Global Health & Medicine. 2025; 7(1):28-38.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2024.01087

Advantages of short-term antimicrobial treatment for pneumonia and aspiration pneumonia in older patients aged over 65: A nationwide inpatient database study

Kei Yamamoto[1,2], Shunsuke Edakubo[1,3], Kiyohide Fushimi[1,*]

[1] Health Policy and Informatics Section, Institute of Science Tokyo, Tokyo, Japan;
[2] Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan;
[3] Department of Anaesthesiology, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: The duration of antimicrobial therapy required to treat community-acquired pneumonia is often longer than expected, likely because of the high number of such inpatients in developed countries with aging populations. In this study, we evaluated the effects of short-term treatments for both pneumonia and aspiration pneumonia in older Japanese adults using the nation's inpatient database. Inpatients aged ≥ 65 years who were admitted to the hospital for pneumonia or aspiration pneumonia between April 1, 2018, and October 31, 2018, were included. We compared patients treated *via* intravenous antibiotics for 3-7 days to control patients treated with a similar regimen for 8-28 days, using inverse probability of treatment-weighted Cox regression. The primary outcome was relapse or readmission for pneumonia and death within 30 days after completing antimicrobial therapy. The secondary outcomes were average treatment effect for *Clostridioides difficile* infection (CDI), chest drainage, and length of hospital stay. The total number of eligible patients was 72,294. The hazard ratio for the primary outcome was 1.04 (95% confidence interval: 0.99-1.10). The mean length of hospital stay was shortened to 9.74 days (range, 9.34-10.1) in the short-term treatment group. The prevalence rates of CDI and chest drainage did not differ significantly between the short- and long-term treatment groups. We observed no statistically significant difference in clinical outcomes between the older adults with pneumonia including aspiration pneumonia who received short- *vs* long-term antimicrobial therapy.

***Keywords*:** aspiration pneumonia, short-term antimicrobial therapy, national inpatient database, older adults, antimicrobial administration

Introduction

Studies on the duration of antimicrobial treatment for various infectious diseases have been conducted recent years, and pneumonia is one of the most commonly studied infectious diseases. In a randomized controlled trial (RCT) of non-severe pneumonia, no significant difference was observed in the rate of re-hospitalization or mortality up to 30 days after treatment between the 3-day and 7-day antimicrobial treatment groups (*1*). In a cohort study of severe community-acquired pneumonia, no difference in mortality or re-hospitalization rate was observed between 7-day and 10-day or longer antimicrobial treatment, using propensity-score matching (*2*). Similarly to these studies, a meta-analysis of severe community-acquired pneumonia showed that there was no difference in the rate of re-hospitalization or mortality between treatment with antibiotics for < 7 days and treatment with antibiotics for 10 days or longer (*3*). Short-term antimicrobial therapy for community-acquired pneumonia may also contribute to controlling the spread of antimicrobial resistance. The guidelines of the Infectious Diseases Society/Respiratory Society of America recommend a minimum antimicrobial therapy duration of 5 days if there is a trend toward improvement within 2 days (*4*). However, in real-world settings, the median duration of treatment for community-acquired pneumonia ranges from 9.5 days in the United States (*5*) to 14 days in Japan (*6*). Moreover, the participants in previous RCTs were relatively young, in their 60s and 70s, and those with aspiration pneumonia (AP) were excluded (*1,2*). However, the median age of patients with moderate or severe community-acquired pneumonia in Japan is 80-85 years (*6*), meaning that physicians in the country may be reluctant to shift to short-term regimens.

Furthermore, there are no data regarding AP from Japan, although it is frequently diagnosed in older patients and may be useful as a reference to justify

shortening antibiotic treatment durations. Although some guidelines state that the duration of treatment for community-acquired AP should be 5-7 days (*7*), Japanese guidelines and manuals on antimicrobial use recommend 7-10 days (*8,9*). We used data from the Diagnosis Procedure Combination (DPC) database, which includes almost all of the acute-care beds and > 50% of all hospital beds in Japan, along with payment claims data for all inpatients from >1,500 participating hospitals (*10*), to determine the outcomes of short-term antimicrobial therapy for pneumonia, including AP, in older patients.

Patients and Methods

Study design and participants

This multicenter, retrospective, observational study used DPC data between April 1 and October 31, 2018. We excluded data after 2020, when the COVID-19 pandemic began, because the COVID-19 would affect the diagnosis of respiratory infections including pneumonia, and there were no major changes in the treatment policy for pneumonia after 2018. In order to avoid any modification due to viral diseases that spread on a large scale in winter, such as influenza, data analysis was conducted using data from April to October. We included patients aged ≥ 65 years who were hospitalized for the first time for pneumonia or AP, as coded by the International Classification of Diseases, 10th revision (ICD-10; Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*).

We excluded patients with pyothorax, pulmonary pyogenic disease, or bacteremia at the time of admission (as noted by ICD-10; Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*); those who had not begun taking antimicrobial agents within 2 days of admission to the hospital; those whose initial antimicrobial treatments were administered for < 3 or > 28 days; those who were discharged from the hospital before the end of antimicrobial therapy with a 2-day antimicrobial-free period (including cases of death); and those with scheduled hospital admissions.

Extracted information

The following information was extracted from the database: age, sex, body mass index (BMI), Japan Coma Scale score at admission, activities of daily living (ADL) assessment scores according to the Barthel index at admission (*11*), comorbidities at admission, length of hospitalization, discharge outcome, ambulance use, medications, procedures, and hospitalization-related piecework medical expenses. Information regarding underlying diseases was extracted if the following ICD-10 codes were present: diseases included in the Charlson comorbidity index (CCI) (*12*), diseases associated with dysphagia, and *Clostridioides difficile* infection (CDI).

The extracted information concerning medications included catecholamines taken within 3 days of admission and antimicrobials to treat pneumonia or AP at admission. Information was extracted for the following drugs if they were prescribed within 6 months following admission and up to 1 week prior to discharge: immunosuppressive agents, corticosteroids, molecular-targeted agents, antitumor agents, angiotensin-converting enzyme inhibitors, cilostazol, *Hange-koboku-to* (Kampo), antihistamines, antiemetic drugs (metoclopramide and domperidone), antipsychotic drugs included in the Screening Tool for Older Person's appropriate Prescriptions in Japanese (*13*), hypnotic sedatives, anxiolytics, antidepressants, and sulpiride.

The inpatient procedures included tabulated receipt processing codes for hemodialysis and nasal nutrition on prior hospitalization within 6 months. Data regarding oxygen administration, high-flow therapy, and ventilator use were collected at administration (Figure 1).

Definitions

The following diseases were defined as being associated with dysphagia: cerebrovascular disease, dementia, Parkinson's disease, Parkinson's syndrome, myofascial junction diseases, cranial nerve palsy, brainstem encephalitis, hyperthyroidism, systemic amyloidosis, Wilson's disease, Arnold-Chiari malformation, esophageal stenosis, esophageal achalasia, dysphagia, and vocal cord paralysis. State of consciousness was assessed in the order of 0, 1, 2, 3, 10, 20, 30, 100, 200, and 300 on the Japan Coma Scale (*14*). Each order was then replaced by 0-9, respectively. The short-term treatment group included patients who received antimicrobial agents for 3-7 days, whereas the longer treatment group included those who received antimicrobial agents for 8-28 days. Antimicrobials were divided according to the antimicrobial spectrum into anti-anaerobic, antipseudomonal, anti-methicillin-resistant *Staphylococcus aureus,* and other antimicrobial agents. Treatment duration was defined by the end of treatment, with 2 consecutive days where no antimicrobial agents were administered.

