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Effectiveness of Ampicillin-Sulbactam Versus Ceftriaxone for the Initial Treatment of Community-Acquired Pneumonia in Older Adults: A Target Trial Emulation Study

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Background. Current guidelines for community-acquired pneumonia (CAP) include ampicillin-sulbactam as an initial treatment option, though they do not mandate routine coverage of anaerobic organisms. This study aimed to compare the effectiveness of ampicillin-sulbactam with that of ceftriaxone as initial treatment for CAP in older adults.

Methods. This study was conducted using the target trial emulation framework, using a nationwide Japanese database (May 2010–June 2023). The study included patients aged ≥65 years, admitted to Diagnosis Procedure Combination hospitals for CAP, who received either ampicillin-sulbactam or ceftriaxone as the initial treatment. The exposure group received ampicillin-sulbactam, while the control group received ceftriaxone, both on the day of hospitalization. The primary outcome was in-hospital mortality; the secondary outcome was the development of *Clostridioides difficile* infection during hospitalization.

Results. The study included 26 633 older patients hospitalized with CAP, with 14 906 receiving ampicillin-sulbactam and 11 727 receiving ceftriaxone as initial treatment. After inverse probability of treatment weighting, the ampicillin-sulbactam group was associated with a higher in-hospital mortality rate than the ceftriaxone group (10.5% vs 9.0%, respectively; adjusted risk difference, 1.5% [95% confidence interval, .7%–2.4%]; adjusted odds ratio, 1.19 [1.08–1.31]). The incidence of *C difficile* infection was numerically higher in the ampicillin-sulbactam group (0.6% vs 0.4%; adjusted risk difference, 0.2% [95% confidence interval, .0%–.4%]; adjusted odds ratio, 1.45 [.99–2.11]). These results were consistent among patients with risk factors for aspiration.

Conclusions. In older patients with CAP, initial treatment with ampicillin-sulbactam was associated with higher mortality compared to treatment with ceftriaxone.

Received 30 October 2024; editorial decision 27 February 2025; accepted 03 March 2025; published online 5 March 2025

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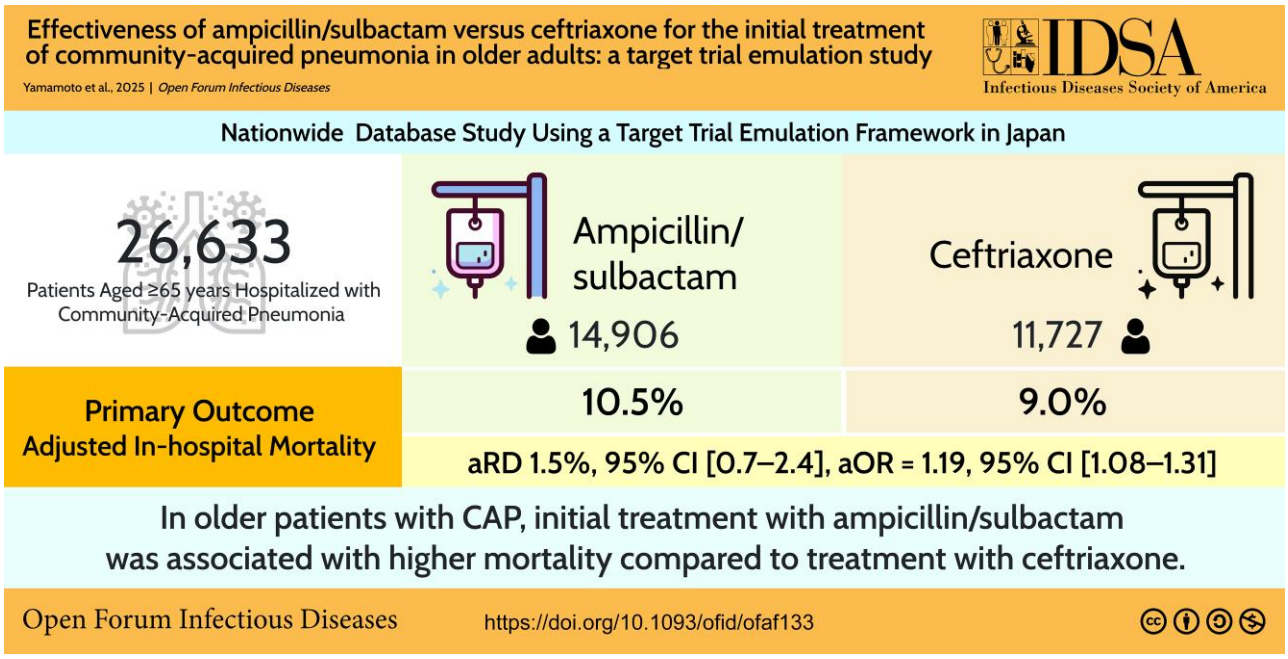
https://doi.org/10.1093/ofid/ofaf133

