Showa Univ J Med Sci 33(2), 55-64, June 2021

Original Paper

# Risk factors for initial antibiotic treatment failure in patients with aspiration pneumonia

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Received: 6 January 2021 / Accepted: 1 February 2021

**Abstract**

Sulbactam/ampicillin (SBT/ABPC) and ceftriaxone (CTRX) are the initial antibiotics recommended for treating aspiration pneumonia without risk factors for drug-resistant pathogens. However, the condition of some patients does not improve with these antibiotics. Therefore, we investigated the new risk factors associated with failure of initial antibiotic treatment in patients with aspiration pneumonia. This study included 487 patients diagnosed with aspiration pneumonia who received initial antibiotic treatment with SBT/ABPC or CTRX, and were hospitalized at the Respiratory Medicine Department of the Yokohama City Minato Red Cross Hospital. The outcome was initial antibiotic treatment failure, which was defined as a change from initial to secondary antibiotic treatment. The characteristics of patients with and without antibiotic treatment failure were compared using univariate analyses, and significant independent risk factors for the initial antibiotic treatment failure were selected using multivariate analyses. The mean age of the patients was 84.1 ± 9.6 years; 302 (62%) of them were men and 93 patients experienced antibiotic treatment failure. Logistic regression analysis extracted no restriction of diet on admission (odds ratio [OR], 3.23; 95% confidence interval [CI], 1.35-7.74), history of hospitalization due to aspiration pneumonia (OR, 1.81; 95%CI, 1.12-2.93), the severity of pneumonia (OR, 1.37; 95%CI, 1.01-1.86), and C-reactive protein (CRP) level (OR, 1.26; 95%CI, 1.09-1.45) as risk factors for initial antibiotic treatment failure. Our results suggested that no restriction of diet on admission, history of hospitalization due to aspiration pneumonia, severity of pneumonia, and increased CRP levels were the risk factors associated with failure of initial antibiotic treatment in patients with aspiration pneumonia. These factors will be useful for determining an effective initial treatment strategy for patients with aspiration pneumonia.

**Key words** :aspiration pneumonia, nursing and healthcare-associated pneumonia, risk factors, treatment failure, initial antibiotic treatment

## Introduction

Aspiration pneumonia in a patient with a predisposition to aspiration is caused by dysphagia[1]. Previously published data demonstrated that 66.8% of patients hospitalized for pneumonia were diagnosed with aspiration pneumonia[2]; aspiration pneumonia accounted for 80.1% and 95% of the cases among those aged ≥ 70 years and ≥ 90 years, respectively. Therefore, most patients hospitalized with pneumonia have the aspiration type, and this proportion is increased among older patients. Aspiration pneumonia is associated with increased severity, high rates of in-hospital mortality and recurrent

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pneumonia[3,4], and poor prognosis.

Pneumonia is classified into three types: community-acquired pneumonia, hospital-acquired pneumonia, and healthcare-associated pneumonia (HCAP). In Japan, HCAP is classified as nursing-and healthcare-associated pneumonia (NHCAP), based on the Japanese medical system. Most patients with NHCAP are older and have aspiration pneumonia[5,6], and the treatment of these patients is performed based on the NHCAP treatment guidelines[7].

Aspiration pneumonia is often caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, and anaerobic bacteria. However, in addition to these bacteria, drug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Acinetobacter*, and extended-spectrum $\beta$-lactamase-producing enteric bacteria have been included as causative agents. The isolation rate of drug-resistant pathogens has been reported as 11% in patients with NHCAP and 3%–54.4% in patients with aspiration pneumonia[4,6,8]. Therefore, antibacterial agents effective against these bacteria are used for initial antibiotic treatment. The initial antibiotic treatment was determined while considering the risk factors for drug-resistant pathogens based on the clinical practice guideline for NHCAP[7]. These risk factors included "history of antibiotic treatment for 2 or more days in the preceding 90 days," or "current tube feeding," or "history of MRSA isolation"[7]. Broad-spectrum antibiotics or anti-MRSA agents are recommended when patients have a minimum of one of these risk factors. In contrast, treatment with sulbactam/ampicillin (SBT/ABPC) or ceftriaxone (CTRX) is recommended as the initial antibiotic treatment for patients without these risk factors.

The conditions of some patients do not improve after treatment with SBT/ABPC or CTRX. Since aspiration pneumonia is common in older people with underlying diseases and poor physical conditions, risk factors other than those[9–14] for drug-resistant pathogens may be involved. However, these factors have not been investigated so far. The initial treatment of aspiration pneumonia is important because initial treatment failure is one of the independent prognostic factors in patients with aspiration pneumonia[8]. Therefore, we aimed to investigate the risk factors for initial antibiotic treatment failure in patients with aspiration pneumonia, other than those for drug-resistant pathogens, to identify new factors that might help to determine the initial antibiotic treatment.

