Original Article

Bacterial etiology and pneumococcal urinary antigen in moderate exacerbation of chronic obstructive pulmonary disease

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Background: This study aimed to establish nationwide data for the distributions of typical and atypical bacterial pathogens in Korean patients with moderate acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and evaluate the clinical usefulness of a urinary antigen test (UAT) to detect *Streptococcus pneumoniae*.

Methods: This study was a post hoc analysis of a randomized controlled trial designed to compare oral zabofloxacin with moxifloxacin for treating outpatients with moderate AECOPD. From clinics across South Korea, 342 subjects with AECOPD were enrolled, and their blood, sputum, and urine samples were collected at baseline. A serologic test, sputum culture and polymerase chain reaction (PCR), and UAT were performed to identify bacterial pathogens. Bacterial prevalence and regional distributions were analyzed. The patients' characteristics and clinical response between UAT-positive and UAT-negative groups were compared, as were the *Streptococcus pneumoniae* detection rates using conventional sputum culture and PCR versus UAT.

Results: The most commonly isolated pathogen was *Haemophilus influenzae* (30.3%), followed by *Streptococcus pneumoniae* (24.7%) and *Pseudomonas aeruginosa* (14.0%), with no significant regional differences in bacterial distribution. Patients with positive UAT for *Streptococcus pneumoniae* showed no clinical failure when treated with respiratory quinolone (0.0%), whereas 11.8% of patients with negative UAT showed clinical failure (P=0.037). UAT showed moderate agreement with sputum culture by kappa coefficient (κ=0.476).

Conclusions: The bacterial prevalence in patients with moderate AECOPD in South Korea showed correlations with the global prevalence, without significant regional differences. In outpatient settings, UAT has the potential to be used as a supplemental tool with sputum culture as a guide for determining the suspicion of bacterial exacerbation.

Keywords: Pulmonary disease; chronic obstructive; outpatients; exacerbation; antibody-coated bacteria test; urinary

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Introduction

Acute exacerbations have significant importance in the management of patients with chronic obstructive pulmonary disease (COPD) because of their impact on disease progression and quality of life. Known triggers of COPD exacerbations include viruses, bacteria, and air pollutants (1). Studies also suggest associations between exacerbation and the presence of bacteria in sputum (2-4), but bacteriologic evaluation in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in outpatient settings is not routinely recommended by the current guideline (5). Antibiotics are recommended if a bacterial infection is suspected from clinical findings and sputum purulence, and the initial choice of antibiotics is usually made empirically in AECOPD, based on the local bacterial prevalence and resistance patterns (5).

Globally, *Haemophilus Influenzae (H. influenzae)*, *Streptococcus pneumoniae (S. pneumoniae)*, *Moraxella catarrhalis (M. catarrhalis)*, and *Pseudomonas aeruginosa (P. aeruginosa)* are the most common bacterial pathogens associated with AECOPD, with prevalence varying in different study settings (3,6-9). In South Korea, Jeong *et al.* reported *S. pneumoniae* and *P. aeruginosa* as the most prevalent bacterial pathogens in hospitalized patients with community acquired pneumonia (CAP) and COPD exacerbations (10), whereas other studies in Seoul, South Korea, reported *P. aeruginosa* as the most prevalent bacteria in this population (11,12). However, most reports on the bacterial prevalence in Korean patients with COPD are solely based on sputum culture results (13,14) and are single-center studies (10,12). In this nationwide multicenter prospective study, four different tools—serologic test, sputum culture, sputum polymerase chain reaction (PCR), and urinary antigen test (UAT)—were used to identify bacterial etiology in patients with moderate AECOPD.

S. pneumoniae is a leading cause of CAP and one of the most common bacteria associated with COPD exacerbations. Although *S. pneumoniae* can be isolated from sputum culture, the infectious etiology is often difficult to prove because of its low detection rate (15). Moreover, current sputum culture tests take at least 2 days, limiting their use in an outpatient setting. Our previous study (16) compared sputum culture and PCR results for *H. influenzae* and *S. pneumoniae* in outpatients with AECOPD and found a higher detection rate with PCR than with culture, likely due to colonization and false-positive results. UATs are also used to detect *S. pneumoniae*; however, they are not routinely recommended for the evaluation of patients with AECOPD per the current guideline. Because the collection of urinary samples is easier, UAT would be a very useful tool for deciding whether to prescribe antibiotics if their clinical values were proven. Lee *et al.* showed that positive UAT results may be associated with favorable clinical outcomes after the use of antibiotics in patients with CAP (17). Nishimura *et al.* compared the detection of *S. pneumoniae* by UAT and sputum culture, and they showed that UAT and sputum culture results did not match in many patients with stable COPD (18). Their study concluded that UAT was not effective for predicting a positive sputum culture in patients with stable COPD. However, the same study reported that patients with AECOPD had both positive pneumococcal UAT and positive sputum culture for *S. pneumoniae*. This finding led us to postulate that UAT and sputum culture results did not match because patients with stable COPD have lower bacterial levels than patients with exacerbated COPD. If UAT can effectively predict a positive *S. pneumoniae* detection on sputum culture in patients with moderate AECOPD, then UAT can be considered a supplemental tool for evaluating whether a patient has bacterial exacerbation in an outpatient setting.