Outcomes

The primary outcome was relapse or death within 30 days after the completion of antimicrobial therapy. Relapse was defined as oxygen administration on the day when antimicrobials were resumed or readmission to the hospital for pneumonia or AP.

The secondary outcomes were hospitalization duration, rate of chest drainage implementation, and

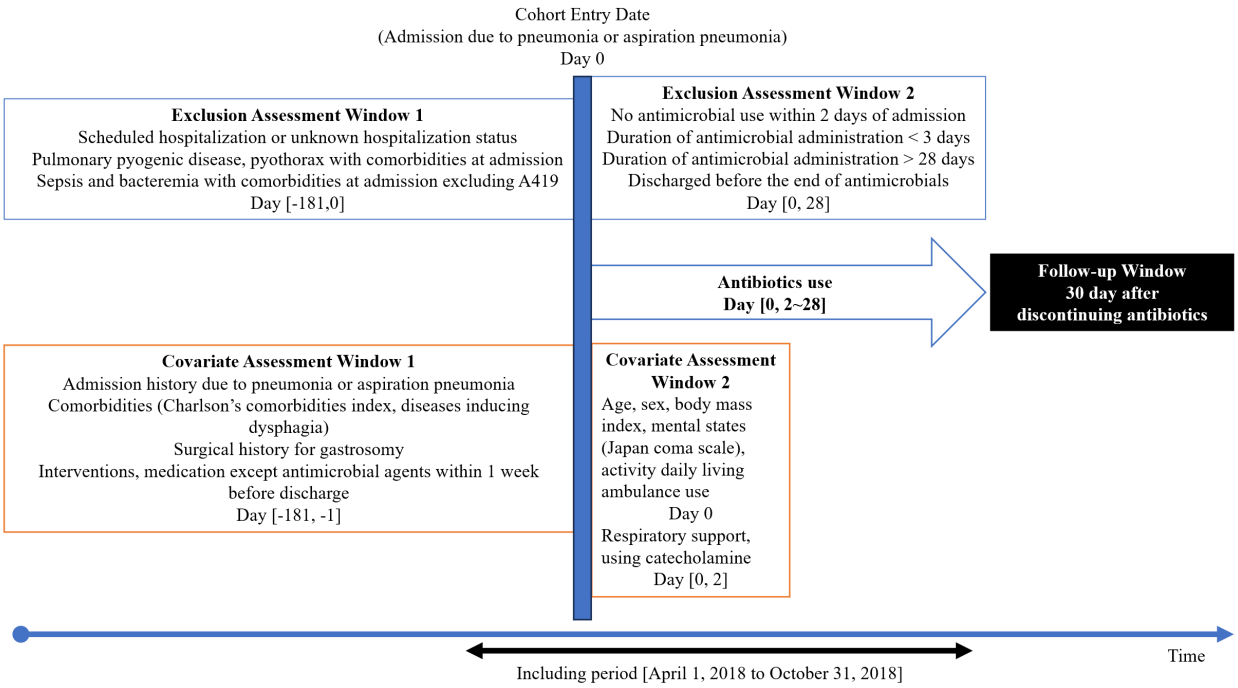

Figure 1. Schematic representation of patient cohort recruitment and covariate sampling processes.

rate of CDI complications following the termination of antimicrobial therapy. Cases were considered complicated by CDI if oral vancomycin, fidaxomicin, or bezlotoxumab were used after the initial antibiotic therapy course was completed or if metronidazole was used after the end of the initial antibiotic regimen and CDI has been noted as a comorbidity.

Statistical analysis

Assuming random missing values, a propensity score for the treatment was calculated after processing the missing values using multiple imputations with chained equations. Following imputation, the primary outcome was subjected to Cox regression after inverse probability of treatment weighting (IPTW). The average treatment effect (ATE) was calculated for each secondary outcome. Propensity score estimates were calculated using a logistic regression model with the following covariates: age, sex, BMI, state of consciousness, ambulance use, ADL assessment score, CCI, comorbidities involving dysphagia, hemodialysis, use of medications that may affect swallowing, use of medications associated with immune suppression, initial antimicrobial agents and combination antimicrobial therapy, nasal tube feeding, surgical history of gastrostomy, admission history for pneumonia or AP, use of advanced respiratory support therapy (*e.g.*, oxygen administration, high-flow therapy, or the use of a ventilator), and the administration of catecholamines within 3 days of admission. To balance the evaluation, absolute standardized mean difference (ASD) values of < 0.10 were considered evaluable. Subgroup analysis was performed according to age group (< 75, 75-89, and ≥ 90 years), oral antibiotics during initial therapy, oral antibiotics on the final prescription, and discharge to another hospital. A *p*-value less than 0.05 was considered statistically significant.

Sensitivity analyses were performed as follows: *i*) the primary outcome was changed to restarting antimicrobials without the use of an oxygen supply, and *ii*) the hazard ratio (HR) was calculated using IPTW Cox regression analysis with death within 30 days of admission as the outcome — including patients who were excluded from the main analysis because their completion of antimicrobial therapy was not confirmed. All statistical analyses were performed using R version 4.3.0 (R Core Team 2023, Vienna, Austria). Multiple imputations *via* chained equations were performed for 20 imputed datasets with 15 iterations through classification and regression tree approaches using the R package "mice". IPTW was performed using the R package "weightthem". A Kaplan–Meier survival curve was created using the "adjustedCurves" R package.

Ethics approval statement

The study was conducted in accordance with the principles of the Declaration of Helsinki, and was approved by the Institutional Review Board of Tokyo Medical and Dental University (M2000-788-23; March 2021). The requirement for informed consent was waived owing to the use of anonymized retrospective data.

Results

Of the 119,564 initially eligible patients, 47,270 met the exclusion criteria, resulting in 72,294 eligible patients across 1,795 institutions. Only 141 facilities treated > 50% of their patients with short-term antibiotic courses (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*). From these facilities, 22,569 patients were included in the short-term treatment group, and 49,725 were included in the long-term treatment group (Figure 2). The mean duration of antimicrobial therapy was 10.3 ± 4.6 days, with values of 5.9 ± 1.2 and 12.2 ± 4.2 in the short- and long-term treatment groups, respectively. The mean patient age was 84.0 ± 8.0 years, and 46.4% were female (Table 1). The mean Charlson's comorbidity index was 1.57 ± 1.59, and the underlying disease had an ASD < 0.1 in both treatment groups (Table 1). The level of respiratory support within 3 days of hospitalization was higher in the long-term treatment group vs the short-term one. The initial use of antipseudomonal antibiotics was slightly higher in the long-term treatment group than in the short-term one. The average length of stay after discontinuing antimicrobial agents was longer for the long-term group (20.8 days) than for the short-term one (16.2 days). The overall crude number of primary outcomes (*i.e.*, relapse and death) was 10,356 (14.3%), which was higher in the long-term treatment group (15.5%) than in the short-term one (11.6%; Table 2). The HR of the primary outcome within 30 days following the completion of antimicrobial therapy without IPTW was 1.11 (95% confidence interval [CI]: 1.06-1.16), and the Kaplan–Meier survival curve indicated a worse prognosis in the long-term treatment group (Figure 3A). A log-log plot of the proportional hazard is shown in Supplemental Figure S2A (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*). The average cost per hospitalization was 1,059,773 ± 861,678 JPY, which was significantly higher in the long-term treatment group (1,177,023 JPY) than in the short-term one (801,441 JPY).

