

Real-World Antibiotic Use in Treating Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) in China: Evidence From The ACURE Study

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Research

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Abstract

Background: The evidence for real-world antibiotic use in treating acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is insufficient. This study aimed to investigate real-world antibiotic use in the management of AECOPD in China.

Methods: All hospitalized AECOPD patients from the acute exacerbation of chronic obstructive pulmonary disease inpatient registry (ACURE) study conducted at 163 sites between January 2018 and December 2019 were screened according to the eligible criteria. The eligible study population was divided into secondary and tertiary hospital groups. Patients' baseline characteristics, antibiotic use, and bacterial pathogen characteristics were retrieved and analyzed using SPSS 23.0.

Results: A total of 1663 patients were included in the study, including 194 patients from secondary hospitals and 1469 patients from tertiary hospitals. Among the 1663 AECOPD patients enrolled, 1434 (86.2%) received antibiotic treatment, comprising approximately 85.6% and 86.3% of patients in the secondary and tertiary hospital groups, respectively. The median antibiotic therapy duration was 9.0 (interquartile range [IQR]: 7.0 - 11.0) days. Regarding the routes of antibiotic use, 1400 (97.6%) patients received intravenous antibiotics, 18 (1.3%) patients received oral antibiotics, 15 (1.0%) patients received both intravenous and oral antibiotics, and one (0.1%) patient received both oral and nebulized antibiotic treatment. In addition, cephalosporin, penicillin, and quinolone were the most commonly prescribed antibiotics (43.6%, 37.0%, and 34.2%, respectively). In total, 990 (56.5%) patients underwent pathogen examinations; the proportion of patients receiving pathogen examinations in the second hospital group was significantly lower than that in the tertiary hospital group (46.4% vs 61.3%, $p < 0.001$).

Conclusion: This study indicates that antibiotics are extensively prescribed to AECOPD patients in China and demonstrates the limited compliance to the AECOPD guidelines in real-world antibiotic use. More well-designed clinical trials are warranted to further help guide the rational antibiotic use in the treatment of AECOPD.

Introduction

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2021 report,[1] chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease, characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities that are usually caused by significant exposure to noxious particles or gases and influenced by host factors, including abnormal lung development. In China, the prevalence of COPD among individuals aged 40 years and older is 13.7%.[2] Additionally, COPD was the fifth leading cause of death in China in a survey during 1980–2013,[3] and is now the third leading cause of death all over the world,[4] indicating that COPD has become a significant public health problem.

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are characterized by episodes of worsening of symptoms, resulting in substantial morbidity and mortality.[5] As there is heterogeneity in

the biological response, COPD exacerbations can be divided into different phenotypes, such as bacteria-, virus-, or eosinophil-associated exacerbations.[6] Specifically, respiratory bacterial infection is a major risk factor for the pathogenesis of COPD.[7] Bacterial infections during AECOPD are common; a recent meta-analysis involving 118 studies between 1980 and 2018 has revealed that the overall estimation of the prevalence of bacterial infection in AECOPD is 49.59%.[8]

Previous studies have suggested that antibiotic use might influence the prognosis of AECOPD, including treatment failure and rehospitalization.[9, 10] The GOLD 2021 report indicates that antibiotics are among the three most commonly used classes of medications for treating COPD exacerbations. Antibiotics should be administered to AECOPD patients with clinical signs of bacterial infection, for a recommended duration of 5-7 days.[1] However, the evidence for antibiotic use in general clinical practice when treating AECOPD is insufficient.

Hospitals in China are classified into grades I, II, and III based on their functions and roles: Grade I hospitals include community health centers and township health centers directly providing preventive care, medical care, and rehabilitation services for residents; Grade II hospitals are secondary hospitals providing comprehensive medical services to a region and conducting limited teaching and scientific research; and Grade III hospitals are tertiary hospitals providing high-level specialized medical services and conducting advanced teaching and scientific research.[11] Significant variations in medical care quality have been observed among these three grades of hospitals.[12] Furthermore, previous studies have demonstrated a relationship between hospital-grade quality of care and patients' clinical outcomes.[13, 14] This study aimed to investigate real-world antibiotic use in AECOPD patients in Chinese hospitals of different grades.

