Analysis of bacterial characteristics in sputum and their relationship with clinical and paraclinical symptoms in acute exacerbations of chronic obstructive pulmonary disease

Running tittle: Bacterial characteristics in acute exacerbations of COPD

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SUMMARY:

Chronic obstructive pulmonary disease (COPD) is a widespread condition with increasing prevalence globally. Sputum bacterial analysis aids in guiding initial antibiotic treatment. This study aimed to analyze bacterial characteristics using Real-Time PCR and sputum culture, and to explore their association with clinical and paraclinical features during acute exacerbations of COPD. A cross-sectional, comparative, prospective study was conducted on 180 inpatients at the Vietnam National Lung Hospital between January 2016 and June 2021. Clinical and paraclinical data were collected from the patients. The mean age of participants was 69.4 ± 9.4 years. Positive bacterial cultures were found in 37.2% of cases, while 62.8% were negative. The predominant Gram-positive bacteria

 https://doi.org/10.5281/zenodo.15052810

identified included *P. aeruginosa* (20.9%), *H. influenzae* (17.9%), *S. pneumoniae* (11.9%), and *A. baumannii* (10.4%). Atypical bacteria detected via PCR included *L. pneumophila* (11.9%) and *M. pneumoniae* (4.5%). *P. aeruginosa*, *H. influenzae*, *S. pneumoniae*, and *A. baumannii* were highly sensitive to moxifloxacin, ceftriaxone, and cefotaxime. Patients with positive cultures had higher white blood cell counts, CRP levels, and procalcitonin ($p<0.05$). These findings support the use of bacterial susceptibility data to inform antibiotic choices, preventing unnecessary use of broad-spectrum antibiotics and reducing the risk of resistance development.

Keywords: COPD, exacerbation, Real-Time PCR, Vietnam.

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent and increasingly common condition worldwide. According to the World Health Organization, 65 million people globally suffer from moderate to severe COPD, making it the third leading cause of death globally, with projections of affecting over 210 million people by 2030(1,2). This disease is severe, debilitating, and imposes a burden on patients and healthcare systems alike. In the Asia-Pacific region, including Vietnam, COPD prevalence is notably high. Research by Ngo Quy Chau and colleagues in Hanoi found a 2% prevalence rate among adults aged 40 and above(3). Another national survey in 2006 by Dinh Ngoc Sy and collaborators reported a 4.2% prevalence rate in the same age group(4).

Exacerbations are critical events in COPD patients, leading to worsened lung function, reduced quality of life, increased risk of future exacerbations, and mortality(5,6). Preventing exacerbations is crucial in COPD management, as they significantly impact

 https://doi.org/10.5281/zenodo.15052810

health status, often leading to hospitalizations, disease progression, rapid decline in lung function, and increased mortality(7).

There are many causes of exacerbations, with respiratory infections being the most common cause of COPD exacerbations(8–10). Recurrent bronchopulmonary infections exacerbate obstructive ventilation disorders and also increase the severity of the disease. Common microbiological causes of COPD exacerbations include bacteria such as *Haemophilus influenzae*, *Streptococcus pneumoniae, Moraxella catarrhalis*, and may also involve certain respiratory viruses(11,12). In addition to these agents, atypical bacteria such as *Mycoplasma pneumoniae, Chlamydia pneumoniae*, and *Legionella pneumophila* are also important, though less common, pathogens(13,14). The prevalence of atypical pathogens in patients with COPD exacerbations varies significantly between studies. In clinical practice, bacterial antibiotic susceptibility test results can provide evidence for doctors to use in developing initial antibiotic regimens for treatment. This helps avoid the misuse of broad-spectrum and potent antibiotics from the outset, thereby limiting the development of resistance to these antibiotics (15–17). However, there is a lack of real-world data on COPD exacerbations among Vietnamese patients, necessitating a thorough consideration of clinical complexities.

Thus, this study aims to analyze the characterization of bacteria using Real-Time PCR in sputum culture, and antibiotic susceptibility testing in acute exacerbations of Chronic Obstructive Pulmonary Disease.