This study aimed to establish nationwide data for distributions of typical and atypical bacterial pathogens in patients with moderate AECOPD in South Korea, considering the results of sputum culture, sputum PCR, serologic test, and UAT. We further aimed to find if there were regional differences in bacterial prevalence. Finally, we aimed to compare the characteristics and clinical outcomes after antibiotic use in patients with positive and negative pneumococcal UAT results and investigate the usefulness of various methods for detecting *S. pneumoniae*, such as UAT, PCR, or sputum culture. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-133/rc).

Methods

Study design and subjects

This was a *post hoc* analysis of a clinical trial examining the efficacy of zabofloxacin versus moxifloxacin to treat patients with COPD exacerbation (19). Patients aged over 40 years with COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report (i.e., a post-bronchodilator forced expiratory volume in

1 second/forced vital capacity <0.7) were eligible for the study. Among them, 342 patients who were experiencing moderate exacerbation of COPD and who also had purulent sputum or an increased volume of sputum were enrolled and prospectively followed up in the outpatient clinics of 31 university hospitals in South Korea (20). "Exacerbation of COPD" was defined as worsening of respiratory symptoms beyond normal day-to-day variations leading to a change in medication, and "Moderate exacerbation" was defined as requiring short-acting bronchodilators (SABD) and antibiotics and/or corticosteroids for treatment but not requiring hospitalization (5). The clinical responses to quinolone monotherapy (either zabofloxacin or moxifloxacin) were assessed by the physician as clinical cure, failure, or indeterminate. Zabofloxacin is an antimicrobial agent of the fluoroquinolones class that targets both deoxyribonucleic acid (DNA) gyrase and topoisomerase IV enzymes and is synthesized by Dong Wha Pharmaceutical Industry, Ltd. of South Korea (21). "Clinical cure" was defined as an improvement in symptoms and signs at the time of assessment compared with the initial visit and "Clinical failure" was defined as a lack of improvement. Pregnant women, patients who received systemic antibiotics and/or antifungal agents within the last 72 h, those with confirmed pneumonia (on chest X-ray) within 48 h, and those with underlying septic shock, bronchiectasis, lung abscess, active tuberculosis, lung malignancy, cystic fibrosis, empyema, or asthma were excluded.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This work was a substudy of a study approved by the institutional ethics board of Ulsan University Hospital (UUH-2012-08-076) and informed consent was obtained from all patients.

Pathogen detection methods

Laboratory tests, an electrocardiogram, and a chest X-ray were performed, and sputum samples were collected on the inclusion day (day 1).

Sputum culture

Sputum was spontaneously expectorated into a sterile pot on the first day of visit before antimicrobial treatment. The sputum samples (n=217) with a Murray-Washington classification criteria IV or V (≤25 epithelial cells and >25 leukocytes per field) were subsequently analyzed by Gram staining and cultured within 4 h of collection (22).

Sputum PCR

Sputum DNA was extracted using Chemagic DNA kits (PerkinElmer, Turku, Finland) and PCR assays for *H. influenzae* and *S. pneumoniae* were performed using Seeplex Pneumobacter ACE Detection kits (Seegene Inc., Seoul, South Korea), according to the manufacturer's protocol (22).

Blood serologic marker test

Serological assays were performed in the central Seegene medical foundation reference laboratory (Seoul, Korea) using the *Mycoplasma pneumoniae (M. pneumoniae)* immunoglobulin (Ig) G/IgM enzyme-linked immunosorbent assay (ELISA) (Vircell, Granada, Spain), the SeroCP™ IgG/IgM kit [*Chlamydia pneumoniae (C. pneumoniae)*, Savyon Diagnostics, Ashdod, Israel], and the *Legionella pneumophila (L. pneumophila)* serogroup 1 IgG/IgM ELISA (Vircell) according to the manufacturers' instructions. A probable acute infection was defined as a positive IgM result on day 1 and a definite acute infection was defined as a 4-fold or greater increase in the IgG titer between day 1 and day 36±7 serum specimens (20).

