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BACTERIOLOGICAL AND CLINICAL PROFILES CORRELATED WITH ANTIBIOTIC RESISTANCE IN PATIENTS WITH ACUTE ATTACKS OF COPD

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ABSTRACT:

Background: In Chronic Obstructive Pulmonary Diseases (COPD), recurrent acute attacks are common and presumed to occur due to repeated bacterial infections. There is a correlation between the acute attacks of COPD and acquiring antibiotic resistance or infection with newer strains of organisms. The present study, a prospective, clinical correlative one was undertaken to isolate the organisms, to know their sensitivity and antibiotic resistance.

Aim of the study: To study and isolate the organism in the sputum of patients admitted with acute attacks of COPD and to correlate their resistance to newer antibiotics with the presenting clinical features.

Materials: 67 consecutive patients diagnosed with acute attacks of COPD attending the Department of General Medicine, Medicover Hospitals, Hyderabad, Telangana were considered for the study. Demographic details, spirometry values as per GOLD 2018 guidelines, antibiograms of the sputum samples were correlated with clinical severity and analyzed and compared with other studies in the literature.

Results: The study of 67 patients included 46 (68.65%) males and 21 (31.34%) females with a male-to-female ratio of 2.19:1. The mean age was 58.25±4.85 years. Patients aged between 45 and 65 years were 50 (74.62%) of the total 67 patients. A history of smoking was present in 44 (65.67%) patients with a smoking index of 224.7 ± 98.32. P. aerugenes (31.34%) was the most commonly isolated and cultured bacteria, followed by Klebsiella Pneumoniae (22.38%), S. Pneumoniae (09.12%), and H. influenzae (08.46%). P. aeruginosa was also the most resistant to Cefoperazone-sulbactam (29%). This was followed by Ciprofloxacin (28%). K. Pneumoniae was the most resistant to Cefoperazone-sulbactam in 63% of the isolates and levofloxacin in 39% of the isolates. S. Pneumoniae was the most resistant to Ciprofloxacin in 41% of the isolates, and Amoxicillin-clavulanic acid in 36%.

Conclusions: Bacteriological Profile in patients with acute attacks of COPD has a significant bearing upon the severity of the disease and its recurrence. The commonest bacteria encountered in the bacterial isolates were P. Aeruginosa and K. Pneumoniae. There was a significant correlation between the bacteriological profile of the sputum samples and their impact on the acute attacks of AECOPD. The study highlighted the differences in bacteriological profile in comparison to other studies. P. Aerugnes was the most common bacteria isolated and confirmed its role in acute attacks of severe degree AECOPD. The prevalence of antibiotic resistance to common bacteria suggested that the severity of the acute attacks of COPD could be attributed to the existence of antibiotic-

resistant strains. The susceptibility of both Gram-positive and Gram Negative bacteriae to broad spectrum Carbapenems was higher when compared to Ceftriaxone and Cefaperazone+sulbactum.

Keywords: Sputum samples, bacterial identification, antibiotic susceptibility testing, prevalence, multidrug-resistant strains, targeted therapy.

INTRODUCTION:

Chronic obstructive pulmonary disease (COPD) is defined as a progressive organic lung disease clinically identified by persistent airflow obstruction, which is fully irreversible. (1) Acute attacks of COPD are defined as persistent enhanced degree of airway symptoms over and above the day-to-day variations occurring normally. Acute attacks are the risk factors for increased morbidity and mortality in COPD patients. (2) Patients with such repeated acute attacks need to be hospitalized to prevent further decline in their lung function, quality of life, and overall prognosis. (3) Multifactorial factors play their role in different degrees in causing the Pathophysiology of COPD within a short period. (4)The factors could be infective or non-infective. (5) Among the infective factors bacterial infections play an important role in the pathogenesis of COPD. Usually, the bacteria form colonies in the lower respiratory tract and at a lower degree produce a continuous inflammatory response. (6) Every attempt should be made by the physician treating acute attacks of COPD, to identify these bacterial pathogens and assess their antibiotic resistance. This would help in turn in choosing the suitable antibiotics to improve the status of the patient and outcomes. (7) Earlier meta-analysis studies showed that bacterial colonization and infection of the lower respiratory tract during exacerbations were associated with increased airway inflammation, systemic inflammation, and prolonged recovery. (8, 9) Many authors from their studies have proved that understanding and identifying the clinical and bacteriological profile and antibiotic resistance pattern of the bacteria in different patients helped them to understand the method of tailoring antimicrobial therapy and optimizing patient management. (10) Hence the present study has attempted to analyze the clinical features and bacteriological profile and correlated them with the bacterial resistance studies in patients with acute attacks of COPD. This information was used to select the appropriate antibiotics and implement targeted therapy to effectively manage exacerbations and reduce the risk of treatment failure. The commonly associated bacteria included were H.influenza, Moraxella-catarrhalis, Streptococcus,-pneumonia, pseudomonas, and others. (11) Nowadays antibiotics are chosen and used in the treatment of acute attacks of COPD in the presence of bacterial infection; (12) but the selection of the antibiotics is based on the locally prevalent bacteria and their resistance pattern. (13)

