Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8867-17
Intern Med 57: 487-495, 2018
http://internmed.jp

【 ORIGINAL ARTICLE 】

Isolation of ESBL-producing Bacteria from Sputum in Community-acquired Pneumonia or Healthcare-associated Pneumonia Does Not Indicate the Need for Antibiotics with Activity against This Class

Hideyuki Horie[1], Isao Ito[1,2], Satoshi Konishi[1,2], Yuki Yamamoto[1,2], Yuko Yamamoto[1,2], Tatsuya Uchida[3], Hideo Ohtani[1] and Yoshiharu Yoshida[1]

Abstract:

Objective In the past decade, extended-spectrum β-lactamase (ESBL)-producing bacteria have increasingly frequently been isolated from various kinds of clinical specimens. However, the appropriate treatment of pneumonia in which ESBL-producing bacteria are isolated from sputum culture is poorly understood. To investigate whether or not ESBL-producing bacteria isolated from sputum in pneumonia cases should be treated as the causative bacteria.

Methods and Patients In this retrospective study, we screened for patients, admitted between January 2009 and December 2015 in whom pneumonia was suspected and for whom sputum cultures yielded *Escherichia coli* or *Klebsiella* spp. isolates. We identified patients with community-acquired pneumonia (CAP) or healthcare-associated pneumonia (HCAP) from whom ESBL-producing bacteria had been isolated from sputum culture and to whom antibiotic treatment had been given with a diagnosis of pneumonia. We analyzed the patients' backgrounds and the effect of the antibiotic treatment for the initial 3-5 days.

Results From 400 patients initially screened, 27 with ESBL-producing bacteria were secondarily screened. In this subset of patients, 15 were diagnosed with pneumonia, including 7 with CAP (5 *E. coli* and 2 *K. pneumoniae*) and 8 with HCAP (8 *E. coli*). These patients exhibited an average age of 84.1 years old, and 9 of 15 were men. No patients were initially treated with antimicrobials that are effective against isolated ESBL-producing bacteria. However, 13 of 15 patients showed improvement of pneumonia following the initial antibiotic treatment.

Conclusion ESBL-producing bacteria isolated from sputum are not likely to be the actual causative organisms of pneumonia.

Key words: community-acquired pneumonia (CAP), healthcare-associated pneumonia (HCAP), extended-spectrum β-lactamase (ESBL)-producing bacteria

(Intern Med 57: 487-495, 2018)
(DOI: 10.2169/internalmedicine.8867-17)

Introduction

Extended-spectrum β-lactamase (ESBL)-producing bacilli are the generic designation for Gram-negative bacilli producing β-lactamase that have acquired the ability to degrade third- and fourth-generation cephalosporins and monobactams (1). This class of bacteria includes four species (*Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis*) that the Clinical Laboratory and Standards Institute (CLSI) suggests should be targeted for the detection of ESBL (2). These bacteria may be isolated from various specimens, including urine, sputum, and blood culture.

[1]Departments of Medicine, Sugita Genpaku Memorial Obama Municipal Hospital, Japan, [2]Department of Respiratory Medicine, Kyoto University Hospital, Japan and [3]Departments of Laboratory Medicine, Sugita Genpaku Memorial Obama Municipal Hospital, Japan
Received: January 16, 2017; Accepted: April 4, 2017; Advance Publication by J-STAGE: October 11, 2017
Correspondence to Dr. Isao Ito, isaoito@kuhp.kyoto-u.ac.jp

In 1983, ESBL-producing bacteria were discovered for the first time in Europe, and the detection frequency since then has been increasing. According to a report published in 2013 (3), the global rate of the *E. coli* ESBL-phenotype was 24.1%, and regional rates of 12.6%, 19.4%, 35.7%, and 57.4% have been reported in North America (NA), Europe and the Mediterranean region (EU), Latin America (LA), and the Asia-Pacific region (APAC), respectively. Among *Klebsiella* spp., the global rate of ESBL-phenotype was 32.5%, and regional rates of 15.4%, 41.9%, 52.6%, and 47.2% have been reported in NA, EU, LA, and APAC, respectively. In Japan, the frequencies of ESBL isolation are lower than those of the APAC, with Japan reporting frequencies of 2.4-8.6% for *K. pneumoniae* and 5.3-10% for *E. coli* (4, 5).

Community-acquired pneumonia (CAP) is most commonly due to *Streptococcus pneumoniae*, atypical bacteria, and respiratory viruses (6). Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) more frequently involve resistant pathogens, such as *Pseudomonas aeruginosa*, Gram-negative Enterobacteriaceae, and methicillin-resistant *Staphylococcus aureus* (MRSA). Pathogens in immunosuppressed patients are even more diverse and include opportunistic pathogens (7, 8). In 2005, the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines introduced a new classification of pneumonia: healthcare-associated pneumonia (HCAP) (9). It has been suggested that HAP, VAP, and HCAP are more frequently associated with antibiotic-resistant pathogens than CAP (8, 9). However, this concept has been the subject of controversy, as several studies have shown that the frequency of isolation of drug-resistant pathogens from HCAP patients is not high (8, 10, 11). As such, in the new guidelines of HAP/VAP published by the ATS/IDSA in 2016, HCAP was addressed separately from HAP/VAP (7). The isolation frequency of ESBL-producing bacteria from sputum has varied among reports: ESBL-producing *E. coli*, *K. pneumoniae*, and *P. mirabilis* have been detected at rates of 0.5%, 0.2-8.7%, and 0%, respectively, in CAP and 0.7-9.5%, 0.2-6.4%, and 0.3-0.4%, respectively, in HCAP (12-21). ESBL-producing bacteria vary in resistance genotypes and separation frequencies by area and hospital source (4, 5, 22).