2. METHODS

2.1. Research Participants

Patients diagnosed with acute COPD and admitted for inpatient treatment at the Vietnam National Lung Hospital between January 2016 and June 2021, regardless of gender, were

 https://doi.org/10.5281/zenodo.15052810

included in the study. Eligible participants were those with a previously diagnosed history of COPD at the Central Lung Hospital who met the criteria for an acute exacerbation upon admission. Only patients who provided consent participated in the study.

The COPD diagnostic criteria, based on GOLD 2015, required patients to be over 40 years old with a history of smoking or tobacco use (18). Clinical symptoms included a persistent cough, excessive sputum production over many years, progressively worsening shortness of breath, and recurrent respiratory infections. Physical examination findings included reduced breath sounds, wheezing, crackles, and bronchial breath sounds, as well as chest expansion and hyperresonance on percussion. Laboratory findings included chest X-rays showing bronchial and vascular patterns, along with emphysematous changes. Pulmonary function tests confirmed irreversible or partially reversible airflow obstruction, with an FEV1/FVC ratio of less than 70% after bronchodilator use.

The diagnosis of acute COPD exacerbation followed Anthonisen's 1987 criteria, which included increased sputum volume, the presence of purulent or mucopurulent sputum, and worsening dyspnea.

2.2. Research Period and Location of the Study

The study was conducted at the Vietnam National Lung Hospital from January 2016 to June 2021.

2.3. Research Design

A cross-sectional, comparative, and prospective study design was employed to analyze the data.

2.4. Data collection method:

2.4.1. Sample size

Applied the sample size formula to a proportion

 https://doi.org/10.5281/zenodo.15052810

$n = Z^2_{1-\alpha/2}\frac{p(1-p)}{\varepsilon^2.p^2}$	In which: - n: the study sample size - Statistical significance level α = 0.05 (corresponding to 95% confidence level). - With 95% confidence level: Z1-α/2 = 1.96 (look up from the table with the selected α value) - ε is the relative deviation between the sample parameter and the population parameter (choose ε = 0.15) - p = 0.5 (Estimating the rate of common bacterial agents in patients with acute COPD exacerbations)

The actual sample size collected was 180 subjects.

2.4.2. Sample Collection Method

A convenient sampling method was used in this study, where patients were directly interviewed using a pre-built structured questionnaire.

2.4.3. Data Collection Method

Clinical Research

The researcher conducted direct interviews with patients to assess their condition, performed clinical examinations on all participants, and monitored the implementation of research-related tests. The collected research information was recorded in the research medical records.

Paraclinical Research

Various laboratory tests were conducted upon the patient's admission to the hospital, including blood count, blood biochemistry, CRP, PCT, and arterial blood gas analysis. Sputum culture was performed to isolate bacteria, and real-time PCR was used to identify atypical bacteria within the first 24 hours of admission. Pulmonary ventilation function was measured once the patient’s clinical condition and/or blood gas levels had stabilized after the acute episode. Additionally, chest X-rays and electrocardiograms were conducted within the first 24 hours of admission.

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3. RESULTS

Among the 180 patients participating in the study, the mean age of the patients was 69.38 ± 9.40 years. The majority were male with 167 cases, accounting for 92.8%. The Figure 1 illustrated the findings of bacterial detection in sputum samples using both sputum culture and real-time PCR methods. The results indicated that 37.2% of the tested samples were positive for bacterial presence, while 62.8% were negative.

