Comparative Study of Pathogens in Patients with Simple Bronchiectasis and Bronchiectasis-COPD Overlap Syndrome: Postprint

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Abstract

Background: China has a large patient population with chronic obstructive pulmonary disease (COPD) and bronchiectasis, both being chronic respiratory diseases with high incidence and mortality rates. Bronchiectasis-COPD overlap syndrome (BCOS) is commonly encountered as a special clinical subtype but is easily overlooked. Infection is often a trigger for acute exacerbations, yet related etiological research remains relatively scarce. Objective: To analyze the distribution of pathogenic bacteria and antimicrobial resistance characteristics in patients with simple bronchiectasis (BE) and BCOS, compare the differences between the two groups, and provide references for rational clinical use of antimicrobial agents. Methods: A total of 584 bronchiectasis patients hospitalized in the Department of Respiratory and Critical Care Medicine of Maanshan People' s Hospital from January 2016 to January 2023 were selected as study subjects. Patients were divided into two groups based on COPD comorbidity: BE group (without COPD, 335 cases) and BCOS group (with COPD, 249 cases). Retrospective analysis was performed on pathogen composition, antimicrobial susceptibility test results, and their changes over time, analyzing differences in pathogen distribution and drug resistance between the two groups. Results: Among the 584 bronchiectasis patients, 299 pathogenic strains were isolated, including 146 strains in the BE group: 87 Gram-negative bacteria (59.59%), 3 Gram-positive bacteria (2.05%), 9 Mycobacteria (6.16%), and 47 fungi (32.19%). The BCOS group had 153 strains: 80 Gram-negative bacteria (52.29%), 1 Gram-positive bacterium (0.65%), 2 Mycobacteria (1.31%), and 70 fungi (45.75%). The proportion of Candida albicans in BCOS patients was higher than in BE patients (2 =5.274, P=0.022). The drug resistance rates of Pseudomonas aeruginosa in BE and BCOS groups were: imipenem 10.64% vs 25.53%, piperacillin-tazobactam 6.98% vs 15.91%, ciprofloxacin 12.77% vs

21.28%, amikacin 2.13% vs 2.13%. The drug resistance rates of Klebsiella pneumoniae were: imipenem 0% vs 14.29%, piperacillin-tazobactam 0% vs 14.29%, ciprofloxacin 15.38% vs 35.71%, amikacin 0% vs 7.14%. The resistance rate of Pseudomonas aeruginosa to ampicillin-sulbactam in the BCOS group was lower than in the BE group (P=0.026). The isolation rates of extended-spectrum β-lactamase Enterobacteriaceae (2 =4.357, P=0.037) and carbapenem-resistant Pseudomonas aeruginosa in the BCOS group were both higher than in the BE group (2 =5.593, P=0.018). From 2016 to 2022, Pseudomonas aeruginosa had the highest number of isolates among bronchiectasis patients, showing a trend of first decreasing then increasing. The number of Klebsiella pneumoniae isolates increased significantly in 2021 and 2022, ranking second only to Pseudomonas aeruginosa. The number of Mycobacteria isolates from 2020 to 2022 and Aspergillus isolates from 2021 to 2022 both showed upward trends. Conclusion: As a special phenotype, BCOS has its own characteristics in pathogen distribution and drug resistance, which deserves attention. Pseudomonas aeruginosa is currently the most common pathogen isolated from both BE and BCOS patients, with the number of Klebsiella pneumoniae isolates ranking second only to Pseudomonas aeruginosa in recent years. The numbers of isolated Mycobacteria and Aspergillus strains have also increased significantly compared with before, which should be taken seriously, especially in BE patients.

Full Text

Comparative Study of Pathogenic Bacteria in Patients with Bronchiectasis with and without Chronic Obstructive Pulmonary Disease

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Abstract

Background

Chronic obstructive pulmonary disease (COPD) and bronchiectasis are both chronic respiratory diseases with high morbidity and mortality in China. Bronchiectasis-COPD overlap syndrome (BCOS) represents a common yet

often overlooked clinical subtype. While infection frequently triggers acute exacerbations, etiological research on this condition remains relatively scarce.

Objective
To analyze and compare the distribution and antimicrobial resistance characteristics of pathogens in patients with bronchiectasis alone (BE) versus those with BCOS, providing evidence for rational antimicrobial use in clinical practice.

Methods
We retrospectively analyzed 584 hospitalized bronchiectasis patients in the Department of Pulmonary and Critical Care Medicine at Ma' anshan People' s Hospital between January 2016 and January 2023. Patients were divided into two groups: BE group (n=335, without COPD) and BCOS group (n=249, with COPD). Pathogen composition, antimicrobial susceptibility results, and their temporal changes were analyzed to identify differences in distribution and resistance patterns between groups.