Methods

Study design

All data were obtained from the database of the acute exacerbation of chronic obstructive pulmonary disease inpatient registry (ACURE) study (ClinicalTrials.gov registry number: NCT02657525). The ACURE study was an ongoing, national, multicenter, observational registry aimed to investigate the overall clinical features and treatment procedures of hospitalized Chinese AECOPD patients in a real-world setting. The enrollment of participants in the ACURE study formally began in September 1, 2017, and the expected end of patient enrollment in all centers was December 2019. The ACURE study planned to recruit 7600 in-hospital AECOPD patients with a 3-year follow-up. By December 2019, 163 secondary and tertiary sites were finally included in the ACURE study, and all sites were distributed in 28 provinces across China. The details of the ACURE study design have been published elsewhere.[15] The study was approved by the Ethics Committee for China-Japan Friendship Hospital (2015-88). Informed consent was obtained from all involved patients. This study was conducted in accordance with the ethical standards formulated in the Helsinki Declaration.

Study participants

Data of all hospitalized AECOPD patients from all 163 sites in the ACURE study conducted between January 2018 and December 2019 were reviewed. The eligible criteria for AECOPD patients were as follows: 1) age no less than 18 years old; 2) who agreed to sign an informed consent for their participation in the ACURE study; 3) who did not participate in other clinical trials or intervention studies; 4) who had a confirmed diagnosis of AECOPD at discharge per the GOLD 2017 report; 5) with spirometry-verified COPD, which was defined as post-bronchodilator forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) <0.70; 6) who had no primary diagnosis of other respiratory diseases related to hospitalization other than AECOPD (including asthma, bronchiectasis, pulmonary tuberculosis, pneumonia, pulmonary interstitial fibrosis, lung cancer, pulmonary artery hypertension, and pulmonary embolism, etc.). The eligible study population was divided into a secondary and a tertiary hospital group based on the grade of admitted hospitals.

Data sources and study outcomes

For each patient, we extracted age, gender, body mass index (BMI), smoking status, comorbidities, hospitalization frequency due to AECOPD in the past year, COPD assessment test (CAT) score at admission and post-bronchodilator FEV₁/FVC. Data of antibiotic use and bacterial pathogen characteristics during admission were also reviewed. The primary outcomes were antibiotic use characteristics and antibiotic prescriptions for AECOPD patients. The secondary outcomes were the bacterial pathogen characteristics of AECOPD patients.

Statistical methods

The median and interquartile range (IQR) were used to describe continuous variables with a skewed distribution, while continuous variables with a normal distribution were presented as the mean and standard deviation (SD). Categorical variables were expressed as frequencies and percentages. The Mann-Whitney U test was performed to compare continuous variables with a skewed distribution, whereas the independent sample T test was conducted to compare continuous variables with a normal distribution. The chi-square test or Fisher's exact test was used to compare categorical variables.

A two-side p-value of less than 0.05 was defined as statistically significant. SPSS Windows Version 23.0 (IBM Corporation, Armonk, NY, USA) was used to perform statistical analysis.

Results

Baseline characteristics of included AECOPD patients

Finally, a total of 1663 patients who met the eligibility criteria were included in the study (Figure 1). In the study population, 194 and 1469 patients were admitted in the secondary and tertiary hospitals, respectively. The baseline characteristics of included AECOPD patients are demonstrated in Table 1. Of the total study population, 1318 (79.3%) were men and 345 (20.7%) were women. The median age of the overall study population was 70.0 (IQR: 64.0 - 77.0) years, and the median BMI was 22.1 (IQR: 19.8 - 24.5)

kg/m². A total of 1122 (67.5%) patients had at least one comorbidity other than COPD. Of the 1663 included patients, the median hospitalization frequency due to AECOPD in the past year was 0.0 (IQR: 0.0 - 1.0). The median of CAT scores at admission and post-bronchodilator FEV₁/FVC were 19.0 (IQR: 15.0 - 24.0) and 0.50 (IQR: 0.42 - 0.59), respectively. There was a markedly higher CAT score at admission in the secondary hospital group than the tertiary hospital group ($p < 0.001$).