UAT

Urine samples were assayed using the Binax NOW *S. pneumoniae* UAT (Binax Inc., Portland, ME, USA) according to the manufacturer's protocol. The sample was placed on a nitrocellulose membrane containing complexes of rabbit antibody against *S. pneumoniae* conjugated with colloidal gold particles. The results were read by the presence or absence of visually detectable pink-to-purple-colored lines after 15 min (20).

Statistical analyses

SPSS version 24 for Windows (IBM Corp., Armonk, New York, USA) was used for statistical analysis. A Chi-square test or Fisher's exact test was used to compare proportions between the groups. Student's *t*-tests were performed to compare continuous variables between the urinary antigen positive and negative groups. To determine the risk factors associated with *P. aeruginosa* isolation, both univariable and multivariable logistic regression models were used. A multivariable logistic regression analysis was performed to examine if positive pneumococcal UAT can predict clinical cure after using respiratory quinolones. The statistical significance was set at P<0.05. To compare the agreement between UAT and sputum culture or PCR, the kappa

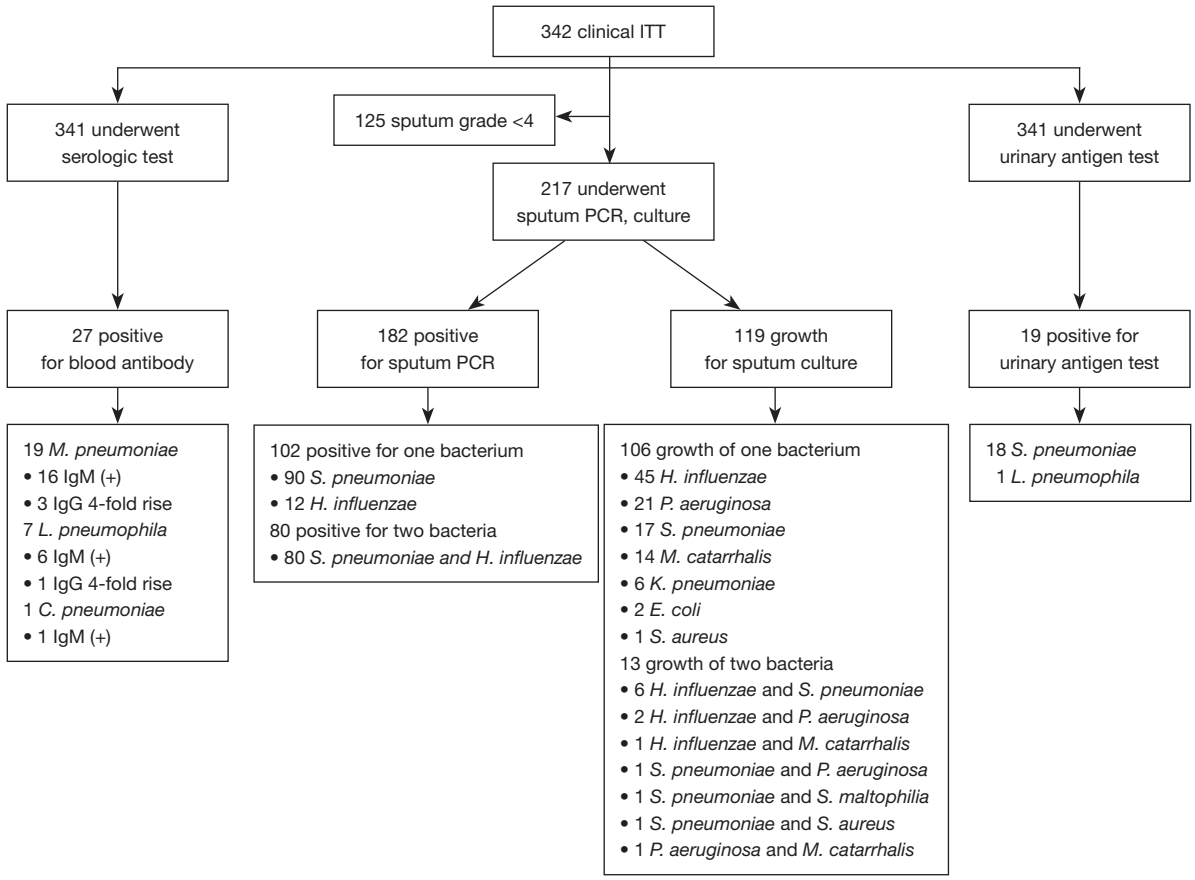

Figure 1 The results of bacterial isolation from 342 intention-to-treat patients with chronic obstructive pulmonary disease via serologic test, sputum PCR assay, sputum culture, and urinary antigen test. ITT, intention-to-treat; PCR, polymerase chain reaction; Ig, immunoglobulin; *M. pneumoniae*, *Mycoplasma pneumoniae; L. pneumophila*, *Legionella pneumophila*; *C. pneumoniae*, *Chlamydia pneumoniae; H. influenzae*, *Haemophilus influenzae; S. pneumoniae*, *Streptococcus pneumoniae; P. aeruginosa*, *Pseudomonas aeruginosa; M. catarrhalis*, *Moraxella catarrhalis; K. pneumoniae*, *Klebsiella pneumoniae; S. aureus*, *Staphylococcus aureus; E. coli*, *Escherichia coli; S. maltophilia*, *Stenotrophomonas maltophilia*.

coefficient was calculated according to the Landis and Koch guidelines (23).

Results

