

## ORIGINAL RESEARCH

# *Streptococcus Pneumoniae* Urinary Antigen Test and Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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### Abstract

**Background:** *Streptococcus pneumoniae* is one of the most common bacteria identified in sputum obtained from subjects with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). **Purpose:** To examine the urinary pneumococcal antigen test in subjects admitted with AECOPD and subjects with COPD, and to evaluate its relationship with AECOPD. **Methods:** Urine samples from 82 subjects with AECOPD involved in 122 consecutive hospitalizations were tested. Additionally, 196 consecutive subjects with stable COPD were tested a total of 607 times at intervals greater than 6 months. **Results:** Pneumococcal antigen was positive in 14 (17.1%) out of all 82 subjects first hospitalized with AECOPD. It was positive in 7 (20.6%) out of the 34 subjects with pneumonic exacerbations of COPD, and in 7 (14.6%) out of the 48 subjects with non-pneumonic exacerbations of COPD. Two subjects with non-pneumonic *S. pneumoniae*-related AECOPD were identified, and they both tested positive. A total of 607 urinary antigen tests were performed on stable COPD subjects, and 16 (2.6%) specimens were positive. Colonization by *S. pneumoniae* was found in the sputum of only 25% of the COPD subjects with positive urinary pneumococcal antigen test results. **Conclusion:** The results of the pneumococcal urinary antigen test were similar for AECOPD subjects with and without pneumonia. This test may be a useful method for preventing the under-diagnosis of *S. pneumoniae*-related exacerbations of COPD. The detection of pneumococcal antigen in the urine is not related to the persistent colonization of the respiratory mucosa by *S. pneumoniae*.

### Abbreviations

AECOPD	acute exacerbations of chronic obstructive pulmonary disease
COPD	chronic obstructive pulmonary disease
<i>S. pneumoniae</i>	<i>Streptococcus pneumoniae</i>
FEV <sub>1</sub>	forced expiratory volume in 1 second
FVC	forced vital capacity
PPM	potentially pathogenic microorganisms
PISP	penicillin-intermediate <i>Streptococcus pneumoniae</i>
PRSP	penicillin-resistant <i>Streptococcus pneumoniae</i>
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>

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**Keywords:** Chronic obstructive pulmonary disease, Acute exacerbations of chronic obstructive pulmonary disease, *Streptococcus pneumoniae*, Urinary antigen

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### Background

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are one of the most common causes of acute hospital admission (1, 2), and are remarkable events in the course of chronic obstructive pulmonary disease (COPD) (3). Since AECOPD is considered to be mostly attributable to airway infection, it is important to examine the infectious organisms that

are responsible for AECOPD. The development of reliable methods to define the etiology of these infectious exacerbations is important to adequately treat these subjects.

Subjects with COPD suffer from the complication of community-acquired pneumonia at a high frequency (4). It would be considered under-treatment if those subjects with exacerbated COPD due to pneumonia were treated only for their pneumonia. Therefore, the therapeutic management of AECOPD with no clinical signs of pneumonia should be the same as for an exacerbation of COPD as a result of pneumonia (5).

Ko *et al.* reported from Hong Kong that the three predominant bacterial species isolated from sputum samples were *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae*, although influenza A is the most common etiologic agent isolated from viral cultures in subjects who were hospitalized with AECOPD (6). *S. pneumoniae* has been one of the most common bacteria identified in the sputum obtained from subjects with AECOPD (7–10). Over the last decade, some studies have proved that the Binax NOW *Streptococcus pneumoniae* urinary antigen test was useful for the rapid and easy diagnosis of community-acquired pneumococcal pneumonia (11–17).

There have only been 2 published studies that addressed whether the *Streptococcus pneumoniae* urinary antigen test would be positive in *Streptococcus pneumoniae*-related infective exacerbations without pneumonia, and whether this screening method would increase the diagnostic yield. Murdoch *et al.* examined the urinary antigen test in 49 cases collected during an exacerbation, and reported that the antigen was detected in 33.3% (1/3) of exacerbated subjects with *S. pneumoniae* isolated from their respiratory samples, and in 4.3% (2/46) of exacerbated subjects without *S. pneumoniae* (17).