Antibiotic use characteristics of included AECOPD patients receiving antibiotic treatment

Among the 1663 AECOPD patients enrolled, 1434 (86.2%) received antibiotic treatment. Approximately 85.6% and 86.3% of patients in the secondary and tertiary hospital groups, respectively, received such treatment. Overall, 1102 (76.8%) patients were treated with monotherapy, while 332 (23.2%) received combination therapy with ≥ 2 antibiotics. In addition, the proportion of patients in the secondary hospital group receiving combination therapy with ≥ 2 antibiotics was significantly lower than that in the tertiary hospital group (7.8% vs 25.2%, $p < 0.001$). As for the duration of antibiotic use, the median time in the overall population was 9.0 (IQR: 7.0 - 11.0) days. Compared with the secondary hospital group, the tertiary hospital group demonstrated a significantly longer median duration of therapy (9.0 vs. 8.0 days, $p < 0.05$). With regard to the routes of antibiotic use, 1400 (97.6%) patients received intravenous antibiotics, 18 (1.3%) received oral antibiotics, 15 (1.0%) received both intravenous and oral antibiotics, and one (0.1%) patient received both oral and nebulized antibiotic treatment (Table 2).

Antibiotic prescriptions of included AECOPD patients receiving antibiotic treatments

Table 3 shows antibiotic prescriptions of the included AECOPD patients who received antibiotic treatment. Of 1434 AECOPD patients receiving antibiotic treatment, the proportions of cephalosporin, penicillin, and quinolone use were 43.6%, 37.0% and 34.2%, respectively. In addition, the proportions of anti-*Pseudomonas* cephalosporin, penicillin and anti-*Pseudomonas* penicillin in the tertiary hospital group were significantly higher than the secondary hospital group (all $p < 0.01$). Moreover, quinolone and anti-*Pseudomonas* quinolone were more commonly prescribed in secondary hospitals in contrast with tertiary hospitals (both $p < 0.01$).

Bacterial pathogen characteristics of included AECOPD patients receiving pathogen examinations

Among 1663 included AECOPD patients, 990 (56.5%) underwent at least one pathogen examination. Notably, the proportion of patients receiving pathogen examinations in the second hospital group was significantly lower than that in the tertiary hospital group (46.4% vs 61.3%, $p < 0.001$). A qualified sputum was the main specimen source of pathogen examination, followed by blood, nasopharyngeal swab, alveolar lavage fluid, and pleural effusion. The proportion of qualified sputum specimen sources in the tertiary hospital group was significantly higher than that in the secondary hospital group (96.2% vs. 65.6%, $p < 0.001$), whereas the proportion of nasopharyngeal swab specimen sources was markedly lower than that in the secondary hospital group (1.6% vs. 34.4%, $p < 0.001$) (Table 4). A total of 775 AECOPD patients had bacterial culture results during admission. The most common bacterial pathogens

isolated were *Pneumonia klebsiella*, *Acinetobacter*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae* isolates (Table 5).

