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An Open-Label, Prospective Clinical Study to Evaluate the Efficacy of Prophylactic Antibiotics after Diagnostic Bronchoscopy

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The aim of this study was to prospectively examine the effect of prophylactic antibiotic use on the development of respiratory infections and on the worsening of symptoms after diagnostic fiberoptic bronchoscopy procedures. This study was an open-label, multicenter, controlled, clinical trial. Patients were alternately assigned to a group given prophylactic antibiotics after bronchoscopy (prophylaxis(+) group) and a group not given antibiotic prophylaxis after bronchoscopy (prophylaxis(-) group), and they were followed-up for 1 week. 158 patients were assigned to the prophylaxis(-) group and 153 to the prophylaxis(+) group. Therapeutic antibiotic administration was needed in 3 patients (1.90%) in the prophylaxis(-) group and 5 patients (3.27%) in the prophylaxis(+) group (risk ratio 1.014, 95% confidence interval 0.978-1.052; p=0.446). Worsening of symptoms after bronchoscopy occurred in 57.6% of all patients by day 7, but no significant differences were observed between the 2 study groups. Prophylactic antibiotic use after bronchoscopy did not prevent the development of infectious events and worsening of symptoms, suggesting that prophylactic antibiotics might not be necessary for routine diagnostic bronchoscopic procedures.

Fiberoptic bronchoscopy (FB) is a commonly used procedure in clinical practice for the diagnosis of various pulmonary diseases, such as lung cancer and interstitial lung diseases. Although diagnostic FB procedures are generally safe, some complications, such as bleeding, pneumothorax, bronchospasm, arrhythmia, and pneumonia, have been reported. Fever and respiratory infection may occur after FB, sometimes requiring antibiotic treatment.

The British Thoracic Society (BTS) guidelines do not recommend use of prophylactic antibiotics prior to diagnostic bronchoscopy routinely in all patients, but only in patients with asplenia, heart valve prosthesis, or a previous history of endocarditis. However, these recommendations are not based on directly applicable studies, and the evidence level is low (Grade C, level IV) (Honeybourne *et al*, 2001). There are few reports of prospective studies

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on the effectiveness of prophylactic antibiotic use to prevent infectious complications after diagnostic FB.

The aim of this study was to prospectively examine the effect of prophylactic antibiotic use on the development of infectious events that require therapeutic antibiotic administration and on the worsening of symptoms after diagnostic FB procedures.

MATERIALS AND METHODS

Study design and participants

The study was conducted with the approval of the Ethics Committees or Institutional Review Board of Kobe University Hospital (Kobe, Japan), Takatsuki Hospital (Takatsuki, Osaka, Japan), and Kasai Municipal Hospital (Kasai, Hyogo, Japan).

Written, informed consent was obtained from all study participants. Subject enrollment was started in August 2008 and completed in July 2010. Outpatients who underwent diagnostic FB were eligible for enrollment in the study.

The study included patients aged 20 years or older who underwent diagnostic FB. The exclusion criteria were: history of systemic antibiotic use within the previous week; suspected infectious disease; FB or surgical treatment within the previous week; tracheal intubation; hemodialysis; and history of severe side effects or allergy to antibiotics.

Patients were alternately assigned to a group given prophylactic antibiotics after bronchoscopy (prophylaxis(+) group) and a group not given antibiotic prophylaxis after bronchoscopy (prophylaxis(-) group). The patients in the prophylaxis(+) group were given antibiotics such as amoxicillin clavulanate 250 mg, amoxicillin 250 mg, cefditoren pivoxil 100 mg, or cefcapene pivoxil hydrochloride hydrate 100 mg 3 times daily for 3 days after FB. These antibiotics were chosen because they show antimicrobial activity against respiratory pathogens and do not have an anti-inflammatory effect, which is reported for macrolides (Desaki *et al*, 2004) such as azithromycin, that may have had an impact on the outcome of the study.

At entry into the study, each patient answered an unvalidated questionnaire about his/her daily respiratory symptoms, such as fever, cough, sputum, and dyspnea, daily from the day before the FB (day -1) to day 7 after the FB. The patients were requested to report fever in the questionnaire when their temperature was over 37.5°C. The severity of symptoms was scored using a 5-point scale (none, weak, moderate, severe, very severe) and is summarized in Table I. Other symptoms, such as diarrhea, were declared as free text answers. The occurrence of respiratory infections associated with respiratory symptoms and fever and necessitating therapeutic antibiotic administration was surveyed from the medical records and the questionnaire responses. At the end of the 7-day follow-up period, the questionnaire was collected from the patients when they visited our clinics.

