

[ ORIGINAL ARTICLE ]

## Comparison between Patients with Chest Infection due to *Klebsiella* spp. and *Streptococcus pneumoniae*

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### Abstract:

**Objective** In Japan, the aging demographic structure is becoming pronounced, and the full-blown graying of society appears not far off, which indicates an increasing population that will require healthcare contact. *Klebsiella* spp. are major pathogens in healthcare-associated infections, and their importance is increasing. The aim of this study was to clarify the characteristics of *Klebsiella* spp. chest infections by evaluating the differences in the characteristics of chest infections caused by *Klebsiella* spp. and *pneumoniae*.

**Methods** We conducted a retrospective study of consecutive patients hospitalized with pneumonia, lung abscess/necrotizing pneumonia, and empyema due to *Klebsiella* spp. and *S. pneumoniae* for 15 years at our institution in Saitama, Japan.

**Patients** Patients with chest infections due to *Klebsiella* spp. (K group, n=76) and *S. pneumoniae* (S group, n=446) were included.

**Results** The K group more frequently was male, older, coinfecting by *Pseudomonas aeruginosa*, and had diabetes mellitus, a history of upper digestive system surgery, alcohol drinking habit, a smoking habit, and an impaired pre-morbid performance status than the S group. The percentages of lung abscesses or necrotizing pneumonia (31.6% vs. 0.9%) and empyema without pulmonary parenchymal shadow (3.9% vs. 0.7%) were higher in the K group than those in the S group. Severity on admission and mortality did not differ between the groups; however, patients in the K group required a longer duration of antibiotics administration and hospital stay than those in the S group.

**Conclusion** *Klebsiella* spp. chest infections have some marked characteristics when compared with pneumococcal infections, and our results serve to differentiate *Klebsiella* spp. infection from pneumococcal infection.

**Key words:** *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, lung abscess, necrotizing pneumonia, pulmonary gangrene

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### Introduction

*Klebsiella* spp. are Gram-negative rods that can lead to a wide range of disease states, most notably chest and urinary tract infections, septicemia, meningitis, diarrhea, and soft tissue infections. Major chest infections due to *Klebsiella* spp. include pneumonia, lung abscess, and empyema. *Klebsiella*

spp. infection is an independent prognostic factor in pneumonia (1, 2), the mortality of which was reported to be 41% (7 of 15 patients) within 14 days after diagnosis (3, 4).

In Japan, the aging demographic structure is becoming pronounced, and the full-blown graying of society appears to be not far off, which indicates an increasing population that will require healthcare contact. *Klebsiella* spp. are major pathogens in healthcare-associated infections, and their im-

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portance appears to be increasing (5). One clinical report from an Asian tertiary teaching hospital showed that *Klebsiella* spp. and *Streptococcus pneumoniae* are two leading pathogens of healthcare-associated pneumonia (6). It has been reported that patients with *K. pneumoniae* chest infection frequently suffer a rapid, fatal outcome (7), and physicians should understand the clinical characteristics of *Klebsiella* chest infections; however, there have been no recent reports investigating how chest infections due to *Klebsiella* spp. differ from those due to other pathogens.

We therefore investigated the characteristics of *Klebsiella* chest infections by comparing the differences in clinical and radiologic features of chest infections due to *Klebsiella* spp. with those due to *S. pneumoniae*, which is a major pathogen of chest infections.

## Materials and Methods

We conducted a retrospective study of consecutive patients hospitalized with pneumonia [community-acquired pneumonia (CAP) or healthcare-associated pneumonia (HCAP)], lung abscess/necrotizing pneumonia, and empyema due to *Klebsiella* spp. and *S. pneumoniae* from January 2002 through November 2017 at our institution in Saitama, Japan.

Lung abscess/necrotizing pneumonia was diagnosed when chest computed tomography (CT) showed cavitory lesions in areas of pulmonary consolidation. Empyema was diagnosed when the pleural effusion was pus or when it met the criteria of class 4 to 7 pleural effusion (8). Parapneumonic effusion was diagnosed when pleural effusion did not meet the above criteria of empyema or could not be evaluated because of its small amount.