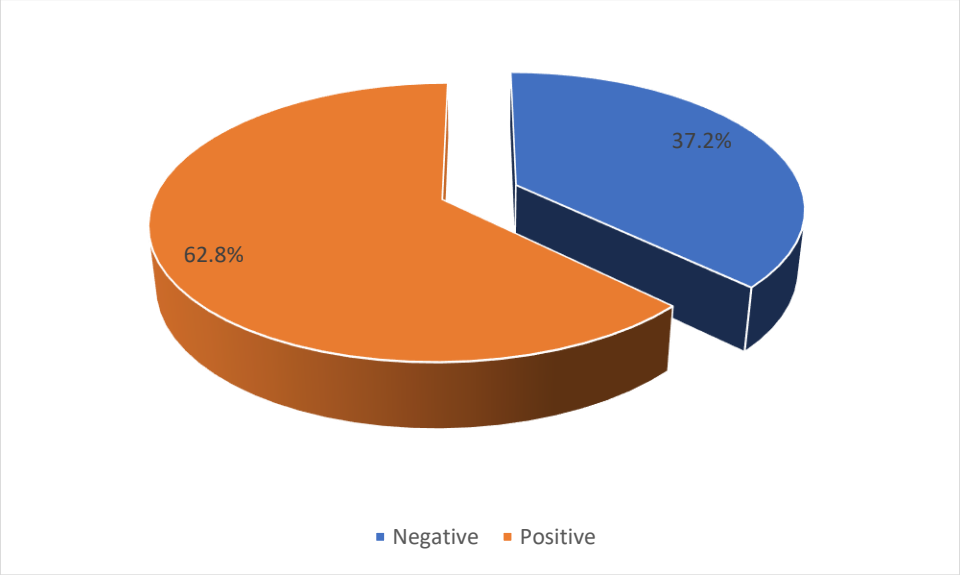

Figure 2. ***Results of bacterial detection in sputum (n=180)***

Table 1 presented the distribution of bacterial species identified in positive sputum specimens. Among the bacteria detected through sputum culture, *Pseudomonas aeruginosa* had the highest proportion, accounting for 20.9% of cases. This was followed by *Haemophilus influenzae* at 17.9%, *Streptococcus pneumoniae* at 11.9%, and *Acinetobacter baumannii* at 10.4%. Other detected bacterial species included *Moraxella catarrhalis* (9.0%), *Klebsiella pneumoniae* (6.0%), *Stenotrophomonas maltophilia* (3.0%), and *Staphylococcus aureus* (3.0%). The table also illustrated the distribution of atypical bacteria identified using real-time PCR. Among these, *Legionella pneumophila*

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accounted for 11.9% of cases, *Mycoplasma pneumoniae* for 4.5%, and *Chlamydia pneumoniae* for 1.5%.

Table 1. Bacterial species isolated in sputum (n=67)

Bacteria		Quantity (n)	Percentage (%)
Pseudomonas aeruginosa,		14	20,9
Haemophilus influenzae,		12	17,9
Streptococcus pneumoniae,		8	11,9
Acinetobacter baumannii,		7	10,4
Moraxella catarrhalis,		6	9,0
Klebsiella pneumoniae,		4	6,0
Stenotrophomanas maltophilia,		2	3,0
Staphylococcus aureus,		2	3,0
Atypical bacteria	*Legionella pneumophila,*	8	11,9
	Mycoplasma pneumoniae,	3	4,5
	Chlamydia pneumoniae	1	1,5
Total		67	100