## Methods

*Study design and patient population*

This study included 489 patients diagnosed with aspiration pneumonia who received initial antibiotic treatment with SBT/ABPC or CTRX and were hospitalized at the Respiratory Medicine Department of the Yokohama City Minato Red Cross Hospital in Japan, between January 2012 and March 2017. Two patients who were not classified as NHCAP and presented with other infections were excluded. Finally, data of 487 patients were analyzed for this study. This study was approved by the clinical committee of the Yokohama City Minato Red Cross Hospital (Permit Number: 2017-42).

*Data collection*

The following data were collected from the medical records of the patients at baseline and before admission. The investigation items before admission included meal route, aspiration episode, history of hospitalization due to aspiration pneumonia, activities of daily living (ADL), residence, the number of NHCAP criteria met[7], and risk factors for drug-resistant pathogens[7]. The specificity (22%) and positive predictive values (17%) of the risk factors for drug-resistant pathogens are low[15]. To validate the accuracy of previously reported risk factors for drug-resistant pathogens, we also analyzed patients with drug-resistant pathogens. Items investigated on admission were age, sex, body weight, height, body mass index, body temperature, respiratory rate, pulse oximetric saturation, systolic blood pressure, C-reactive protein (CRP) level, white blood cells, albumin, creatinine (Crea), and blood urea nitrogen (BUN) levels, past medical history/comorbidities (cerebrovascular disease, neuromuscular disease, dementia, chronic obstructive pulmonary disease, a gastrointestinal disease associated with gastroesophageal reflux, cancer, and/or diabetes mellitus), severity of pneumonia, diet restriction, type of initial antibiotics, and the numbers and types of medications. The severity of pneumonia was assessed using the following parameters: age, dehydration, respiration, orientation, and pressure (A-DROP) score[16], and was classified as mild, moderate, severe, and very severe. Investigation items during admission were intervention by a speech therapist, intervention by a dentist, length of hospitalization, duration of fasting, duration of initial antibiotic, types of secondary antibiotics, and in-hospital mortality rate.

*Definitions*

NHCAP was defined as patients who met a minimum of one of the following criteria[7]: resident of an extended care facility or nursing home; discharged from a hospital within the preceding 90 days; an elderly or disabled person receiving nursing care (performance status ≥ 3); and an outpatient receiving regular endovascular treatment (dialysis, antibiotic therapy, chemotherapy, or immunosuppressant therapy). The risk factors for drug-resistant pathogens[7] were history of antibiotic treatment for ≥ 2 days in the preceding 90 days, current tube feeding, and history of MRSA isolation. The ADL was evaluated using the "Criteria for determination of the daily life independence level (bedridden level) of the older with a disability"[17]. Medication details were collected from the medical records of the patients (excluding medicine taken only when necessary), and the category of drugs was classified based on the Therapeutic Category of Drugs in Japan (Standard Commodity Classification of Japan "division 87-dugs and related commodities") posted on the Kyoto Encyclopedia of Genes and Genomes website.

*Outcome*

The outcome was the failure of initial antibiotic treatment. This was defined as a change from initial antibiotics to secondary antibiotics (meropenem [MEPM], doripenem [DRPM], tazobactam/piperacillin [TAZ / PIPC], cefepime [CFPM] plus clindamycin [CLDM], ciprofloxacin [CPFX] plus SBT / ABPC, or vancomycin [VCM]), which can effectively act on patients with risk factors for drug-resistant pathogens. Death was not included as a factor of initial antibiotic treatment failure because it could have been caused by factors other than initial antibiotic treatment failure.

*Statistical analysis*

The characteristics of patients with and without antibiotic treatment failure were compared using the Chi-squared test or Fisher's exact test for categorical variables; the Mann–Whitney U test or Student's t-test was used for continuous variables. The severity of pneumonia was classified as mild and moderate, severe, and very severe, according to the patient's A-DROP scores. Variables with a p-value of $< 0.1$ extracted through the univariate analysis were applied to the multivariate analysis. We confirmed that these variables did not correlate with each other. Multivariate analysis of the risk factors for initial antibiotic treatment failure in patients with aspiration pneumonia was performed using the stepwise selection method. In addition, the relationship between initial antibiotic treatment failure and medications at admission were evaluated using the univariate and multivariable analyses. All data were analyzed using SPSS software version 25 (IBM Japan Inc., Tokyo, Japan). A p-value of $< 0.05$ was considered statistically significant.

## Results

*Patient characteristics*

The characteristics of patients before, on, and during admission are shown in Table 1. The mean age was 84.1 ± 9.6 years and 302 (62%) of them were men. The types of initial antibiotic treatment included SBT / ABPC (91.8%) and CTRX (8.2%). A history of hospitalization due to aspiration pneumonia was observed in 167 (34.4%) patients. Severe and very severe aspiration pneumonia was observed for 244 (50.1%) of the total patients. Older or disabled people receiving nursing care accounted for 483 (99.2%) of the total patients. The risk factors for drug-resistant pathogens were observed in 219 (45%) of the total patients.