Regarding the treatment of pneumonia, recommendations of antibiotics are based on the pathogen, disease severity, and patient background (6, 9, 23). When ESBL-producing bacteria are isolated from sputum or when the bacteria are expected to be the causative infecting organisms of pneumonia, the use of carbapenems has been recommended (9). Notably, however, it is difficult to determine whether the drug-resistant bacteria (including ESBL-producing bacteria) isolated from sputum are the causative organisms of pneumonia or simply colonizing the patient. In fact, although the use of broad-spectrum antibiotics has been increasing after the 2005 ATS/IDSA guidelines introduced the classification of HCAP (24), it has been reported that pneumonia improves even when treatment is not performed in accordance with the guidelines (11, 25-28). For this reason, some commenters have suggested that treatment according to the guidelines may not always be appropriate (14, 25-27). Some researchers advocate the use of carbapenems only in the most seriously ill cases in an effort to avoid the selection of carbapenem-resistant bacteria (29, 30). Furthermore, the use of wide-spectrum antibiotics incurs the risk of selecting for resistance in other (bystander) bacteria (31, 32).

How often ESBL-producing bacteria cause pneumonia and whether targeted treatment is needed for cases in which these bacteria have been isolated from sputum cultures is unclear. To examine the need to treat ESBL-producing bacteria, we retrospectively analyzed antibiotic treatment and the initial treatment effectiveness in patients with pneumonia from whom ESBL-producing bacteria had been isolated via sputum culture.

Materials and Methods

Subjects

The screening process used in this retrospective study is shown in Fig. 1. We performed primary screening in a laboratory examination database for cases/patients (admitted between January 2009 and December 2015) in whom culture of expectorated or aspirated sputum had been performed due to suspicion of pneumonia, with *E. coli* or *Klebsiella* spp. subsequently isolated. If the same species was detected twice or more in a given patient within the study period, only the first occurrence was counted and screened at the next step. If different species were detected in a given patient within the study period, each occurrence was counted as a separate event. In the second screening step, we extracted cases/patients from whom ESBL-producing bacteria had been isolated and determined the isolation rate of each ESBL-producing species as a fraction of the samples identified via the primary screening. For instance, for *E. coli*, the isolation rate was calculated as the number of patients with ESBL-producing *E. coli* divided by the number of patients with *E. coli*. In a third screening step, from among the secondarily screened cases, we screened for those patients who had been diagnosed with pneumonia. In the final screening step, we extracted those patients with CAP or HCAP in order to analyze the efficacy of initial treatment with antibiotics.

The diagnosis of pneumonia was based on respiratory (expectoration, coughing, dyspnea) and/or constitutional (a fever or lassitude, disturbance of consciousness) symptoms with newly developed shadow(s) in chest X-ray and elevated levels of C-reactive protein (CRP) and/or changes in white blood cell counts (WBCs).

The exclusion criteria were as follows (Fig. 1): infectious diseases aside from pneumonia among secondarily screened patients; HAP, VAP, and concomitant infection in other organs among the tertiarily screened patients.