Statistical Analysis

To determine the sample size, the results of previous reports were used (Kanazawa, 2007), even though there have been only a few reports on the incidence of infectious events after FB. The risk of developing respiratory infection was estimated to be 5.6%, and it was calculated that 400 patients would be needed in each study group to identify a 33% risk reduction by prophylactic antibiotic use with 95% precision and 80% power.

Continuous data are summarized as means and standard deviation (SD), and categorical data are summarized as numbers, percentages, relative risks (RR), and related 95% confidence intervals (CI). Differences between continuous variables were assessed with analysis of variance. The chi-square test was used to analyze categorical data. Statistical

analysis was conducted with the PASW Statistics 18 software package (SPSS Inc., Chicago, IL). A p value < 0.05 was considered significant.

TABLE I. The severity score of symptoms

Symtoms	Grade
Cough	
No cough at all	none
Cough less than a few times in an hour	weak
Cough more than 10 times in an hour	moderate
Frequent cough during daytime	severe
Cough so much that it is difficult to sleep	very severe
Sptum	
No sputum at all	none
Feeling of sputum in the throat, but cough not productive	weak
Cough with sputum, but not causing too much discomfort	moderate
Hard to clear one's throat	severe
Feel agonized with continuous sputum production	very severe
Dyspnea	
No dyspnea	none
Not troubled by breathlessness	weak
Short of breath when walking	moderate
Short of breath even at rest	severe
Too breathless to even move about in the room	very severe

RESULTS

Patients' characteristics

The study enrolled 438 patients; 220 patients were assigned to the prophylaxis(-) group and 218 to the prophylaxis(+) group. The data of 311 patients were analyzed, since the remaining 127 patients failed to bring or fill in their questionnaires at the final follow-up (Figure 1). As shown in Table II, the patients' characteristics did not differ significantly between the 2 groups. Overall, there were 23 patients with diabetes, 5 patients with renal failure, and 11 patients on immunosuppressant treatment (including corticosteroids); however, there were no patients with a history of valvular heart disease, endocarditis, or asplenia. The diagnostic procedures performed and the duration of FB did not differ significantly between the 2 groups.

Therapeutic antibiotic administration

Therapeutic antibiotic administration was needed in 3 patients (1.90%) in the prophylaxis(-) group and 5 patients (3.27%) in the prophylaxis(+) group. These patients' profiles are summarized in Table III. No significant reduction in the risk of respiratory infections associated with respiratory symptoms or fever that necessitated therapeutic

antibiotic administration was observed with prophylactic antibiotic use (RR 1.014, 95% CI 0.978-1.052, p=0.446). It is noteworthy that patients who underwent a minimally invasive procedure such as bronchial lavage or observation only did not develop respiratory infections.

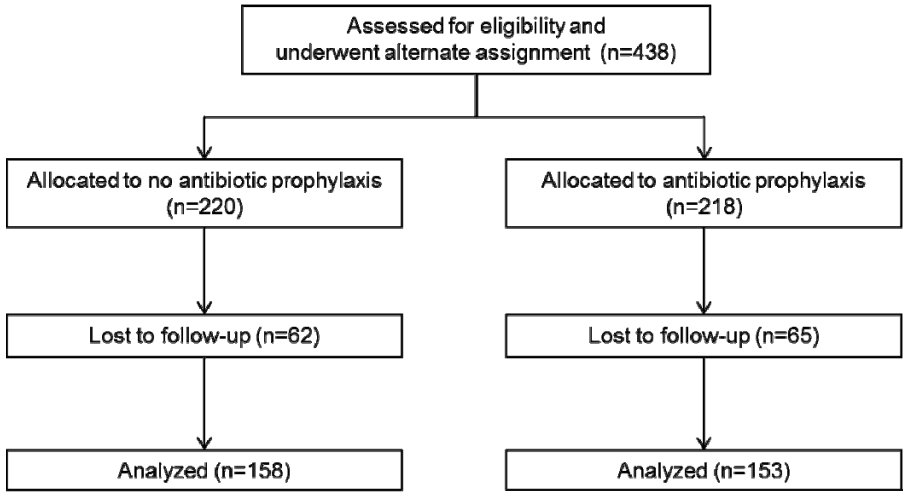

Figure 1. Study profile. The study initially enrolled 438 patients. The analysis finally included 158 patients who were assigned to the group not given antibiotic prophylaxis after bronchoscopy and 153 patients who were assigned to the group given antibiotic prophylaxis after bronchoscopy.