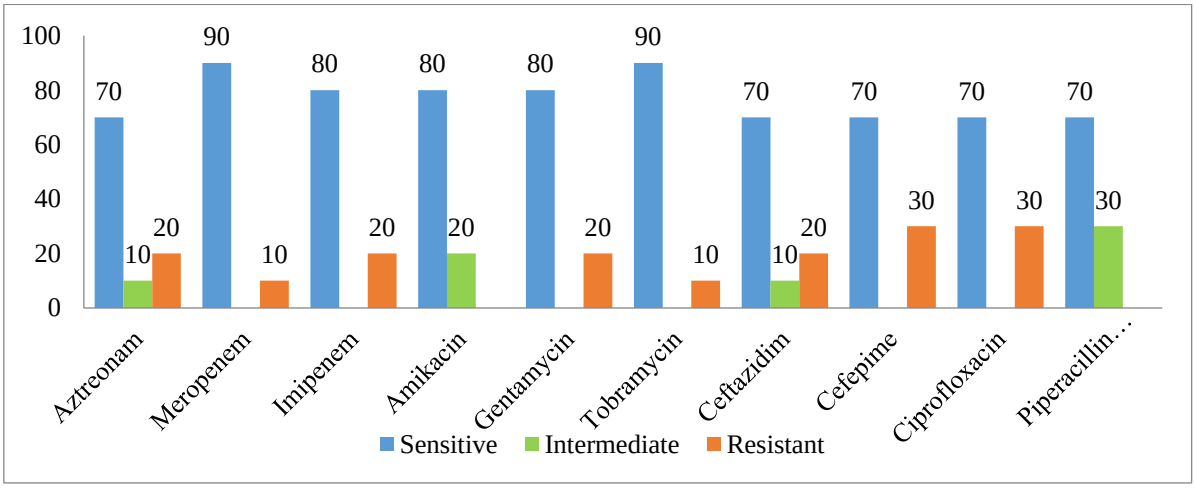

Figure 3. ***Antibiogram results of Pseudomonas aeruginosa (n=14)***

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The Figure 4 illustrated the sensitivity of *P. aeruginosa* to various antibiotics. The results indicated that the bacteria exhibited the highest sensitivity to Meropenem and Tobramycin, both at 90%. Imipenem, Amikacin, and Gentamicin demonstrated an 80% sensitivity rate. Meanwhile, Aztreonam, Ceftazidime, Ciprofloxacin, and Piperacillin/Tazobactam each showed a sensitivity rate of 70%. These findings highlighted the varying degrees of antibiotic susceptibility in *P. aeruginosa*, providing essential insights for selecting effective treatment options.

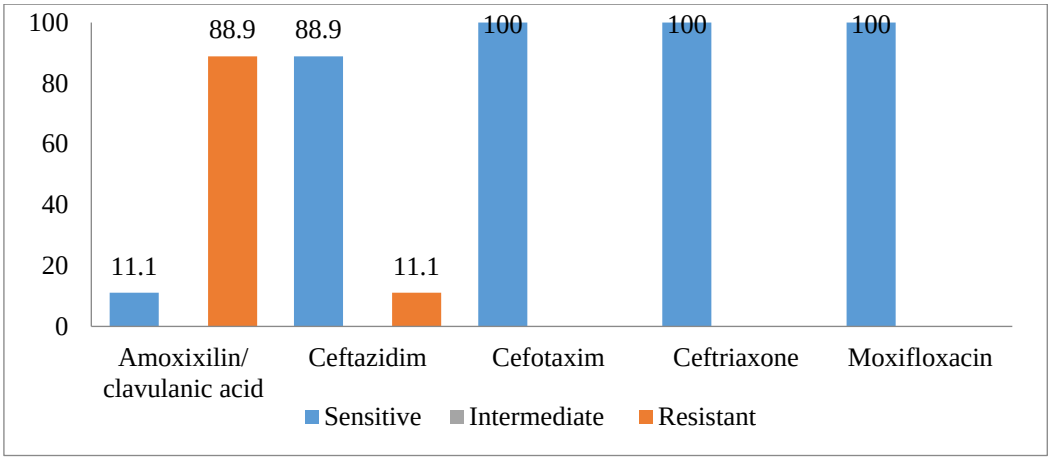

Figure 5. ***Antibiogram results of Haemophilus influenzae*** *(n=12)*

Figure 6 illustrated the antibiogram results of *Haemophilus influenzae*, showing its high sensitivity to several antibiotics. The bacteria exhibited complete sensitivity (100%) to Moxifloxacin, Ceftriaxone, and Cefotaxime, while Ceftazidime showed a slightly lower sensitivity rate of 88.9%. However, *H. influenzae* demonstrated a high resistance rate of 88.9% to Amoxicillin/Clavulanic acid, with only 11.1% sensitivity. These findings highlighted the effectiveness of certain antibiotics in treating *H. influenzae* infections while also emphasizing the significant resistance to Amoxicillin/Clavulanic acid. (*Figure 3*)