Andreo *et al.* also investigated the pneumococcal urinary antigen test in 50 subjects with AECOPD, and reported that the antigen was positive in 17.6% (3/17) of subjects with *S. pneumoniae* isolated from sputum samples, and in 3% (1/33) of subjects without *S. pneumoniae* (16). Therefore, the overall results for exacerbated subjects were similar to those reported by Murdoch *et al.* It has been reported that over 80% of *Streptococcus pneumoniae* urinary antigen test specimens from subjects with pneumococcal pneumonia tested positive, and that the *Streptococcus pneumoniae* urinary antigen test result was sometimes positive in *Streptococcus pneumoniae*-related AECOPD subjects without pneumonia. Their results may represent the difference in the positive rate between non-pneumonic and pneumonic exacerbations related to *Streptococcus pneumoniae*.

We hypothesized that pneumococcal urinary antigen would be detected in both pneumonic and non-pneumonic exacerbations related to *Streptococcus pneumoniae*. We included not only subjects with AECOPD due to respiratory infection without pneumonia, but also subjects with COPD complicated by pneumonia in the present study. On the other hand,

Patel *et al.* reported that the presence of lower airway bacterial colonization in stable patients was significantly correlated with the exacerbation frequency (18).

Andreo *et al.* also reported that pneumococcal urinary antigen was detected in some subjects with stable COPD (16). Therefore, their results now question whether urinary pneumococcal antigen is related to subsequent exacerbations of COPD. The purpose of the present study was to evaluate the urinary pneumococcal antigen test, and to compare sputum cultures in subjects hospitalized due to pneumonic versus non-pneumonic AECOPD, and in subjects with stable COPD and bacterial colonization. Additionally, we also analyzed whether the pneumococcal urinary antigen test result can be a predictor of subsequent exacerbations.

## Methods

### Subjects

A total of 122 consecutive hospitalizations due to AECOPD in 82 subjects were recruited from the Respiratory division of Kyoto-Katsura Hospital, a general hospital that provides health care mainly for the western part of the city of Kyoto. The subjects were hospitalized and treated for AECOPD between November 2006 and June 2008. All subjects were evaluated and treated based on the clinical pathway for AECOPD. Therefore, the inclusion and exclusion criteria were identical to the clinical pathway for AECOPD that has been described elsewhere (19).

The inclusion criteria were: 1) a clinical diagnosis of COPD, 2) age over 40 years, 3) a history of smoking (10 pack-years or greater), 4) a  $FEV_1/FVC < 0.7$  on or before the first day of admission, 5) the absence of previous inflammatory changes on chest radiographs that influenced pulmonary function (for example, a previous thoracoplasty or tubercular sequelae), and 6) the presence of aggravated symptoms of COPD compatible with exacerbations. The exclusion criterion was non-infective exacerbations, including exacerbations due to pneumothorax or cardiac failure alone.

Additionally, in a longitudinal study on subjects with stable COPD, a total of 196 consecutive subjects with stable COPD were also recruited from the outpatient clinic of the Respiratory division of Kyoto-Katsura Hospital between May 2006 and September 2008. The entry criteria for stable COPD included: 1) a diagnosis of COPD, 2) age over 40 years, 3) a history of smoking (10 pack-years or greater), 4) regular attendance at our clinic for more than 6 months to avoid substantial changes in subjective parameters brought about by new medical interventions, and 5) no changes in the treatment regimen for more than 4 weeks. Subjects with any history suggestive of asthma, an exacerbation of their COPD over the preceding 8 weeks, previous inflammatory changes revealed on chest radiographs that influenced pulmonary function (for example, a previous thoracoplasty or tuberculous sequelae), or any other illness, were excluded.

## Measurements

All AECOPD subjects hospitalized during this study period were evaluated and treated based on the clinical pathway for AECOPD. Regardless of whether the treatment was completed based on the clinical pathway or they dropped out, the same clinical pathway was used to evaluate the subjects immediately after seeing them. The details of this clinical pathway for AECOPD have been described elsewhere (19). Briefly, the implemented clinical pathway for AECOPD consists of the following interventions: 1) frequent evaluations and laboratory testing, 2) pharmacological treatment, 3) instructions on the method of drug administration by a ward pharmacist, 4) respiratory management, 5) pulmonary rehabilitation during the acute phase, 6) nutritional support, and 7) early discharge planning. The pharmacological treatment included high-dose, frequent inhalation of a bronchodilator under supervision, the oral administration of 0.5 mg/kg of prednisolone every morning for 10–14 days and antibiotics administration until the inflammatory markers disappeared.