*Outcome*

Ninety-three patients experienced failure of initial antibiotic treatment. The secondary antibiotics used were MEPM monotherapy (44 patients), DRPM monotherapy (9 patients), TAZ/PIPC monotherapy (20 patients), CFPM plus CLDM (2 patients), CPFX plus SBT/ABPC (2 patients), and VCM monotherapy or combination therapy (16 patients).

Patients with initial antibiotic treatment failure had a significantly longer duration of hospitalization than those without initial antibiotic treatment failure (median 25 days [8.0–196 days] vs. 17 days [1.0–126 days]; $P < 0.01$). The rate of in-hospital mortality was significantly higher in patients with initial antibiotic treatment failure than in those without initial antibiotic treatment failure (25.8% vs. 9.4%; $P < 0.01$).

*Characteristics of patients with antibiotic treatment failure analyzed using univariate analysis*

Table 2 shows the results of the univariate analysis. The proportion of males, meal intake on admission, and rate of high severity of pneumonia were significantly higher in patients with treatment failure than in those without treatment failure. Additionally, the levels of CRP, BUN, and Crea were significantly higher in patients with treatment failure

Table 1. Patient characteristics

| Characteristics | Total (n=487) |
|---|---|
| **Investigation item on admission** | |
| Age (years) | 84.1 ± 9.6 |
| Sex, male | 302 (62) |
| Body weight (kg) | 42 (21.3–77.4) |
| Height (cm) | 155.8 ± 10.4 |
| BMI ($kg/m^2$) | 18.1 ± 4.0 |
| Body temperature (℃) | 37.4 ± 0.9 |
| Respiratory rate (times) | 22 (11–57) |
| $SpO_2$ (%) | 88 (40–99) |
| WBC ($\times 10^2/\mu l$) | 105 (12–395) |
| CRP (mg/dl) | 6.5 (0–38.1) |
| BUN (mg/dl) | 22.5 (4.7–164.3) |
| Crea (mg/dl) | 0.71 (0.15–7.14) |
| Alb (g/dl) | 3.2 ± 0.5 |
| Systolic blood pressure (mmHg) | 124.2 ± 24.5 |
| Past medical history / comorbidities | |
| Cerebrovascular disease | 174 (35.7) |
| Neuromuscular disease | 69 (14.2) |
| Dementia | 210 (43.1) |
| COPD | 48 (9.9) |
| Gastrointestinal disease associated with gastroesophageal reflux | 38 (7.8) |
| Cancer | 126 (25.9) |
| Diabetes | 92 (18.9) |
| No restriction of diet | 26 (5.3) |
| The severity of pneumonia | |
| Mild / Moderate / Severe / Very severe | 4 (0.8) / 239 (49.1) / 160 (32.9) / 84 (17.2) |
| Drug-resistant pathogens[a] | 115 (23.6) |
| Type of initial antibiotic | |
| SBT / ABPC / CTRX | 447 (91.8) / 40 (8.2) |
| **Investigation item before admission** | |
| Meal route | |
| Oral / Tubal feeding / Infusion | 430 (88.3) / 58 (11.9) / 6 (1.2) |
| Aspiration episode | 196 (40.2) |
| History of hospitalization due to aspiration pneumonia | 167 (34.3) |
| ADL[b] | |
| Rank J / A / B / C | 5 (1.0) / 44 (9.0) / 173 (35.5) / 265 (54.4) |
| Residence | |
| Home / Care facility or nursing home | 285 (58.7) / 201 (41.3) |
| Definition of NHCAP[a] | |
| Resident of an extended care facility or nursing home | 198 (40.7) |
| Discharge from a hospital within the preceding 90 days | 129 (26.5) |
| An elderly or the disabled person receiving nursing care[c] | 483 (99.2) |
| Person who is receiving regular endovascular treatment as an outpatient[d] | 23 (4.7) |
| Risk factors for drug-resistant pathogens[a] | |
| History of antibiotic therapy for 2 or more days in the preceding 90 days | 180 (37.0) |
| Current tube feeding | 64 (13.1) |
| History of MRSA isolation | 39 (8.0) |
| **Investigation item during admission** | |
| Intervention by a speech therapist | 298 (61.2) |
| Intervention by a dentist | 110 (22.6) |
| Length of initial antibiotic treatment (day) | 8 (1–31) |
| Length of hospitalization (day) | 18 (1–196) |
| The fasting duration (day) | 4 (0–62) |