Results
A total of 299 pathogen strains were isolated from 584 bronchiectasis patients. In the BE group (146 strains), Gram-negative bacteria accounted for 87 strains (59.59%), Gram-positive bacteria for 3 strains (2.05%), Mycobacterium for 9 strains (6.16%), and fungi for 47 strains (32.19%). In the BCOS group (153 strains), Gram-negative bacteria accounted for 80 strains (52.29%), Gram-positive bacteria for 1 strain (0.65%), Mycobacterium for 2 strains (1.31%), and fungi for 70 strains (45.75%). The proportion of *Candida albicans* was significantly higher in the BCOS group than in the BE group (^{2}=5.274, P=0.022). Resistance rates of *Pseudomonas aeruginosa* in BE and BCOS groups were: imipenem 10.64% vs. 25.53%, piperacillin-tazobactam 6.98% vs. 15.91%, ciprofloxacin 12.77% vs. 21.28%, and amikacin 2.13% vs. 2.13%. Resistance rates of *Klebsiella pneumoniae* were: imipenem 0% vs. 14.29%, piperacillin-tazobactam 0% vs. 14.29%, ciprofloxacin 15.38% vs. 35.71%, and amikacin 0% vs. 7.14%. The resistance rate of *P. aeruginosa* to ampicillin-sulbactam was significantly lower in the BCOS group (P=0.026). The isolation rates of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (^{2}=4.357, P=0.037) and carbapenem-resistant *P. aeruginosa* (CRPA) (^{2}=5.593, P=0.018) were significantly higher in the BCOS group. From 2016 to 2022, *P. aeruginosa* remained the most frequently isolated pathogen, showing a trend of initial decline followed by increase. The isolation of *K. pneumoniae* strains rose significantly in 2021-2022, becoming the second most common pathogen. Isolation rates of Mycobacterium (2020-2022) and *Aspergillus* (2021-2022) also showed upward trends.

Conclusion
As a distinct phenotype, BCOS exhibits unique characteristics in pathogen distribution and antimicrobial resistance that warrant attention. *Pseudomonas aeruginosa* remains the most common pathogen in both BE and BCOS patients, though *K. pneumoniae* isolation has recently become the second most frequent. Notably, isolation rates of Mycobacterium and *Aspergillus* have increased signif-

icantly, particularly in BE patients, requiring heightened clinical vigilance.

Keywords
Bronchiectasis; Pulmonary disease, chronic obstructive; Bronchiectasis-COPD overlap syndrome; *Pseudomonas aeruginosa*; Drug resistance

Introduction

Bronchiectasis is a chronic lung disease characterized by impaired mucociliary clearance, airway infection, and inflammation leading to structural airway damage and abnormal bronchial dilation. Clinical manifestations include chronic cough, sputum production, recurrent acute exacerbations, hemoptysis, and dyspnea. The global incidence of bronchiectasis has been increasing in recent years, representing the third most common chronic respiratory disease after COPD and asthma. In Asian populations, particularly China, the prevalence among adults increased 2.31-fold between 2013-2017, with an average annual growth rate of 32.8%, significantly increasing healthcare costs and mortality risk. Despite this burden, bronchiectasis receives far less attention than other chronic airway diseases.

Bronchiectasis is a highly heterogeneous disease that can present as an independent chronic infectious lung disease or coexist with other pulmonary conditions, including COPD. The concept of bronchiectasis-COPD overlap syndrome (BCOS), first proposed by Hurst et al., refers to the coexistence of both conditions in the same patient. Currently, no clinical guidelines address this overlap, and the causal relationship between the two diseases remains unclear. However, BCOS is increasingly recognized as associated with poorer prognosis and higher mortality compared to either disease alone. While most research has focused on differences between BCOS and COPD alone, BCOS as a special subtype of bronchiectasis has received limited attention despite its clinical importance. Respiratory infections are key triggers for acute exacerbations in both bronchiectasis and COPD, necessitating comparative studies of pathogen distribution and resistance patterns between pure bronchiectasis (BE) and BCOS to guide more precise antimicrobial therapy.