Of the 342 patients with moderate AECOPD who visited an outpatient clinic, 341 (excluding one patient who could not complete the test) underwent serologic tests, 217 (excluding 125 patients with sputum samples of poor quality, <grade 4) underwent sputum culture and PCR for *S. pneumoniae* and *H. influenzae* (*Figure 1*), and 341 (excluding the same patient who could not complete the test) underwent UAT. Potentially pathogenic microorganisms (PPMs) were identified by serologic tests from 27 patients (7.9%). A total of 182 patients (53.2%) had positive sputum PCR and 80 of these showed two pathogens. PPMs isolated in sputum culture samples were from 119 patients (34.8%) with 13 of these having two pathogens. PPMs were identified by UAT from 19 patients (5.6%). Of the 168 pathogens, the most common typical bacteria were *H. influenzae* (30.3%), followed by *S. pneumoniae* (24.7%) and *P. aeruginosa* (14.0%). Atypical pathogens such as *M. pneumoniae*, *L. pneumophilia*, and *C. pneumoniae* accounted for 15.7% of all pathogens (*Figure 2*).

We investigated the 18 patients with *S. pneumoniae*-positive UAT for their corresponding sputum culture results. Four patients had two pathogens isolated, and three patients had none. Two patients had no available sputum culture due to poor quality. From the remaining patients (9 of 18), one pathogen was isolated. The most

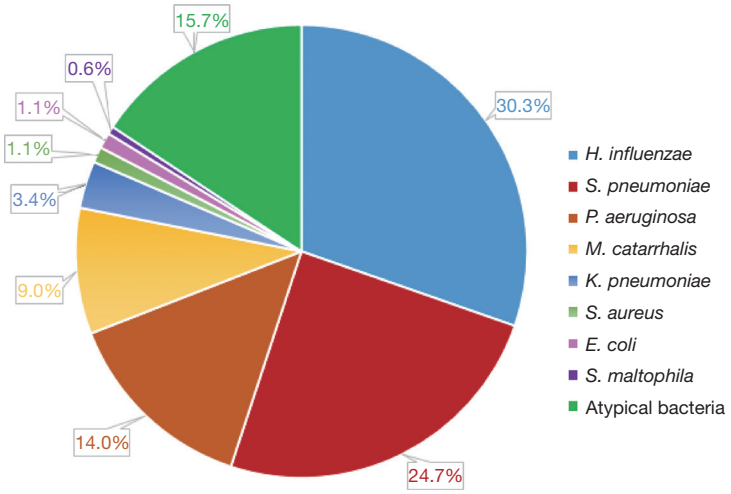

Figure 2 Prevalence of bacterial species retrieved from patients with acute exacerbations of chronic obstructive pulmonary disease in South Korea. The most commonly isolated typical bacteria were *H. influenzae* (30.3%), followed by *S. pneumoniae* (24.7%) and *P. aeruginosa* (14.0%). Atypical bacteria are 15.7% of all isolated pathogens. *H. influenzae*, *Haemophilus influenzae; S. pneumoniae*, *Streptococcus pneumoniae; P. aeruginosa*, *Pseudomonas aeruginosa; M. catarrhalis*, *Moraxella catarrhalis; K. pneumoniae*, *Klebsiella pneumoniae; S. aureus*, *Staphylococcus aureus; E. coli*, *Escherichia coli; S. maltophilia*, *Stenotrophomonas maltophilia*.

commonly isolated pathogen was *S. pneumoniae* (11 out of 18). Two *H. influenzae*, one *Staphylococcus aureus (S. aureus)*, and one *Stenotrophomonas maltophilia (S. maltophilia)* were isolated along with *S. pneumoniae*. One *S. aureus* and one *M. catarrhalis* were isolated without *S. pneumoniae*. There was no *P. aeruginosa* isolation in any sputum culture results of UAT-positive patients.