Discussion

Per the GOLD 2021 report, AECOPD can be classified as mild, moderate, and severe, based on the severity of the disease.[1] Patients with mild AECOPD should only be treated with short-acting bronchodilators (SABDs), those with moderate AECOPD are treated with SABDs plus antibiotics and/or oral corticosteroids, while those with severe AECOPD require hospitalization or visits to the emergency room. Our results demonstrate that 86.2% of included AECOPD patients received antibiotic treatment during admission. The median antibiotic therapy duration was 9.0 days. Cephalosporins, penicillin, and quinolones were the most commonly prescribed antibiotics. Furthermore, 56.5% of the included AECOPD patients underwent pathogen examinations. Importantly, a significantly lower proportion of patients receiving pathogen examinations was found in the second hospital group when comparing with the tertiary hospital group. Moreover, the most common bacterial pathogens isolated from the study population were *Pneumonia klebsiella*, *Acinetobacter*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae* isolates.

Prompt treatment improves recovery from exacerbation, reduces the risk of hospitalization, and is associated with a better health-related life quality of AECOPD patients.[16] Antibiotics play an important role in the treatment of AECOPD. However, evidence for the choice of antibiotic type and treatment duration remains insufficient. The GOLD 2021 report suggested that antibiotic choice should be based on the local bacterial resistance pattern, and the initial empirical treatment is usually an aminopenicillin with clavulanic acid, macrolide, or tetracycline; importantly, the report emphasized the potential likelihood of gram-negative bacterial infection (e.g., *Pseudomonas* species).[1] UK NICE guideline for AECOPD management provides a list of the first-choice oral antibiotics (including amoxicillin, doxycycline, and clarithromycin) and first-choice intravenous antibiotic (including amoxicillin, co-amoxiclav, clarithromycin, co-trimoxazole, and piperacillin with tazobactam); notably, the guideline stresses that clinicians should assess the effects of intravenous antibiotics within 48 hours and consider stepping down to oral antibiotics when possible.[17] In this study, only 1% patients received both intravenous and oral antibiotics, which was inconsistent with stepping-down mode for antibiotic use in NICE guideline; besides, this study suggested that the median antibiotic therapy duration from real-world data was significantly longer than guidelines.(1, 17) Above evidence reflect that there potentially exists insufficient monitoring of respiratory infection symptoms signs, disease prognosis, and pathogens in the clinical practice of AECOPD. Precision medicine has drawn more and more attention recently, and individualized treatment is also necessary for AECOPD patients. In order to dynamically adjust the most suitable antibiotic treatment for AECOPD patients, physicians need to record the infection symptoms of phlegm and fever, and reexamine potential pathogens more timely and comprehensively. As for the Chinese expert consensus for AECOPD, the preferred antibiotic is initially selected based on the results of *Pseudomonas aeruginosa* infection risk assessment; namely, for those with no risk factors of *Pseudomonas aeruginosa* infection, antibiotics including amoxicillin/clavulanic acid, levofloxacin, and moxifloxacin are suggested;

meanwhile, ciprofloxacin, levofloxacin, or a beta-lactam with anti-*Pseudomonas aeruginosa* activity combining with aminoglycosides (optional) is suggested for patients with risk factors for *Pseudomonas aeruginosa* infection, for a recommended duration of 5-10 days.[18] In general, the guidelines and expert consensus all propose the necessity of monitoring *Pseudomonas aeruginosa* infection. In this study, antibiotic use with a high coverage rate of *Pseudomonas aeruginosa* was observed, which was consistent with current international guidelines and national expert consensus. Interestingly, we found that anti-*pseudomonas* cephalosporin and anti-*pseudomonas* penicillin were main choices for patients in tertiary hospitals, while anti-*pseudomonas* quinolones were more commonly prescribed in secondary hospitals. We speculate that this may result from physicians' medication experience varies in different-grade hospitals, and the safety of quinolones is much easier to guarantee than cephalosporin and penicillin.