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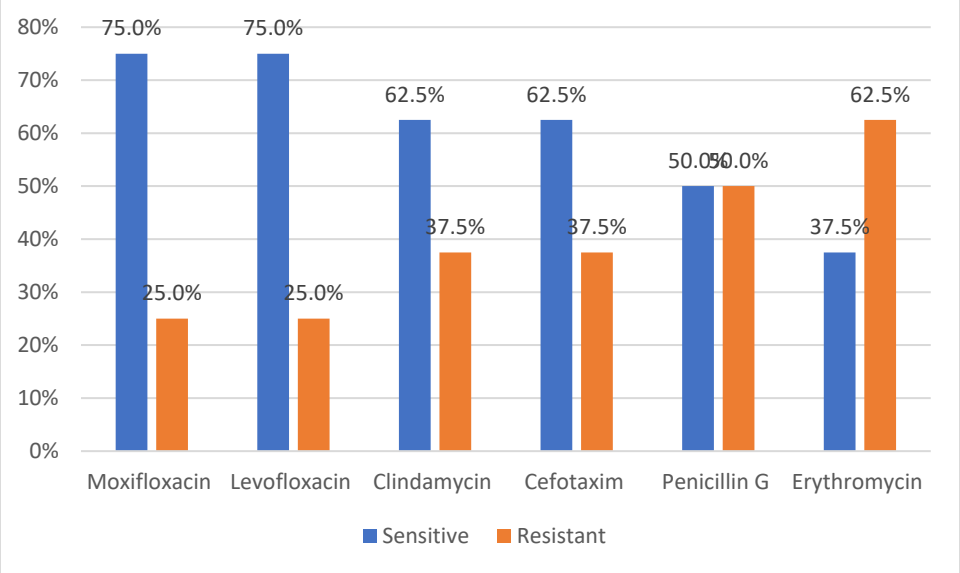

Figure 7. ***Antibiogram results of Streptococcus pneumoniae (n=8)***

Figure 4 depicted the antibiogram results of *Streptococcus pneumoniae*, illustrating its varying sensitivity to different antibiotics. The bacteria showed a sensitivity rate of 75% to both Moxifloxacin and Levofloxacin, corresponding to 6 out of 8 cases. Clindamycin and Cefotaxime exhibited a sensitivity rate of 62.5% (5 out of 8 cases). However, *S. pneumoniae* demonstrated lower sensitivity to Penicillin G, with only 50% (4 out of 8 cases) being responsive. Notably, the bacteria exhibited a high resistance rate of 62.5% to Erythromycin, with 5 out of 8 cases showing resistance. (*Figure 4*)

The table displayed the antibiogram results of *Acinetobacter baumannii*, illustrating its sensitivity and resistance patterns to various antibiotics. The bacteria exhibited sensitivity to Meropenem, Imipenem, and Doxycycline, with 5 out of 7 cases showing responsiveness to each. Amikacin, Gentamicin, Tobramycin, Ciprofloxacin, and Ampicillin/Sulbactam demonstrated lower sensitivity, with only 2 out of 7 cases being responsive. Ceftazidime, Minocycline, and Piperacillin/Tazobactam showed even lower sensitivity, with just 1 out of 7 cases being sensitive. The resistance rates were notably high for several antibiotics. Amikacin, Gentamicin, Tobramycin, Ceftazidime,

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Minocycline, Piperacillin/Tazobactam, Ampicillin/Sulbactam, and Trimethoprim/Sulfamethoxazole all exhibited resistance in 5 out of 7 cases. These findings highlighted the significant antibiotic resistance of *A. baumannii*, emphasizing the challenge of effective treatment selection. (*Table 2*)

Table 2. Antibiogram results of Acinetobacter baumannii (n=7)

Antibiotic	Sensitive	Intermediate	Resistant
Meropenem	5/7	0	2/7
Imipenem	5/7	0	2/7
Amikacin	2/7	0	5/7
Gentamycin	2/7	0	5/7
Tobramycin	2/7	0	5/7
Doxycycline	5/7	0	2/7
Ceftazidim	1/7	1/7	5/7
Ciprofloxacin	2/7	0	5/7
Minocycline	1/7	1/7	5/7
Ampicillin /Sulbactam	2/7	0	5/7
Trimethoprim/Sultamethoxazole	0	2/7	5/7
Piperacillin /Tazobactam	1/7	1/7	5/7

