Dr. Hariom Sharan (41.12%).[9] Gram stain positivity in our study was 91.2% (185/203) which matches with all the other studies. Of the culture positive cases, 79.8 percent cases grew gram negative organism which was higher than the study of Dr. Hariom Sharan (61.54%) and comparable with that of Chawla et al (74.03%) and Madhabi et al (74.0%). The cause for higher prevalence of gram negative organisms in cultures could be because of the fact that the cases included in the study were mostly advanced (stage 3 and stage 4) COPD.

Of the pathogenic organisms that were grown in cultures, Klebsiella species was the commonest comprising of 49.2 percent (100/203) which was in accordance to the study conducted by Madhabi et al as well as Dr. Hariom Saran. Staphylococcus aureus was isolated in 18.7 % (38/203) cases while Pseudomonas aeruginosa was isolated in 12.8 percent (26/203) cases. This was in contrary to the study conducted by Chawla et al where Pseudomonas aeruginosa was the most common isolate from the sputum of hospital in-patients or the study by Anand K et al[10] in

which Streptococcus pneumonia was the most common isolate. In our study there were only 3 samples from which Streptococcus pneumonia could be isolated.

Amongst the gram negative organisms, Carbapenem had the highest sensitivity (90.2%) followed by Amikacin (70.4%), Ciprofloxacin (68.0%), Piperacillin-Tazobactam (64.0%) and Ceftriaxone (37.0%). Among the gram positive organisms, Linezolid was found to be sensitive in all the cases. Vancomycin was sensitive in 68% cases. Vancomycin resistant Staphylococcus aureus was detected in 34.2% cases. Amoxicillin Clavulanate was sensitive in only 5.24 percent gram negative cases and 36.0% gram positive cases. Azithromycin was found to be sensitive in 23.0 percent gram negative cases while 41.0 percent gram positive cases showed sensitivity to the same. It is believed that the low sensitivity profile of both Amoxicillin Clavulanate and Azithromycin could primarily be because of their easily available oral formulations and their over the counter usage as well as widespread application of the injectable form of the former at all levels of health care both of which mostly end up in incomplete course of medication. Besides the predominance of gram negative organisms in our study has resulted in the overall low sensitivity profile of these two drugs. 5 out of the 100 (5.0%) positive cases were multi drug resistant.

CONCLUSION: Klebsiella species are the most common organisms responsible for AECOPD in this part of the country. Carbapenems have been found to show the best sensitivity amongst the Gram negative cases followed by Amikacin, Ciprofloxacin and Piperacillin-Tazobactam whilst Linezolid showed extremely good results against the Gram positive isolates. However, Carbapenems being reserve drugs, Amikacin, Ciprofloxacin or Piperacillin-Tazobactam and Linezolid may be used as the first empirical antibiotics of choice, should their respective organisms be found or suspected in similar scenarios. Further-more the overall low sensitivity of the much commonly used Amoxicillin Clavulanate and Azithromycin faces us with a situation which warrants a much more judicious use of both of these drugs probably restricted only to cases with a confirmed sensitivity report to a positive culture.

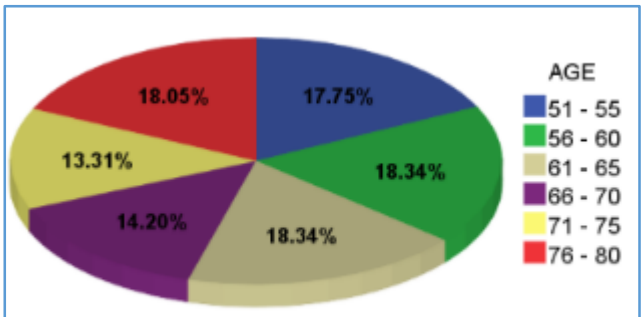

FIGURE 1: PIE DIAGRAM SHOWING AGE DISTRIBUTION OF CASES

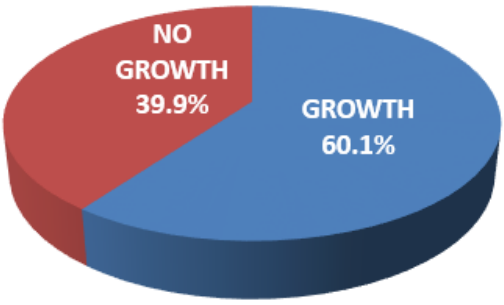

FIGURE 2: PIE DIAGRAM SHOWING CASES WITH PATHOGENIC ORGANISMS VS NO PATHOGENIC ORGANISMS ON CULTURE

Total Sputum Samples 338, growth of pathogenic organisms in 203(60.1%) cases no pathogenic organism growth in 135(39.9%).