The lung microbiome, including bacteria, detected in COPD patients, is a dynamic organism, and its composition seems to be dependent upon the heterogeneity of disease, disease progression, and treatment.[19] Patel et al.[20] found that lower airway bacterial colonization in a stable COPD state could modulate the character and frequency of exacerbations. Sanjay et al.[21] clarified that there existed associations between COPD exacerbations and new isolations of bacterial pathogens. Mayhew et al.[22] proved that the stability of the lung microbiome over time was more likely to be decreased in exacerbations and individuals with more frequent exacerbations; additionally, bacterial exacerbations were more likely to be relapse in subsequent exacerbations within a subject. In addition, MAESTRAL study suggested that complete bacteria eradication involved in the exacerbation was of vital importance to the successful treatment of AECOPD.[23] Thus, monitoring the lung microbiome is critical for AECOPD patients. In this study, 61.3% AECOPD patients in tertiary hospitals underwent pathogen examination, while this proportion was significantly lower in secondary hospitals. This suggest that it is necessary to further increase physicians' awareness of the importance of conducting pathogen examination in AECOPD patients to better guide the treatment, as pathogen examination provides the best evidence for precise antibiotic medication. Herrera et al. [24] reported that both swab and sputum specimens had good specificity in polymerase chain reaction tests for the diagnosis of community-acquired pneumonia (CAP) caused by atypical bacteria, but there was a significantly lower sensitivity in swab specimens than in sputum specimens. Moreover, a recent French study showed that the diagnostic efficacy of pulmonary samples for *Legionella pneumophila* was clearly superior to that of nasopharyngeal aspirates in adult patients with CAP or AECOPD.[25] Furthermore, Cho et al.[26] found that sputum was more efficacious than nasopharyngeal swabs for the simultaneous detection of *Legionella pneumophila*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae* using multiplex PCR in CAP. Therefore, specimen type is crucial for accurately detecting bacterial infections, and the sensitivity of sputum specimens may be superior to that of swab specimens. This also suggests the necessity of improving the proportion of sputum specimens collected from AECOPD patients in China, especially in secondary hospitals. Regarding the types of cultured bacterial pathogens, *Pneumonia klebsiella* isolates, *Acinetobacter* isolates, *Haemophilus influenzae* isolates, *Pseudomonas aeruginosa* isolates, and *Streptococcus pneumoniae* isolates were commonly detected, which was consistent with the findings of previous

studies. Millares et al. [27] reported that *Streptococcus*, *Pseudomonas*, *Moraxella*, *Haemophilus*, *Neisseria*, *Achromobacter* and *Corynebacterium* genera were found by an increase in the relative abundance over 20 % during exacerbations of COPD. In a Chinese study, the predominant bacteria included *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Haemophilus influenzae* and *Streptococcus pneumoniae*. [28] Therefore, monitoring potential bacterial pathogens based on clinical characteristics and territories seems crucial to the management of AECOPD patients in real clinical practice.

This study had some limitations. Firstly, the prescribing of antibiotics according to the international nonproprietary names (INNs), which might cause the absence of a more detailed pharmacotherapeutic approach. Secondly, there were missing data (e.g., duration of antibiotic use) in a portion of the patients. Thirdly, the proportion of patients from secondary hospitals was relatively lower than that from tertiary hospitals; nevertheless, a professional steering committee was employed to monitor the study, and its scientific integrity can be absolutely guaranteed. Future studies focusing on antibiotic use among AECOPD patients in secondary hospitals are needed. Fourthly, due to the limited follow-up duration, no prognostic analysis was performed to investigate the relationship between antibiotic use and long-term clinical outcomes.

To the best of our knowledge, this is the first multicenter retrospective observational study to describe the real-world antibiotic use in AECOPD patients in Chinese hospitals of different grades. This study indicated that antibiotics are extensively prescribed to AECOPD patients in China and demonstrated the limited compliance to the AECOPD guidelines in real-world antibiotic use. More well-designed clinical trials are warranted to further help guide the rational antibiotic use in the treatment of AECOPD.

Conclusion

In summary, this study indicates that antibiotics are extensively prescribed to AECOPD patients in China and demonstrates the limited compliance to the AECOPD guidelines in real-world antibiotic use. More well-designed clinical trials are warranted to further help guide the rational antibiotic use in the treatment of AECOPD.