The geographic region with the most pathogens isolated was Seoul (31.5%), followed by Gyeongsang (26.8%) and cities near Seoul (grouped as "Seoul suburb") (19.6%) (*Figure 3*). Atypical pathogens were mostly isolated in Seoul (48.3%), followed by Gyeongsang (34.5%) and Seoul suburbs (13.8%). No atypical pathogen was isolated in Chungcheong. Of the 25 cultivated *P. aeruginosa*, the highest number (10; 40.0%) was grown from sputum samples taken from patients in Seoul. The remaining 15 samples (60.0%) came from areas outside Seoul: 5 (20.0%) from Chungcheong, 4 (16.0%) from Seoul suburb, 3 (12.0%) from Jeju, and 3 (12.0%) from Jeolla. The demographics and baseline characteristics of patients with or without *P. aeruginosa* isolation were analyzed (Table S1). The variables associated with *P. aeruginosa* isolation in the univariable analysis were female sex (40.0% *vs.* 6.8%; P<0.001), younger age (66.3±9.6 *vs.* 68.7±7.4; P=0.018), nonsmoking (44.0% *vs.* 3.9%; P<0.001), and bronchiectasis (24.0% *vs.* 8.8%; P=0.031). However, these factors were not statistically significant in a multivariable logistic regression analysis.

There were no differences in sex, body mass index (BMI), smoking status, pulmonary function, GOLD grade, COPD Assessment Test (CAT) scores, the EXAcerbations of Chronic pulmonary disease Tool—Patient-Reported Outcome (EXACT-PRO) scores, or eosinophil count between patients who tested positive and those who tested negative for *S. pneumoniae* on UAT (*Table 1*); however, patients in UAT-positive group were older (72.4±6.5 *vs.* 68.4±7.9; P=0.035) and had a lower albumin level (3.9±0.5 *vs.* 4.2±0.4; P=0.007) than patients in UAT-negative group. There were no differences in systemic steroids or inhaled corticosteroid use or underlying disease such as malignancy, cardiovascular disease, diabetes mellitus, bronchitis, or bronchiectasis. The details of clinical responses to quinolone monotherapy (either zabofloxacin or moxifloxacin) according to an assessment performed by the physician as clinical cure, failure, or indeterminate have already been described (16,19). When patients with indeterminate responses were excluded from the analysis, no clinical failure (0.0%) was found in UAT-positive patients, whereas 11.8% of UAT-negative patients showed clinical failure (P=0.037). However, after adjusting for potential confounders, UAT positivity did not predict clinical cure (odds ratio 2.366; 95% CI: 0.517–10.838; P=0.267; Table S2).