Smoking status was classified into current smoker (someone who has smoked greater than 100 cigarettes in their lifetime and has smoked in the last 28 days), ex-smoker (someone who has smoked greater than 100 cigarettes in their lifetime but has not smoked in the last 28 days), and never-smoker (someone who has not smoked greater than 100 cigarettes in their lifetime and does not currently smoke). Alcohol habit (drinking level) was classified into 3 levels: heavy drinking (consumption of 8 or more drinks per week for women and 15 or more drinks per week for men) (9), moderate drinking (up to 1 drink per day for women and up to 2 drinks per day for men), and slight drinking (fewer than the moderate level) or non-drinking. The performance status (PS) (10) of the patients for performing daily life activities before the development of chest infections was recorded on admission based on anamnesis from the patients and their families. Excluded patients comprised those with tuberculosis or a confirmed alternative diagnosis lasting until the end of the follow-up period.

Diagnosis of causative microorganisms was based on the results from the semiquantitative culture of respiratory samples or blood, paired sera, urinary antigen tests for *S. pneumoniae* and *Legionella pneumophila*, and nasopharyngeal

rapid diagnostic test and reverse transcription polymerase chain reaction for influenza virus, as reported previously (11, 12). Biochemical bacterial identification of the isolated bacteria from patients was performed with an automated bacterial identification system (Vitek 2 GN; Sysmex bioMérieux, Tokyo, Japan). Broth microdilution was carried out according to the Clinical and Laboratory Standards Institute (CLSI) guidelines for antibiotics (13). The production of extended-spectrum beta-lactamase (ESBL) was screened and confirmed in accordance with the standards of the CLSI (12). HCAP was defined according to the criteria of the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines (4). Severe disease was defined when at least 1 major criterion (invasive mechanical ventilation, septic shock with the need for vasopressors) or 3 minor criteria (respiratory rate  $\geq 30$  breaths/min, partial pressure of arterial oxygen (PaO<sub>2</sub>)/fraction of inspiratory oxygen (FiO<sub>2</sub>) ratio  $\leq 250$ , multilobar infiltrates, confusion/disorientation, uremia, leukopenia, thrombocytopenia, hypothermia, hypotension requiring aggressive fluid resuscitation) of the IDSA/ATS guidelines (14) were present.

Approval for this study was obtained from the institutional clinical research ethics board of Saitama Cardiovascular and Respiratory Center.

## Statistical analyses

The results are presented as numbers and percentages, median (range) or means  $\pm$  standard deviation unless otherwise indicated. Fisher's exact test and Student's *t*-test were used for categorical and continuous data, respectively. In all instances, a 2-tailed *p* value of  $<0.05$  was considered to indicate statistical significance. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, USA).

## Results

### Patients

From January 2002 to December 2017, 76 patients with *Klebsiella* spp. (K group) and 446 patients with pneumococcal (S group) chest infections were admitted to our institution. All patients were  $\geq 18$  years old. There were no HIV-positive patients, patients with non-resected lung cancer, or those undergoing chemotherapeutic treatment. Three patients had mixed infection of both *S. pneumoniae* and *Klebsiella* spp. and were excluded.

Clinical features of each group are listed in Table 1. The K group was older and had more males and patients with an impaired pre-morbid PS than the S group. Alcohol habit in the K group included heavy drinking in 10, moderate drinking in 18, and slight/no drinking in 46 patients. The frequencies of heavy drinking and moderate drinking were greater in the K group than in the S group. Diabetes mellitus and a history of upper digestive system surgery were more frequent in the K group than in the S group.