Urine was collected at the time of admission for the Binax NOW *Streptococcus pneumoniae* urinary antigen test. Bacterial cultures of the sputum were performed for three consecutive days. Chest radiographs were obtained before admission in all subjects. Pulmonary function tests were performed after the inhalation of 200 µg of salbutamol using a MDI with a spacer on the day after the completion of a 10–14 day oral course of glucocorticosteroids, or before discharge (20).

All eligible subjects with stable COPD underwent the following examinations on the same day every 6 months: Binax NOW *Streptococcus pneumoniae* urinary antigen

testing, bacterial culture of the sputum, chest radiography, and pulmonary function tests. Those subjects with positive urinary antigen also reported the frequency of their AECOPD since the last examination. An AECOPD was defined as a worsening of respiratory symptoms that required treatment with oral corticosteroids or antibiotics, or both. The examinations were repeated every 6 months throughout the study period.

In this study, the Binax NOW *Streptococcus pneumoniae* urinary antigen test was performed only on non-concentrated urine. Only spontaneous sputum was collected, and neither induced sputum nor blood cultures were used in the present study (21).

## Statistical analysis

All results are expressed as means ± SD. Unpaired *t*-tests or chi-square tests were used to compare the values between urinary pneumococcal antigen negative and positive groups. Chi-square tests were performed to compare the results between the urinary antigen and sputum culture tests. A *p*-value of less than 0.05 was considered to be statistically significant.

## Results

A total of 122 hospitalizations of 82 subjects were analysed in the present study. Fifty-seven subjects were hospitalized only once due to AECOPD during the study period, and 16 subjects were hospitalized twice. Five subjects were hospitalized three times, 2 patients 4 times, and 2 subjects 5 times. The average age of the 82 subjects at their initial hospitalization was 74.4 years (Table 1). Spirometry was performed in 113 out of 122 episodes

**Table 1.** Demographic details and outcomes of all 82 subjects first hospitalized with acute exacerbations of chronic obstructive pulmonary disease and a comparison between subjects positive and negative for pneumococcal urinary antigen

		All subjects first hospitalized with AECOPD			Urinary Pneumococcal Antigen						P- value
		N	Mean ± SD or	N(%)	Negative			Positive			
		N	Mean ± SD or	N(%)	N	Mean ± SD or	N(%)	N	Mean ± SD or	N(%)	
Age	(years)	82	74.4 ± 8.8		68	74.2 ± 7.9		14	75.5 ± 12.7		0.62
Gender	(male)	82	69 (84.1%)		68	58 (85.3%)		14	11 (78.6%)		0.69
History of smoking	(pack-years)	82	77 ± 39		68	79 ± 39		14	68 ± 37		0.33
Body mass index	(kg/m <sup>2</sup> )	76	20.2 ± 3.1		63	20.4 ± 3.1		13	19.7 ± 3.3		0.47
Pneumonia as a complication	(present)	82	34 (41.5%)		68	27 (39.7%)		14	7 (50.0%)		0.56
Ambulance transportation	(yes)	82	30 (36.6%)		68	25 (36.8%)		14	5 (35.7%)		0.99
Arterial blood gases at the beginning of treatment											
PaO <sub>2</sub>	(mmHg)	82	61.9 ± 22.1		68	61.8 ± 23.8		14	62.4 ± 10.8		0.93
PaCO <sub>2</sub>	(mmHg)	82	44.4 ± 15.5		68	45.6 ± 16.2		14	38.1 ± 9.9		0.10
pH		82	7.409 ± 0.071		68	7.406 ± 0.071		14	7.429 ± 0.067		0.27
Pulmonary function tests after treatment											
FVC	(L)	76	2.40 ± 0.80		63	2.44 ± 0.75		13	2.19 ± 1.00		0.30
FVC	(%predicted)	76	80.5 ± 22.4		63	81.8 ± 21.5		13	74.5 ± 26.3		0.29
FEV <sub>1</sub>	(L)	76	1.10 ± 0.52		63	1.10 ± 0.51		13	1.11 ± 0.62		0.98
FEV <sub>1</sub>	(%predicted)	76	56.5 ± 25.1		63	56.0 ± 24.7		13	59.2 ± 27.5		0.68
FEV <sub>1</sub> /FVC	(%)	76	45.9 ± 14.5		63	44.9 ± 14.4		13	50.9 ± 14.0		0.18
Length of stay	(days)	82	19.4 ± 17.9		68	20.1 ± 19.4		14	15.6 ± 4.5		0.40
Re-admission within 30 days	Number (%)	77	10 (13.0%)		63	9 (14.3%)		14	1 (7.1%)		0.68
Mortality during hospitalization	Number (%)	82	3 (3.7%)		68	3 (4.4%)		14	0 (0%)		0.99
Mortality within 30 days	Number (%)	81	4 (4.9%)		67	3 (4.5%)		14	1 (7.1%)		0.54
Mortality within 90 days	Number (%)	77	7 (9.1%)		64	4 (6.3%)		13	3 (23.1%)		0.09