n (%) or mean ± standard deviation (SD) or median (range)
SBT / ABPC, sulbactam / ampicillin; CTRX, ceftriaxone; MRSA, methicillin-resistant *Staphylococcus aureus*; COPD, chronic obstructive pulmonary disease; TPN, total parenteral nutrition; NHCAP, nursing-and healthcare-associated pneumonia; BMI, body mass index; WBC, white blood cells; CRP, C-reactive protein; BUN, blood urea nitrogen; Crea, creatinine; Alb, albumin; SpO2, pulse oximetric saturation; ADL, activities of daily living
[a] : Clinical practice guidelines for NHCAP
[b] : Criteria for determination of the daily life independence level (bedridden level) of the elderly with disability
[c] : Patients whose performance status is performance status 3 (capable of only limited self-care, confined to a bed or a chair, more than 50% of their waking hours) or more
[d] : dialysis, antibiotic therapy, chemotherapy, immunosuppressant therapy

Table 2. Characteristics of patients with antibiotic treatment failure analyzed using the univariate analysis

| Characteristics | Patients without treatment failure n=394 | Patients with treatment failure n=93 | p-value |
|---|---|---|---|
| **Investigation item on admission** | | | |
| Age (years) | 84.0 ± 10.0 | 84.6 ± 7.8 | 0.637 |
| Sex, male | 234 (59) | 68 (73) | 0.014 |
| Body weight (kg) | 42.1 (21.3–77.4) | 41.0 (30–65.5) | 0.810 |
| Height (cm) | 155.5 ± 10.4 | 156.8 ± 10.1 | 0.399 |
| BMI ($kg/m^2$) | 18.2 ± 4.2 | 17.8 ± 3.2 | 0.632 |
| Body temperature (℃) | 37.4 ± 0.9 | 37.5 ± 1.0 | 0.350 |
| Respiratory rate (times) | 23.0 (11–50) | 22.0 (13–57) | 0.244 |
| $SpO_2$ (%) | 88.0 (40–99) | 87.0 (54–99) | 0.627 |
| WBC ($\times 10^2/\mu l$) | 105.0 (12–395) | 102.0 (24–288) | 0.304 |
| CRP (mg/dl) | 6.2 (0–38.1) | 7.3 (0.1–35) | 0.020 |
| BUN (mg/dl) | 22.0 (4.7–164.3) | 24.8 (7.2–85.8) | 0.024 |
| Crea (mg/dl) | 0.7 (0.15–7.14) | 0.8 (0.22–6.14) | 0.022 |
| Alb (g/dl) | 3.2 ± 0.5 | 3.1 ± 0.5 | 0.137 |
| Systolic blood pressure (mmHg) | 123.2 ± 24.2 | 128.4 ± 25.0 | 0.064 |
| Past medical history / comorbidities | | | |
| Cerebrovascular disease | 142 (36.0) | 32 (34.4) | 0.768 |
| Neuromuscular disease | 54 (13.7) | 15 (16.1) | 0.547 |
| Dementia | 177 (44.9) | 33 (35.5) | 0.098 |
| COPD | 37 (9.4) | 11 (11.8) | 0.478 |
| Gastrointestinal disease associated with gastroesophageal reflux | 29 (7.4) | 9 (9.7) | 0.454 |
| Cancer | 105 (26.6) | 21 (22.6) | 0.420 |
| Diabetes | 72 (18.3) | 20 (21.5) | 0.474 |
| No restriction of diet | 17 (4.3) | 9 (9.7) | 0.041 |
| The severity of pneumonia | | | 0.013 |
| Mild & Moderate | 208 (53) | 35 (38) | |
| Severe | 118 (30) | 42 (45) | |
| Very severe | 68 (17) | 16 (17) | |
| Investigation item before admission | | | |
| Meal route | | | |
| Oral | 348 (88.3) | 82 (88.2) | 0.967 |
| Tubal feeding | 46 (11.7) | 11 (11.8) | 0.978 |
| Infusion | 6 (1.5) | 0 (0) | 0.278 |
| Aspiration episode | 158 (40.1) | 38 (40.9) | 0.893 |
| History of hospitalization due to aspiration pneumonia | 128 (32.5) | 39 (41.9) | 0.084 |
| ADL[a] | | | 0.714 |
| Rank J | 5 (1.3) | 0 (0) | |
| Rank A | 34 (8.6) | 10 (10.8) | |
| Rank B | 139 (35.3) | 34 (36.6) | |
| Rank C | 216 (54.8) | 49 (52.7) | |
| Residence | | | 0.564 |
| Home | 228 (58.1) | 57 (61.3) | |
| Care facility or nursing home | 165 (41.9) | 36 (38.7) | |
| Definition of NHCAP[b] | | | |
| Resident of an extended care facility or nursing home | 162 (41.1) | 36 (38.7) | 0.671 |
| Person who has been discharged from a hospital within the preceding 90 days | 103 (26.1) | 26 (28.0) | 0.721 |
| An elderly or disabled person who is receiving nursing care[c] | 391 (99.2) | 92 (98.9) | 0.573 |
| Person who is receiving regular endovascular treatment as an outpatient[d] | 19 (4.8) | 4 (4.3) | 0.544 |
| Risk factors for drug-resistant pathogens[b] | | | |
| History of antibiotic therapy for 2 or more days in the preceding 90 days | 142 (36.0) | 38 (40.9) | 0.386 |
| Current tube feeding | 53 (13.5) | 11 (11.8) | 0.677 |
| History of MRSA isolation | 31 (7.9) | 8 (8.6) | 0.815 |

n (%) or mean ± SD or median (range)