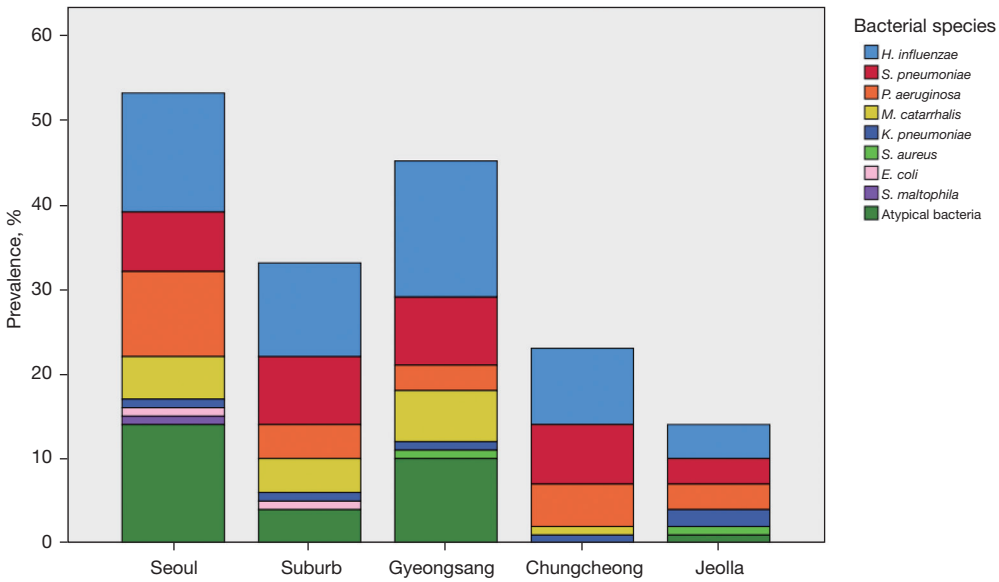

Figure 3 Prevalence of bacterial species in five regional districts of South Korea. The region with most pathogens isolated was Seoul (31.5%), followed by Gyeongsang (26.8%) and Seoul suburb (19.6%) The term *suburb* indicates regional districts close to Seoul, including Gyeongin and Gangwon. *H. influenzae*, *Haemophilus influenzae; S. pneumoniae*, *Streptococcus pneumoniae; P. aeruginosa*, *Pseudomonas aeruginosa; M. catarrhalis*, *Moraxella catarrhalis; K. pneumoniae*, *Klebsiella pneumoniae; S. aureus*, *Staphylococcus aureus; E. coli*, *Escherichia coli; S. maltophilia*, *Stenotrophomonas maltophilia*.

S. pneumoniae UAT results were compared with the results of sputum culture and PCR in sputum samples from 217 and 167 patients, respectively, by calculating the kappa coefficient (*Table 2*). UAT had moderate agreement with sputum culture (κ=0.476) and poor agreement with sputum PCR (κ=0.023). Sputum culture and PCR also showed poor agreement (κ=0.043, not shown in *Table 2*).

Discussion

Although there have been several reports on bacterial distributions in patients with COPD exacerbations in South Korea, most were single-center studies and only took sputum culture results into consideration (12-14). This study analyzed bacterial prevalence using blood and urine tests in addition to sputum culture, all collected from a prospective, nationwide multicenter clinical trial. Furthermore, the regional prevalence was analyzed, including 342 patients with COPD in outpatient settings with a high suspicion of bacterial exacerbation from 31 university hospitals in five different regional districts.

Overall, *H. influenzae* was the most prevalent species, followed by *S. pneumoniae* and *P. aeruginosa*, consistent with the known global prevalence (3,6-9) and previous nationwide reports (13,14). It is possible that our large sample size and multicenter approach provide more reliable results than some previous studies from South Korea that reported no *H. influenzae* or *M. catarrhalis* detection: these were single-centered studies with less than 200 samples (13,14). A recent multicenter retrospective study conducted in South Korea reported that *P. aeruginosa* was the most prevalent bacterial species (11). The study included patients with moderate-to-severe AECOPD, whereas our study only included patients with moderate AECOPD who were not hospitalized. Noteworthy, our prospective findings showed that atypical pathogens accounted for approximately 15.7% of all isolated pathogens and were mainly concentrated in Seoul and Gyeongsang; however, only 4.7% had atypical pathogens with no other bacteria, suggesting that atypical pathogens are not a major cause of AECOPD in South Korea. Nevertheless, regional differences might have to be considered if there is clinical suspicion of an atypical bacterial infection. Further studies are required to identify the significance of atypical bacterial AECOPD and clinical importance of any regional difference.

P. aeruginosa was the third most common bacteria and its prevalence was 14.0%, even more than that of *M. catarrhalis* (9.0%), which is noticeably different from the

Table 1 Baseline characteristics of patients positive (+) and negative (–) for pneumococcal UAT

Variable	UAT (+) (n=18)	UAT (–) (n=323)	P value[a]
Sex, female	0 (0.0%)	30 (9.2%)	0.176
Age, years	72.4±6.5	68.4±7.9	0.035
BMI, kg/m^2	21.0±2.5	22.2±3.4	0.159
Smoker	18 (100.0%)	302 (93.5%)	0.264
Alcohol drinker	15 (83.3%)	279 (86.4%)	0.715
PFT			
Post-BD FEV_1, % pred	52.7±21.7	49.5±17.4	0.468
Post-BD FVC, % pred	75.0±19.2	75.6±16.8	0.888
Post-BD FEV_1/FVC, %	48.8±16.4	46.5±12.5	0.460
Performance			
CAT score	25.5±8.1	22.7±7.2	0.132
EXACT-PRO score	46.6±16.5	45.0±12.3	0.601
Initial laboratory tests			
Eosinophil count	251.3±297.9	219.5±229.1	0.574
Albumin	3.9±0.5	4.2±0.4	0.007
Previous medications			
Systemic steroid use	6 (33.3%)	86 (26.6%)	0.533
Inhaled corticosteroid use	11 (61.1%)	220 (68.1%)	0.536
Underlying diseases			
Any malignancy	3 (16.7%)	31 (9.6%)	0.330
Cardiovascular disease	8 (44.4%)	154 (47.7%)	0.789
Diabetes Mellitus	2 (11.1%)	38 (11.8%)	0.933
Bronchitis	7 (38.9%)	129 (39.9%)	0.929
Bronchiectasis	3 (16.7%)	26 (8.0%)	0.202
Clinical failure after antibiotics[b]	0 (0.0%)	38 (11.8%)	0.037