The table 3 presented the antibiogram results of *Moraxella catarrhalis*, highlighting its sensitivity and resistance to various antibiotics. The bacterium showed sensitivity to Amoxicillin/Clavulanic acid in 4 out of 6 cases, Ceftriaxone in 4 out of 6 cases, Ceftazidime in 5 out of 6 cases, Levofloxacin in 5 out of 6 cases, and Amikacin in 3 out of 6 cases. Conversely, *M. catarrhalis* exhibited resistance to several antibiotics. Gentamicin demonstrated resistance in 3 out of 6 cases, while Clarithromycin was resistant in 4 out of 6 cases. The highest resistance rate was observed with Erythromycin,

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with 5 out of 6 cases showing resistance. These results emphasized the varying degrees of antibiotic susceptibility in *M. catarrhalis*, providing essential insights for effective treatment strategies. (*Table 3*)

Table 3. Antibiogram results of Moraxella catarrhalis (n=6)

Antibiotic	Sensitive	Intermediate	Resistant
Amoxixilin/clavulanic acid	4/6	1/6	1/6
Cefotaxim	3/6	1/6	2/6
Ceftriaxon	4/6	0	2/6
Ceftazidim	5/6	0	1/6
Penicillin G	2/6	1/6	3/6
Erythromycin	1/6	0	5/6
Clarythromycin	2/6	0	4/6
Amikacin	3/6	0	3/6
Gentamycin	2/6	1/6	3/6
Levofloxacin	5/6	0	1/6

The table 4 showed the correlation between bacterial culture results and paraclinical characteristics. Patients with a white blood cell count > 10 G/l had a higher positive bacterial culture rate (46.3%) than those with ≤ 10 G/l (27.4%), with a statistically significant difference (p = 0.04). For CRP levels, the highest positive bacterial culture rate (48.4%) was observed in patients with CRP > 40 mg/l, compared to 45.9% in the 20–40 mg/l group and 24.1% in those with CRP < 20 mg/l (p = 0.001). Regarding procalcitonin, patients with PCT ≥ 0.25 ng/mL had a lower positive culture rate (33.3%) than those with PCT < 0.25 ng/mL (79.5%), with p = 0.01. These results highlighted the association between bacterial infections and inflammatory markers. (*Table 4*)

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Table 4. ***Correlation between the results of bacteria isolated in sputum and some paraclinical characteristics***

Characteristics \ *Bacterial results*		**Positive *bacteria***		**Negative *bacteria***		**OR 95%CI**	**p**
		n	**%**	**n**	**%**		
White blood cell count (n=180)	≤ 10 G/l	17	27.4	45	72.6	1	0.04
	> 10 G/l	50	46.3	68	53.7	1.95 (0.96 - 4.06)	
	Total	67	37.2	113	62.8		
CRP level (n=180)	< 20 mg/l	19	24.1	60	75.9	1	0.001
	20 - 40 mg/l	17	45.9	20	54.1	2.68 (1.37 - 6.45)	
	> 40 mg/l	31	48.4	33	51.6	2.97 (1.07 - 6.65)	
	Total	67	37.2	113	62.8		
PCT (n=51)	< 0.25 ng/mL	31	79.5	8	20.5	1	0.01
	≥ 0.25 ng/mL	4	33.3	8	66.7	0.13 (0.02 - 0.66)	
	Total	35	70.6	16	29.4		