MATERIALS: In total 67 consecutive patients diagnosed with acute attacks of COPD attending the Department of General Medicine of Family Physicians, Appollo Health & Lifestyle Limited, Hyderabad, Telangana were considered for the prospective analytical study. An institution ethics committee approval was obtained before commencing the study and a committee-approved consent form was used. The study period was between August 2017 and July 2018.

Inclusion Criteria: Patients with acute attacks of COPD were included. Patients aged between 35 years and 75 years were included. Patients of both genders were included. Patients with complaints of breathlessness at rest, fever, tachypnoea, and low oxygen saturation levels below 75% at rest were included. All the patients willing to join the study were included with the consent of the attendees of the patients.

Exclusion Criteria: Patients aged below 35 and above 75 years were excluded. Patients with associated infections of other systems like urinary tract infections, GIT infections, and localized infections were excluded. Patients with Diabetes Mellitus were excluded. Patients with immune-compromised diseases (AIDS) were excluded. Patients under treatment for pulmonary Tuberculosis, Bronchial asthma, Bronchiectasis, Lung malignancies, and community-acquired pneumonia were

excluded. Patients on antibiotic treatment for earlier attacks within 21 days were excluded. Patients earlier managed within the ward or treated on an outpatient basis. Patients admitted directly to the emergency department or respiratory ICU was excluded. The patients who received antibiotic therapy in the past 21 days; those managed in an outpatient or emergency department; those admitted inpatient department or intensive care unit; and those with ischemic heart disease were excluded from the study. Criteria for grouping as Acute Attack of COPD: The study used Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2018 criteria. (9) **The criteria included were:** 1. Patients requiring admission inwards. 2. Patients with adequate sputum samples showed more than 10 squamous epithelial cells and more than 25 pus cells. The demographic data of the patients included age, gender, presenting symptoms, history of smoking, duration of smoking, and smoking index. A thorough history taking was adopted followed by thorough general and systemic examinations of the patients. Spirometry was undertaken in all the patients to study the airflow resistance and volumes of the lungs. Spirometry was done before and after bronchodilator administration. When the forced expiratory volume in one second to forced vital capacity (FEV1/FVC) was less than 0.70, it was taken as the clinical diagnosis of COPD. As per GOLD 2018 guidelines, all the patients with acute attacks of COPD were considered and classified as 1. Mild when the post-bronchodilator FEV1 was equal to or more than (≥) 80% predicted 2. Moderate when the post-bronchodilator FEV1 was less than 80% predicted 3. Severe when post-bronchodilator FEV1 was less than 50% predicted 4. Very severe when post-bronchodilator FEV1 was less than 30%. **Method of isolating the organism:** All the patients were advised to collect sputum and give it for analysis; for isolation of organism before starting the antibiotics empirically. The sputum smear was tested for Gram's staining and incubated for bacterial culture, and antibiotic sensitivity testing. **Sputum sample collection and culture:** The sputum sample was collected early in the morning after the patient was encouraged to cough deeply to bring it out. The sample is collected in a sterile bottle with a screw cap. Oral contamination of the sample was avoided by asking the patients to gargle with plain water. The time taken to transport the sputum sample was less than 2 hours. The samples were cultured on two sheep blood agar, chocolate agar, and McConkey agar plates at the Microbiology laboratory of the Hospital. One of the sheep blood agar plates was streaked with staphylococci to encourage the growth of the H. influenza organism. All the plates were incubated at 37°C for 24–48 hours. The sheep blood agar plates were kept in a 05–10% CO2 incubator. Bartlett's grading system was used to report Gram's stain, and standard techniques were used to isolate cultures. The Kirby-Bauer method was used to test the antibiotic sensitivity of the pathogenic organisms isolated in culture. The variables in this study were Age, Gender, Presenting symptoms, History of smoking, duration of smoking, and smoking index.