**Table 2.** Comparison of the results from the urinary antigen test and sputum culture and the distribution of positive results by COPD severity

	Urinary antigen positive			Urinary antigen negative			Total
	<i>Streptococcus pneumoniae</i> from sputum culture		sputum not available	<i>Streptococcus pneumoniae</i> from sputum culture		sputum not available	
	positive	negative		positive	negative		
<b>All episodes (N = 122)</b>							
GOLD stage I	1	1	0	0	13	2	17
GOLD stage II	3	2	2	1	32	1	41
GOLD stage III	1	4	0	0	38	2	45
GOLD stage IV	1	1	0	0	14	3	19
Total	6	8	2	1	97	8	122
<b>All patients (N = 82)</b>							
GOLD stage I	1	1	0	0	12	2	16
GOLD stage II	3	2	1	1	18	0	25
GOLD stage III	1	3	0	0	25	2	31
GOLD stage IV	1	1	0	0	7	1	10
Total	6	7	1	1	62	5	82
<b>Non-pneumonic exacerbation (N = 48)</b>							
GOLD stage I	0	0	0	0	6	2	8
GOLD stage II	1	1	1	0	8	0	11
GOLD stage III	0	2	0	0	18	2	22
GOLD stage IV	1	1	0	0	4	1	7
Total	2	4	1	0	36	5	48
<b>Pneumonic exacerbation (N = 34)</b>							
GOLD stage I	1	1	0	0	6	0	8
GOLD stage II	2	1	0	1	10	0	14
GOLD stage III	1	1	0	0	7	0	9
GOLD stage IV	0	0	0	0	3	0	3
Total	4	3	0	1	26	0	34

before discharge or after completing oral corticosteroids for 10–14 days. In 76 out of 82 subjects, the post-bronchodilator FEV<sub>1</sub> was 1.10 L (56.5%pred) on average, and the FEV<sub>1</sub>/FVC was 45.9% (Table 1).

In the other 6 out of 82 subjects (7.3%), the disease severity of COPD was determined using spirometric results performed prior to admission. According to the GOLD criteria (3), there were 16 (19.5%), 25 (30.5%), 31 (37.8%), and 10 (12.2%) subjects, respectively, at stages I, II, III, and IV. In 34 (41.5%) out of the 82 subjects, since their chest radiographs revealed infiltration compatible with pneumonia, they were diagnosed with a pneumonic exacerbation of COPD.

The urinary pneumococcal antigen test was positive in 14 subjects (17.1%) and negative in 68 subjects (82.9%) out of all 82 subjects first hospitalized with AECOPD during the study period. In the 34 subjects with pneumonic exacerbations of COPD, it was positive in 7 subjects (20.6%) and negative in 27 subjects (79.4%). On the other hand, in the 48 subjects with non-pneumonic exacerbations of COPD, the test was positive in 7 subjects (14.6%) and negative in 41 subjects (85.4%).

Sputum was saved for culture in 76 subjects (92.7%), but was not available in only 6 subjects (7.3%) out of all 82 subjects with AECOPD (Table 2). Only normal flora were isolated or no organisms were grown in 52

subjects (63.4%). The possible pathogenic bacteria were confirmed by culturing the sputum in 24 subjects (29.3%). *Streptococcus pneumoniae* was isolated from sputum culture in 7 subjects (8.5%), but not in 75 subjects (91.5%).