After multiple imputations, the convergence and distribution of the assignments were confirmed (Supplemental Figure S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*). After IPTW, the balance assessment showed that the ASD values were <0.1 for all covariates (Figure 4; Supplemental Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*). The HR of the primary outcome within 30 days following antimicrobial therapy completion was 0.99 (95% CI: 0.95-1.04), and the Kaplan–Meier survival curve indicated a similar prognosis between the short- and long-term treatment groups (Figure 3B). Regarding ATE, we found no significant differences in the proportion of chest drainage implementations and CDI complications between the two groups at 0.01% (95% CI: –0.06 to 0.07) and 0.07% (95% CI: –0.03 to 0.17), respectively. No significant differences were observed in the HRs for death and relapse (Table 2). Regarding length of hospital stay, the ATE for short-term treatment was –9.65 days (95% CI: –10.05 to –9.25). In our subgroup analysis, the primary outcome

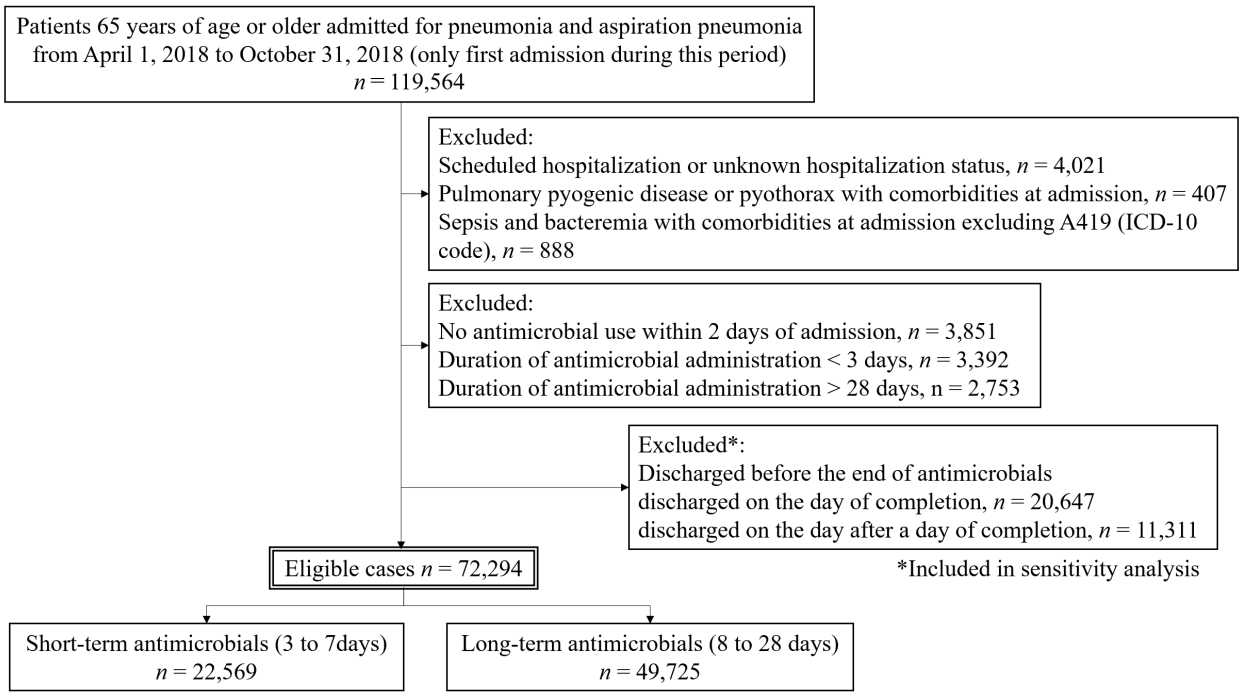

Figure 2. Flowchart of the study procedure.

Table 1. Characteristics of patients admitted with pneumonia and aspiration pneumonia