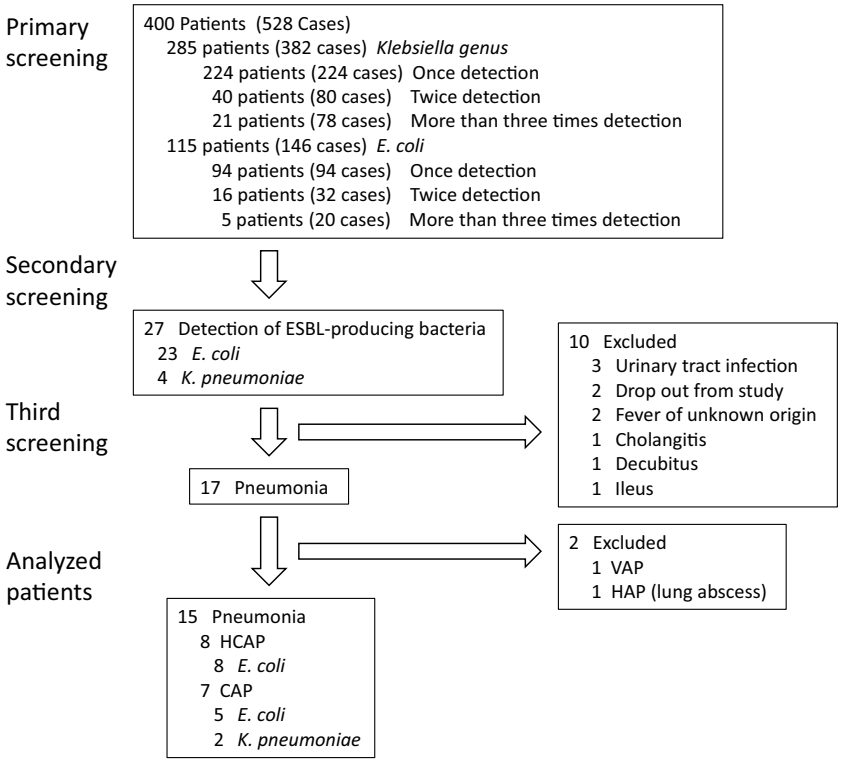

Figure 1. **Profile of study enrollment. ESBL-producing bacteria were identified in 27 of 400 patients. Fifteen patients exhibited a diagnosis of pneumonia. Twelve patients were not enrolled for the following reasons (numbers in parentheses): urinary tract infection (3), dropped out of study (2), a fever of unknown origin (2), cholangitis (1), decubitus (1), ileus (1), ventilator-associated pneumonia (1), or hospital-acquired pneumonia (1).**

Detection of ESBL-producing bacteria

In this study, we searched for three of the species of bacteria (*E. coli*, *K. pneumoniae*, *K. oxytoca*) that the CLSI has targeted for the detection of ESBL-producing bacteria. Enterobacterial organisms were identified, and antimicrobial susceptibilities were determined via the MicroScan Neg Combo Panel NENC1J (Beckman Coulter, Brea, USA) using a Microscan WalkAway 40SI (Beckman Coulter) and the standard criteria of the CLSI (2). ESBL production was assessed by the double-disk synergy (DDS) test. The DDS test was performed using ceftazidime and cefotaxime (30 μg) disks with and without clavulanic acid (10 μg) (Eiken Chemical, Tokyo, Japan). The ESBL production phenotype was defined as a ≥5-mm increase in zone diameter for at least 1 of the combination disks relative to the corresponding single antibiotic disk (33, 34). *E. coli* strain ATCC 25922 and *K. pneumoniae* strain ATCC 700603 were used as negative and positive controls, respectively, for ESBL production.

Evaluation of the subjects and sputum samples

The severity of pneumonia was assessed by CURB-65 (35). The quality of the sputum was evaluated by Geckler's classification (36). The results of semi-quantitative sputum culture were expressed as follows: no growth as - (minus), light growth (equivalent to 10^4 CFU/mL or less) as 1+, moderate growth (equivalent to 10^5 to 10^6 CFU/mL) as 2+, and heavy growth (equivalent to 10^7 CFU/mL or more) as 3+. The degree of independence in daily life was determined by the Performance Status (PS) scale of the Eastern Cooperative Oncology Group (ECOG). HCAP was defined according to ATS/IDSA guidelines (9). CAP was defined as pneumonia that developed in the community but did not meet the definition of HCAP.

Judgment of treatment efficacy

To determine retrospectively whether or not the isolated ESBL-producing bacteria were causative organisms of pneumonia, we systematically judged the effect of the initial antibiotics administered to the patients. We evaluated the following seven items at three to five days after the initiation of treatment: five physical findings (body temperature, respiratory rate, SpO_2, pulse rate, blood pressure), chest X-ray findings, and WBCs (Table 1) (6, 23, 37-40). If only one or two items showed improvement, we judged the case as exhibiting no initial antibiotic effect. The judgment was performed by two independent respiratory physicians with final agreement.

Table 1. Criteria for Judging the Treatment Efficacy.

	Improvement	No improvement
Body temperature	<37.2°C	Findings other than those in the Improvement' column
Respiration rate	<20 min^{-1}	
Pulse rate	<100 min^{-1}	
SpO_2	>92%	
Systolic blood pressure	≥90 mmHg	
Chest Xp	Improvement or no worsening	
White blood cell count	Lower than the initial data on Day 1	

Improvement in ≥4 items was interpreted as efficacy. Improvement in ≤3 items was interpreted as non-efficacy.

Table 2. Baseline Clinical Characteristics.

Men/women, n (%)	9 (60)/6 (40)
Age, years (IQR)	84.1 (68-95)
Nursing home residence, n (%)	5 (33)
Smoker Active/Past, n (%)	0 (0)/6 (40)
Performance status 0/1/2/3/4, n	0/6/0/2/7
Past antibiotic therapy (3 months), n (%)	11 (73)
Past hospitalization (3 months), n (%)	4 (27)
Comorbidity, n (%)	
Pulmonary disease	
Chronic obstructive pulmonary disease	6 (40)
Bronchiectasis	5 (33)
Pneumoconiosis	1 (7)
Old pulmonary tuberculosis	1 (7)
Hypertension	12 (80)
Congestive heart failure	2 (13)
Cerebrovascular accident	3 (20)
Diabetes mellitus	3 (20)
Chronic kidney disease	3 (20)
Dementia	5 (33)
Malignancy Active/Past	1 (7)/6 (40)
Immunosuppression	2 (13)
Probable aspiration, n (%)	12 (80)
Severity score (CURB-65) 0/1/2/3/4/5, n	0/2/6/4/3/0
Chest radiographic features	
Bilateral involvement, n (%)	11 (73)
Pleural effusion, n (%)	3 (20)
Clinical parameters upon admission, mean	
Respiration rate, min^{-1}	21.1
Systolic blood pressure, mmHg	122
Diastolic blood pressure, mmHg	68
Pulse rate, min^{-1}	87.6
Body temperature, °C	37.9
SpO_2 <90%/90%-95%/>95% , n	7/4/2
Laboratory values upon admission, mean	
CRP, mg/dL	9.5
WBC, /μL	11,600
Hemoglobin, g/dL	10
Creatinine, mg/dL	0.93
Chronic liver disease	0 (0)
Dementia	5 (33)
Malignancy Active/Past	1 (7)/6 (40)
Immunosuppression	2 (13)