**Table 1. Patient Characteristics, Laboratory Data, and Outcomes.**

Characteristic	<i>Klebsiella</i> spp. infection (n=76)	Pneumococcal infection (n=446)	p value
Infection type			
Pneumonia	45 (59.2%)	436 (97.8%)	<0.0001
Lung abscess/necrotizing pneumonia	24 (31.6%)	4 (0.9%)	<0.0001
Pneumonia plus empyema	2 (2.6%)	2 (0.4%)	0.1032
Lung abscess/necrotizing pneumonia plus empyema	2 (2.6%)	1 (0.2%)	0.0569
Empyema	3 (3.9%)	3 (0.7%)	0.0428
Sex, male	66 (86.8%)	308 (69.1%)	0.0014
Age, mean years (standard deviation)	72.3 (10.95)	68.8 (13.90)	0.0337
Vaccine history, yes			
PPV	2 (2.6%)	20 (4.5%)	0.7561
Influenza	3 (3.9%)	29 (6.5%)	0.6035
Smoking status, current smokers	61 (80.3%)	283 (63.5%)	0.0039
Alcohol habit, Heavy drinking/Usual/Slight or no drinking	10/18/5	8/27/411	<0.0001
LTOT	5 (6.6%)	35 (7.8%)	0.8192
Premorbid PS, 0/1-2/3-4	27/25/11	240/114/34	0.0158
Type of pneumonia, CAP	47 (61.8%)	303 (67.9%)	0.2943
Underlying diseases, yes			
COPD	15 (19.7%)	106 (23.8%)	0.5563
Bronchiectasis	6 (7.9%)	20 (4.5%)	0.2475
Pulmonary non-tuberculous mycobacteria	7 (9.2%)	19 (4.3%)	0.0831
Old tuberculosis	4 (5.3%)	22 (4.9%)	0.7814
Chronic pulmonary aspergillosis	0 (0.0%)	7 (1.6%)	0.6009
Interstitial pneumonia	3 (3.9%)	31 (7.0%)	0.4528
History of lung cancer surgery	3 (3.9%)	11 (2.5%)	0.4407
Pneumoconiosis	0 (0.0%)	7 (1.6%)	0.6009
Other pulmonary diseases	3 (3.9%)	4 (0.9%)	0.0671
Hypertension	11 (14.5%)	45 (10.1%)	0.3138
Congestive heart failure	4 (5.3%)	26 (5.8%)	1.0000
Ischemic heart disease	1 (1.3%)	21 (4.7%)	0.2279
Diabetes mellitus	20 (26.3%)	47 (10.5%)	0.0006
Cerebral vascular disease	4 (5.3%)	32 (7.2%)	0.8058
Dementia	2 (2.6%)	4 (0.9%)	0.2126
Neuromuscular disease	4 (5.3%)	5 (1.1%)	0.0295
History of upper digestive system surgery	7 (9.2%)	14 (3.1%)	0.0222
Chronic liver disease	2 (2.6%)	12 (2.7%)	1.0000
Connective tissue diseases	4 (5.3%)	14 (3.1%)	0.3150
Steroid or immunosuppressant	3 (3.9%)	27 (6.1%)	0.6006
Malignant disease	1 (1.3%)	13 (2.9%)	0.7041
CKD	2 (2.6%)	8 (1.8%)	0.6448
None	9 (11.8%)	94 (21.1%)	0.0628
Blood tests, median (range) [number measured]			
WBC (/mm <sup>3</sup> )	10,600.0 (1,300-240) [76]	11,300.0 (600-47,100) [446]	0.1170
Platelets (×10 <sup>4</sup> /mm <sup>3</sup> )	26.9 (0.8-64.8) [62]	22.9 (4.8-86.8) [117]	0.0068
AST (IU/L)	24.0 (7-514) [75]	25.0 (9-431) [442]	0.3553
LDH (IU/L)	208.0 (41-978) [76]	218.0 (17-923) [437]	0.8215
CK (IU/L)	76.5 (13-1,384) [58]	73.0 (7-20,485) [400]	0.4981
BUN (mg/dL)	16.0 (7-123) [65]	18.0 (5-98) [437]	0.5943
Creatinine (mg/dL)	0.7 (0.3-2.4) [65]	0.7 (0.3-3.4) [440]	0.9052
Na (mmol/L)	138.0 (127-153) [60]	137.0 (116-148) [143]	0.1019
CRP (mg/dL)	13.3 (0.8-54.6) [65]	13.5 (0.09-54.3) [445]	0.6862
Duration, days, mean±standard deviation			
Antibiotic administration	13.3±6.2	9.5±4.6	<.0001
Hospital stay	22.6±19.7	17.0±19.2	0.0179
Hospital mortality	5 (6.6%)	22 (4.9%)	0.5731