Characteristics	All	Short-term treatment	Long-term treatment	ASD
n	72,294	22,569	49,725	
Age, years (mean [SD])	83.97 (7.96)	83.89 (8.03)	84.01 (7.93)	0.015
Sex, female (%)	33,570 (46.4)	11,323 (50.2)	22,247 (44.7)	0.109
Body mass index (mean [SD])	19.90 (3.92)	20.12 (3.98)	19.80 (3.89)	0.08
Missing value	8,151 (11.2)	2,439 (10.8)	5,712 (11.5)	
Japan coma scale (mean [SD])*	1.11 (1.82)	1.02 (1.73)	1.15 (1.86)	0.069
ADL assessment score				
Feeding (%)				0.12
unable	32,359 (44.8)	9,353 (41.4)	23,006 (46.3)	
needs help cutting, spreading butter, *etc.*, or requires modified diet	15,396 (21.3)	5,060 (22.4)	10,336 (20.8)	
independent	20,994 (29.0)	7,198 (31.9)	13,796 (27.7)	
missing value	3,545 (4.9)	958 (4.2)	2,587 (5.2)	
Transfers (bed to chair and back) (%)				0.122
unable, no sitting balance	37,655 (52.1)	10,888 (48.2)	26,767 (53.8)	
major help (one or two people, physical), can sit	5,747 (7.9)	1,806 (8.0)	3,941 (7.9)	
minor help (verbal or physical)	14,972 (20.7)	5,084 (22.5)	9,888 (19.9)	
independent	12,584 (17.4)	4,401 (19.5)	8,183 (16.5)	
missing value	1,336 (1.8)	390 (1.7)	946 (1.9)	
Grooming (%)				0.084
needs to help with personal care	52,835 (73.1)	16,006 (70.9)	36,829 (74.1)	
independent face/hair/teeth/shaving (implements provided)	17,203 (23.8)	5,923 (26.2)	11,280 (22.7)	
missing value	2,256 (3.1)	640 (2.8)	1,616 (3.2)	
Getting on and off toilet (%)				0.118
dependent	42,044 (58.2)	12,260 (54.3)	29,784 (59.9)	
needs some help, but can do something alone	14,282 (19.8)	4,830 (21.4)	9,452 (19.0)	
independent (on and off, dressing, wiping)	14,416 (19.9)	5,021 (22.2)	9,395 (18.9)	
missing value	1,552 (2.1)	458 (2.0)	1,094 (2.2)	
Bathing self (%)				0.076
dependent	54,610 (75.5)	16,796 (74.4)	37,814 (76.0)	
independent (or in shower)	12,198 (16.9)	4,220 (18.7)	7,978 (16.0)	
missing value	5,486 (7.6)	1,553 (6.9)	3,933 (7.9)	
Walking on level surface (%)				0.116
immobile or < 50 yards	42,957 (59.4)	12,686 (56.2)	30,271 (60.9)	
wheelchair independent, including corners, > 50 yards	4,498 (6.2)	1,525 (6.8)	2,973 (6.0)	
walks with help of one person (verbal or physical) > 50 yards	8,213 (11.4)	2,816 (12.5)	5,397 (10.9)	
independent (but may use any aid; for example, stick) > 50 yards	12,672 (17.5)	4,432 (19.6)	8,240 (16.6)	
missing value	3,954 (5.5)	1,110 (4.9)	2,844 (5.7)	
Ascend and descend stairs (%)				0.094
unable	45,913 (63.5)	13,825 (61.3)	32,088 (64.5)	
needs help (verbal, physical, carrying aid)	7,843 (10.8)	2,705 (12.0)	5,138 (10.3)	
independent	11,168 (15.4)	3,876 (17.2)	7,292 (14.7)	
missing value	7,370 (10.2)	2,163 (9.6)	5,207 (10.5)	
Dressing (%)				0.109
dependent	42,765 (59.2)	12,562 (55.7)	30,203 (60.7)	
needs help but can do about half unaided	14,927 (20.6)	5,022 (22.3)	9,905 (19.9)	
independent (including doing buttons, zips, laces, *etc*.)	13,106 (18.1)	4,548 (20.2)	8,558 (17.2)	
missing value	1,496 (2.1)	437 (1.9)	1,059 (2.1)	
Controlling bowels (%)				0.114
incontinent (or needs to be given enemas)	40,262 (55.7)	11,778 (52.2)	28,484 (57.3)	
occasional accident	9,803 (13.6)	3,191 (14.1)	6,612 (13.3)	
continent	20,221 (28.0)	7,027 (31.1)	13,194 (26.5)	
missing value	2,008 (2.8)	573 (2.5)	1,435 (2.9)	
Controlling bladder (%)				0.114
incontinent, or catheterized and unable to manage alone	40,483 (56.0)	11,842 (52.5)	28,641 (57.6)	
occasional accident	10,114 (14.0)	3,311 (14.7)	6,803 (13.7)	
continent	19,817 (27.4)	6,882 (30.5)	12,935 (26.0)	
missing value	1,880 (2.6)	534 (2.4)	1,346 (2.7)	
Underlying diseases and medications for daily use				
Charlson comorbidity index (mean (SD))	1.57 (1.59)	1.55 (1.59)	1.58 (1.58)	0.016
Admission history of aspiration pneumonia (%)	3,368 (4.7)	894 (4.0)	2,028 (4.1)	0.006
Admission history of pneumonia (%)	2,922 (4.0)	999 (4.4)	2,369 (4.8)	0.016

*The state of consciousness is assessed in the order 0, 1, 2, 3, 10, 20, 30, 100, 200, and 300, whereas each of these in turn was replaced from 0 to 9. ASD, absolute standardized mean difference; SD, standard deviation; ADL, active daily living; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 1. Characteristics of patients admitted with pneumonia and aspiration pneumonia (continued)

Characteristics	All	Short-term treatment	Long-term treatment	ASD
Diseases with dysphagia (%)	31,661 (43.8)	9,771 (43.3)	21,890 (44.0)	0.015
Surgical history of gastrostomy (%)	342 (0.5)	99 (0.4)	243 (0.5)	0.007
Nasal tube feeding (%)	425 (0.6)	113 (0.5)	312 (0.6)	0.017
Hemodialysis (%)	30 (0.0)	7 (0.0)	23 (0.0)	0.008
Medications associated with immune suppression				
corticosteroid (%)	638 (0.9)	208 (0.9)	430 (0.9)	0.006
antitumor agents (%)	3 (0.0)	2 (0.0)	1 (0.0)	0.009
immunosuppressants (%)	8 (0.0)	2 (0.0)	6 (0.0)	0.003
Medications involved in swallowing				
angiotensin-converting enzyme inhibitors (%)	212 (0.3)	53 (0.2)	159 (0.3)	0.016
cilostazol (%)	6 (0.0)	3 (0.0)	3 (0.0)	0.007
antiemetic agents (metoclopramide and domperidone) (%)	8 (0.0)	4 (0.0)	4 (0.0)	0.009
psychiatric agents (%)	50 (0.1)	14 (0.1)	36 (0.1)	0.004
Hange-koboku-to (Kampo) (%)	3 (0.0)	0 (0.0)	3 (0.0)	0.011
About admission of pneumonia				
Aspiration pneumonia (%)	31,112 (43.0)	9,504 (42.1)	21,608 (43.5)	0.027
Ambulance use (%)	32,313 (44.7)	9,566 (42.4)	22,747 (45.7)	0.068
Most advanced respiratory support therapy within three days of admission (%)				0.246
none	26,113 (36.1)	9,887 (43.8)	16,226 (32.6)	
oxygen administration by oxygen canula or mask	43,794 (60.6)	12,229 (54.2)	31,565 (63.5)	
high-flow therapy	440 (0.6)	73 (0.3)	367 (0.7)	
mechanical ventilator support	1,947 (2.7)	380 (1.7)	1,567 (3.2)	
Catecholamine use within 3 days of admission(%)	1,524 (2.1)	264 (1.2)	1,260 (2.5)	0.101
Combination antimicrobial therapy (%)	6,971 (9.6)	1,859 (8.2)	5,112 (10.3)	0.071
Initial antimicrobial agents				
anti-pseudomonal agents (%)	19,648 (27.2)	5,067 (22.5)	14,581 (29.3)	0.157
anti-anaerobic agents (%)	50,782 (70.2)	14,796 (65.6)	35,986 (72.4)	0.148
anti-MRSA agents(%)	236 (0.3)	43 (0.2)	193 (0.4)	0.037
oral antibiotics (%)	11,001 (15.2)	1,147 (5.1)	2,374 (4.8)	0.014
Oral antibiotics for final administration (%)	3,521 (4.9)	3,050 (13.5)	7,951 (16.0)	0.07
Length of hospital stay, days (mean, [SD])	29.6 (28.8)	22.1 (23.4)	33.1 (30.3)	0.404

*The state of consciousness is assessed in the order 0, 1, 2, 3, 10, 20, 30, 100, 200, and 300, whereas each of these in turn was replaced from 0 to 9. ASD, absolute standardized mean difference; SD, standard deviation; ADL, active daily living; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 2. Outcomes associated with treatment duration for pneumonia by using inverse probability of treatment weighting Cox regression