COPD, chronic obstructive pulmonary disease; TPN, total parenteral nutrition; MRSA, methicillin-resistant *Staphylococcus aureus*; NHCAP, nursing-and healthcare-associated pneumonia; BMI, body mass index; WBC, white blood cells; CRP, C-reactive protein; BUN, blood urea nitrogen; Crea, creatinine; Alb, albumin; $SpO_2$, pulse oximetric saturation; ADL, activities of daily living

[a] : Criteria for determination of the daily life independence level (bedridden level) of the elderly with disability

[b] : Clinical practice guidelines for NHCAP

[c] : Patients whose performance status is performance status 3 (capable of only limited self-care, confined to a bed or a chair, more than 50% of their waking hours) or more

[d] : dialysis, antibiotic therapy, chemotherapy, immunosuppressant therapy

Table 3. Multivariable analysis of risk factors for initial antibiotic treatment failure

| Factors | | β | OR | 95%CI | p-value |
|---|---|---|---|---|---|
| The severity of pneumonia | Mild vs Moderate vs Severe vs Very severe | 0.31 | 1.37 | 1.01–1.86 | 0.045 |
| History of hospitalization due to aspiration pneumonia | No vs Yes | 0.59 | 1.81 | 1.12–2.93 | 0.016 |
| No restriction of diet on admission | No vs Yes | 1.17 | 3.23 | 1.35–7.74 | 0.008 |
| CRP (mg/dl) | 5 mg/dl | 0.23 | 1.26 | 1.09–1.45 | 0.002 |

CRP, C-reactive protein; OR, odds ratio; CI, confidence interval.
Dementia, severity of pneumonia, history of hospitalization due to aspiration pneumonia, CRP, Crea, and no restriction of diet on admission were incorporated into the multivariable analysis.

when compared to those in patients without treatment failure.

*Multivariable analysis of the risk factors for initial antibiotic treatment failure*

Multivariable logistic regression analysis was performed using the following variables: dementia, the severity of pneumonia, history of hospitalization due to aspiration pneumonia, levels of CRP and Crea, and no restriction of diet on admission. Sex, BUN, and systolic blood pressure are included in the A-DROP; hence, these factors were excluded from the multivariable analysis. The significant, independent risk factors for antibiotic treatment failure in patients with aspiration pneumonia included the following: severity of pneumonia (odds ratio [OR], 1.37; 95% confidence interval [CI], 1.01–1.86), history of hospitalization due to aspiration pneumonia (OR, 1.81; 95%CI, 1.12–2.93), no restriction of diet on admission (OR, 3.23; 95%CI, 1.35–7.74), and CRP levels (OR, 1.26; 95%CI, 1.09–1.45; Table 3).

*Medications at admission associated with initial antibiotic treatment failure*

In the univariate analysis, the use of antacids, other agents affecting the digestive organs, urinary disturbance agents other than overactive bladder agents, and anti-tubercular agents at admission were significantly higher in patients with treatment failure than in those without treatment failure (Table 4). The multivariable analysis was performed using dementia, severity of pneumonia, history of hospitalization due to aspiration pneumonia, CRP and Crea levels, no restriction of diet on admission, urinary disturbance agents other than overactive bladder agents, antacids, other agents affecting the digestive organs, anti-tubercular agents, sex hormone preparations, and other agents related to blood and body fluids (antiplatelet agents). The significant independent risk factors for initial antibiotic treatment failure in patients with aspiration pneumonia were history of hospitalization due to aspiration pneumonia (OR, 1.79; 95%CI, 1.10–2.90), no restriction of diet on admission (OR, 3.26; 95% CI, 1.36–7.81), CRP level (OR, 1.28; 95%CI, 1.10–1.47), and urinary disturbance agents other than overactive bladder agents (OR, 2.56; 95%CI, 1.34–4.88) (Table 5). In this study, the urinary disturbance agents other than overactive bladder agents included urapidil, tamsulosin, silodosin, naftopidil, and Chimaphila umbellata extract, Populus tremula extract, Pulsatilla pratensis mill extract, Equisetum arvense extract, and wheat germ oil.