Other pathogens were positive in 17 subjects (20.7%). Sputum was available in all 34 subjects with pneumonic exacerbations of COPD, and *Streptococcus pneumoniae* was confirmed by culturing the sputum in 5 subjects (14.7%), but not in the other 29 subjects (85.3%). On the other hand, in the 48 subjects with non-pneumonic exacerbations of COPD, *Streptococcus pneumoniae* was confirmed by culturing the sputum in 2 subjects (4.2%), but not in the other 40 subjects (83.3%), and sputum was not available in 6 subjects (12.5%). The overall results of the sputum cultures for all 122 episodes included in the present study are listed in Table 3. *Streptococcus pneumoniae* was the most frequently detected, and *Klebsiella pneumoniae* followed in that order.

The results of the urinary antigen test and sputum culture were compared for all 122 episodes of AECOPD during the study period, for all 82 subjects first hospitalized with AECOPD, for the 48 subjects with non-pneumonic exacerbations of COPD, and for the 34 subjects with pneumonic exacerbations of COPD (Table 2). Although urinary antigen was positive

**Table 3.** Results of a sputum culture in all 122 episodes hospitalized with acute exacerbations of chronic obstructive pulmonary disease

Number (Percentage) of Bacterial Isolates	Pathogen
7 (5.7%)	<i>Streptococcus pneumoniae</i> (including 4 episodes with PISP and one with PRSP)
6 (4.9%)	<i>Klebsiella pneumoniae</i>
5 (4.1%)	<i>Staphylococcus aureus</i> (including 3 episodes with MRSA)
5 (4.1%)	<i>Haemophilus influenza</i>
3 (2.5%)	<i>Serratia marcescens</i>
3 (2.5%)	<i>Moraxella catarrhalis</i>
2 (1.6%)	<i>Stenotrophomonas maltophilia</i>
2 (1.6%)	<i>Escherichia coli</i>
2 (1.6%)	<i>Enterobacter cloacae</i>
1 (0.8%)	<i>Proteus mirabilis</i>
1 (0.8%)	<i>Pseudomonas aeruginosa</i>
1 (0.8%)	<i>Enterobacter aerogenes</i>
1 (0.8%)	<i>Morganella morganii</i>
1 (0.8%)	<i>Chryseobacterium indologenes</i>
1 (0.8%)	<i>Citrobacter freundii</i>
1 (0.8%)	<i>Klebsiella oxytoca</i>

(Multiple pathogens were isolated in six episodes.)

1) PISP: penicillin-intermediate *Streptococcus pneumoniae*; 2) PRSP: penicillin-resistant *Streptococcus pneumoniae*; 3) MRSA: methicillin-resistant *Staphylococcus aureus*.

in 16 out of 122 episodes of AECOPD, *Streptococcus pneumoniae* was found from sputum culture in 7 episodes ( $p < 0.001$ ). Although urinary antigen was positive in 14 out of 82 subjects first hospitalized with AECOPD during the study period, *Streptococcus pneumoniae* was found from sputum culture in 7 subjects ( $p < 0.001$ ).

Although both tests were significantly related to each other, when compared with sputum culture, the urinary antigen test is more sensitive, and may increase the diagnostic yield for *Streptococcus pneumoniae*-related exacerbations of COPD. However, since few patients had positive results at each individual COPD stage, it was not clear that the frequency of positive results in the urinary antigen test and sputum culture was related to the COPD severity.

For all 82 subjects first hospitalized with AECOPD during the study period, the demographic details, as well as their outcomes during and after the AECOPD, were compared between subjects positive and those negative for pneumococcal urinary antigen (Table 1). However, none of the values was significantly different between the subjects positive and those negative for urinary pneumococcal antigen.

An additional study was performed to compare the results of the urinary antigen test and sputum culture in 196 consecutive subjects with stable COPD (170 males). Since the examinations were repeated every 6 months and often for more than one repetition during the study period, 26 subjects received the examination 5 times, 68 received it 4 times, 36 received it 3 times, 31 received it twice, and 35 subjects received it only once. The average age of the 196 subjects at the initial examination was

71.7  $\pm$  8.8 years, their FVC was 95.6  $\pm$  22.1% pred, FEV<sub>1</sub> was 1.50  $\pm$  0.70L (67.3  $\pm$  27.1% pred), and their FEV<sub>1</sub>/FVC was 48.0  $\pm$  13.2%.

The urinary antigen test was performed 607 times, and 16 specimens were positive. Twelve of these subjects received the test more than once, and tested positive only once (three subjects received the test 5 times and tested positive once, six received it 4 times and tested positive once, and three received it twice and tested positive once). They tested negative at all other times. There was one patient who received the test only once, and tested positive that time.