PPV: pneumococcal polysaccharide vaccine, LTOT: long-term oxygen therapy, PS: performance status, CAP: community-acquired pneumonia, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, WBC: white blood cell count (/mm<sup>3</sup>), AST: aspartate transaminase, LDH: lactate dehydrogenase, CK: creatine kinase, BUN: blood urea nitrogen, CRP: C-reactive protein

**Table 2. Diagnostic Methods and Results of the Patients in the Present Study (n=522).**

Method	No. of samples studied	No. of positive diagnostic studies (%)		
		Overall pathogens	<i>Klebsiella</i> spp. infection	Pneumococcal infection
Paired sera	343	36 (10.5)	4 (10.8)	32 (10.5)
Rapid influenza diagnostic test	497	41 (8.2)	4 (7.1)	36 (8.3)
Urinary antigen	484	394 (81.4)	1 (2.0)	386 (90.4)
Culture				
Sputum	477	215 (45.0)	53 (89.8)	157 (39.3)
Transbronchial aspirate	23	9 (39.1)	6 (60.0)	3 (25.0)
Protected specimen brush	15	13 (86.7)	12 (100)	1 (33.3)
Bronchial washing	18	12 (66.7)	7 (77.8)	5 (62.5)
Bronchoalveolar lavage fluid	7	3 (42.9)	1 (14.3)	2 (33.3)
Blood	340	26 (7.6)	4 (9.8)	22 (7.4)
Pleural fluid	18	9 (50.0)	4 (66.7)	4 (36.4)

**Table 3. Etiologies of Mixed Infection.**

Species	<i>Klebsiella</i> spp. infection	Pneumococcal infection	p value
Mixed infection	19 (25.0%)	104 (23.3%)	0.7704
<i>Haemophilus influenzae</i>	1 (1.3%)	17 (3.8%)	0.4934
<i>Legionella</i> sp.	0 (0.0%)	6 (1.3%)	0.5997
Influenza virus	4 (5.3%)	53 (11.9%)	0.1101
<i>Pseudomonas aeruginosa</i>	6 (7.9%)	2 (0.4%)	0.0002
<i>Moraxella catarrhalis</i>	0 (0.0%)	5 (1.1%)	1.0000
Enterobacteriaceae other than <i>Klebsiella</i> spp.	1 (1.3%)	1 (0.2%)	0.2702
<i>Streptococcus</i> sp. other than pneumococcus	2 (2.6%)	1 (0.2%)	0.0569
<i>Chlamydomphila pneumoniae</i>	2 (2.6%)	16 (3.6%)	1.0000
<i>Chlamydomphila psittaci</i>	1 (1.3%)	1 (0.2%)	0.2702
MSSA	1 (1.3%)	5 (1.1%)	1.0000
Others	1 (1.3%)	1 (0.2%)	0.2702

MSSA: methicillin-sensitive *Staphylococcus aureus*

### Types of chest infections

Pulmonary infection was found in 73 (pneumonia in 45 and lung abscess in 28) of the 76 patients in the K group and in 443 (pneumonia in 438 and lung abscess in 5) of the 446 patients in the S group (Table 1). Empyema was found in 5 of the 76 patients in the K group and in 6 of the 446 patients in the S group. Two of the 5 patients with empyema in the K group were complicated with pulmonary infection, and 3 did not show any pulmonary shadows. Compared with the S group, the K group had a higher frequency of patients with a lung abscess or necrotizing pneumonia alone (31.6% vs. 0.9%) and empyema alone (3.9% vs. 0.7%) but a lower frequency of patients with pneumonia alone (59.2% vs. 99.1%).

### *Klebsiella* subspecies

The *Klebsiella* subspecies identified included *K. pneumoniae* (n=72), *K. rhinoscleromatis* (n=1), *K. oxytoca* (n=1), and *K. ozaenae* (n=2).

### Etiology of mixed infection

Diagnostic methods used to identify etiologies in both the

K and S groups are shown in Table 2. Mixed infection was found on admission in 19 patients (25.0%). The most common microorganism causing mixed infection in the K group was *Pseudomonas aeruginosa* (n=6), followed by influenza virus (n=4) and other microorganisms (Table 3). Patients in the K group were more frequently coinfecting by *P. aeruginosa* than those in the S group (7.9% vs. 0.4%, p=0.0002).