## Discussion

We investigated the risk factors for initial antibiotic treatment failure in patients with aspiration pneumonia other than those for drug-resistant pathogens, to identify new factors that would help to determine the initial treatment. The severity of pneumonia, history of hospitalization due to aspiration pneumonia, no restriction of diet on admission, and CRP levels were identified as significant independent risk factors for initial antibiotic treatment failure in this study.

To date, the study of risk factors has focused on drug-resistant pathogens[9–14]. Since aspiration pneumonia is common in older adults with underlying diseases and poor physical conditions, we assumed that unknown risk factors, other than those for drug-resistant pathogens, might be involved. Our findings strongly suggested that the diet status, deterioration of the general condition of the patient, and intensity of inflammation in the lung tissues are factors that will prove beneficial when determining the therapeutic strategy. Thus, taking these factors along with the currently existing risk factors into account might help

Table 4. Medications at admission that were associated with antibiotic treatment failure

| medications | Patients without treatment failure n=394 | Patients with treatment failure n=93 | p-value |
|---|---|---|---|
| Number of medications | 5 (0–16) | 6 (0–18) | 0.261 |
| Agents affecting central nervous system | 231 (58.6) | 52 (55.9) | 0.633 |
| Hypnotics and sedatives, antianxiety drugs | 61 (15.5) | 18 (19.4) | 0.362 |
| Antiepileptics | 30 (7.6) | 7 (7.5) | 0.977 |
| Antipyretics, analgesics, and anti-inflammatory agents | 23 (5.8) | 6 (6.5) | 0.822 |
| Antiparkinsonism agents | 31 (7.9) | 12 (12.9) | 0.124 |
| Psychotropic agents | 116 (29.4) | 26 (28.0) | 0.777 |
| Agents used for common cold | 1 (0.3) | 0 (0) | 0.809 |
| Other agents affecting central nervous system | 93 (23.6) | 24 (25.8) | 0.655 |
| Agents affecting peripheral nervous system | 9 (2.3) | 4 (4.3) | 0.223 |
| Skeletal muscle relaxants | 1 (0.3) | 0 (0) | 0.809 |
| Autonomic agents | 6 (1.5) | 2 (2.2) | 0.471 |
| Antispasmodics | 2 (0.5) | 2 (2.2) | 0.166 |
| Antimotion sickness agents | 6 (1.5) | 1 (1.1) | 0.601 |
| Cardiovascular agents | 238 (60.4) | 55 (59.1) | 0.822 |
| Cardiotonics | 15 (3.8) | 3 (3.2) | 0.539 |
| Antiarrhythmic agents | 16 (4.1) | 4 (4.3) | 0.551 |
| Diuretics | 91 (23.1) | 17 (18.3) | 0.315 |
| Antihypertensives | 108 (27.4) | 29 (31.2) | 0.467 |
| Vasoconstrictors | 2 (0.5) | 0 (0) | 0.654 |
| Vasodilators | 97 (24.6) | 26 (28.0) | 0.505 |
| Agents for hyperlipidemias | 63 (16.0) | 14 (5.1) | 0.824 |
| Other cardiovascular agents | 27 (6.9) | 6 (6.5) | 0.890 |
| Agents affecting respiratory organs | 96 (24.4) | 22 (23.7) | 0.886 |
| Antitussives | 3 (0.8) | 1 (1.1) | 0.573 |
| Expectorants | 77 (19.5) | 21 (22.6) | 0.511 |
| Antitussives and expectorants | 1 (0.3) | 0 (0) | 0.809 |
| Bronchodilators | 22 (5.6) | 2 (2.2) | 0.130 |
| Agents affecting digestive organs | 254 (64.5) | 66 (71.0) | 0.235 |
| Antidiarrheals, intestinal regulators | 40 (10.2) | 11 (11.8) | 0.635 |
| Agents for peptic ulcer | 173 (43.9) | 44 (47.3) | 0.553 |
| Stomachics and digestives | 4 (1.0) | 1 (1.1) | 0.655 |
| Antacids | 0 (0) | 2 (2.2) | 0.036 |
| Purgatives and clysters | 142 (36.0) | 36 (38.7) | 0.631 |
| Cholagogues | 14 (3.6) | 1 (1.1) | 0.185 |
| Other agents affecting digestive organs | 29 (7.4) | 14 (15.1) | 0.019 |
| Hormone preparations | 23 (5.8) | 9 (9.7) | 0.179 |
| Thyroid and para-thyroid hormone preparations | 11 (2.8) | 2 (2.2) | 0.534 |
| Adrenal hormone preparations | 11 (2.8) | 4 (4.3) | 0.317 |
| Sex hormone preparations | 3 (0.8) | 3 (3.2) | 0.087 |
| Urinary disturbance agents other than overactive bladder agents | 36 (9.1) | 17 (18.3) | 0.011 |
| Vitamin preparations | 68 (17.3) | 15 (16.1) | 0.794 |
| Nutrients, tonics and alteratives | 47 (11.9) | 10 (10.8) | 0.751 |
| Calcium compounds and preparations | 5 (1.3) | 0 (0) | 0.345 |
| Mineral preparations | 42 (10.7) | 10 (10.8) | 0.979 |
| Agents relating to blood and body fluids | 136 (34.5) | 35 (37.6) | 0.571 |
| Hemostatics | 2 (0.5) | 0 (0) | 0.654 |
| Anticoagulants | 42 (10.7) | 8 (8.6) | 0.556 |
| Other agents relating to blood and body fluids | 98 (24.9) | 31 (33.3) | 0.096 |
| Other agents affecting metabolism | 107 (27.2) | 24 (25.8) | 0.792 |
| Agents for liver disease | 2 (0.5) | 0 (0) | 0.654 |
| Agents for treatment of gout | 57 (14.5) | 14 (15.1) | 0.885 |
| Antidiabetic agents | 40 (10.2) | 13 (14.0) | 0.287 |
| Other agents affecting metabolism | 23 (5.8) | 2 (2.2) | 0.112 |
| Antineoplastic agents | 12 (3.0) | 5 (5.4) | 0.209 |
| Antiallergic agents | 44 (11.2) | 10 (10.8) | 0.909 |
| Antihistamines | 3 (0.8) | 2 (2.2) | 0.244 |
| Agents for stimulation therapy | 3 (0.8) | 1 (1.1) | 0.573 |
| Other antiallergic agents | 40 (10.2) | 7 (7.5) | 0.441 |
| Crude drug and Chinese medicine formulations | 47 (11.9) | 17 (18.3) | 0.103 |
| Antibiotic preparations | 17 (4.3) | 4 (4.3) | 0.628 |
| Chemotherapeutics | 7 (1.8) | 3 (3.2) | 0.294 |
| Sulfonamide preparations | 0 (0) | 1 (1.1) | 0.191 |
| Anti-tuberculous agents | 0 (0) | 2 (2.2) | 0.036 |
| Synthetic antibacterials | 2 (0.5) | 0 (0) | 0.654 |
| Other chemotherapeutics | 5 (1.3) | 0 (0) | 0.345 |
| Narcotics | 0 (0) | 1 (1.1) | 0.191 |