RESULTS

Out of 67 patients included in the study after satisfying the inclusion and exclusion criteria, there were 46 (68.65%) males and 21 (31.34%) females with a male-to-female ratio of 2.19:1. The mean age was 58.25±4.85 years. Patients aged between 35 and 45 years were 08 (11.94%), Patients aged between 45 and 55 years were 19 (28.35%), Patients aged between 55 and 65 years were 31 (46.26%) and Patients aged between 65 and 75 years were 09 (13.43%). The commonest presenting symptom was Dyspnea in 51 (76.11%) patients, followed by symptoms of cough in 49 (73.13%) patients, and symptoms of expectoration in 47 (70.14%) patients. History of smoking was present in 44 (65.67%) patients and no history in 23 (34.32%) patients. Duration of smoking for less than 05 years was noted in 15 (22.38%) patients, 05 to 10 years of smoking in 17 (25.37%) patients, 10 to 15 years of smoking was observed in 22 (32.83%) patients, and more than 15 years of smoking in 13 (19.40%) of patients. The mean smoking index was 224.7 ± 98.32. The majority of the patients had a smoking index of 100–300 (51.7%) followed by < 100 (21.4%). A similar pattern was observed in males, i.e., 61.7% followed by 19.5%, respectively, while the majority of the females had a smoking index of < 100 (58.7%) followed by > 300 (21.7%), (Table 1).

Observation	Number	Percentage	P value
Age			
35 to 45 years	08	11.94	0.101
45 to 55 years	19	28.35	
55 to 65 years	31	46.26	
65 to 75 years	09	13.43	
Gender			
Male	46	68.65	0.521
Female	21	31.34	
Presenting Symptoms			
Dyspnea	51	76.11	0.317
Cough	49	73.13	
Expectoration	47	70.14	
Smoking			0.431
Yes	44	65.67	
No	23	34.32	
Duration of Smoking			
Less than 5 years	15	22.38	
05 to 10 years	17	25.37	0.435
10 to 15 years	22	32.83	
More than 15 years	13	19.40	
Smoking Index			
Less than 100	16	23.88	0.211
100 to 300	34	50.74	
More than 300	17	25.37	

Table 1: Showing the Demographic data of the patients with Acute COPD (n-67)

Based on the Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2018 criteria classification the Spirometry values were analyzed in this study and found that there were 07 (10.44%) patients with a mild degree, 28 (41.79%) patients with a moderate degree, 20 (29.85%) patients with a severe degree and 12 (17.91%) patients with a very severe degree. (Table 2)

GOLD Grading of Spirometry values	Number	Percentage	P value
Mild	07	10.44	0.510
Moderate	28	41.79	0.001
Severe	20	29.85	0.001
Very severe	12	17.91	0.001

Table 2: Showing the Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2018 criteria classification based on Spirometry values (n-67).

On bacteriological culture, P. aerugnes (31.34%) was the most commonly isolated and cultured bacteria, followed by Klebsiella pneumoniae (22.38%), S. pneumoniae (09.12%), and H. influenzae (08.46%). The least common bacteria were Acinetobacter (01.49%) and M. catarrhalis (01.49%). But S. aureus was isolated in 04.37%, and S. pyogenes in 05.97% of patients (Table 3).

Organism isolated	Number	Percentage
Pseudomonas Aeruginosa	21	31.34
Klebsiella Pneumoiniae	15	22.38
Normal flora	07	10.44
Strepto. Pneumoniae	06	09.12

H.Influenza	05	08.46
E.Coli	04	05.97
Strepto. Pyogenes	04	05.97
Staph, aureus	03	04.37
Moraxella catarrhalis	01	01.49
Acinebacter	01	01.49
Total	67	100

Table 3: Showing the various types of Bacteria isolated in COPD patients (n-67).