Characteristics	Overall	Short-term treatment	Long-term treatment	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
a) Relapse as resumption of antimicrobial therapy and oxygen supply					
primary outcome (%)	10,356 (14.3)	2,626 (11.6)	7,730 (15.5)	1.11 (1.06 to 1.16)	0.99 (0.95 to 1.04)
relapse during hospitalization (%)	4,877 (6.7)	1,085 (4.8)	3,792 (7.6)	1.07 (1.01 to 1.13)	0.97 (0.92 to 1.03)
readmission due to pneumonia or aspiration pneumonia (%)	2,202 (3.0)	754 (3.3)	1,448 (2.9)		
death during hospitalization (%)	3,080 (4.3)	717 (3.2)	2,363 (4.8)	1.21 (1.12 to 1.32)	1.03 (0.95 to 1.12)
death during re-hospitalization (%)	197 (0.3)	70 (0.3)	127 (0.3)		
b) Relapse as resumption of antimicrobial therapy					
primary outcome (%)	15,343 (21.2)	3,801 (16.8)	11,542 (23.2)	1.17 (1.13 to 1.22)	1.08 (1.04 to 1.12)
relapse during hospitalization (%)	10,127 (14.0)	2,316 (10.3)	7,811 (15.7)	1.16 (1.12 to 1.21)	1.09 (1.05 to 1.14)
readmission due to pneumonia or aspiration pneumonia (%)	2,152 (3.0)	738 (3.3)	1,414 (2.8)		
death during hospitalization (%)	2,872 (4.0)	679 (3.0)	2,193 (4.4)	1.21 (1.12 to 1.32)	1.02 (0.94 to 1.11)
death during re-hospitalization (%)	192 (0.3)	68 (0.3)	124 (0.2)		

"Unadjusted HR" was calculated without inverse probability of treatment weighting, and "Adjusted HR" was calculated after inverse probability of treatment weighting. HR, hazard ratio; CI, confidence interval.

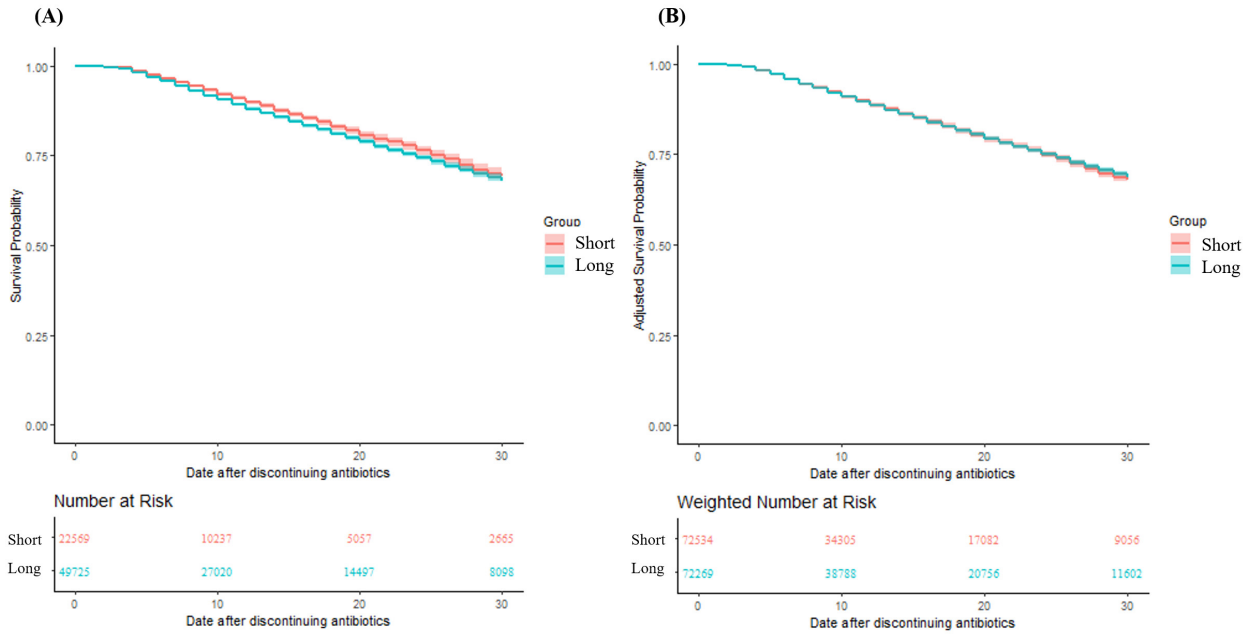

Figure 3. Kaplan–Meier survival curve for relapse and death. (A) Analysis after multiple imputations; **(B)** Analysis after multiple imputation and inverse probability of treatment weighting.

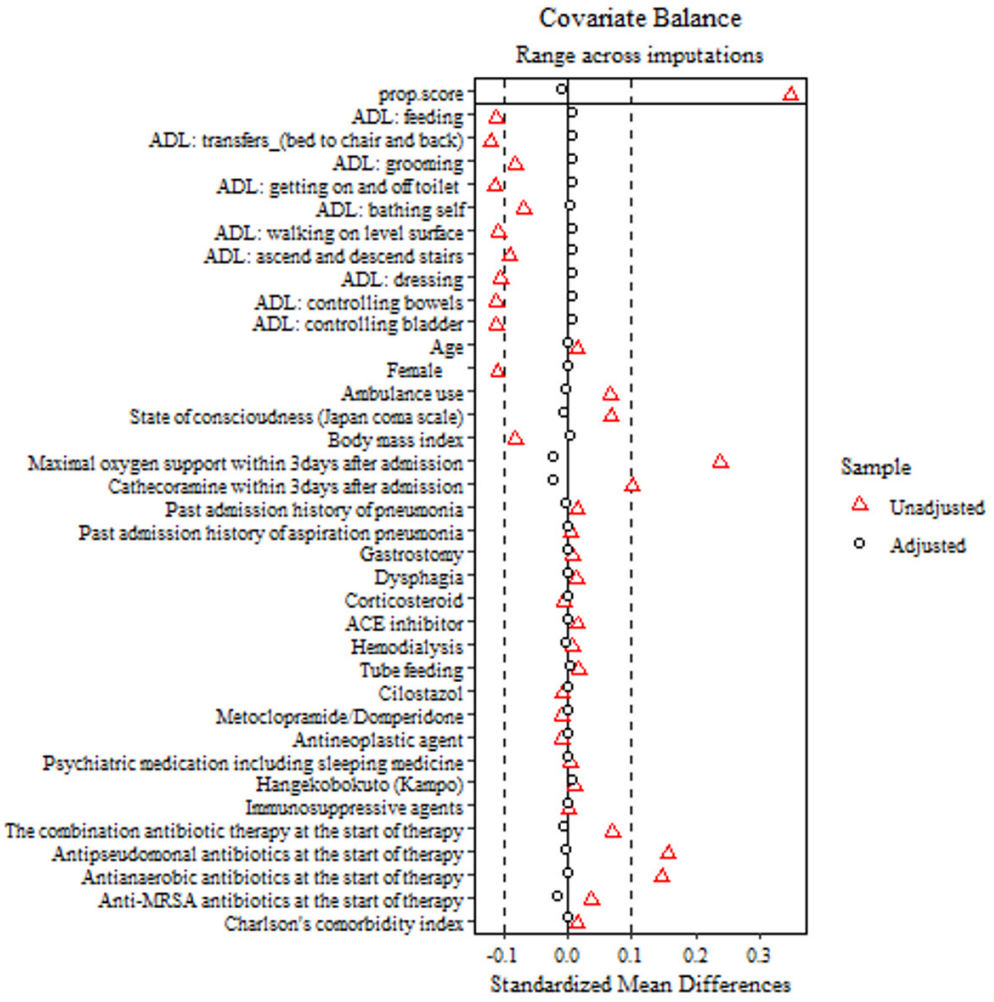

Figure 4. Balance evaluation after the inverse probability of treatment weighting. After multiple imputations for each covariate, standard mean differences are plotted before (red triangles) and after (white circles) inverse probability of treatment weighting. Values of < 0 indicate covariates that were more common in the control group, while those with values > 0 were more common in the short-term treatment group.