IQR: interquartile range, CRP: C-reactive protein, WBC: white blood cell count

Results

Patient enrollment

Klebsiella spp. or *E. coli* was isolated in 400 cases (400 patients), consisting of 285 patients harboring members of the genus *Klebsiella* (including 261 cases with *K. pneumoniae*) and 115 patients harboring *E. coli*. ESBL-producing bacteria were isolated in 27 patients (23 with *E. coli*, 4 with *K. pneumoniae*). ESBL-producing *K. oxytoca* was not isolated from any of these patients. Twelve of the 27 patients were excluded, and the remaining 15 were diagnosed with pneumonia, including 7 with CAP (5 with *E. coli*, 2 with *K. pneumoniae*) and 8 with HCAP (8 with *E. coli*) (Fig. 1).

Characteristics of patients with CAP/HCAP from whom ESBL-producing bacteria were isolated

The patient characteristics are shown in Table 2. The average age was 84.1 years old (range 68-95 years), and 9 patients (60%) were men. As for the degree of independence in daily life, the PS scores of 9 patients were more than 2. In terms of disease severity, no cases required admission to the intensive-care unit or mechanical ventilation. Seven patients were diagnosed with respiratory failure (SpO_2 <90%) at the time of starting antibiotic therapy. On chest X-ray, bilateral infiltrates were seen in 11 patients, and pleural effusion was seen in 3 patients. Nine patients had risk factors for aspiration, namely a history of cerebrovascular diseases or neuromuscular diseases or a PS score of greater than 2. The simultaneously isolated organisms from these 15 patients are shown in Table 3. MRSA was most frequently isolated concomitantly with ESBL-producing bacteria, reflecting the patients' complicated conditions. The details of the 15 patients are shown in Table 4. Geckler's classification of sputum was as follows: classifications of 1/2/3/4/5/6 were reported in 0/4/2/2/3/4 patients, respectively.

Effect of initial antibiotic treatment

Table 4 shows the details of the 15 patients. All 15 patients received initial antibiotic treatment for pneumonia. Fig. 2 shows the antibiotic(s) used for treatment and the outcome. In the initial antibiotic treatment, 12 patients were treated with a single antibiotic, and 3 patients were treated

Table 3. Simultaneously Detected Micro-organisms Other than ESBL-producing Bacteria.

	n (%)
MRSA	9 (60)
Candida	3 (20)
Intraoral indigenous bacterium	2 (13)
Corynebacterium sp.	1 (7)
Enterococcus faecium	1 (7)
Klebsiella pneumoniae (ESBL-)	1 (7)
Proteus mirabilis (ESBL-)	1 (7)
MSSA	1 (7)
Streptococcus pneumoniae	1 (7)

MSSA: Methicillin-sensitive *Staphylococcus aureus*, MRSA: Methicillin-resistant *Staphylococcus aureus*, ESBL-: extended-spectrum β-lactamase non-producer

with a combination of antibiotics. No patients were treated with either carbapenems or cephamycins, compounds that were expected to show efficacy against ESBL-producing bacteria, as initial antibiotics.

All of the patients were followed by physicians. The initial antibiotics were either continued to the end of the treatment of pneumonia (8 patients; Group 1), changed to oral antibiotics (6 patients; Group 2), or changed to another antibiotic (due to lack of efficacy of the initial antibiotics) (1 patient; Group 3).

In Group 1, 5 patients improved, and 3 patients died. One patient (case 14) was considered to have died from pneumonia. This patient had been in end-stage condition with multiple comorbidities and had been bed-ridden, preventing her family members and the physician from using antibiotics known to target ESBL-producing bacteria. Another two patients were considered to have died due to worsening of their underlying heart failure.

The sole patient in Group 3 (case 6) was treated with Ceftriaxone (CTRX) as the initial antibiotic without improvement of pneumonia. After the isolation of ESBL-producing *E. coli* from sputum, the antibiotic was switched to Meropenem (MEPM), resulting in improvement of pneumonia.

A retrospective judgment of the treatment efficacy of the initial antibiotics on Days 3-5 revealed that 13 patients (87%) were successfully treated with the initial antibiotics, while 2 did not show any improvement.

Discussion

In this study, the examination of 400 sputum cultures resulted in the isolation of ESBL-producing bacteria in 27 (6.75%) cases. This rate of isolation was equivalent to that reported in a previous study in Japan (5). Despite the isolation of ESBL-producing bacteria from these patients, it was difficult to determine whether these microbes represented the source of pneumonia or were simply colonizing these patients. Among the 27 patients, 10 (37%) ultimately were diagnosed with diseases other than infections of the lower respiratory tract. This result suggests that the ESBL-producing bacteria that are colonizing the respiratory tract frequently can be isolated from sputum cultures.