Antibiotic sensitivity pattern was observed in the study and found that both the Gram-positive and Gram-negative bacteriae were usually sensitive to Meropenem (89%) followed by Amoxicillin-clavulanic acid (78%) and Ceftriaxone (73%). These bacteria were resistant to Cefoperazone-sulbactam (47%) followed by Levofloxacin (49%) and Amikacin (41%), (Table 4).

Antibiotic	Sensitive percentage (%)	Resistant percentage (%)
Piperacillin-tazobactam	72	28
Ceftriaxone	73	27
Cefoperazone-sulbactam	47	53
Levofloxacin	49	51
Amoxicillin-clavulanic acid	78	22
Amikacin	41	59
Ciprofloxacin	63	37
Meropenem	89	11

Table 4: Showing the prevalence of antibiotic sensitivity and antibiotic resistance in the bacteria isolated in the study (n-67).

When the antibiotic resistance pattern was observed in the study, it was observed that the most commonly isolated organism, P. aerugnes was also the most resistant to Cefoperazone-sulbactam (29%). This was followed by Ciprofloxacin (28%). It was observed that K. pneumoniae was the most resistant to Cefoperazone-sulbactam in 63% of the isolates, followed by Levofloxacin in 39% of the isolates. S. pneumoniae was the most resistant to Ciprofloxacin in 41% of the isolates, followed by Amoxicillin-clavulanic acid 36%), (Table 5).

Antibiotic	P. aeruginosa (%)	K. pneumoniae (%)	S. pneumoniae (%)
Piperacillin-tazobactam	26%	34%	16%
Ceftriaxone	25%	25%	21%
Cefoperazone-sulbactam	29%	63%	13%
Levofloxacin	19%	39%	24%
Amoxicillin-clavulanic acid	18%	34%	36%
Amikacin	17%	23%	15%
Ciprofloxacin	28%	27%	41%
Meropenem	0%	075%	03%

Table 5: Showing the pattern of Bacterial resistance among the bacteria isolated in the study (n-67).

The incidence of organisms and the Spirometry "GOLD grading" were correlated in the study and found that the bacteria such as Ps. Aerogenosa and K. Pneumoniae accounted for 20 (29.85%), (Ps.Aerogenosa-15, K. Pneumoniae- 05) of the patients with GOLD severe and very severe acute

attacks of COPD. The S. pneumoniae and H. Influenza organisms accounted for 04/67 (05.97%) of the total subjects diagnosed with severe and very severe Spirometry "GOLD grading". (Table 6) There was a statistical significance in this observation with a p-value less than 0.05 (p- 0.001).

GOLD Grading of Spirometry values	Number	P. Aeruginosa 21	K. pneumonia 15	S. pneumonia 06	H. Influenza 05
Mild	07- 10.44	01	02	02	01
Moderate	28- 41.79	05	08	01	01
Severe	20- 29.85	06	03	01	01
Very severe	12- 17.91	09	02	01	01

Table 6: Showing the correlation between the Spirometry "GOLD grading" and the incidence of the bacteria isolated in the study (n-67).