Graphical Abstract



This graphical abstract is also available at Tidbit: https://tidbitapp.io/tidbits/effectiveness-of-ampicillin-sulbactam-versus-ceftriaxone-for-the-initial-treatment-of-community-acquired-pneumonia-in-older-adults-a-target-trial-emulation-study?utm_campaign=tidbitlinkshare&utm_source=lO

Keywords. ampicillin/sulbactam; anaerobic bacteria; aspiration pneumonia; ceftriaxone; community-acquired pneumonia.

Community-acquired pneumonia (CAP) is a common and potentially life-threatening infection, especially in older adults [1]. Studies conducted in the 1970s revealed that anaerobic bacteria were isolated more frequently in aspiration pneumonia than in those conducted recently. Therefore, past practice guidelines recommended regimens covering anaerobic bacteria to treat aspiration pneumonia [2, 3]. Recent studies have detected fewer anaerobic bacteria in aspiration pneumonia [4–6]. A Canadian retrospective study using a clinical database compared antimicrobial agents with limited anaerobic coverage (mainly ceftriaxone) with those with extended anaerobic coverage (ceftriaxone plus metronidazole or moxifloxacin) for treating aspiration pneumonia. They found no difference in efficacy between the 2 groups. However, regimens with extended anaerobic coverage had a higher incidence of *Clostridioides difficile* infection (CDI) [7]. Current guidelines, as stated in the 2019 guideline and supported by the 2023 guideline, indicate that routine anaerobic bacterial coverage is unnecessary even in patients with suspected aspiration pneumonia unless the condition is suggestive of a lung abscess or empyema [8, 9]. However, anaerobic coverage is common, especially for aspiration pneumonia [10].

Ampicillin-sulbactam and ceftriaxone provide broad-spectrum coverage against the typical bacterial pathogens associated with CAP and are the initial empirical treatment options for hospitalized patients with CAP [8, 11]. However, their activity against anaerobic bacteria differs somewhat. Ampicillin-sulbactam provides broad coverage against anaerobes including *Peptostreptococcus*, *Fusobacterium*, *Prevotella*, and *Bacteroides* species, whereas ceftriaxone has limited activity, particularly against *Bacteroides* and *Prevotella* species [12]. A meta-analysis including 3 observational studies and 1 quasi–randomized controlled trial (RCT) comparing ampicillin-sulbactam with ceftriaxone as initial therapy for CAP could not determine the more effective therapy regarding death and clinical cure owing to the small sample size [13].

RCTs are the reference standard for causal inference. However, they are time consuming, expensive, and, in certain instances, infeasible. Target trial emulation represents a promising complement to RCTs. It uses existing data sources to emulate the design and analysis of a hypothetical target trial [14]. The target trial framework can reduce common biases in observational studies and enhance transparency regarding design and analytic decisions in real-world settings [14]. This study aimed to determine whether ampicillin-sulbactam is superior to ceftriaxone as an initial treatment for CAP in older patients. To achieve this, we used a target trial framework to analyze an anonymously processed database of medical information derived from electronic medical records (EMRs).

MATERIALS AND METHODS

Study Design and Data Sources

We emulated a hypothetical target trial in which older patients with CAP received ampicillin-sulbactam or ceftriaxone on the

day of hospitalization [14]. Supplementary Table 1 summarizes the key components of the protocol [14]. Supplementary Figure 1 depicts the study design diagram, which illustrates the temporality of key study parameters and data observability [15]. We used data from the Real World Data database, a nationwide Japanese database maintained by the Health, Clinic, and Education Information Evaluation Institute with support from Real World Data. The study period was between May 2010 and June 2023.