n (%) or mean ± standard deviation (SD) or median (range)

Table 5. Multivariable analysis of risk factors for antibiotic treatment failure including medications

| Factors | | β | OR | 95%CI | p-value |
|---|---|---|---|---|---|
| History of hospitalization due to aspiration pneumonia | No vs Yes | 0.58 | 1.79 | 1.10–2.90 | 0.019 |
| No restriction of diet on admission | No vs Yes | 1.18 | 3.26 | 1.36–7.81 | 0.008 |
| CRP (mg/dl) | 5 mg/dl | 0.24 | 1.28 | 1.10–1.47 | 0.001 |
| Urinary disturbance agents other than overactive bladder agents | No vs Yes | 0.94 | 2.56 | 1.34–4.88 | 0.005 |

CRP, C-reactive protein; OR, odds ratio; CI, confidence interval.
Dementia, the severity of pneumonia, history of hospitalization due to aspiration pneumonia, CRP, Crea, no restriction of diet on admission, other agents affecting digestive organs, urinary disturbance agents other than overactive bladder agents, antacids, anti-tuberculous agents, sex hormone preparations, and other agents relating to blood and body fluids were incorporated into the multivariable analysis.

in deciding an effective initial treatment strategy for patients with aspiration pneumonia. In addition to the antibiotic treatment, appropriate management of the general condition, such as water management, respiratory management, and oral care, will lead to an improvement in aspiration pneumonia.

The risk of treatment failure increased 3.23-fold in patients without restriction of diet on admission. There are three possible explanations for this observation. Firstly, food residue and ADL decrease are significantly associated with an increase in bacteria in the saliva of older people requiring care[18]. Moreover, the swallowing function decreases in patients with aspiration pneumonia[19]. Based on previous findings, we assumed that when a patient with impaired swallowing function ingests food on admission, it remains in the oral cavity leading to an increase in the number of bacteria. Secondly, the pathogens that cause pneumonia colonize on the surface of the tongue and promote further colonization in the pharynx[20]. Aspiration of pharyngeal bacteria is the major infection route in the development of pneumonia[21]. Therefore, pneumonia continues owing to bacterial colonization from the tongue to the pharynx. Thirdly, in patients with aspiration pneumonia with reduced cough reflex[22], aspiration may continue. Therefore, in a patient with impaired swallowing function, the ingestion of food might increase bacterial colonization in the oral cavity, which could move and colonize within the pharynx resulting in a lack of therapeutic effects of SBT / ABPC and CTRX. Thus, oral care and fasting may be beneficial to prevent repeated aspiration to reduce ongoing pneumonia by reducing bacteria in the oral cavity.