Combinations of beta-lactamase inhibitors, fourth-generation cephalosporins, aminoglycosides, fluoroquinolones, and cephamycins may show good efficacy against ESBL-producing bacteria, but such combinations are not considered to be first-line therapy for treating infections by these microbes (9, 41, 42). David and Emery reported that even when ESBL-producing bacteria exhibited *in vitro* susceptibility (minimum inhibitory concentration (MIC) ≤8 μg/mL) to cephalosporins (but not cephamycins), treatment with these compounds failed in the clinical context. Therefore, regardless of the results of *in vitro* antibiotic drug susceptibility tests, such results should be interpreted with caution (42, 43). It has been reported that carbapenems show antibacterial activity against more than 98% of ESBL-producing *E. coli*, *K. pneumoniae*, and *P. mirabilis* isolates (44). The HCAP guidelines recommend the use of carbapenems for the antibiotic treatment of pneumonia caused by ESBL-producing bacteria. There are no randomized trials for the clinical treatment of pneumonia caused by ESBL-producing bacteria (45). In addition, there is little evidence on the efficacy of treating pneumonia with carbapenems in cases where ESBL-producing bacteria are isolated from sputum cultures.

In the present study, we identified 15 patients who had been diagnosed with pneumonia and yielded ESBL-producing bacterial isolates. None of these 15 cases were initially treated with antibiotics such as carbapenems, fourth-generation cephalosporins, aminoglycosides, or cephamycins. In Group 1, fluoroquinolone was used in one patient with ESBL-producing *E. coli*; testing subsequently revealed that this isolate was resistant to this drug. However, except for 1 patient who died of pneumonia in Group 1 and 1 whose condition was relieved with carbapenem in Group 3, 13 patients (87%) were successfully treated with the initial antibiotics. In other words, although this study could not determine whether or not the ESBL-producing bacteria isolated from sputum cultures were the actual pathogenic cause of pneumonia, the findings from our analysis of the treatments and results suggest that the use of broad-spectrum antibiotics with activity against ESBL-producing bacteria was not required in these cases.

When the concept of HCAP was established in the 2005 ATS/IDSA guidelines, patients with HCAP were considered at risk of harboring multi-drug-resistant (MDR) bacteria (9). Recently, however, it has been reported that HCAP itself may not be associated with an increased frequency of MDR bacteria (8, 10, 11). Furthermore, many researchers have reported that guideline-concordant therapy does not improve the outcome in HCAP (25-28). Instead, death in patients with HCAP may reflect the patient's condition (e.g. age, initial general status, underlying diseases, disease severity of pneumonia, and anamnesis) rather than the presence of re-

Table 4. Case Summary of 15 Patients from Whom ESBL-producing Bacteria were Isolated from Sputum.

Patient	Age (years)/ Sex	CAP or HCAP	Past history*	CURB-65	Geckler classification	Species of bacteria of ESBL-producing bacteria	Other bacteria detected	Initial antibiotic†	Effect of initial treatment	Change in antibiotic†	Outcome of pneumonia
1	75/F	HCAP	A, F, I, J	2	Absorbed sputum, 6	*E. coli*, 3+	no	LVFX 500 mg/day p.o.	effective	no	improvement
2	79/F	HCAP	A, E, F	2	Absorbed sputum, 5	*E. coli*, 1+	MRSA, *Corynebacterium*sp, 3+	A/S 6 g/day div	effective	no	improvement
3	95/M	CAP	A, H	4	Absorbed sputum, 6	*E. coli*, 3+	MRSA, *Candida*, 2+	A/S 6 g/day div+MINO 200 mg/day p.o.	effective	no	improvement
4	84/M	CAP	A, G, H	2	Absorbed sputum, 2	*E. coli*, 3+	MRSA, *Candida*, 3+	CTRX 2 g/day div	effective	MINO 200 mg/ day p.o	improvement
5	85/M	CAP	A, G, H	3	Absorbed sputum, 3	*E. coli*, 3+	MRSA, *Enterococcus faecium*, 2+	CTRX 2 g/day div+AZM 500 mg/day p.o.	effective	GRNX 400 mg/ day p.o	improvement
6	95/F	HCAP	A, C, E	4	Absorbed sputum, 2	*E. coli*, 3+	Intraoral indigenous bacterium, 3+	CTRX 2 g/day div	not effective	MEPM 1 g/day div	improvement
7	86/M	CAP	A, G, H	1	Absorbed sputum, 3	*E. coli*, 3+	*K. pneumoniae*, 3+	S/C 3 g/day div	effective	no	improvement
8	76/M	CAP	A, D	3	Absorbed sputum, 6	*K. pneumoniae*, 3+	*Streptococcus pneumoniae*, *Staphylococcus aureus*, 3+	A/S 6 g/day div	effective	no	improvement
9	86/M	HCAP	A, G, H	2	Expectorated sputum, 2	*E. coli*, 3+	MRSA, 2+	CTRX 2 g/day+AZM 2 g/day p.o	effective	AMPC/CVA 1,000 mg/day p.o	improvement
10	86/M	HCAP	A, G, H	2	Absorbed sputum, 4	*E. coli*, 3+	MRSA, 1+	A/S 9 g/day div	effective	trimethoprim-sulfamethoxazole 4 T/day p.o	improvement
11	68/M	CAP	C, D, F, J	3	Absorbed sputum, 4	*K. pneumoniae*, 3+	MRSA, 3+	A/S 6 g/day div	Effective	MINO 200 mg/ day p.o	improvement
12	88/F	HCAP	A, E, G, J	3	Expectorated sputum, 5	*E. coli*, 1+	MRSA, 2+	CTRX 2 g/day+CLDM 1,200 mg/day div	effective	no	improvement
13	78/M	CAP	A, G, H, I	1	Expectorated sputum, 5	*E. coli*, 3+	Intraoral indigenous bacterium, 3+	T/P 13.5 g/day div	effective	LVFX 500 mg/ day p.o	improvement
14	93/F	HCAP	A, C, D, E	4	Expectorated sputum, 6	*E. coli*, 3+	*Proteus mirabilis*, 1+	A/S 6 g/day div	not effective	no	died due to pneumonia
15	87/F	HCAP	A, E, J	2	Expectorated sputum, 2	*E. coli*, 3+	MRSA, *Candida*, 3+	T/P 13.5 g/day div	effective	no	improvement