Data are expressed as mean ± standard deviation or numbers (percentages). [a], Student's *t*-test was used to calculate P value for categorical variables, and Chi-square test was used for continuous variables. [b], antibiotics: zabofloxacin or moxifloxacin. UAT, urinary antigen test; BMI, body mass index; PFT, pulmonary function test; BD, bronchodilator; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; CAT, COPD Assessment Test; EXACT, The EXAcerbations of Chronic pulmonary disease Tool; PRO, Patient-Reported Outcome.

global prevalence. Previous studies also reported a high incidence rate of *P. aeruginosa* isolation (11,13,14), which is expected and may be attributed to more severe patients being transferred to large metropolitan hospitals clustered in this area after being treated at smaller local hospitals. Furthermore, since the patients in this study had moderate COPD exacerbation and were recruited in outpatient settings without a mandatory computed tomography scan, it is possible that some of them had co-existing bronchiectasis but were unaware about its presence, contributing to the high incidence of *P. aeruginosa*. *P. aeruginosa* has been previously reported to be isolated in patients with advanced COPD (24-27) or those with bronchiectasis comorbidities (28,29). Indeed, we found that *P. aeruginosa* isolation was more common in patients with bronchiectasis and in females, although these factors were not significant on a

Table 2 Agreement between UAT and results from sputum culture or PCR to detect *S. pneumoniae*

Test		UAT		Total	Kappa
		Positive	Negative		
Sputum culture	Positive	11	15	26	0.476
	Negative	5	186	191	
	Total	16	201	217	
Sputum PCR	Positive	13	116	129	0.023
	Negative	2	36	38	
	Total	15	152	167	

UAT, urinary antigen test; PCR, polymerase chain reaction.

multivariable logistic regression analysis, probably due to small numbers of these groups.

A single-center study on patients hospitalized with severe AECOPD in South Korea reported that although viruses showed seasonal variations, three bacteria (*P. aeruginosa*, *S. pneumoniae*, and *H. influenzae*) showed no seasonal variations (12). We also aimed to determine the seasonal variations for bacterial pathogens in this study. But, most of the participants were enrolled in winter and spring; therefore, it was impossible to accurately analyze seasonal variations. Overall, it seemed that there was no correlation between bacterial species and specific seasons (Figure S1).

Although bacterial infection is one of the major causes of COPD exacerbations, treatment with antibiotics remains controversial (30-32). Antibiotics are recommended if there are clinical signs of bacterial infection such as increased sputum purulence. Because this approach can often be subjective and not quantifiable, objective markers such as blood levels of C-reactive proteins (CRP) and procalcitonin are suggested as candidates to help guide the initiation of antibiotics (33-36). However, these biomarkers do not provide information about antibiotic resistance. Sputum culture analysis can be used to determine the drug resistance profile and recommend different antibiotics to target the specific bacteria, but the current methodology requires at least 2 days for the results to be obtained, and good-quality sputum samples can be difficult to obtain in some cases. In this regard, urine samples are easier to collect and test; thus, UAT could be a promising supplemental test, although it is not yet developed enough to detect all bacterial species. Using an immunochromatographic membrane assay, pneumococcal UAT detects capsular polysaccharide antigen, a cell wall component of *S. pneumoniae* excreted in urine. It provides results within 15 minutes and is reported to have a sensitivity of 50–80% and a specificity of over 90% for detecting *S. pneumoniae* (37,38). Urine can be easier to obtain than sputum, and UAT will show positive results for up to three days after antibiotics are initiated. These advantages make UAT a good candidate for routine examination in outpatient settings when AECOPD is suspected.

To evaluate the clinical impact of UAT in our study, we compared the clinical response to respiratory quinolones in UAT-positive and UAT-negative patients. UAT-positive patients showed less clinical failure of respiratory quinolones than UAT-negative patients (0.0% *vs.* 11.8%). Although statistical significance was not achieved after adjusting for potential confounders, it should be noted that this study was not originally designed for the purpose of evaluating clinical responses according to UAT results; nonetheless, the trend for clinical cure favored the UAT-positive group, suggesting that UAT has potential as a supplemental test in determining whether bacterial exacerbation should be suspected. We believe that further studies with a larger sample size specifically designed to test this research question are required.

UAT is well studied in the field of CAP, but the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guideline does not recommend routine UAT for diagnosing CAP (39) as there is no difference in the clinical outcomes between guideline-directed treatment and pathogen-directed treatment on the basis of UAT results. However, in case of patients with AECOPD, no specific antibiotics is recommended empirically by any guideline and whether to use antibiotics or not in addition to systemic steroids is a major clinical question (5). UAT can help determine whether COPD exacerbation is bacterial or viral, helping clinicians to make decisions around antibiotics prescription.