In a survey conducted by general internal physicians and respiratory specialists on fasting as a strategy to treat aspiration pneumonia, 89.4% of the clinicians recommended temporary fasting[23]. However, no studies have reported the benefits of fasting on admission. To the best of our knowledge, this is the first study to demonstrate that no restriction of diet on admission on admission in patients with aspiration pneumonia affected the therapeutic efficacy of antibiotic treatment. Our results strongly suggest that it might be necessary to restrict the diet of patients with aspiration pneumonia at admission and evaluate their swallowing function before resuming their diet.

The risk of treatment failure increased 1.81-fold in patients with a history of hospitalization due to aspiration pneumonia. An increased risk of treatment failure may be associated with a history of antibiotic treatment. If there was a history of hospitalization due to aspiration pneumonia, the patients might have received antibiotic treatment. The use of broad-spectrum antibiotics for more than 2 days within the previous 90 days carried an increased risk of developing drug-resistant pathogens[9]. It is, therefore, likely that patients with a history of hospitalization due to aspiration pneumonia might have a reduced response to SBT / ABPC or CTRX. If patients are previously treated with antibiotics for aspiration pneumonia, broad-spectrum antibiotics should be recommended as initial antibiotic treatment. This study aimed to investigate the risk factors of antibiotic treatment failure, other than those related to drug-resistant pathogens. However, the risk factor for drug-resistant pathogens was extracted. The reason was that some patients in this study presented with risk factors related to drug-resistant pathogens. Therefore, a history of hospitalization due to aspiration pneumonia might be associated with drug-resistant pathogens.

The risk of treatment failure increased 1.37-fold in

patients with a higher level of severity of pneumonia. This was possibly owing to the worsening of the systemic dysfunction caused by an increase in the severity of pneumonia, progressing it to a state that could not be improved using antibiotic treatment. This study used the A-DROP score to assess the severity of pneumonia. It has been previously reported that the survival rates in patients with mild, moderate, severe, and very severe pneumonia classified using A-DROP scores were 100%, 90.5%, 82.8%, and 71.7%, respectively[24], suggesting that patients with higher A-DROP scores have extremely poor general conditions and poor prognosis. In addition, as the components of A-DROP include dehydration and respiratory status, patients with increased severity of pneumonia have worsened dehydration and respiratory status. Therefore, in addition to antibiotic treatment, systemic management such as water and respiratory management might be necessary during the initial treatment of patients with severe aspiration pneumonia.

The risk of treatment failure was increased by 1.26-fold with a 5 mg/dl increase in CRP. CRP is a marker of inflammation and may correlate with the spread of inflamed tissue in the lungs. Chest radiography findings have demonstrated that the inflammation in pneumonia increases with the increase in the width of the infiltrated area in the lung[25]. Therefore, the inflammation of the lung tissue might be widespread when the CRP levels are high. Therefore, it is considered that patients with high CRP levels had strong lung tissue inflammation and, therefore, did not respond to SBT / ABPC or CTRX.

Although drugs causing an increased risk of aspiration pneumonia have been reported previously[26], there are no reports on the association between medications at admission and the risk factors for antibiotic treatment failure in patients with aspiration pneumonia. Therefore, we investigated whether the medications at admission were associated with failure of initial antibiotic treatment for aspiration pneumonia. The administration of urinary disturbance agents other than overactive bladder agents at the time of hospitalization resulted in a 2.56-fold increase in the risk of treatment failure. Dry mouth is an adverse reaction of urinary disturbance agents other than overactive bladder agents. Previous studies have shown that the presence of dry mouth significantly increases the incidence of aspiration pneumonia[27], and carries a 2-fold higher risk of death owing to pneumonia[28]. Therefore, the administration of urinary disturbance agents other than overactive bladder agents might increase the risks of death from pneumonia and also increase the risk of antibiotic treatment failure. Older people tend to take multiple inappropriate medications inadvertently. If a patient is taking urinary disturbance agents other than overactive bladder agents at the time of hospitalization for aspiration pneumonia, discontinuation of the drug should be considered.

A limitation of this study is that the history of hospitalization due to aspiration pneumonia was recorded only if the patient was previously hospitalized in the surveyed hospital. The study did not include a history of hospitalization at other hospitals. Therefore, the rate of previous hospitalization due to aspiration pneumonia might be underreported.

## Conclusion

Our results suggested that no restriction of diet on admission, history of hospitalization due to aspiration pneumonia, severity of pneumonia, and increased CRP levels were risk factors associated with failure of initial antibiotic treatment in patients with aspiration pneumonia. These factors will be useful for determining an effective initial treatment strategy for patients with aspiration pneumonia. Furthermore, we expect that taking these factors into account will lead to an improvement in the management and treatment of patients with aspiration pneumonia.

### Conflict of interest disclosure

The authors have no conflicts of interest to declare for this manuscript.

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