E. coli: *Escherichia coli*, MRSA: Methicillin-resistant *Staphylococcus aureus,* ESBL: Extended-spectrum β-lactamase, CAP: Community-acquired pneumonia, HCAP: Healthcare-associated pneumonia, LVFX: Levofloxacin, A/S: Sulbactam/Ampicillin, MINO: Minocycline, CTRX: Ceftriaxone, AZM: Azithromycin, GRNX: Garenoxacin, MEPM: Meropenem, S/C: Sulbactam/Cefoperazone, AMPC/CVA: Amoxicillin/ Clavulanate, CLDM: Clindamycin, T/P: Tazobactam/Piperacillin

*Past history: A: heart trouble (hypertension, chronic heart disease, coronary heart disease), B: chronic liver injury, C: chronic renal failure, D: cerebrovascular disease, E: dementia, F: diabetes mellitus, G: malignant disease, H: lung disease (COPD, bronchiectasis, asthma, tuberculosis, pneumoconiosis, pneumonomycosis), I: use of immunosuppressant or steroid, J: others.

Intern Med 57: 487-495, 2018 DOI: 10.2169/internalmedicine.8867-17

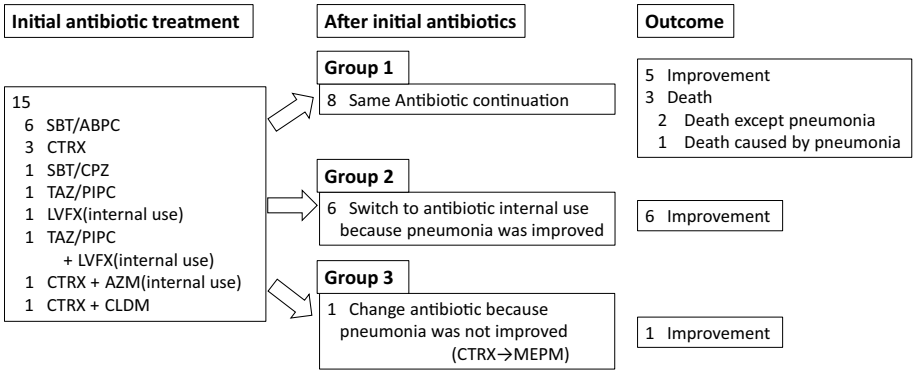

Figure 2. Initial antibiotic treatment and the outcome. Group 1: continued initial antibiotic, Group 2: changed to an oral medicine because of improvement in response to initial antibiotic treatment, Group 3: changed antibiotic because of a lack of improvement in response to initial antibiotic, based on the judgment of the chief physician.

sistant bacteria that failed to respond to the administered antimicrobial treatment (8, 13, 15, 46). Therefore, whether or not all patients who need hospitalization and are at risk of harboring resistant bacteria should receive wide-spectrum antibiotic therapy as the initial treatment remains unclear.

The unnecessary use of wide-spectrum antibiotics is discouraged because their use can increase the possibility of selection for MDR bacteria (12, 47, 48). An analysis by Ito and Mishima (49) indicated that, although patients who expectorated resistant bacteria in their sputum have a worse prognosis than those without resistant bacteria, the cause of death was not attributable to therapies not covering the resistant pathogens; those results implied that wide-spectrum antibiotics are not always suitable when drug-resistant bacteria are isolated in sputum culture. Maruyama et al. showed that HCAP patients with more than 2 MDR risk factors (antibiotic use within 180 days, Barthel Index less than 50, hospitalization more than 2 days within 90 days, immunocompromised state) had a significantly higher 30-day death rate and detection rate of MDR bacteria than did HCAP patients with 0 or 1 MDR risk factor. Therefore, those authors recommended that physicians avoid excessive use of wide-spectrum antibiotics in initial treatment of HCAP by considering the severity of pneumonia and the number of MDR risk factors (15). Even in cases with ESBL-producing bacteria in their sputum samples, the usage of wide-spectrum antibiotics such as carbapenems can be limited in severe cases (29, 30).