DISCUSSION

The present study was conducted to study and isolate the organism in the sputum of patients admitted with acute attacks of COPD and to correlate their resistance to newer antibiotics with the presenting clinical features. The subjects with acute attacks of chronic obstructive pulmonary disease (COPD) were evaluated by their clinic-bacteriological spectrum and antibiotic resistance sequences. The study provided knowledge about the prevalence of bacterial species and their susceptibility patterns during acute attacks of COPD. In comparison to other studies, this study showed a higher incidence of positive isolates and cultures from the sputum of the patients. On bacteriological culture, P. aerugnes (31.34%) was the most commonly isolated and cultured bacteria, followed by Klebsiella pneumoniae (22.38%), S. pneumoniae (09.12%), and H. influenzae (08.46%). The least common bacteriae were Acinetobacter (01.49%) and M. catarrhalis (01.49%). But S. aureus was isolated in 04.37%, and S. pyogenes in 05.97% patients (Table 3). Sethi et al in 2016 (14), reported positive sputum cultures in 60% of COPD exacerbations. They concluded that the exacerbations in COPD were triggered by newer bacterial infections and they underscored the importance of analyzing bacterial sensitivity and resistance and their clinical correlation. The most common isolated pathogens in a similar study by Mood et al (15) showed the isolation of organisms like Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis, which were consistent with previous literature. A study by Soler et al. (16) in 2013 reported that the commonest bacteria were Haemophilus influenza and Streptococcus pneumoniae being acute attacks of COPD. The bacteria colonize in the lower respiratory tract and produce chronic inflammatory changes in the bronchial mucosa and submucosal layers. (17) They also observed that these bacteria were resistant to multiple antibiotics. Bacterial species are known to colonize the lower respiratory tract and contribute to the inflammatory response, leading to exacerbations. One concerning finding in our study was the presence of multidrug-resistant strains among the isolated bacteria. Antibiotic sensitivity pattern was observed in the study and found that both the Gram-positive and Gram-negative bacteriae were usually sensitive to Meropenem (89%) followed by Amoxicillin-clavulanic acid (78%) and Ceftriaxone (73%). These bacteria were resistant to Cefoperazone-sulbactam (47%) followed by Levofloxacin (49%) and Amikacin (41%), (Table 4). Soler et al (16) form their study concluded that the odds of a patient developing an acute attack of COPD is based on the bacteria and it was 1.69, 1.77, and 2.96 respectively for H. influenzae, S. pneumoniae, and M. catarrhalis. Garch DS, Thurston SJ et al (18) from their study showed that H. influenzae, S. pneumoniae, and M. catarrhalis were isolated in patients with stable COPD in much higher loads than those found during acute attacks of COPD. Domenech A, Puig C, Marti S et al (19) from their study found that the most common species were S. pneumoniae followed by H. influenzae, M. catarrhalis, and Legionella pneumophila, which caused more severe forms of COPD patients, and the organism isolated in acute exacerbation of COPD patients the commonly found organism were Ps. Aerogenosa species. They also found in their study that the presence of Ps. Aerogenosa in the patients was associated with a higher risk of morbidity and mortality with 30 to 90 day death rates. In this study, the organism isolated in the order of of decreasing incidence were P. aerugnes (31.34%), Klebsiella pneumoniae (22.38%), S.pneumoniae (09.12%), and H. Influenza (08.46%). (Table 3) In the present