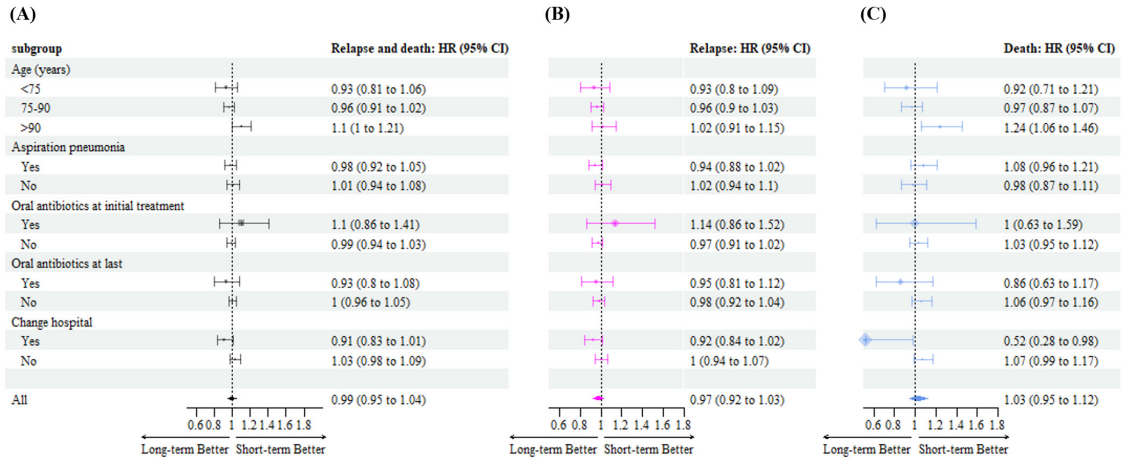

Figure 5. Subgroup analysis. (A) Primary outcome; **(B)** Relapse; **(C)** Death. Hazard ratios for outcomes after the inverse probability of treatment weighting in each subgroup are shown; whisker ends indicate 95% confidence intervals.

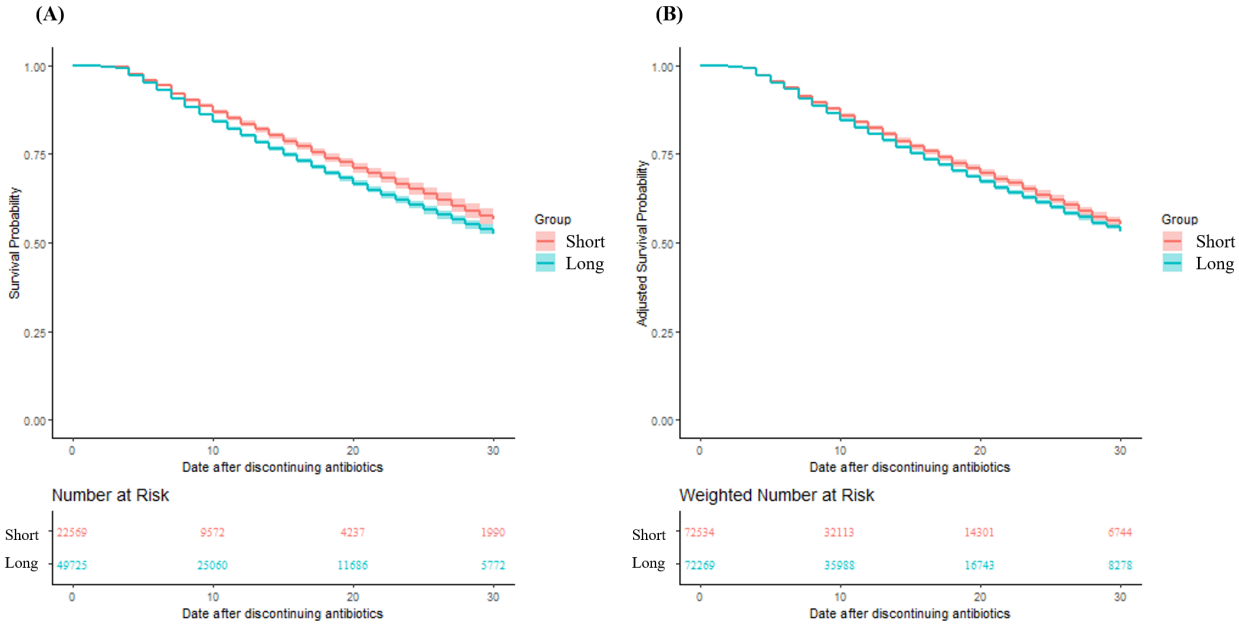

Figure 6. Kaplan–Meier survival curve for death and relapse (defined as resumption of antimicrobial therapy).

was slightly more common in the long-term treatment group for patients who initially received anti-anaerobic antimicrobials. No significant difference was observed in the prevalence of AP between the groups (Figure 5).

Sensitivity analysis

Our analysis with in-hospital pneumonia relapse, defined as all cases where antimicrobial agents were restarted, showed significant differences in the HRs for the primary outcome and relapse, at 1.08 (95% CI: 1.04-1.12) and 1.09 (95% CI: 1.05-1.14), respectively, but showed no significant difference for death (Table 2, Figure 6; Supplemental Figure S2B, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*).

To compare the duration of antimicrobial therapy, we had initially excluded > 30,000 patients for whom completion of antimicrobial therapy was not confirmed (Figure 2). We performed a second survival analysis with death at 30 days following admission as the outcome, with these patients re-included. Although the covariates were balanced *via* the same approach used in the main analysis (Supplemental Figure S4A, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*), the HR for death was 0.42 (95% CI: 0.40-0.43) — indicating a higher mortality rate in the short-term treatment group. The Kaplan–Meier survival curve showed that the occurrence of death within 7 days was higher in the short-term treatment group (Supplemental

Figure S4B, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*).

Discussion

Short-term antimicrobial treatment did not increase the risk of relapse or death at 30 days following completion of initial antibiotic therapy for pneumonia, including AP, in older Japanese patients aged ≥ 65 years who were indexed in the DPC database between April 1 and October 31, 2018. Many RCTs have focused on reducing the duration of antimicrobial therapy for various infectious diseases, including pneumonia. Our results were consistent with theirs; however, many of these studies included relatively younger patients (*i.e.*, aged between 40 and 79) (*1-3*). Few such studies have focused exclusively on older adults (*15*). The mean patient age in this study was 80 years, which is appropriate for pneumonia treatment in a country such as Japan with an aging population. Although the median duration of antimicrobial treatment was shorter than what was reported in a previous related study (*6*), it was nevertheless relatively long (≥ 10 days). A few centers in Japan still actively provide short-term antimicrobial treatments. Although short-term antimicrobial treatment did not decrease the occurrence of CDI in this study, it shortened the length of hospital stay. Before adjustment, there was an average difference of ~300,000 JPY between our treatment groups regarding medical costs related to hospitalization. Although the cost difference is expected to be smaller when illness severity and other factors are accounted for, shortening the duration of antimicrobial treatment may reduce medical costs, as has been previously reported (*3*).