Abbreviations

AECOPD	acute exacerbations of chronic obstructive pulmonary disease
ACURE	acute exacerbation of chronic obstructive pulmonary disease inpatient registry
IQR	interquartile range
GOLD	Global Initiative for Chronic Obstructive Lung Disease
COPD	chronic obstructive pulmonary disease
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
BMI	body mass index
CAT	COPD assessment test
SD	standard deviation
CAP	community-acquired pneumonia
INNs	international nonproprietary names

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee for China-Japan Friendship Hospital (2015-88). Informed consent was obtained from all involved patients. This study was conducted in accordance with the ethical standards formulated in the Helsinki Declaration.

Consent for publication

Not applicable

Availability of data and material

Data are available from chenyan99727@csu.edu.cn with reasonable requests.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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Tables

Table 1. Baseline characteristics of included AECOPD patients.

Characteristics	Overall (n=1663)	Secondary hospital (n=194)	Tertiary hospital (n=1469)	p - value
Age, years	70.0 (64.0 - 77.0)	71.5 (65.8 - 77.0)	70.0 (64.0 - 77.0)	0.149
Gender, male	1318 (79.3)	160 (82.5)	1158 (78.8)	0.239
BMI, kg/m ²	22.1 (19.8 - 24.5)	22.4 (20.1 - 25.0)	22.0 (19.8 - 24.4)	0.358
Smoking status				0.750
Current smoker	480 (28.9)	54 (27.8)	426 (29.0)	
Ex-smoker	704 (42.3)	87 (44.8)	617 (42.0)	
Never smoking	479 (28.8)	53 (27.3)	426 (29.0)	
Any comorbidity	1122 (67.5)	127 (65.5)	995 (67.7)	0.526
Cardiovascular diseases	748 (50.5)	98 (50.5)	650 (44.2)	0.099
Endocrine and metabolic diseases	167 (10.0)	16 (8.2)	151 (10.3)	0.376
Digestive diseases	57 (3.4)	4 (2.1)	53 (3.6)	0.266
Other diseases	645 (38.8)	67 (34.5)	578 (39.3)	0.196
Hospitalization frequency due to AECOPD in the past year, times	0 (0 - 1.0)	0 (0 - 2.0)	0 (0 - 1.0)	0.238
CAT score at admission	19.0 (15.0 - 24.0)	22.0 (15.0 - 29.0)	19.0 (15.0 - 24.0)	< 0.001
Post-bronchodilator FEV ₁ /FVC	0.50 (0.42 - 0.59)	0.50 (0.40 - 0.59)	0.50 (0.43 - 0.59)	0.285

Notes: Values are presented as median (IQR) or number (percentage).

Legend: AECOPD – acute exacerbation of chronic obstructive pulmonary disease; BMI - body mass index; CAT - COPD Assessment Test; FEV₁ - forced expiratory volume in one second; FVC: forced vital capacity.

Table 2. Antibiotic using characteristics of included AECOPD patients receiving antibiotic treatment.

Characteristics	Overall (n=1434)	Secondary hospital (n=166)	Tertiary hospital (n=1268)	p - value
Types of antibiotic use				< 0.001
Monotherapy	1102 (76.8)	153 (92.2)	949 (74.8)	
Combination therapy with ≥ 2 antibiotics	332 (23.2)	13 (7.8)	319 (25.2)	
Duration of antibiotic use, days (n=1400)	9.0 (7.0 – 11.0)	8.0 (6.0 – 11.0)	9.0 (7.0 – 11.0)	0.030
Routes of antibiotic use				0.242
Oral	18 (1.3)	0 (0)	18 (1.4)	
Intravenous	1400 (97.6)	166 (100)	1234 (97.3)	
Oral + intravenous	15 (1.0)	0 (0)	15 (1.2)	
Oral + nebulized	1 (0.1)	0 (0)	1 (0.1)	

Notes: Values are presented as median (IQR) or number (percentage).