study it was observed that when the incidence of the organism and the Spirometry "GOLD grading" were correlated, the bacteriae such as Ps. Aerogenosa and K. Pneumoniae accounted for 20 (29.85%), (Ps.Aerogenosa-15, K. Pneumoniae- 05) of the patients with GOLD severe and very severe acute attacks of COPD. The S. Pneumoniae and H. Influenza organisms accounted for 04/67 (05.97%) of the total subjects diagnosed with severe and very severe Spirometry "GOLD grading". There was a statistical significance in this observation with a p-value less than 0.05 (p- 0.001), (Table 6). A similar study was reported by Pérez-Lazo G., Abarca-Salazar S (20) and Barnsteiner S., Baty F., Albrich W. C., et al (21) and they reported P. Aerugenes as the most common isolate in the hospitalized patients. However, studies by Cižman M., Mioč V., Bajec T et al (22) and Miravitlles M, Anzueto A et al (23) reported K. pneumoniae as the most common isolate in their patients with acute attacks of COPD. Studies by Shashibhushan et al. (24) reported S. Pneumoniae as the most common isolate. There were a few more studies from Jacobs et al, and Eklof et al who found the correlation between the Ps. Aeroginosa infections in patients with acute Attacks of COPD with the severity of symptoms but also helped in as a marker of worsening disease with greater risk of morbidity and mortality and longer durations of Hospital stay. (25, 26) The protocol of selecting an antibiotic, based on the information provided by the microbiologist on the resistance pattern, of the organism is compulsory to achieve efficient and economical management with reduced chances of the organism developing resistance and preventing morbidity, mortality and prolonged Hospitalization. (27) Antibiotic sensitivity pattern observed in this study showed both the Gram-positive and Gram-negative bacteriae sensitive to Meropenem in 89% of patients followed by Amoxicillin-clavulanic acid in 78% and Ceftriaxone in 73% of patients. These bacteria were resistant to cefoperazone-sulbactam in 47% of patients followed by Levofloxacin in 49% and Amikacin in 41% of patients (Table 4). In a similar study by Mood, N, Katta S.R et al (15) the sensitivity testing reported significant resistance empirically used common antibiotics and the resistance observed was 17 to 43%. Resistance was observed in Both Gram-positive and Gram-negative bacteria, especially towards Cefoperazone-sulbactam followed by Levofloxacin and Amikacin. In terms of sensitivity observed by the above authors, most of the isolated bacteria were sensitive to Meropenem followed by Amoxicillin-clavulanic acid and Ceftriaxone. Hassan et al., from their study, showed the bacteriae isolated were resistant to Amoxicillin, Amoxicillin-clavulanic acid, and Cephalosporins mostly whereas the resistance was moderate to Fluoroquinolones (ofloxacin, levofloxacin, ciprofloxacin); and least against Carbapenems. (28). The antibiotic resistance pattern observed in this study showed the most commonly isolated organism, P. aerugenes was also the most resistant to Cefoperazone-sulbactam (29%). This was followed by Ciprofloxacin (28%). It was observed that K. pneumoniae was the most resistant to Cefoperazone-sulbactam in 63% of the isolates, followed by Levofloxacin in 39% of the isolates. S. pneumoniae was the most resistant to Ciprofloxacin in 41% of the isolates, followed by Amoxicillin-clavulanic acid in 36% of patients (Table 5). In the present study of 67 patients, males were 46 (68.65%) and 21 (31.34%) were females with a male-to-female ratio of 2.19:1. The prevalence of acute attacks of COPD in males could be attributed to their outside profession and activities and environmental pollutions. The mean age was 58.25±4.85 years. Patients aged between 45 and 65 years were 50 (74.62%) of the total 67 patients. This fact could be attributed to the higher prevalence of chronic Bronchitis in this age group. A history of smoking was present in 44 (65.67%) patients with a smoking index of 224.7 ± 98.32. History of smoking and the smoking index was lower among the females in the study with < 100 (58.7%) followed by > 300 (21.7%) respectively, (Table 1). In a similar study by Mood, N, Katta S.R, et al (15) the male-to-female ratio was 3.9:1 with most of the patients with a history of smoking but fewer smokers among the female gender. Hence smoking was recognized as a risk factor for acute attacks of COPD. Smoking and environmental pollutants tend to reduce the mucociliary clearance of the terminal bronchi ultimately leading to reduced inborn immunity. Colonization of the bacteria increases paving the way for another organism also once the immunity is lowered. Persistent colonization leads to chronic inflammatory changes and changes in the smooth muscle cells of the bronchi leading to increased airway resistance. (29) In non-smokers, acute attacks of COPD are explained by the presence of indoor air pollution (30). The commonest

presenting symptom in the present study was dyspnea in 51 (76.11%) patients, followed by symptoms of cough in 49 (73.13%) patients, and symptoms of expectoration in 47 (70.14%) patients. Mullerova et al. (31) reported from their study that the chances of developing increase with the increased airway resistance and it is 1.2 and 2.4 for moderate and very severe limitation, respectively. (31) Au et al. (32) found the rate of hospitalization increased in their patients with increased airway resistance. (32)

CONCLUSIONS:

The Bacteriological Profile in patients with acute attacks of COPD has a significant bearing on the severity of the disease and its recurrence. The commonest bacteria encountered in the bacterial isolates were P. Aeruginosa and K. Pneumoniae. There was a significant correlation between the bacteriological profile of the sputum samples and their impact on the acute attacks of AECOPD. The study highlighted the differences in bacteriological profile in comparison to other studies. P. Aerugenes was the most common bacteria isolated and confirmed its role in acute attacks of severe degree AECOPD. The prevalence of antibiotic resistance to common bacteria suggested that the severity of the acute attacks of COPD could be attributed to the existence of antibiotic-resistant strains. The susceptibility of both Gram-positive and Gram Negative bacteriae to broad-spectrum Carbapenems was higher when compared to Ceftriaxone and Cefaperazone+sulbactum. The bacteriological profile of the study warrants regular watch on emerging newer bacterial populations, and their antibiotic resistance patterns, and to keep a vigil over the antibiograms and antimicrobial resistance patterns while treating acute attacks of COPD.

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