### Laboratory data on admission

Laboratory data on admission are shown in Table 1. The platelet count of patients in the K group was significantly higher than that of patients in the S group (median,  $26.9 \times 10^4/\text{mm}^3$  vs.  $22.9 \times 10^4/\text{mm}^3$ , p=0.007). The ratios of blood cultures positive for *Klebsiella* spp. and *S. pneumoniae* were 4 of 41 (9.8%) and 22 of 294 (7.5%), respectively, in the tested patients.

### Antibacterial susceptibility of isolated *Klebsiella* spp.

The antibacterial susceptibilities of the isolated *Klebsiella* spp. are listed in Table 4. Susceptibility to penicillins was low; however,  $\beta$ -lactamase inhibitors apparently restored the activities of the penicillins. ESBL-producing *Klebsiella* spp. were found in one patient.



**Table 4. Antibacterial Susceptibility of Isolated *Klebsiella* species.**

	Number tested	Susceptible	(%)
ABPC	50	0	0
AMPC/CVA	16	14	87.5
ABPC/SBT	28	26	92.9
PIPC	56	29	51.8
PIPC/TAZ	9	7	77.8
CAZ	57	56	98.2
CEZ	56	56	100
CMZ	55	55	100
CTRX	12	12	100
CFPM	28	28	100
IPM	56	56	100
MEPM	26	26	100
GM	58	58	100
AMK	58	57	98.3
LVFX	26	26	100
CPF	28	27	96.4
MINO	57	54	94.7
AZT	58	48	85.8

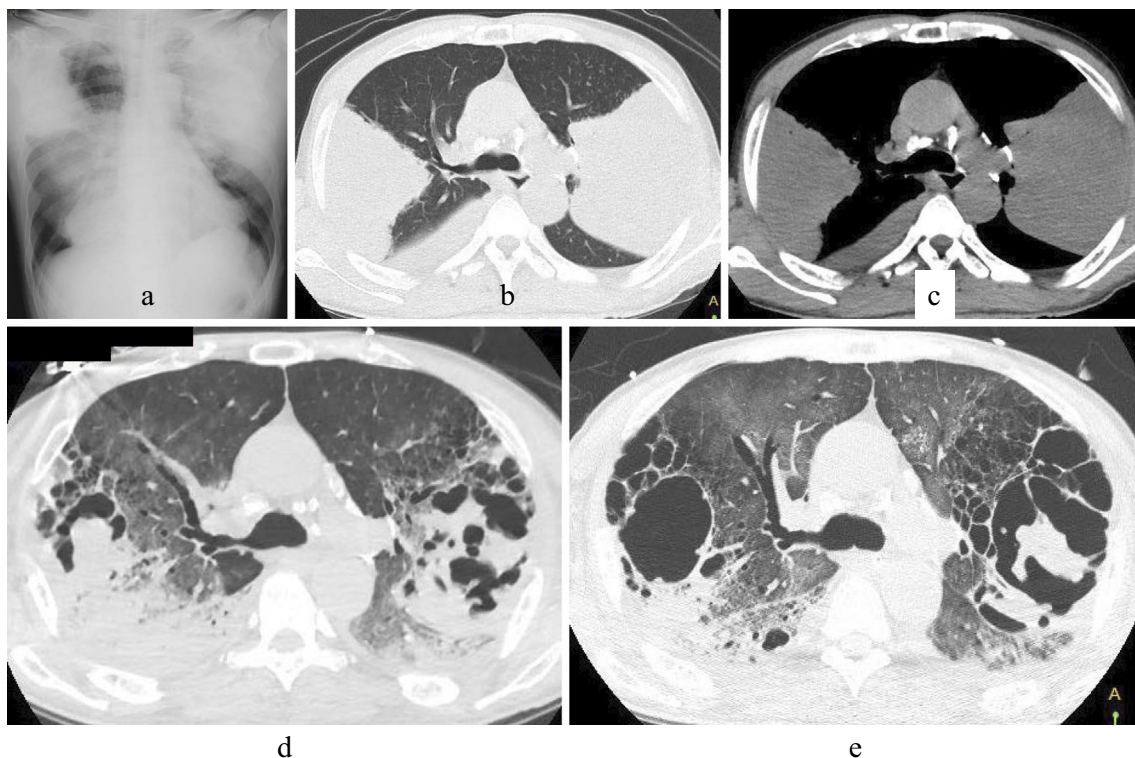
ABPC: ampicillin, AMPC: amoxicillin, CVA: clavulanic acid, SBT: sulbactam, PIPC: piperacillin, TAZ: tazobactam, CAZ: ceftazidime, CEZ: cefazolin, CMZ: cefmetazole, CTRX: ceftriaxone, CFPM: cefepime, IPM: imipenem, MEPM: meropenem, GM: gentamicin, AMK: amikacin, LVFX: levofloxacin, CPF: ciprofloxacin, MINO: minocycline, AZT: aztreonam