Legend: AECOPD – acute exacerbation of chronic obstructive pulmonary disease.

Table 3. Antibiotic prescriptions of included AECOPD patients receiving antibiotic treatment.

Characteristics	Overall (n=1434)	Secondary hospital (n=166)	Tertiary hospital (n=1268)	p - value
Cephalosporin	625 (43.6)	72 (43.4)	553 (43.6)	0.954
Anti - pseudomonas cephalosporin	281 (19.6)	19 (11.4)	262 (20.7)	0.005
Penicillin	530 (37.0)	30 (18.1)	500 (39.4)	< 0.001
Anti - pseudomonas penicillin	465 (32.4)	21 (12.7)	444 (35.0)	< 0.001
Quinolone	491 (34.2)	76 (45.8)	415 (32.7)	0.001
Anti - pseudomonas quinolone	329 (22.9)	56 (33.7)	273 (21.5)	0.001
Aminoglycoside	48 (3.3)	0 (0)	48 (3.8)	0.011
Macrolide	48 (3.3)	0 (0)	33 (2.6)	0.068
Carbapenem	33 (2.3)	1 (0.6)	29 (2.3)	0.255
Aztreonam	30 (2.1)	0 (0)	5 (0.4)	> 0.999> 0.999
Clindamycin	5 (0.3)	0 (0)	4 (0.3)	
	4 (0.3)			

Notes: Values are presented as median (IQR) or number (percentage).

Legend: AECOPD – acute exacerbation of chronic obstructive pulmonary disease.

Table 4. Specimen sources of included AECOPD patients receiving pathogen examinations.

Characteristics	Overall (n=990)	Secondary hospital (n=90)	Tertiary hospital (n=900)	p - value
Qualified sputum	925 (93.4)	59 (65.6)	866 (96.2)	< 0.001
Nasopharyngeal swabs	45 (4.5)	31 (34.4)	14 (1.6)	< 0.001
Blood	53 (5.4)	7 (7.8)	46 (5.1)	0.409
Alveolar lavage fluid	13 (1.3)	0 (0)	13 (1.4)	0.508
Pleural effusion	1 (0.1)	0 (0)	1 (0.1)	> 0.999

Notes: Values are presented as number (percentage).

Legend: AECOPD – acute exacerbation of chronic obstructive pulmonary disease.

Table 5. Distribution of positive bacterial pathogens in included AECOPD patients with bacterial culture results.

Characteristics	Overall (n=775)	Secondary hospital (n=59)	Tertiary hospital (n=716)	p - value
<i>Pseudomonas aeruginosa</i> isolates	9 (1.2)	2 (3.4)	7 (1.0)	0.145
<i>Pneumonia klebsiella</i> isolates	43 (5.5)	3 (5.1)	40 (5.6)	> 0.999
<i>Acinetobacter</i> isolates	10 (1.3)	1 (1.7)	9 (1.3)	0.549
<i>Escherichia coli</i> isolates	4 (0.5)	0 (0)	4 (0.6)	> 0.999
<i>Aerobacter cloacae</i> isolates	2 (0.3)	0 (0)	2 (0.3)	> 0.999
<i>Bacillus proteus</i> isolates	3 (0.4)	0 (0)	3 (0.4)	> 0.999
<i>Haemophilus influenzae</i> isolates	10 (1.3)	1 (1.7)	9 (1.3)	0.549
<i>Pseudomonas maltophilia</i> isolates	2 (0.3)	0 (0)	2 (0.3)	> 0.999
<i>Staphylococcus aureus</i> isolates	1 (0.1)	0 (0)	1 (0.1)	> 0.999
<i>Streptococcus pneumoniae</i> isolates	8 (1.0)	0 (0)	8 (1.1)	> 0.999

Notes: Values are presented as number (percentage).

Legend: AECOPD – acute exacerbation of chronic obstructive pulmonary disease.