Worsening of symptoms after FB

The severity of respiratory symptoms at an arbitrary follow-up period and worsening of the severity of symptoms as compared with the severity at baseline are summarized in Figure 2 and 3, respectively. Grades higher than at baseline were counted as worsening of symptoms. Fever higher than 37.5°C occurred in 19 patients by day 7 after FB, and 1% to 4% of the patients developed fever by 2 to 7 days after FB in both study groups. Although the incidence of fever actually tended to be higher in the prophylaxis(+), the risk of developing fever after FB did not differ significantly between the 2 groups (Figure 3). Around 20% to 30% of the patients in both study groups experienced worsening of cough and sputum, with no significant differences between the 2 groups. Worsening of dyspnea was recorded in approximately 10% of the patients, with no significant difference between the 2 groups. Worsening of 1 or more symptoms, including fever, cough, sputum, and dyspnea, occurred in 57.6% of all patients by day 7 after FB, with no significant differences between the 2 study groups. Other symptoms were recorded in 28 and 29 patients in the prophylaxis(-) and prophylaxis(+) groups, respectively. Symptoms including common cold and diarrhea were declared at frequencies that did not differ significantly between the 2 groups. No fatal complications were reported during the study period in either group.

DISCUSSION

The present results suggest that prophylactic antibiotic use did not prevent the development of infectious events that necessitated therapeutic antibiotic administration or improve the severity of patients' symptoms after routine diagnostic FB procedures.

Several studies have examined the frequency of bacteremia after FB and associated diagnostic procedures and reported that, while up to 10% of patients had bacteremia, a large percentage of the cases with bacteremia did not go on to develop severe complications (Kane *et al*, 1975; Steinfort *et al*, 2010; Witte *et al*, 1986; Yigla *et al*, 1999). No severe systemic infectious complications were encountered in the present study. These findings do not contradict the current suggestion of the necessity of prophylactic antibiotic use in patients with risk factors, such as valvular heart disease or a history of infectious endocarditis or splenectomy, since this study did not include such high-risk patients.

TABLE II. Patient characteristics and procedures of fiberoptic bronchoscopy

Characteristics	**Prophyraxis(-) (n=158)**	**Prophyraxis(+) (n=153)**	**p value**
Age			
Median, year	70	70	0.259
Range	26-88	35-96	
Gender			
Male	113	101	0.295
Female	45	52	
Smoker			
Never	51	58	0.067
Former	49	56	
Current	58	37	
Diabetes	9	14	0.283
Renal failure	2	3	0.681
Immunosuppressant	5	6	0.767
History of aspiration pneumonia	0	1	0.494
Type of FOB procedure			
Curettage	105	99	0.745
TBB	58	63	0.454
TBLB	13	7	0.326
BAL	11	10	0.881
TBAC/TBNA	58	57	0.921
Bronchial lavage	9	7	0.601
Observation only	9	10	0.589
Duration of procedure			
-15 min	18	19	0.534
15-30 min	123	112	
30- min	17	22	

FOB, fiberoptic bronchoscopy; TBB, transbronchial biopsy; TBLB, transbronchial lung biopsy; BAL, bronchoalveolar lavage; TBAC, transbronchial needle-aspiration cytology; TBNA, transbronchial needle aspiration.

TABLE III. Summary of cases of the development of respiratory infection

Characteristics	Prophyraxis(-) (n=3)	Prophyraxis(+) (n=5)	Total (n=8)
Age			
Median, year	60	66	64
Range	52-81	56-82	52-82
Gender (M/F)	1/2	4/1	5/3
Smoker (never/former/current)	2/0/1	2/1/2	4/1/3
Diabetes	1	0	1
Renal failure	0	0	0
Immunosuppressant	0	0	0
History of aspiration pneumonia	0	0	0
Type of FOB procedure			
Curettage	2	3	5
TBB	2	3	5
TBLB	1	0	1
BAL	1	0	1
TBAC/TBNA	0	3	3
Bronchial lavage	0	0	0
Observation only	0	0	0
Duration of procedure (-15, 15-30, 30- min)	0/3/0	0/5/0	0/8/0
Worsening of Symptoms (none/weak/moderate/severe/very severe)*	3	4	7
Fever (>37.5 degrees Celsius)	0	1	0
Cough	2 (0/0/2/0/0)	1 (0/1/0/0/0)	3 (0/1/2/0/0)
Sputum	1 (0/1/0/0/0)	2 (0/1/1/0/0)	3 (0/2/1/0/0)
Dyspnea	1 (0/1/0/0/0)	1 (0/0/1/0/0)	2 (0/1/1/0/0)