Methods

1.1 Study Subjects We retrospectively enrolled 584 bronchiectasis patients hospitalized in the Department of Pulmonary and Critical Care Medicine at Ma' anshan People' s Hospital between January 2016 and January 2023. Patients were divided into two groups based on COPD comorbidity: BE group (n=335, without COPD) and BCOS group (n=249, with COPD). Inclusion criteria were: (1) age $ $18 years; (2) complete clinical and microbiological data. Exclusion criteria were: (1) age <18 years; (2) cystic fibrosis; (3) incomplete clinical data. This retrospective study involved only clinical data collection without clinical intervention, posing no risk to participants. It was approved by the Ma' anshan People's Hospital Ethics Committee [Approval No. Medical Ethics (2023) 01-06]

with a waiver of informed consent.

Diagnostic criteria for bronchiectasis were based on the 2012 Chinese Expert Consensus on Diagnosis and Treatment of Adult Bronchiectasis, incorporating history, clinical presentation, physical examination, and high-resolution CT findings. COPD diagnosis followed the 2013 Guidelines for Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (Revised Edition) by the Chinese Thoracic Society, based on history, symptoms, physical examination, chest imaging, and pulmonary function tests.

1.3 Data Collection We retrospectively collected general patient information including gender, age, BCOS disease duration (time since concurrent diagnosis of bronchiectasis and COPD), hospitalization days, smoking history (pack-years = years smoked × packs per day), sputum microbiology culture results, and antimicrobial susceptibility data.

1.4 Pathogen Culture and Antimicrobial Susceptibility Testing All 584 patients provided deep sputum specimens collected under nursing supervision on the morning following admission, immediately placed in sterile containers and sent for testing. Pathogen culture, fungal culture, and routine acid-fast staining were performed according to the National Clinical Laboratory Procedures. Bacterial identification and antimicrobial susceptibility testing were conducted using the VITEK 2-Compact automated microbiology system (bioMérieux, France). Results were interpreted according to 2017 Clinical and Laboratory Standards Institute (CLSI) criteria. Quality control strains included *Staphylococcus aureus* ATCC25923, *Escherichia coli* ATCC25922, *Klebsiella pneumoniae* ATCC700603, and *Pseudomonas aeruginosa* ATCC27853 (from the National Quality Control Center). Pathogen resistance rate was calculated as (number of resistant strains / total tested strains) × 100%, and isolation rate as (number of isolated pathogens / number of patients) × 100%.

1.5 Statistical Methods Antimicrobial susceptibility data were analyzed using Whonet 5.6 software. Survey data were processed using Excel 2021 and SPSS 26.0. Normally distributed continuous variables were expressed as mean ± standard deviation and compared using independent samples t-test. Categorical data were expressed as percentages and compared using ^{2} test or Fisher' s exact test. Statistical significance was defined as $P<0.05$.

Results

2.1 Patient Characteristics Among 584 bronchiectasis patients, 297 (50.86%) were male and 287 (49.14%) female, with a mean age of 66.8$±$12.4 years. The BCOS group had significantly higher proportions of male patients, older age, longer BCOS disease duration, longer hospitalization days, and higher smoking history rates compared to the BE group ($P<0.05$). There was no significant difference in smoking pack-years between the two groups .

2.2 Pathogen Distribution A total of 299 pathogen strains were isolated from 584 bronchiectasis patients. The BE group yielded 146 strains: 87 Gram-negative bacteria (59.59%), 3 Gram-positive bacteria (2.05%), 9 Mycobacterium (6.16%), and 47 fungi (32.19%). The BCOS group yielded 153 strains: 80 Gram-negative bacteria (52.29%), 1 Gram-positive bacterium (0.65%), 2 Mycobacterium (1.31%), and 70 fungi (45.75%). The proportion of *Candida albicans* was significantly higher in the BCOS group than in the BE group (^{2}=5.274, P=0.022). No significant differences were observed in other pathogen distributions between groups .

2.3 Antimicrobial Resistance Patterns The predominant pathogens in both groups were *P. aeruginosa*, *K. pneumoniae*, and *Acinetobacter baumannii*. Resistance rates were calculated and compared [TABLE:3-5]. For *P. aeruginosa*, resistance rates in BE vs. BCOS groups were: imipenem 10.64% vs. 25.53%, piperacillin-tazobactam 6.98% vs. 15.91%, ciprofloxacin 12.77% vs. 21.28%, and amikacin 2.13% vs. 2.13%. For *K. pneumoniae*: imipenem 0% vs. 14.29%, piperacillin-tazobactam 0% vs. 14.29%, ciprofloxacin 15.38% vs. 35.71%, and amikacin 0% vs. 7.14%. For *A. baumannii*: imipenem 20.00% vs. 66.67%, piperacillin-tazobactam 20.00% vs. 66.67%, ciprofloxacin 20.00% vs. 100.00%, and amikacin 0% vs. 66.67%. The resistance rate of *P. aeruginosa* to ampicillin-sulbactam was significantly lower in the BCOS group (P=0.026). Although most resistance rates were higher in the BCOS group, no other statistically significant differences were observed.