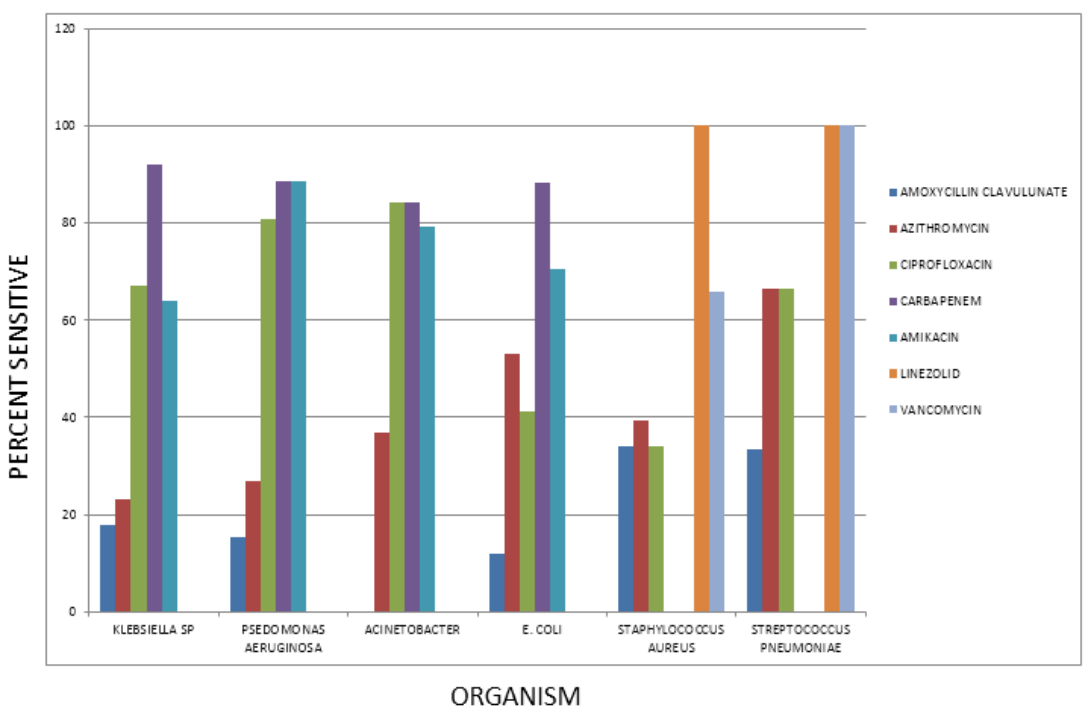

FIGURE 3: BAR DIAGRAM SHOWING DISTRIBUTION OF SENSITIVITY PATTERN OF ANTIBIOTICS ACROSS DIFFERENT PATHOGENIC ORGANISMS

Organism	Amoxycillin clavulunate			Azithromycin			Ciprofloxacin			Carbapenem			Amikacin			Linezolid			Vancomycin		
	S	R	PS	S	R	PS	S	R	PS	S	R	PS	S	R	PS	S	R	P	S	R	PS
Klesiella SP.	18 (18.0%)	68 (68.0%)	14 (14.0%)	23 (23.0%)	68 (68.0%)	9 (9.0%)	67 (67.0%)	27 (27.0%)	6 (6.0%)	92 (92.0%)	2 (2.0%)	6 (6.0%)	64 (64.0%)	27 (27.0%)	9 (9.0%)	N/D	N/D	N/D	N/D	N/D	N/D
Pseudomonas Aeruginosa	4 (15.4%)	18 (69.2%)	4 (15.4%)	7 (27.0%)	17 (65.4%)	2 (7.6%)	21 (80.8%)	1 (3.8%)	4 (15.4%)	23 (88.5%)	2 (7.7%)	1 (3.8%)	23 (88.5%)	2 (7.7%)	1 (3.8%)	N/D	N/D	N/D	N/D	N/D	N/D
Acinetobacter	0 (0.0%)	15 (79.9%)	4 (21.1%)	7 (36.8%)	12 (63.2%)	0 (0.0%)	16 (84.2%)	3 (15.8%)	0 (0.0%)	16 (84.2%)	2 (10.5%)	1 (5.3%)	15 (79.0%)	4 (21.0%)	0 (0.0%)	N/D	N/D	N/D	N/D	N/D	N/D
E. Coli	2 (11.8%)	15 (88.2%)	0 (0.0%)	9 (53.0%)	6 (35.3%)	2 (11.7%)	7 (41.2%)	9 (53.0%)	1 (5.8%)	15 (88.2%)	2 (11.8%)	0 (0.0%)	12 (70.6%)	5 (29.4%)	0 (0.0%)	N/D	N/D	N/D	N/D	N/D	N/D
Staphylococcus aureus	13 (34.2%)	23 (60.5%)	2 (5.3%)	15 (39.5%)	20 (52.6%)	3 (7.9%)	13 (34.2%)	19 (50.0%)	6 (15.8%)	N/D	N/D	N/D	N/D	N/D	N/D	38 (100.0%)	0 (0.00%)	0 (0.00%)	25 (65.8%)	12 (31.6%)	1 (2.6%)
Streptococcus pneumoniae	2 (33.4%)	0 (0.0%)	1 (66.6%)	2 (66.6%)	0 (0.0%)	1 (33.4%)	2 (66.6%)	1 (33.4%)	0 (0.0%)	N/D	N/D	N/D	N/D	N/D	N/D	3 (100.0%)	0 (0.00%)	0 (0.00%)	3 (100%)	0 (0.0%)	0 (0.0%)
Total	39 (19.2%)	139 (68.5%)	25 (12.3%)	63 (31.0%)	123 (60.6%)	17 (8.4%)	126 (62.0%)	60 (29.6%)	17 (8.4%)	146 (90.2%)	8 (4.9%)	8 (4.9%)	114 (70.4%)	38 (23.5%)	10 (6.1%)	38 (100.0%)	0 (0.00%)	0 (0.00%)	28 (68.3%)	12 (29.3%)	1 (2.4%)

Table 1: Distribution of sensitivity pattern of antibiotics across different pathogenic organisms

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