The database comprises anonymized patient data from EMRs, claims data, and Diagnosis Procedure Combination (DPC) data from approximately 240 medical institutions, including 26 million patients in Japan, as of 2022 [16]. The DPC is a case-mix classification system for acute inpatient care in Japan administered by the Ministry of Health, Labour, and Welfare. It is similar to the Diagnosis-Related Group classification system used in the United States [17–19]. Data were systematically extracted from the EMR of each medical institution using an automated process. Patients were deidentified and assigned unique identifiers within each medical institution. In accordance with local regulations, informed consent was waived, and an opt-out approach was used due to the use of anonymized data in the database. A previous study confirmed that the DPC database has a sensitivity of 63% and a specificity of 94.8% for bacterial pneumonia diagnosis [20].

This study adheres to the principles of the Declaration of Helsinki. In adherence to local regulations, ethical review was not required for the anonymized and de-identified patient data. This study complies with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement (Supplementary Table 2) [21].

Eligibility Criteria

We included patients aged ≥65 years admitted to DPC hospitals for CAP who received ampicillin-sulbactam or ceftriaxone as an initial treatment on the day of admission. CAP was defined as having a primary diagnosis or reason for admission of the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes J12, J13, J14, J15, J16, J18, or J690 and labeled as CAP in the DPC code. Only the first admission was included for patients with multiple admissions during the study period. Patients were excluded if they received both ampicillin-sulbactam and ceftriaxone on the day of admission.

Treatment Strategies and Assignment

The exposure group comprised patients who received ampicillin-sulbactam on the day of admission. The control group comprised patients who received ceftriaxone on the day of hospitalization. The 1-day period was selected as the duration of exposure to treatment to estimate the effectiveness of the initial antimicrobials, minimize the risk of combination antimicrobials serving as intermediate variables, and emulate clinical trials [22]. To determine the intention-to-treat effect, we maintained the grouping with the baseline treatment strategy, even if a change occurred in treatment. Supplementary Table 3 lists the definitions of the medications.

Eligible individuals were assigned at baseline to the treatment strategy that matched their data. To emulate randomization, we used the inverse probability of treatment weighting (IPTW) method based on the propensity score to balance the baseline characteristics of both groups.

Time Zero, Follow-up Period, and Outcomes

Emulation assumed that time zero was the day of admission. Emulation end at the date of death, hospital discharge, or transfer from an acute care unit to a long-term care unit in the same hospital, after which the patient is no longer covered by DPC; the transfer date was set as the discharge date. The primary outcome was all-cause in-hospital mortality. The secondary outcome was the development of CDI (*ICD-10* code A047) during hospitalization.

Covariates

We extracted the following data at admission a priori as potentially clinically meaningful confounders/prognostic factors based on clinical experience and previous studies. Supplementary Figure 2 depicts the directed acyclic graph, which guided the selection of covariates [23]. We selected the following variables as potential confounders: age, sex, admission year, admission department, Barthel Index, body mass index, nursing and healthcare-associated pneumonia (NHCAP), aspiration pneumonia, pneumonia severity classification (including dehydration, hypoxia, altered mental status, hypotension, immunocompromised, and severe pneumonia), the Charlson Comorbidity Index, laboratory results on admission (including serum sodium, serum urea nitrogen, creatinine, albumin, hematocrit, white blood cell count, arterial pH, arterial carbon dioxide, arterial oxygen, blood glucose, and total bilirubin levels) [11, 24–28], aspiration risk factors (including a history of cerebral infarction, dementia, psychiatric disorder, underweight, tube feeding, bedridden, and admission from a long-term care facility) [6], and the use of a high-flow nasal cannula or mechanical ventilation on the day of admission.

NHCAP is a pneumonia classification unique to Japan, introduced by the Japanese Respiratory Society in 2011. It includes patients who meet ≥1 of the following criteria: residing in a long-term care facility, recent hospitalization within 90 days, older or disabled individuals requiring care, or receipt of outpatient infusion therapy [11]. We included the following concomitant antimicrobials as confounding variables: macrolides, fluoroquinolones, tetracyclines, clindamycin, and metronidazole, all administered on the day of admission [29]. We used initial data in cases of patients with

multiple blood test results. Supplementary Tables 3–6 list the details and definitions of the variables.

Statistical Analysis

Categorical variables are shown as numbers and percentages and continuous variables as median and interquartile range (Supplementary Table 4). To emulate a target trial and estimate the effectiveness of initial antibiotic treatment with ampicillin-sulbactam versus ceftriaxone as an intention-to-treat effect [30], we used the IPTW method based on the propensity score and estimated odds ratios (ORs) [31, 32]. Using a logistic regression model, we estimated the propensity scores for receiving ampicillin-sulbactam based on confounders mentioned above.