CI: Confidence Interval. CRP: C-reactive protein. PCT: Procalcitonin

The table presented the relationship between Gram-positive, Gram-negative, and atypical bacteria with some clinical characteristics. The average duration of illness was 5.59 ± 2.84 years for patients with Gram-negative bacterial culture results, 5.81 ± 2.71 years for those with Gram-positive bacteria, and 5.95 ± 2.82 years for patients with atypical bacteria. The number of acute episodes per year was also similar across groups, with 2.57 ± 1.63 for Gram-negative bacteria, 3.31 ± 2.91 for Gram-positive bacteria, and 2.60 ± 1.81 for atypical bacteria. Regarding disease severity, Type 1 cases accounted for 65.9% in the Gram-negative group, 63.6% in the Gram-positive group, and 66.7% in the atypical bacterial group. Type 2 severity cases were observed at 34.1%, 36.4%, and 33.3%, respectively. These differences were not statistically significant ($p > 0.05$), suggesting no

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clear association between bacterial classification and these clinical characteristics. (*Table 5*).

Table 5. ***Relationship between gram positive (+), gram negative (-), and atypical bacteria groups with some clinical characteristics***

Characteristics		***Gram negative (-) bacteria***	***Gram positive (+) bacteria***	***Atypical bacteria***	**P**
Duration of illness (years)		5.59 ± 2.84	5.81 ± 2.71	5.95 ± 2.82	>0.05
Number of acute times per year (times)		2.57 ± 1.63	3.31 ± 2.91	2.60 ± 1.81	>0.05
Severity level	Type 1	29 (65.9%)	7 (63.6%)	8 (66.7%)	>0.05
	Type 2	15 (34.1%)	4 (36.4%)	4 (33.3%)	

4. DISCUSSION

The role of bacteria in triggering exacerbations and perpetuating chronic inflammation in COPD is well-established. Consequently, it is crucial to gain a deeper understanding of how bacterial infections evolve after an acute exacerbation of COPD (AECOPD) and how our treatment decisions affect these dynamics(19,20).

We observed that the positive bacterial rate was 37.2%, while the negative bacterial rate was 62.8%. Among Gram-positive bacteria identified in sputum cultures, *P. aeruginosa* was the most prevalent (20.9%), followed by *H. influenzae* (17.9%), *S. pneumoniae* (11.9%), *A. baumannii* (10.4%), *M. catarrhalis* (9.0%), *K. pneumoniae* (6.0%), *S. maltophilia* (3.0%), *and S. aureus* (3.0%). For atypical bacteria identified using real-time PCR, *L. pneumophila* was present in 11.9% of cases, *M. pneumoniae* in 4.5%, and *C. pneumoniae* in 1.5%. These findings aligned with other research conducted in Asia. The

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average infection rates for *M. pneumoniae and C. pneumoniae* vary, with Japan at 13%, South Korea at 16%, Taiwan at 22%, China at 16%, Thailand at 9%, Malaysia at 13%, and Singapore at 7%, depending on the study(13). Typically, atypical bacteria are more common in younger patients, are often managed on an outpatient basis, and rarely cause severe pneumonia. Our study showed that *L. pneumophila* is the most frequently encountered atypical pathogen in these patients.

Our study found that 14 isolates of *P. aeruginosa* were still relatively sensitive to several antibiotics, including Meropenem (90%), Tobramycin (90%), Imipenem (80%), Amikacin (80%), Gentamicin (80%), Aztreonam (70%), Ceftazidime (70%), Ciprofloxacin (70%), and Piperacillin/Tazobactam (70%). Despite the fact that over 80% of *Pseudomonas* strains are responsive to antibiotics typically effective against this bacterium, *P. aeruginosa* infections during exacerbations are linked to poorer clinical outcomes. Patients with COPD who were admitted for an exacerbation caused by *P. aeruginosa* demonstrated worse lung function, increased shortness of breath, and a higher frequency of hospitalizations in the previous year(21).

S. pneumoniae is a leading cause of high rates of illness and death globally. Resistance to antibiotics among *S. pneumoniae* strains varies, with resistance developing to several types of antibiotics, including penicillin, cephalosporins (beta-lactams), macrolides, and fluoroquinolones, with some strains even exhibiting multidrug resistance. The extent of penicillin-resistant *S. pneumoniae* (PRSP) and other forms of multidrug resistance differs across regions. EARSS data from 2008 indicate that 95% of invasive *S. pneumoniae* isolates were still susceptible to erythromycin. However, in 32 countries (1,655 isolates), 15% of the isolates showed resistance to erythromycin. Surveillance from the same period found that erythromycin resistance was highest in Tunisia and Malta, with rates of 39%

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and 46%, respectively(22).