In this study, because the timing of pneumonia relapse could not be determined from the data, re-administration of antimicrobials and oxygenation was defined as relapse. Because hypoxemia was found in 90% of the patients with AP who required hospitalization (*16*) and in ~60% of those with healthcare-associated pneumonia (*17*), we considered the need for re-administration of antimicrobials and oxygen to represent a more appropriate indicator of relapse than antimicrobial re-administration alone. Our sensitivity analysis examining only the re-initiation of antimicrobials determined that relapse was more frequent in the long-term treatment group. This group also had a longer average hospital stay and was at a higher risk of developing common nosocomial infections such as urinary tract infections (UTIs), surgical site infections, and catheter-related bloodstream infections (*18*). Bacteremic UTI is occasionally associated with respiratory symptoms, which can be difficult to distinguish from pneumonia in ~10% of cases (*19*). These infectious diseases can be difficult to distinguish from pneumonia using this definition.

In one multicenter cohort study conducted in Japan, 625 of 677 (92%) patients with pneumonia and AP were hospitalized for treatment (*20*). Therefore, the results of our present study are likely representative of most older patients with these conditions. Cases of pneumonia that are treated using oral antimicrobial agents, without hospitalization, are typically milder than those requiring hospitalization, meaning that our present results may also be generalizable to outpatients. However, it remains unclear whether such a generalization is possible for patients with pneumonia or AP that occurs under similar conditions to healthcare-associated pneumonia (*17*), which has higher rates of both mortality and detection of antibiotic-resistant bacteria. Our results may nevertheless be generalizable to healthcare-associated AP because previous RCTs were not limited by administering short-term antibiotic treatments in cases of severe healthcare-associated pneumonia (*e.g.*, ventilator-associated pneumonia) (*21*).

This study has several key limitations. First, although we could not obtain information about race of patients, this study included older adults who were almost certainly Japanese. Therefore, it had limited generalizability for other races or in other health systems. Moreover, it was limited to a time when the effects of seasonal influenza and COVID-19, which are epidemic respiratory viral diseases, could be avoided, so it may be difficult to generalize to the current situation where sporadic outbreaks of COVID-19 occur or during the winter flu season.

Second, information regarding predictors of severity, such as vital signs and laboratory tests (*22*), was not available in the DPC database. Given that such determinants of severity were more prevalent in the long-term treatment group, the pneumonia severity determinant was considered an unmeasured confounder that could undermine the causal relationship. For example, elevated C-reactive protein level predicts complex pneumonia (such as pyothorax and pulmonary pyogenic disease), for which long-term antimicrobial therapy is preferred (*23,24*). Further, although hyponatremia, thrombocytopenia, alcohol abuse, and hypoalbuminemia have been reported to be associated with complex pneumonia (*25*), it was difficult to adjust such factors using DPC data. However, death and chest drainage — which is often performed in cases of complex pneumonia — were not more prevalent in the long-term treatment group. Given the absence of information regarding microbiological tests, the organisms responsible for the assessed pneumonia cases were unknown. *Pseudomonas aeruginosa* is known to represent a common cause of recurrent pneumonia (*3,26*); however, pneumonia and AP in older adults are typically caused by mixed infections of oral commensal bacteria, thereby excluding *P. aeruginosa* as a main causative organism (9.7%) (*27*). It was difficult to determine whether the type of antimicrobial agent selected and the dosage of the antimicrobial agent

were appropriate because the causative pathogens of pneumonia and accurate kidney function could not be acquired due to the limitations of the DPC data. It seems unlikely that the antimicrobial spectrum was less consistent in the long-term treatment group, as antimicrobials with activity against *Pseudomonas aeruginosa* and obligate anaerobes tended to be selected more frequently in the long-term treatment group, but this was not measured in the data. Therefore, their influence as unmeasured confounders in this study was considered negligible.

Third, antimicrobials administered before hospitalization were not adjusted for. Community-acquired pneumonia in Japan is administered to ~18% of patients before hospitalization (*20*). However, this information could not be captured in this study.

Fourth, this is a problem with the validation of the diagnosis (ICD-10). Although, in this study, the diagnosis is the disease that led to the patient being admitted to the hospital, a recent diagnostic validation study of pneumonia and AP using the DPC database revealed that AP had low sensitivity and positive predictive value (*28*). However, that study had a small sample size in AP and the sample was difficult to assess. The sensitivity and positive predictive value reported by the study for pneumonia were 63.0% and 73.0%, respectively (*28*), which is comparable to what has been reported in other similar database studies (*29*). Although there was no significant difference in the adjusted hazard ratio for AP and pneumonia in the stratified analysis, this was a limitation because the diagnosis of AP was included in many cases.

Finally, the indicators for assessing the patients' responses to pneumonia treatment, which typically determine treatment durations in general situations or clinical trials (*4*), could not be tracked using this database. The duration of antibiotic treatment may have been prolonged because of poor clinical progress in a few of the patients who received short-term treatment and vice-versa. However, after adjusting for propensity scores, in-hospital mortality showed no bias toward the long-term treatment group, so we concluded that our adjustment was likely adequate.

In conclusion, although the effect of unadjusted confounding cannot be excluded, short-term antimicrobial therapy for older adults with pneumonia—including AP—did not increase the risk of pneumonia relapse or death in our cohort of older Japanese patients as in past reports of short-term treatments for pneumonia. Although it should be needed to re-evaluate this conclusion in future randomized prospective studies, short-term antibiotic therapy may be suitable for patients with complicated and severe pneumonia in real-world clinical practice if considered carefully.

Funding: This work was supported by a Grant-in-Aid for Research on Policy Planning and Evaluation from the Ministry of Health, Labour, and Welfare of Japan (grant number: 22AA2003), received by K. F.

Conflict of Interest: K.Y. has received research grants from Fujirebio Inc., Canon Medical Systems Corp., Sanyo Chemical Industries Ltd., CarbGeM Inc., Sysmex Corp., and Toyobo Co. Ltd., unrelated to this study. The other authors have no conflicts of interest to disclose.