2.4 Special Drug-Resistant Strains The isolation rates of ESBL-producing Enterobacteriaceae (^{2}=4.357, P=0.037) and carbapenem-resistant *P. aeruginosa* (CRPA) (^{2}=5.593, P=0.018) were significantly higher in the BCOS group. No significant differences were found in carbapenem-resistant Enterobacteriaceae (CRE) or carbapenem-resistant *A. baumannii* (CRAB) isolation rates between groups .

2.5 Co-infection with *Candida albicans* In the BE group, 39 *C. albicans* strains were isolated, while 60 were isolated from the BCOS group. Patients often had concurrent isolation of other pathogens, commonly *P. aeruginosa*, Mycobacterium, and *K. pneumoniae*. No significant difference was observed in co-infection patterns between groups .

2.6 Temporal Trends in Pathogen Distribution (2016-2022) *Pseudomonas aeruginosa* remained the most frequently isolated pathogen from 2016-2022, with isolation rates initially decreasing then increasing. *Klebsiella pneumoniae* isolation rose significantly in 2021-2022, becoming the second most common pathogen. Isolation rates of Mycobacterium (2020-2022) and *Aspergillus* (2021-2022) showed upward trends [Figure 1: see original paper].

2.7 Trends in *P. aeruginosa* Isolation (2016-2022) *Pseudomonas aeruginosa* isolation was highest in the first three years and last two years of the study period. CRPA isolation peaked in 2016 (60.00%, 9/15) and 2017 (19.05%, 4/21), then declined overall. Difficult-to-treat resistant *P. aeruginosa* (DTR-PA) was isolated only in 2016 (3 strains, 20.00% of *P. aeruginosa* isolates) [Figure 2: see original paper].

Discussion

Bronchiectasis is a chronic respiratory disease characterized by impaired mucociliary clearance, airway infection, and inflammation that leads to structural airway damage and abnormal bronchial dilation. Clinical manifestations include chronic cough, sputum production, recurrent acute exacerbations, hemoptysis, and dyspnea. The global incidence of bronchiectasis has been increasing, imposing a substantial healthcare burden. Infection is a key factor driving disease exacerbation, and current guidelines recommend annual sputum cultures with microbiological examination during exacerbations to guide targeted antimicrobial therapy. Similarly, respiratory infections are major triggers for COPD exacerbations, with bacterial infection being a common cause of acute worsening. Therefore, rational antimicrobial therapy is critically important.

This study compared BE and BCOS groups to identify differences in pathogen distribution and resistance patterns, aiming to guide targeted antimicrobial therapy for this special subtype. Among 584 bronchiectasis patients, 335 (57.36%) were in the BE group and 249 (42.64%) in the BCOS group. The BCOS group had significantly more male patients ($P<0.05$), likely related to higher smoking rates among men predisposing to COPD. Indeed, smoking history was significantly more prevalent in the BCOS group ($P<0.05$), though pack-years did not differ significantly between smoking patients in both groups—an interesting finding that may relate to smoking-induced immune barrier impairment and repeated infections leading to bronchiectasis in the BE group, warranting further investigation. BCOS patients were significantly older with longer disease duration and hospitalization days ($P<0.05$), indicating a heavier healthcare burden that deserves greater attention.

Our findings align with yet differ from previous studies. Xie et al. retrospectively analyzed 508 BCOS patients from 2015-2018, isolating 230 pathogens with *P. aeruginosa* as the most common, similar to our results, but followed by *A. baumannii* and *Haemophilus influenzae*. Yu et al. studied 43 BCOS patients from 2015-2017, also identifying *P. aeruginosa* as most common, but with *A. baumannii*, *H. influenzae*, and *K. pneumoniae* as subsequent pathogens. These discrepancies may reflect different enrollment periods and temporal changes in BCOS pathogens. Notably, these studies compared BCOS with COPD alone, whereas a Spanish multicenter observational study (2002-2011) of 1,790 bronchiectasis patients (158 with BCOS) found *P. aeruginosa* as the predominant pathogen in both groups, similar to our findings, but with *H. influenzae* and *Streptococcus pneumoniae* as subsequent pathogens, possibly reflecting regional differences in

pathogen distribution. That study found no significant difference in pathogen distribution between BCOS and BE groups, similar to our results, but did not include fungal comparisons.