Figures

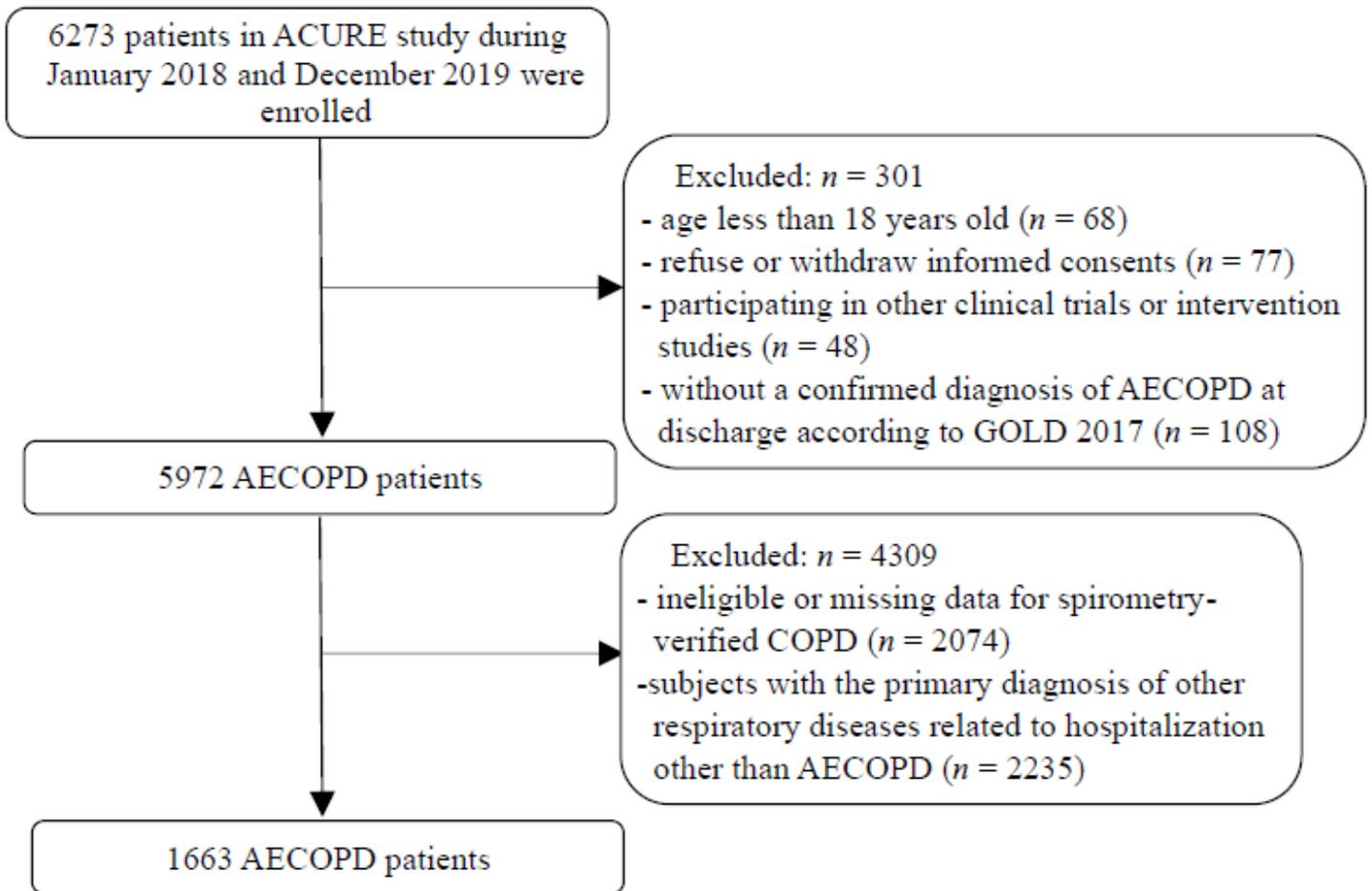


Figure 1

Flowchart diagram of eligible study population.