References

1. Dinh A, Ropers J, Duran C, *et al.* Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): A double-blind, randomised, placebo-controlled, non-inferiority trial. Lancet. 2021; 397:1195-1203.
2. Choudhury G, Mandal P, Singanayagam A, Akram AR, Chalmers JD, Hill AT. Seven-day antibiotic courses have similar efficacy to prolonged courses in severe community-acquired pneumonia — a propensity-adjusted analysis. Clin Microbiol Infect. 2011; 17:1852-1858.
3. Pugh R, Grant C, Cooke RP, Dempsey G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. Cochrane Database Syst Rev. 2015; 2015:CD007577.
4. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA, Griffin MR, Metersky ML, Musher DM, Restrepo MI, Whitney CG. Diagnosis and treatment of adults with community-acquired pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019; 200:e45-e67.
5. Yi SH, Hatfield KM, Baggs J, Hicks LA, Srinivasan A, Reddy S, Jernigan JA. Duration of antibiotic use among adults with uncomplicated community-acquired pneumonia requiring hospitalization in the United States. Clin Infect Dis. 2018; 66:1333-1341.
6. Kimura T, Ito M, Onozawa S. Switching from intravenous to oral antibiotics in hospitalized patients with community-acquired pneumonia: A real-world analysis 2010-2018. J Infect Chemother. 2020; 26:706-714.
7. Mandell LA, Niederman MS. Aspiration pneumonia. N Engl J Med. 2019; 380:651-663.
8. Gilbert DN, Chambers HF, Saag MS, *et al.* The Sanford Guide to Antimicrobial Therapy 2022. Sperryville, VA, USA: Antimicrobial Therapy, Inc; 2022.
9. Mikasa K, Aoki N, Aoki Y, *et al.* JAID/JSC Guidelines for the Treatment of Respiratory Infectious Diseases: The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy - The JAID/JSC Guide to Clinical Management of Infectious Disease/Guideline-preparing Committee Respiratory Infectious Disease WG. J Infect Chemother. 2016; 22:S1-S65.
10. Hayashida K, Murakami G, Matsuda S, Fushimi K. History and profile of diagnosis procedure combination (DPC): Development of a real data collection system for acute inpatient care in Japan. J Epidemiol. 2021; 31:1-11.
11. Mahoney FI, Barthel DW. Functional evaluation: The Barthel index. Md State Med J. 1965; 14:61-65.
12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity

in longitudinal studies: development and validation. J Chronic Dis. 1987; 40:373-383.
13. Kojima T, Mizukami K, Tomita N, *et al.* Screening tool for older persons' appropriate prescriptions for Japanese: Report of the Japan Geriatrics Society Working Group on "Guidelines for medical treatment and its safety in the elderly". Geriatr Gerontol Int. 2016; 16:983-1001.
14. Nakajima M, Okada Y, Sonoo T, Goto T. Development and validation of a novel method for converting the Japan Coma Scale to Glasgow Coma Scale. J Epidemiol. 2023; 33:531-535.
15. Shorr AF, Zadeikis N, Xiang JX, Tennenberg AM, Wes Ely E. A multicenter, randomized, double-blind, retrospective comparison of 5- and 10-day regimens of levofloxacin in a subgroup of patients aged > or =65 years with community-acquired pneumonia. Clin Ther. 2005; 27:1251-1259.
16. Suzuki J, Ikeda R, Kato K, *et al.* Characteristics of aspiration pneumonia patients in acute care hospitals: A multicenter, retrospective survey in Northern Japan. PLoS One. 2021; 16:e0254261.
17. Shindo Y, Sato S, Maruyama E, Ohashi T, Ogawa M, Hashimoto N, Imaizumi K, Sato T, Hasegawa Y. Health-care-associated pneumonia among hospitalized patients in a Japanese community hospital. Chest. 2009; 135:633-640.
18. Stewart S, Robertson C, Pan J, Kennedy S, Dancer S, Haahr L, Manoukian S, Mason H, Kavanagh K, Cook B, Reilly J. Epidemiology of healthcare-associated infection reported from a hospital-wide incidence study: considerations for infection prevention and control planning. J Hosp Infect. 2021; 114:10-22.
19. Denis E, Martis N, Guillouet-de Salvador F, Demonchy E, Degand N, Carles K, Roger PM. Bacteraemic urinary tract infections may mimic respiratory infections: a nested case-control study. Eur J Clin Microbiol Infect Dis. 2016; 35:1601-1605.
20. Morimoto K, Suzuki M, Ishifuji T, Yaegashi M, Asoh N, Hamashige N, Abe M, Aoshima M, Ariyoshi K; Adult Pneumonia Study Group-Japan (APSG-J). The burden and etiology of community-onset pneumonia in the aging Japanese population: a multicenter prospective study. PLoS One. 2015; 10:e0122247.
21. Mo Y, Booraphun S, Li AY, Domthong P, Kayastha G, Lau YH, Chetchotisakd P, Limmathurotsakul D, Tambyah PA, Cooper BS; REGARD-VAP investigators. Individualised, short-course antibiotic treatment versus usual long-course treatment for ventilator-associated pneumonia (REGARD-VAP): A multicentre, individually randomised, open-label, non-inferiority trial. Lancet Respir Med. 2024; 12:399-408.
22. Seo H, Cha SI, Lee WK, Park JE, Choi SH, Lee YH, Yoo SS, Lee SY, Lee J, Kim CH, Park JY. Prognostic factors in patients hospitalized with community-acquired aspiration pneumonia. J Infect Chemother. 2022; 28:47-53.
23. Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. Am J Med. 2008; 121:219-225.
24. Cillóniz C, Ewig S, Polverino E, Muñoz-Almagro C, Marco F, Gabarrús A, Menéndez R, Mensa J, Torres A. Pulmonary complications of pneumococcal community-acquired pneumonia: incidence, predictors, and outcomes. Clin Microbiol Infect. 2012; 18:1134-1142.
25. Chalmers JD, Singanayagam A, Murray MP, Scally C, Fawzi A, Hill AT. Risk factors for complicated parapneumonic effusion and empyema on presentation to hospital with community-acquired pneumonia. Thorax. 2009; 64:592-597.
26. Ishifuji T, Sando E, Kaneko N, Suzuki M, Kilgore PE, Ariyoshi K, Morimoto K, Hosokawa N, Yaegashi M, Aoshima M; Adult Pneumonia Study Group - Japan (APSG-J). Recurrent pneumonia among Japanese adults: Disease burden and risk factors. BMC Pulm Med. 2017; 17:12.
27. Hayashi M, Iwasaki T, Yamazaki Y, Takayasu H, Tateno H, Tazawa S, Kato E, Wakabayashi A, Yamaguchi F, Tsuchiya Y, Yamashita J, Takeda N, Matsukura S, Kokubu F. Clinical features and outcomes of aspiration pneumonia compared with non-aspiration pneumonia: A retrospective cohort study. J Infect Chemother. 2014; 20:436-442.
28. Awano N, Urushiyama H, Yamana H, Yokoyama A, Ando T, Izumo T, Inomata M, Ito Y, Jo T. Validity of diagnoses of respiratory diseases recorded in a Japanese administrative database. Respir Investig. 2023; 61:314-320.
29. Hanquet G, Theilacker C, Vietri J, Sepúlveda-Pachón I, Menon S, Gessner B, Begier E. Best practices for identifying hospitalized lower respiratory tract infections using administrative data: A systematic literature review of validation studies. Infect Dis Ther. 2024; 13:921-940.

Received November 19, 2024; Revised January 28, 2025; Accepted February 3, 2025.

Released online in J-STAGE as advance publication February 6, 2025.

**Address correspondence to*:
Kiyohide Fushimi, Health Policy and Informatics Section, Tokyo Medical and Dental University Graduate School (TMDU), 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan.
E-mail: kfushimi.hci@tmd.ac.jp