### Severity on admission

In the K group, 15 patients (19.7%) were in a severe condition on admission (Table 1) (*K. pneumoniae*, n=12, *K. oryzae*, n=2, *K. rhinoscleromatis*, n=1, *K. oxytoca*, n=1), and 7 (12.3%) patients required mechanical ventilation. The disease in one patient diagnosed with lung abscess/necrotizing pneumonia was compatible with pulmonary gangrene clinically (Figure). The frequency of patients with a severe condition did not differ significantly between the K and S groups (19.7% vs. 18.2%, p=0.7494).

### Treatment and outcomes

Antibiotics were administered to all patients following admission (Table 5). When compared with the patients in the S group, those in the K group more frequently received single penicillins, penicillins combined with  $\beta$ -lactamase inhibitors, and single antibiotic therapy as initial (empirical) antibiotics therapy. Piperacillin was administered to 4 patients of the K group who received single penicillins. Susceptibility of the isolated *K. pneumoniae* to piperacillin was good, and the patients recovered. Patients in the K group required antibiotics for a longer duration and showed a longer hospital stay than those in S group (Table 1). Five patients in the K group died (*K. pneumoniae*, n=4, *K. oryzae*, n=1), but the in-hospital mortality did not differ significantly between the K and S groups.



**Figure.** Images from chest X-ray and computed tomography (CT) performed at the local hospital of a 64-year-old man with a history of hypertension showed bilateral consolidation (a-c). On the 10th day after referral to our hospital (7th hospital day at our institution), CT showed bilateral consolidation with a hyperlucent area (d), and consolidation was replaced by cavitary lesions (e).

**Table 5. Treatment and Outcomes.**

	<i>Klebsiella</i> spp. infection (n=76)	Pneumococcal infection (n=446)	p value
Mechanical ventilation	7 (9.2%)	19 (4.3%)	0.0831
Initial antibiotics			
Carbapenems, 3rd- or 4th-generation cephalosporins plus macrolides	3 (3.9%)	62 (13.9%)	0.0135
Carbapenems, 3rd- or 4th-generation cephalosporins plus fluoroquinolones	1 (1.3%)	9 (2.0%)	1.0000
Carbapenems, 3rd- or 4th-generation cephalosporins plus minocyclines	1 (1.3%)	2 (0.4%)	0.3769
Single carbapenems, 3rd- or 4th-generation cephalosporins	9 (11.8%)	41 (9.2%)	0.5255
Penicillins plus macrolides	0 (0%)	2 (0.4%)	1.0000
Single penicillins	4 (5.3%)	4 (0.9%)	0.0184
Penicillins combined with $\beta$ -lactamase inhibitors	27 (35.5%)	109 (24.4%)	0.0480
Penicillins combined with $\beta$ -lactamase inhibitors plus macrolides	27 (35.5%)	179 (40.1%)	0.5258
Penicillins combined with $\beta$ -lactamase inhibitors plus fluoroquinolones	1 (1.3%)	13 (2.9%)	0.7041
Penicillins combined with $\beta$ -lactamase inhibitors plus minocyclines	1 (1.3%)	3 (0.7%)	0.4681
Others	1 (1.3%)	5 (1.1%)	1.0000
Number of antibiotics for initial treatment			
Single drug	40 (52.66%)	171 (38.3%)	0.0227
$\geq 2$ drugs	36 (47.4%)	275 (61.7%)	