Eight of these subjects were asked about the frequency of their AECOPD at the next visit, but there were no clear episodes. We were unable to ask about acute exacerbations after the positive test results in 5 subjects. However, one patient received the test 4 times, and tested positive 3 times. This patient was followed for 18 months during the study period with no apparent AECOPD. Sputum was taken from this patient three times, but pneumococcal bacteria were not detected.

The subjects were encouraged to submit sputum samples for a total of 607 examinations. However, sputum culture was not available in 218 examinations (35.9%) because they were either unable to produce sputum or forgot to submit it. Sputum was examined for bacteria by routine culture methods in 389 tests. Only normal flora were found in 331 tests (54.5%). *S. pneumoniae* was detected in 23 tests (3.8%), but only 4 of those also tested positive on the urinary antigen test. *S. pneumoniae* was detected in 3 tests in 3 subjects who received the test 4 or more times, but only one of them tested positive once using the urinary antigen test. Table 4 shows the results of the urinary antigen test and *S. pneumoniae* isolated from cultured sputum in all stable COPD subjects.

## Discussion

To our knowledge, this is the first comprehensive report to evaluate the urinary pneumococcal antigen test and its relationship with AECOPD. Our analysis of AECOPD and stable COPD subjects revealed two important findings. First, pneumococcal urinary antigen was positive in both pneumonic and non-pneumonic exacerbations related to *Streptococcus pneumoniae*, and the positive rate of the

**Table 4.** Comparison of the results of the urinary antigen test and sputum culture in all 607 evaluations with stable chronic obstructive pulmonary disease

Stable COPD		<i>Streptococcus pneumoniae</i> from sputum culture		sputum not available	Total
		positive	negative		
Urinary antigen	Positive	4	10	2	16
	Negative	19	356	216	591
Total		23	366	218	607

urinary pneumococcal antigen test was similar between pneumonic and non-pneumonic exacerbations. On the other hand, the positive rate of the urinary pneumococcal antigen test was low in subjects with stable COPD and *S. pneumoniae* colonization in their sputum. In addition, since the presence of urinary pneumococcal antigen in subjects with stable COPD was not related to subsequent exacerbations, it is not a predictor of exacerbation.

Although the role of bacteria remains controversial (2, 22, 23), it is understood that the mechanism of bacterial exacerbations in COPD appears to be the acquisition of new strains of bacterial pathogens from the environment that are able to establish an infection in the tracheobronchial tree in COPD, and that the bacteria isolated from the sputum during an acute exacerbation in many instances reflects a cause-effect relationship.

The present study also demonstrated that the urinary pneumococcal antigen test was negative in many subjects with stable COPD, but was positive in those cases of AECOPD caused by *S. pneumoniae*. From the viewpoint of urinary pneumococcal antigen, its relationship with non-pneumonic infective exacerbations is not different from its relationship with pneumonia.

On the other hand, it has also been reported that some subjects with COPD are colonized by potentially pathogenic microorganisms (PPM) during their stable period, and that AECOPD is associated with the overgrowth of PPMs. Thus, lower airway bacterial colonization in the stable state may modulate the character and frequency of AECOPD (10, 18, 24).

Our study results revealed that *S. pneumoniae* was rarely detectable in the sputum of stable COPD subjects who tested positive for urinary pneumococcal antigen, and that the urinary pneumococcal antigen test results were negative in many subjects whose sputum culture was positive for *S. pneumoniae* colonization. Therefore, we concluded that the urinary pneumococcal antigen test is not useful in predicting a positive sputum culture in stable COPD patients. Moreover, a positive urinary pneumococcal antigen test result was not associated with the subsequent onset of AECOPD.

This may be explained by the colonization of *S. pneumoniae* on the surface without penetration into the body. Marin *et al.* recently reported that bronchial colonization was observed in 70.9% of moderate COPD cases, and was mainly due to *Haemophilus influenzae*, *Pseudomonas aeruginosa* and enterobacteria (24). Our findings were similar. Therefore, *S. pneumoniae* itself does not play an important role from the viewpoint of bronchial colonization. In other words, if the urinary pneumococcal antigen test is positive in an AECOPD patient, then this implies that the antigen detected cannot be residual, and must be related to the present episode.