Correlation between the results of bacteria isolated in sputum and some paraclinical characteristics

Our study found that patients with a white blood cell count > 10 G/l had a higher rate of positive bacterial cultures in their sputum compared to patients with a white blood cell count ≤ 10 G/l. This difference was statistically significant with a p-value < 0.05. Our results are similar to the study by Patrick Mallia et al. (2012), which showed that higher white blood cell counts were observed in patients with acute COPD exacerbations who had positive bacterial cultures(23). The study by Bafadhel M et al. (2015) also showed a positive correlation between the bacterial load in sputum and an increased white blood cell count(24). These patients exhibited more clinical symptoms and had poorer outcomes. Acute COPD exacerbations associated with bacterial pathogens showed significantly more neutrophilic inflammation in the airways compared to non-bacterial exacerbations(21). The severity of the exacerbation and the concentration of bacteria in the airways were related to the extent of neutrophilic inflammation(25).

In our research findings, the proportion of patients with CRP levels > 40 mg/l and positive bacterial results was 48.4%. This rate was higher compared to the group with CRP levels between 20 and 40 mg/l, which had a positive bacterial result of 45.9%. This difference was statistically significant with p < 0.05. According to Bircan A (2008), high CRP levels during acute exacerbations in COPD patients could be an indicator of an exacerbation due to secondary infection, and it was associated with increased sputum production and elevated peripheral blood white cell counts(26). In 2020, a study by Janie Bates, along with Nick A. Francis and colleagues, found that purulent sputum was the best predictive indicator of bacterial infection during acute exacerbations, while elevated CRP levels

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were associated with infection but could not replace the purulent sputum indicator(27). Also, the proportion of patients with PCT levels > 0.25 ng/mL and positive bacterial results in our study was 33.3%, lower than the group with positive bacterial results and PCT levels < 0.25 ng/mL (79.5%). We did not observe any difference between COPD exacerbations with positive bacterial results in the group with PCT > 0.25 ng/mL. In a case-control study by Chang C and colleagues in 2009, a PCT cutoff of 0.155 µg/L showed a sensitivity of 93.3% and a specificity of 60% for diagnosing bacterial infection in patients with COPD exacerbations(28). In patients with COPD exacerbations admitted to the ICU, Nseir and colleagues concluded that a cutoff value of 0.5 µg/L suggested bacterial isolation(29). A study by Ergan and colleagues showed that the optimal PCT threshold for hospitalization was 0.25 µg/L to identify patients with bacterial infection during COPD exacerbations(30). However, some studies by Soler (2012) and Gao (2017) concluded that PCT values did not significantly differ between bacterial and non-bacterial COPD exacerbations(31,32).

Our study had some limitations. The follow-up period for each patient in the study was short (from the time of patient admission), so we were unable to assess changes in indicators before and after the study. We only used the real-time PCR method to detect atypical bacteria (L. pneumophila, M. pneumoniae, C. pneumoniae), so we did not have comprehensive results regarding the microbiological profile in acute COPD episodes. The research period also overlapped with the COVID-19 pandemic, which caused delays in the progress of the study.

5. CONCLUSION

A study on 180 inpatients at the Vietnam National Lung Hospital from January 2016 to June 2021 showed that the positive bacterial rate accounts for 37.2%, and the negative

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bacterial rate accounts for 62.8%. The bacterial antibiotic susceptibility test results provided evidence for doctors to develop initial antibiotic regimens, helping to avoid the misuse of broad-spectrum and potent antibiotics from the outset and limiting the development of resistance to these drugs.

Conflict of Interest Statement: The authors affirm that they have no conflicts of interest to disclose.

Funding Statement: The authors confirm that this study received no financial support.

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 https://doi.org/10.5281/zenodo.15052810