To determine whether UAT can be feasibly substituted for sputum culture or PCR in an outpatient setting, we compared the results of UAT, sputum culture, and PCR detection of *S. pneumoniae*. Only 7.4% of patients tested positive in UAT, while 12.0% tested positive in sputum culture. There was moderate agreement between UAT and sputum culture, with 42.3% patients positive in both tests. In the case of UAT and sputum PCR, 77.2% tested positive for *S. pneumoniae* in sputum PCR and showed poor agreement with UAT. The capability of PCR to detect colonization may have led to false-positive results and poor agreement with UAT, as was the case in the

comparison between sputum culture and PCR (16). Although the agreement between UAT and sputum culture was only moderate, there was no clinical failure after treatment of UAT-positive patients with respiratory quinolone. Moreover, the decision of whether to use anti-pseudomonal antibiotics is important as minimizing the duration of broad-spectrum antibiotics exposure is recommended to prevent new antibiotic resistance (40,41). The fact that sputum culture results for UAT-positive patients did not show any *P. aeruginosa* suggests that UAT results provide a clue to the presence or absence of *P. aeruginosa* infection. Although further studies designed to test this idea are required, performing UAT in patients with AECOPD might be helpful, especially in outpatient settings where sputum culture is often unavailable or inconvenient.

There are several limitations to this study. First, even though the sample size was large, with over 300 patients, only 18 patients had positive UAT results. Further studies with larger sample sizes are required for application in clinical practice. Second, the clinical response was evaluated as cure, failure, or indeterminate according to subjective assessments performed by physicians. An objective assessment of symptoms or signs would have increased the credibility of this study. However, it is very difficult to evaluate clinical response in a perfectly objective way because symptom relief itself is a subjective opinion of a patient. Third, this study was a post hoc analysis of a clinical trial for examining the efficacy of zabofloxacin versus moxifloxacin; therefore, all patients received one of these antibiotics. Moreover, a direct comparison between patients who were prescribed antibiotics and those who were not was impossible; therefore, the results of our study should not be generalized to the routine use of UAT alone for determining whether or not to take antibiotics and, if so, which antibiotics to use. Furthermore, the study result is not sufficient to evaluate UAT as a therapeutic biomarker. In the future, further study comparing patients with antibiotic use versus a placebo group according to UAT results is warranted. Fourth, CRP was not measured in this study, which might have affected the decision to use antibiotics. However, it should be noted that CRP measurement is often not feasible in outpatient settings. Finally, there was no way to distinguish between a true pathogen and colonization based on the test results. Quantitative culture using the protected specimen brush is the "gold standard" for the diagnosis of distal airway infections (8,42); however, its invasiveness prevents routine use. A recent meta-analysis showed that purulent sputum during AECOPD, defined by yellow or green color, was associated with a significantly higher probability of potentially pathogenic bacteria (43). This finding supports the recommendations of current guidelines to use sputum purulence to help guide antibiotic treatment in patients. Most participants in the present study had purulent sputum; hence, we believe that the sputum culture results were not associated with colonization. In this study, we regarded sputum culture as the gold standard test and found that UAT showed a higher agreement than PCR. Although UAT could detect pneumococcal antigen during an exacerbation, the antigen can also be detected during stable periods because of a previous exacerbation or combined pneumonia and because of the long excretion time of urinary pneumococcal antigen. This issue applies also to other tests, including sputum culture and PCR, contributing to large differences in the detection of *S. pneumoniae* in this study. Therefore, when using these test results to diagnose pneumococcal exacerbation in patients with COPD, caution should be taken and the patients' symptoms and signs should be taken into consideration when making clinical decisions.

In conclusion, the bacterial prevalence in patients with moderate AECOPD in South Korea in this study showed correlations with the globally reported prevalence, with *H. influenzae* being the most commonly isolated pathogen, followed by *S. pneumoniae* and *P. aeruginosa*. There was no significant regional difference in bacterial prevalence. Patients with positive UAT for *S. pneumoniae* showed no clinical failure when treated with respiratory quinolone. This finding suggests that UAT, with convenience as its strength, plays a potential role as a supplemental examination tool in determining the suspicion of bacterial exacerbation for patients in an outpatient setting.

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Footnote

Reporting Checklist: The authors have completed the

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Ethical Statement: The authors are accountable for all the aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The work was a substudy of a study approved by the institutional ethics board of Ulsan University Hospital (UUH-2012-08-076) and informed consent was obtained from all patients.

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