## Discussion

To our knowledge, there have been few reports comparing clinical features between *Klebsiella* and pneumococcal chest infection. Lin et al. compared the characteristics of bacteremic lobar pneumonia due to *Klebsiella* spp. (mean patient age, 73 years old) and *S. pneumoniae* (mean patient age, 76 years old), and patients with bacteremic *Klebsiella* pneumonia showed a lower white blood cell count, higher frequency of bilateral involvement on chest X-ray, greater disease severity on admission, more frequent admission to the intensive-care unit, and higher mortality rate than those with bacteremic pneumococcal pneumonia (15). In that report, the frequencies of male gender, diabetes mellitus, alcoholism, and cavitary lesions on chest X-ray did not differ markedly between the two groups (15).

In the present study, there were significant differences in several patient demographics and laboratory data, but no differences were noted in the frequency of patients with severe conditions or mortality between the two groups. Severity and mortality are affected by several factors, including patient demographics and treatment (11, 12). In addition, the prevalence of virulent factors differs across countries and regions (16). For example, the prevalence of K1 isolates is higher in Japan than in the United States or Europe but lower than in Taiwan (16). These differences are likely the cause of the difference in results between the previous studies (15, 17) and ours.

Pneumonia caused by *Klebsiella* spp. has been reported to occur predominantly in men in their 60s, in chronic alcoholics (18), and in patients with conditions such as chronic bronchopulmonary diseases, cardiac diseases, diabetes mellitus, and malignancy (18, 19). Our patients in the K group showed impaired premorbid PS, suggesting that debilitated

patients may be predisposed to *Klebsiella* spp. infection (18). The major underlying conditions in patients with *Klebsiella* spp. infection tend to be chronic diseases that require contact with healthcare providers, and the frequency of *Klebsiella* spp. infection was reported to be lower in patients with CAP than in those with HCAP (18). An impaired PS is not included in the diagnostic criteria of HCAP but is included in those of nursing- and healthcare-associated pneumonia, which is a Japanese variant of HCAP (20). The higher proportion of patients with an impaired PS in the K group than in the S group suggests that a higher proportion of patients in the K group likely had nursing- and healthcare-associated pneumonia. These characteristics may be one reason for the longer duration of antibiotics treatment and hospital stay in the K group patients, which is compatible with the findings of a previous report (21). The higher proportion of lung abscesses, necrosis, and empyema in the K group may also explain the longer duration of antibiotic treatment, as empyema and lung abscesses frequently require longer antibiotics administration than pneumonia (22).

Although *K. pneumoniae* remains the primary species causing human diseases such as pneumonia, numerous causative *Klebsiella* species have been identified, including *K. pneumoniae* (*K. pneumoniae* subsp. *pneumoniae*), *K. rhinoscleromatis* (*K. pneumoniae* subsp. *rhinoscleromatis*), *K. ozaenae* (*K. pneumoniae* subsp. *ozaenae*), *K. planticola*, and *K. ornithinolytica*. *Klebsiella* spp. can colonize or cause chronic upper and lower respiratory tract infections, septicemia, and severe pneumonia (18-21, 23-25), and severe cases of infection were also found in our patients with *K. rhinoscleromatis*, *K. ozaenae*, and *K. oxytoca*.

Polymicrobial infection was found in 19 of our 76 (25.0%) patients in the K group, which was similar to the 27% frequency in a previous report of *Klebsiella* pneumo-

nia (4). *P. aeruginosa* was the leading pathogen of coinfection with *Klebsiella* species in our study. The K group patients had an impaired PS more frequently than those in the S group, suggesting that the K group patients may have received nursing and home-care service more frequently than those in the S group (20) with a risk of multidrug-resistant pathogen infection, including *P. aeruginosa* (20). Previously reported results investigating mixed infection were mainly based on culture results (26). We evaluated the etiology of mixed infection by paired sera and rapid diagnostic tests. As a result, influenza virus was the second-most frequent pathogen found to be coinfecting with *K. pneumoniae*. Damaged epithelium and an impaired defense mechanism in local and systemic immune systems may induce infections caused by *Klebsiella* species (27). There have been few reports of pneumonia due to coinfection of influenza and *Klebsiella* species (28), but the frequency of coinfection with influenza in the K group did not differ markedly from that in the S group. Influenza is a common disease, and such coinfection may be underrecognized. The investigation of polymicrobial infection seems to result in both a better selection of appropriate antibiotics and better infection control, especially in patients with influenza coinfection.