There are several limitations to the present investigation. First, this study was conducted in a single hospital, and the population size was too small to permit a conclusive recommendation. Nonetheless, these results suggest that clinicians should use caution in distinguishing between the isolation of MDR organisms and assignment of those bacteria as the pneumonia-causing pathogen. Second, the retrospective design of this study incorporates various biases, including observer bias and diagnosis bias. Furthermore, we did not consistently search for the possibility of pneumonia caused by atypical pathogens and viruses. Moreover, because the final population analyzed included only hospitalized patients, whether our results would also apply for outpatients is unclear.

In conclusion, even when ESBL-producing bacteria are isolated from sputum cultures in CAP or HCAP patients, antibiotics with activity against ESBL-producing bacteria are not always necessary.

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

Acknowledgement

We thank Drs. Norihito Homma, Toshikazu Takasaki, and Ryo Yamamura for their recruitment and medical care of the patients.

References

1. Bush K, Jacoby GA. Update functional classification of β-lactamases. Antimicrob Agents Chemother **54**: 969-976, 2010.
2. Wayne PA. Performance standards for antimicrobial susceptibility testing. 2012. CLSI Document M100-S22. Clinical and Laboratory Standards Institute .
3. Sader HS, Flamm RK, Jones RN. Tigecycline activity tested against antimicrobial resistant surveillance subsets of clinical bacteria collected worldwide (2011). Diagn Microbiol Infect Dis **76**: 217-221, 2013.
4. Yamaguchi K, Saikawa T, Yanagihara K, et al. *In vitro* susceptibilities to levofloxacin and various antibacterial agents of 12,919 clinical isolates obtained from 72 centers in 2007. Jpn J Antibiot **62**: 346-370, 2009.
5. Hirakata Y, Inoue M, Turnidge JD, et al. Regional variation in the prevalence of extended-spectrum β-lactamase-producing clinical isolates in the Asia-Pacific region (SENTRY 1998-2002). Diagn Microbiol Infect Dis **52**: 323-329, 2005.
6. Mandell LA, File TM Jr, Musher DM, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis **44**: S27-S72, 2007.
7. Kalil AC, Roberts JA, Waterer GW, et al. Executive summary: management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American thoracic society. Clin Infect Dis **63**: 575-582, 2016.
8. Chalmers JD, Rother C, Salih W, Ewig S. Healthcare-associated pneumonia does not accurately identify potentially resistant patho-

gens a systematic review and meta-analysis. Clin Infect Dis **58**: 330-339, 2014.

9. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med **171**: 388-416, 2005.

10. Gross AE, Olsen KM, Rupp ME, et al. Epidemiology and predictors of multidrug-resistant community-acquired and health care-associated pneumonia. Antimicrob Agents Chemother **58**: 5262-5268, 2014.

11. Valles J, Jimenez R, Seoane E, et al. Epidemiology, antibiotic therapy and clinical outcomes of healthcare-associated pneumonia in critically ill patients: a Spanish cohort study. Intensive Care Med **40**: 572-581, 2014.

12. Shindo Y, Taniguchi H, Suzuki R, et al. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. Am J Respir Crit Care Med **188**: 985-995, 2013.

13. Seong GM, Lee J, Lee JH, et al. Healthcare-associated pneumonia among hospitalized patients: Is it different from community acquired pneumonia? Tuberc Respir Dis (Seoul) **76**: 66-74, 2014.

14. Webb BJ, Dangerfield BS, Pasha JS, Agrwal N, Vikram HR. Guideline-concordant antibiotic therapy and clinical outcomes in healthcare-associated pneumonia. Respir Med **106**: 1606-1612, 2012.

15. Maruyama T, Takei Y, Miyashita N, et al. A new strategy for healthcare-associated pneumonia: a 2-year prospective multicenter cohort study using risk factors for multidrug-resistant pathogens to select initial empiric therapy. Clin Infect Dis **57**: 1373-1383, 2013.

16. Ma HM, Hui DS, Lui GC, et al. Risk factors for drug-resistant bacterial pneumonia in older patients hospitalized with pneumonia in a Chinese population. QJM **106**: 823-829, 2013.

17. Jung JY, Kim YS, Park BH, et al. Healthcare-associated pneumonia among hospitalized patients in a Korean tertiary hospital. BMC Infect Dis **11**: 61, 2011.

18. Shindo Y, Ogawa M, Hashimoto N, et al. Health-care-associated pneumonia among hospitalized patients in a Japanese community hospital. Chest **135**: 633-640, 2009.

19. Oshitani Y, Nagai H, Matsui H, Aoshima M. Reevaluation of the Japanese guideline for healthcare-associated pneumonia in a medium-sized community hospital in Japan. J Infect Chemother **19**: 579-587, 2013.

20. Cao G, Chen X, Wu S. Analysis of clinical efficacy of different initial antimicrobial treatment in healthcare associated pneumonia patients in emergency department. Chin Med J (Engl) **127**: 1814-1819, 2014.

21. Park HK, Suh GY, Chung MP, et al. Clinical characteristics of health care-associated pneumonia in Korean teaching hospital. Respir Med **104**: 1729-1735, 2010.

22. Shibata N, Ozawa Y, Shibayama K, et al. PCR classification of CTX-M-type β-lactamase genes identified in clinically isolated gram-negative bacilli in Japan. Antimicrob Agents Chemother **50**: 791-795, 2006.