The detection of pneumococcal urinary antigen has been presented as an alternative method for the diagnosis of pneumococcal pneumonia in adults. Dominguez *et al.* tested urine samples from subjects with pneumo-

coccal pneumonia, and detected *S. pneumoniae* antigen in 23 out of 28 bacteremic subjects (82%), and in 18 out of 23 non-bacteremic subjects (78%) (11). Marcos *et al.* reported that *S. pneumoniae* antigen was detected in all 68 (100%) subjects tested with definitive pneumococcal pneumonia (13).

In the present study, pneumococcal urinary antigen was detected in 4/5 (80%) subjects with pneumonic exacerbations caused by *S. pneumoniae*. This test is known to produce a high percentage of positive test results when used on patients with pneumococcal pneumonia, and our test results confirmed this. There were 2 cases of *S. pneumoniae*-related AECOPD without pneumonia in this study, and they were both positive for pneumococcal urinary antigen. Therefore, the pneumococcal urinary antigen test results were similar in AECOPD subjects with and without pneumonia.

In this study, the examinations were repeated every 6 months for at least 6 months in stable COPD subjects. Twelve subjects received the examinations twice or more, and tested positive only once and were negative all other times. It has also been reported that there is a long persistence of specific pneumococcal antigens in the urine after pneumococcal pneumonia. However, all of the single positive test results turned negative 6 months later, and hence the residual effects were estimated to remain for less than 6 months.

Only one case received the test 4 times, and was positive 3 times. However, persistent colonization of the respiratory mucosa with *S. pneumoniae* was not present, and thus the mechanism remains unclear in this instance. What does the finding of a positive test for pneumococcal urinary antigen in patients with stable COPD mean? In the case of stable COPD, a positive test for pneumococcal urinary antigen but a negative sputum culture may suggest micro-colonization with *S. pneumoniae*, which cannot be diagnosed by routine sputum culture. If we had used a more sensitive method such as a PCR study, then micro-colonization with *S. pneumoniae* could have been confirmed. Another possibility is a false positive or a random error in the pneumococcal urinary antigen tests. In either case, unfortunately, we have no definitive answer to this important question.

We should mention that one of the main limitations of the current evaluation is that the sputum samples were analyzed only by routine culture, and not by PCR study. Without more advanced technology in the detection of microbials in the sputum, the number of *S. pneumoniae*-related sputum samples may have been underestimated. Another problem was that the present study was limited by the small number of *S. pneumoniae*-related cases included.

However, this represents all of the patients with AECOPD and stable COPD in this hospital during the study period. Although it has been reported that the prevalence of COPD is similar in Japan to that in western countries by a general population sample study (25), Japanese health-care providers still feel that COPD is less frequent.

## Conclusions

The pneumococcal urinary antigen test was able to detect pneumococcal antigen during an exacerbation in subjects with COPD. In the present study, the antigen was positive in 85.7% (6/7) of subjects with *S. pneumoniae* isolated from their sputum samples, and 80.0% (4/5) of subjects with pneumonic exacerbations caused by *S. pneumoniae*. There were 2 cases of *S. pneumoniae*-related AECOPD without pneumonia in this study, and they were both positive for pneumococcal urinary antigen. Therefore, the pneumococcal urinary antigen test results are similar in AECOPD subjects with and without pneumonia. This test may be a useful method for preventing the under-diagnosis of *Streptococcus pneumoniae*-related exacerbations of COPD.

Our study results revealed that *S. pneumoniae* was rarely detectable in the sputum of stable COPD subjects who tested positive for urinary pneumococcal antigen. However, the urinary pneumococcal antigen test results were negative in many subjects whose sputum culture was positive for *S. pneumoniae* colonization. Therefore, the detection of pneumococcal antigen in the urine is not related to the persistent colonization of the respiratory mucosa with *S. pneumoniae*. Urinary pneumococcal antigen is not predictive of subsequent exacerbations of COPD.

## Competing interests

KN has received lecture fees from Boehringer-Ingelheim and GlaxoSmith-Kline, but not in relation to the topic of the current manuscript. The other authors declare that they have no competing interests.

## Authors' contributions

KN was the physician responsible for all participants, planned the study design, and prepared the manuscript. TN participated in the data collection and in providing care for the participants. TO performed the statistical analyses. All authors read and approved the final manuscript.

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