FOB, fiberoptic bronchoscopy; TBB, transbronchial biopsy; TBLB, transbronchial lung biopsy; BAL, bronchoalveolar lavage; TBAC, transbronchial needle-aspiration cytology; TBNA, transbronchial needle aspiration. *, severity grade of symptoms after FOB described in Table I

In a previous study, Kanazawa showed the efficacy of prophylaxis post FB (Kanazawa, 2007). It is thought that the difference in outcome mainly came from the different antibiotics used. He showed that a 3-day course of azithromycin was well-tolerated and effective in preventing infections post FB. However, careful attention needs to be paid to the emergence, or increase, of bacterial resistance associated with continuous use of macrolides for prophylaxis, because excessive use of antibiotics would contribute to an increase in antimicrobial resistance. It is noted that, in one of the study areas, a significant increase in the number of erythromycin-resistant, penicillin-susceptible pneumococci was reported with increased use of macrolides, especially azithromycin (Arason *et al*, 2006). Therefore, several

antibiotics other than azithromycin were chosen for the present study. However, since these drugs also have a rather broad antibacterial spectrum that increases the risk of emergence of resistant bacteria, careful attention also needs to be paid to the emergence, or increase, of bacterial resistance. In the report by Kanazawa, pneumonia and empyema occurred in 2.0% and 0.9% of cases, respectively, in the prophylaxis(-) group and prophylaxis(+) groups (Kanazawa, 2007). These rates are rather high for routine diagnostic procedures in FB (Karabay, 2007). Further, 1.9% of the patients in the present study needed therapeutic antibiotic administration for respiratory infection, whereas no cases with severe pneumonia or empyema were reported. Patient background and risk factors, such as diabetes, may also need to be taken into account as factors with some influence. Since the outcome might have been influenced by the prevalence of infectious diseases and the subjects' background, a larger prospective study is needed to elucidate which risk factors for respiratory infection might necessitate prophylactic antibiotic use. Although the patients with infectious endocarditis needs high dose of antibiotics for prophylaxis, we think that our dose regimens of antibiotics, which is approved in Japan and recommended by The Japan Society for Respiratory Endoscopy at 2005 did not affect the result because this study did not include such high-risk patients.

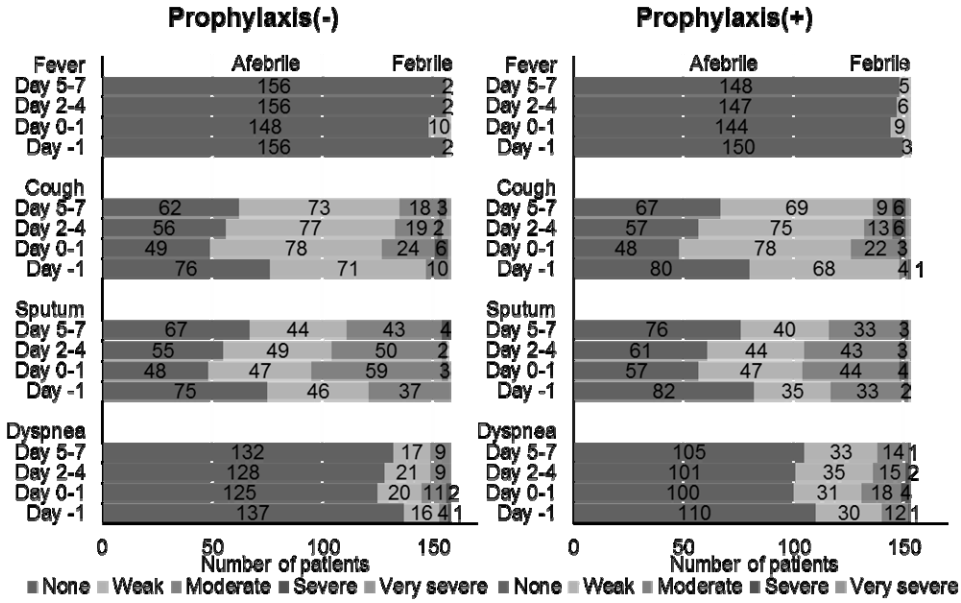

Figure 2. Symptom grade from the questionnaire. The stacked bar graph indicates the number of patients with each severity grade of symptoms in the prophylaxis(-) group and the prophylaxis(+) group. The severity of fever is graded as afebrile (≤37.5°C) or febrile (>37.5°C).