23. Lim WS, Read RC, Roberts HJ, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax **64**: 1-55, 2009.

24. Jones BE, Sauer B, Madaras-Kelly K, et al. Trends in antibiotic use and nosocomial pathogens in hospitalized veterans with pneumonia at 128 medical centers, 2006-2010. Clin Infect Dis **61**: 1403-1410, 2015.

25. Attridge RT, Lawson KA, Ryan L, et al. Guideline-concordant therapy and outcomes in healthcare-associated pneumonia. Eur Respir J **38**: 878-887, 2011.

26. Teshome BF, Attridge RT, Koeller J, et al. Application of a methicillin-resistant *Staphylococcus aureus* risk score for community-onset pneumonia patients and outcomes with initial treatment. BMC Infect Dis **15**: 380, 2015.

27. Chen LA, She DY, Liang ZX, et al. Healthcare-associated pneumonia clinical features and retrospective analysis over 10 years. Chin Med J (Engl) **128**: 2707-2713, 2015.

28. Webb BJ, Dangerfield BS, Pasha JS, et al. Guideline-concordant antibiotic therapy and clinical outcomes in healthcare-associated pneumonia. Respir Med **106**: 1606-1612, 2012.

29. Paterson DL, Bonomo RA. Extended-spectrumβ-lactamases: a clinical update. Clin Microbiol Rev **18**: 657-686, 2005.

30. Kumar D, Singh AK, Ali MR, Chander Y. Antimicrobial susceptibility profile of extended spectrum β-lactamase (ESBL) producing *Escherichia coli* from various clinical samples. Infect Dis (Auckl) **7**: 1-8, 2014.

31. Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med **157**: 531-539, 1998.

32. Gaynes R. Health-care associated bloodstream infections: a change in thinking. Ann Intern Med **137**: 850-851, 2002.

33. Choi SH, Lee SO, Jeong JY, et al. Emergence of antibiotic resistance during therapy for infections caused by Enterobacteriaceae producing AmpC beta-lactamase: implications for antibiotic use. Antimicrob Agents Chemother **52**: 995-1000, 2008.

34. Jacoby GA, Han P. Detection of extended-spectrum beta-lactamases in clinical isolates of *Klebsiella pneumoniae* and *Escherichia coli*. J Clin Microbiol **34**: 908-911, 1996.

35. Lim WS, Boersma WG, Karalus N, et al. Defining community-acquired pneumonia severity on presentation to hospital:an international derivation and validation study. Thorax **58**: 377-382, 2003.

36. Geckler RW, Gremillion DH, McAllister CK, Ellenbogen C. Microscopic and bacteriological comparison of paired sputa and transtracheal aspirates. J Clin Microbiol **6**: 396-399, 1977.

37. The JRS guidelines for the management of community-acquired pneumonia in adults 2005.

38. Halm EA, Marrie TJ, Coley CM, et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia. JAMA **279**: 1452-1457, 1998.

39. Bruns AH, Oosterheert JJ, Hak E, Hoepelman AI. Usefulness of consecutive C-reactive protein measurements in follow-up of severe community-acquired pneumonia. Eur Respir J **32**: 726-732, 2008.

40. Gilbert DN. Clinical end points of therapy for patients with mild community-acquired pneumonia. Clin Infect Dis **47**: 140-144, 2008.

41. Queenan AM, Foleno B, Gownley C, Wira E, Bush K. Effects of inoculum and β-lactamase activity in AmpC- and extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* clinical isolates tested by using NCCLS ESBL methodology. J Clin Microbiol **42**: 269-275, 2004.

42. Paterson DL, Klugman KP, Bonomo RA, et al. Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended-spectrum β-lactamases: implications for the clinical microbiology laboratory. J Clin Microbiol **39**: 2206-2212, 2001.

43. Emery CL, Weymouth LA. Detection and clinical significance of extended-spectrum β-lactamases in a tertiary-care medical center. J Clin Microbiol **35**: 2061-2067, 1997.

44. Perez F, Endimiani A, Hujer KM, Bonomo RA. The continuing challenge of ESBLS. Curr Opin Pharmacol **7**: 459-469, 2007.

45. Yang K, Guglielmo BJ. Diagnosis and treatment of extended-spectrum and AmpC beta-lactamase-producing organisms. Ann Pharmacother **41**: 1427-1435, 2007.

46. Dobler CC, Waterer G. Healthcare-associated pneumonia: a US disease or relevant to the Asia Pacific, too? Respirology **18**: 923-932, 2013.

47. Tebano G, Augustin P, Thabut G, et al. Epidemiology and risk factors of multidrug-resistant bacteria in respiratory samples after

lung transplantation. Transpl Infect Dis **18**: 22-30, 2016.

48. Huang X, Li G, Yi L, Li M, Wang J. The epidemiology of multidrug-resistant bacteria colonization and analysis of its risk factors in intensive care unit. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue **27**: 667-671, 2015.

49. Ito I, Mishima M. Isolation of drug-resistant pathogens does not always require use of broad-spectrum antibiotics in pneumonia. Am J Respir Crit Care Med **189**: 756-757, 2014.