A previous report that investigated chest CT findings of *Klebsiella* pneumonia in 23 cases showed pleural effusion in 8 cases and necrosis or cavities in all cases. Two cases showed clinical courses compatible with pulmonary gangrene (29). In our study, we defined lung abscess/necrotizing pneumonia when cavities were found in areas of pulmonary consolidation. A cavity is the result of pathological processes, including suppurative necrosis, caseous necrosis, ischemic necrosis, and cystic dilatation of lung structures. *K. pneumoniae* is associated with extensive pyogenic lung necrosis and frequent cavitation, and this organism is also disproportionately represented among cases of pulmonary gangrene, in which there is extensive pulmonary necrosis and infarction. These findings suggest that the organism possesses pathogenic determinants that lead to pulmonary necrosis and cavitation more frequently than *S. pneumoniae* (30, 31). A previous report of 205 patients with lung abscess included 10 cases (4.9%) due to *Klebsiella* spp. but only 3 cases (1.5%) due to *S. pneumoniae* (32). Another study from Taiwan implicated *K. pneumoniae* as the most common single cause of lung abscess, isolated from 28 of 90 (31%) patients with lung abscesses (33). These results suggest that the detection of cavity formation suggests a *Klebsiella* spp. infection rather than a *S. pneumoniae* infection.

Our study showed a higher percentage of empyema alone in the K group than in the S group; however, the number of patients with empyema alone was 3 in both groups. Because *S. pneumoniae* is a common cause of chest infection, it may cause a significant fraction of empyema cases, even though pneumococcal pneumonia complicated empyema less frequently than *Klebsiella* pulmonary infection (pneumonia and lung abscess/necrotizing pneumonia). Certainly, the etiology

of empyema in a previous study included *Klebsiella* spp. in 23 (3.5%) and *S. pneumoniae* in 81 (12.5%) of 650 patients (8). Thus, we think it difficult to differentiate *Klebsiella* spp. infection and pneumococcal infection based on complication of empyema.

*S. pneumoniae* is generally susceptible to penicillins; however, *K. pneumoniae* is frequently resistant to penicillins because it produces a penicillin-specific  $\beta$ -lactamase (34), which may result in treatment failure of the initial antibiotics. Results of the antibacterial susceptibility of isolated *Klebsiella* species in our patients were similar to those reported throughout Japan (35). Our K group patients frequently received single penicillins as initial antibiotics. Fortunately, the single penicillin administered in these patients was piperacillin, to which the isolated *Klebsiella* spp. were susceptible; however, about half of the isolated *Klebsiella* spp. showed resistance to piperacillin, which may cause an unfavorable clinical course in other patients. Correct prediction of *Klebsiella* spp. infection results in better antibiotics selection. Our results indicated that patients' demographics and radiologic findings (cavity formation) may be clues to differentiate between infections caused by these two pathogens.

There are several limitations in the present study. It is a retrospective, single-center study with a limited number of patients, so the results may not be applicable to other settings. In addition, we did not investigate the presence of certain factors (K1 and K2 antigen), genes (*rmp A* and *mag A*), or phenotypes (hypermucoviscosity) with increased pathogenicity. It may be best to investigate these factors in future studies when assessing the clinical features of *Klebsiella* infections. We adopted the 2007 IDSA/ATS severity criteria for CAP to compare the disease severity between the K and S groups. This score can also be applied to HCAP (36); however, our study included a small number of patients (6 cases) with empyema without pulmonary parenchymal shadow, so the application of another severity score might be more appropriate.

In conclusion, the characteristics of *Klebsiella* chest infections as investigated by comparing them with pneumococcal chest infection included an old age, male predominance, impaired pre-morbid PS, an alcohol habit, some underlying diseases, a high frequency of developing lung abscess/necrotizing pneumonia and empyema, and a long duration of antibiotics administration and hospital stay. Severe cases of infection were also found in patients with *Klebsiella* spp. other than *K. pneumoniae*.

**The authors state that they have no Conflict of Interest (COI).**

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