The present study also evaluated the influence of prophylactic antibiotic use on the worsening of symptom severity after FB. About half of the patients experienced worsening of respiratory symptoms by day 7 after FB. FB procedures sometimes cause symptoms such as cough, sputum, and dyspnea, not only during the procedure, but also several days after the FB, which, as seen in the present results, cannot be prevented by prophylactic antibiotic use. A randomized trial reported by Park et al. showed that transient post-bronchoscopy fever was detected in no less than 25% of patients up to 24 h after FB and could not be prevented by

prophylactic antibiotic use, suggesting that microbiological factors might not be responsible for the development of post-bronchoscopy fever (Park *et al*, 2011). Their study group contained a substantial number of patients with infectious diseases, including tuberculosis and pneumonia. The present study group excluded such patients from the analysis. Patients in the prophylaxis(+) group had a rather high incidence of fever after FB, and a few patients of this group also reported transient diarrhea, although not severe, on the questionnaire (data not shown), suggesting that antibiotics may rather induce side effects such as skin rash, diarrhea, and fever. From the above results, it is suggested that prophylactic antibiotics do not have significant benefit in decreasing patients' symptoms after FB.

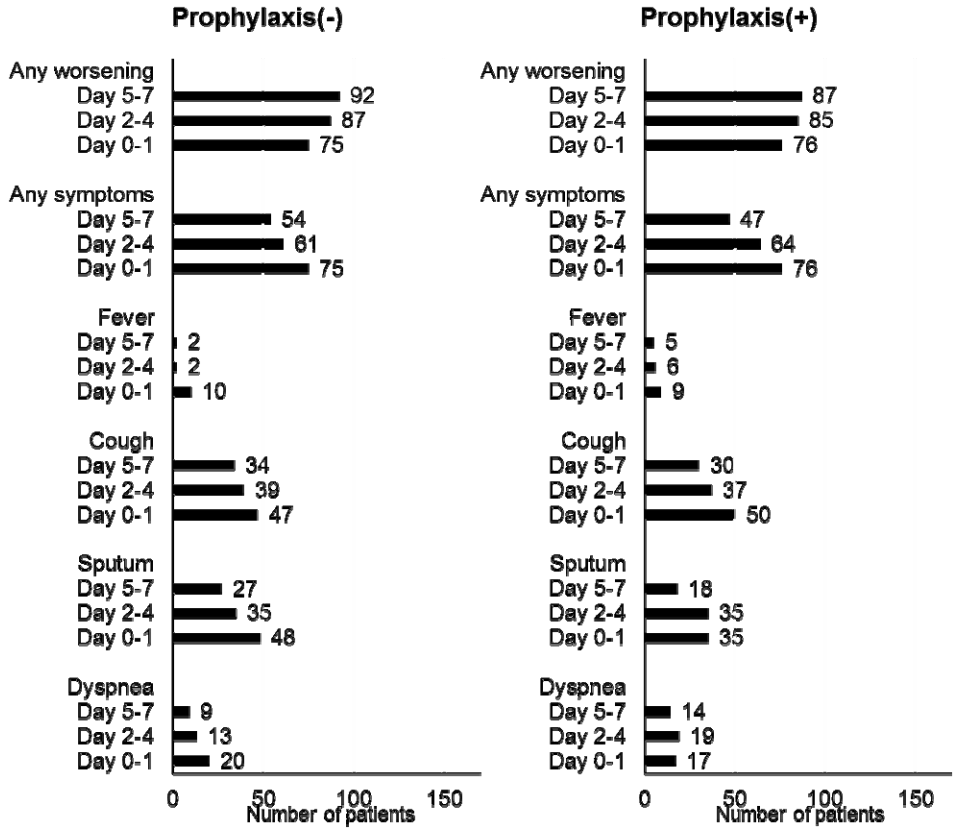

Figure 3. Worsening of symptom severity. The bar graph shows worsening of the severity of symptoms as compared with the severity at baseline. Grades higher than at baseline are counted as worsening of symptoms.

The number of subjects included in this analysis was smaller than expected. The questionnaire may have been rather confusing for elderly persons, resulting in relatively many patients being lost to follow-up. In addition, our methods of randomization have a potential for slight selection bias, although we made an effort to minimize selection bias by designating someone other than the attending physician to assign patients to the study group. Therefore, no definitive conclusion about the efficacy of prophylactic antibiotic use after diagnostic FB could be made based on the results of the present study. However, this is the first report of a prospective analysis of the incidence of infectious events requiring

therapeutic antibiotic administration and of the changes in the severity of symptoms with prophylactic antibiotic use after diagnostic FB.

In conclusion, prophylactic antibiotic use did not prevent infectious events necessitating therapeutic antibiotic administration or ameliorate the worsening of the patients' symptoms after routine diagnostic FB procedures. The present results might be of considerable help for the current recommendations in guidelines, such as those of the BTS, in regard to prophylactic antibiotic use in patients undergoing diagnostic FB.

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