The significantly higher *C. albicans* proportion in BCOS patients ($P<0.05$) may relate to chronic use of inhaled corticosteroids, intermittent systemic corticosteroids, and compromised airway barrier function. While fungal spore inhalation has minimal impact on healthy individuals, chronic lung diseases like bronchiectasis and COPD promote fungal growth due to impaired mucociliary clearance, viscous mucus, and fungal immune evasion mechanisms. We also found that *C. albicans* often coexisted with other pathogens (*P. aeruginosa*, Mycobacterium, *K. pneumoniae*, *Aspergillus*), though their pathogenic significance and correlation with airway inflammation and disease severity require further microbiome studies.

Pseudomonas aeruginosa, *K. pneumoniae*, and *A. baumannii* are common pathogens and important causes of lower respiratory tract infections. Except for significantly higher ampicillin-sulbactam resistance in BE group *P. aeruginosa* ($P<0.05$), no other significant resistance differences were observed, though resistance rates were generally higher in the BCOS group. This may relate to more frequent exacerbations, hospitalizations, broader-spectrum antibiotic exposure, and impaired airway defense in BCOS patients, requiring confirmation with larger samples. Clinicians should pay greater attention to this special subtype and prescribe antibiotics rationally.

BCOS patients showed significantly higher isolation rates of ESBL-producing Enterobacteriaceae and CRPA ($P<0.05$). For refractory BCOS patients with Gram-negative bacilli on rapid sputum smear, empirical therapy should cover ESBL-producers and CRPA using agents like piperacillin-tazobactam, amikacin, aztreonam, or carbapenems. While BE group *K. pneumoniae* remained susceptible to carbapenems, the BCOS group isolated 2 CRE strains. CRAB isolation was also higher in BCOS (2 strains) versus BE (1 strain), though not statistically significant, warranting continued surveillance.

Pseudomonas aeruginosa was the most common pathogen in both groups. Its infection correlates with disease duration, annual hospitalization frequency, and inflammatory markers. This organism' s strong virulence stems from secreted exotoxins and pathogenic factors that bind specific host sites, plus its ability to form protective biofilms and quorum-sensing systems that confer antimicrobial resistance. Bronchiectasis is a structural lung disease, and COPD comorbidity further complicates pulmonary architecture and internal environment, facilitating *P. aeruginosa* colonization and chronic infection. Management requires comprehensive approaches beyond antibiotics, including airway clearance techniques, anti-inflammatory therapy, and anti-biofilm treatments.

While bacterial infection dominates bronchiectasis exacerbations, fungal impacts remain understudied, particularly as triggering factors. Our finding of higher *C. albicans* isolation in BCOS highlights the need for increased fungal surveillance,

especially given rising *Aspergillus* isolation rates in 2021-2022. For patients with poor antibiotic response, clinicians should consider fungal pathogens and enhance detection efforts.

The emergence of CRPA and difficult-to-treat resistant *P. aeruginosa* (DTR-PA) poses major treatment challenges. From 2016-2022, *P. aeruginosa* isolation remained high, with CRPA peaking in 2016 (60.00%) and 2017 (19.05%) before declining. DTR-PA was isolated only in 2016 (3 strains, 20.00% of *P. aeruginosa* isolates), suggesting that restricted carbapenem use has been effective. However, BCOS patients showed significantly higher CRPA isolation, requiring vigilant monitoring. Notably, many CRPA strains remain susceptible to other antibiotics and are often mucoid, suggesting carbapenem-associated resistance. Clinicians should restrict carbapenem use and consider alternatives like piperacillin-tazobactam, ceftazidime, or amikacin. Given the complex pulmonary structure in BCOS that facilitates *P. aeruginosa* colonization, adding anti-biofilm agents such as low-dose macrolides or inhaled tobramycin may be beneficial.

In conclusion, BCOS represents a common and special bronchiectasis subtype with unique pathogenic and resistance characteristics requiring continuous monitoring. *Pseudomonas aeruginosa* remains the predominant pathogen, though *K. pneumoniae* isolation now ranks second. Rising isolation of Mycobacterium and *Aspergillus* demands attention, particularly in BE patients. Real-time surveillance of pathogen distribution and resistance patterns in this special subtype is essential for rational antimicrobial therapy, improved quality of life, and reduced healthcare burden.

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Author Contributions: WU Jun conceived and designed the study, analyzed data, performed statistical analysis, and drafted the manuscript; ZHANG Ling performed microbiological testing; GU Dongwei and ZHENG Lei collected data; ZHAO Zhuxiang and ZHAO Ziwen conceptualized and revised the manuscript. All authors approved the final version.

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Note: Figure translations are in progress. See original paper for figures.