The IPTW approach creates a pseudo-population in which the distribution of measured confounders is balanced across treatment groups. Weights were calculated as the inverse probability of receiving the treatment actually assigned, ensuring that each patient's contribution to the analysis is proportional to how likely they were to receive their observed treatment. This method reduces confounding by measured variables, mimicking the conditions of an RCT.

To evaluate the success of the weighting process, we examined the standardized mean differences (SMDs) for each covariate before and after weighting. The SMD is calculated as the difference in means between 2 groups divided by their pooled standard deviation, representing the difference in "standard deviation units." Unlike *P* values, which can be influenced by large sample sizes, SMDs highlight meaningful differences between groups. Balance was considered achieved if the absolute SMD was <0.1, which is a widely accepted threshold [33].

We also calculated an E-value to estimate the strength of association (ORs) that unmeasured confounders would need to have with both the exposure and outcome to fully explain the observed relationship [34, 35]. To provide context for the E-value, we calculated the observed covariate E-value and the observed bias effect, subsequently creating an observed bias plot (detailed in Supplementary Methods) [36]. To examine whether the results were robust when limited to populations at high risk of aspiration pneumonia, we performed similar analyses based on patients with ≥1 risk factor for aspiration as a subgroup analysis.

This database allowed for tracking patient visits to the same hospital even after discharge, provided that patients had subsequent visits to the same hospital. Therefore, for patients who survived and continued to receive care at the same institution, postdischarge survival could be confirmed. However, patients discharged within 90 days and without subsequent visits likely represent a population whose deaths could not be detected within the same hospital (ie, informative censoring). For example, severely ill patients might have been more likely to be transferred to other healthcare facilities and less likely to return to the original hospital during the follow-up period. To address this limitation, we conducted a sensitivity analysis by plotting cumulative incidence functions and using a Fine-Gray model. Using this approach, we estimated the subdistribution hazard ratio, which quantifies the relative incidence of death while accounting for competing risks, such as discharge within 90 days without subsequent visits. This metric considers the likelihood of death occurring within the follow-up period. The analysis adjusted for the same covariates as in the primary analysis using IPTW.

We set the α level at 5% and calculated ORs and 95% confidence intervals (CIs). We obtained the risk difference (RD) using the fitted logistic regression model to generate predicted risks for each patient in the dataset under the ampicillin-sulbactam and ceftriaxone scenarios [37]. Subsequently, we obtained the standard error by bootstrapping the entire procedure 1000 times [38]. We imputed missing data using multiple imputations with chained equations, assuming that data were missing at random [39, 40]. We defined a variance-covariance matrix by bootstrap standard errors for each imputed dataset and combined the results of the 50 imputed datasets using Rubin's rule (detailed in Supplementary Methods). We analyzed the data using R software, version 4.3.2 (R Foundation for Statistical Computing).

RESULTS

This emulated study included 26 633 older patients hospitalized with CAP, with 14 906 patients receiving ampicillin-sulbactam and 11 727 receiving ceftriaxone (Figure 1). Table 1 presents the baseline characteristics of the eligible patients. In the ampicillin-sulbactam group, 65.3% of patients were ≥81 years old, compared with 59.1% in the ceftriaxone group. The mean Barthel Index was lower in the ampicillin-sulbactam group (SMD, 0.19). The ampicillin-sulbactam group had a higher proportion of diagnosis codes for aspiration pneumonia (10.4% vs 3.5%; SMD, 0.27) and altered mental status (16.1% vs 11.7%; 0.14). Both groups had no patients with human immunodeficiency virus. The ampicillin-sulbactam group had a higher proportion of patients with ≥2 aspiration risk factors (33.9% vs 26.1%; SMD, 0.2). The concomitant use of macrolides (SMD, 0.13), tetracyclines (0.12), and clindamycin (0.14) was higher in the ceftriaxone group. The median length of hospital stay (LOS) (interquartile range) before adjustment was 13 (8–22) days in the ampicillin-sulbactam group and 11 (7–19) days in the ceftriaxone group (SMD, 0.1).

Figure 2 shows the maximum absolute SMDs for each covariate across the imputed datasets before and after IPTW. The absolute SMDs after IPTW were all <0.1, and the 2 groups were well balanced.

Outcomes

The unadjusted in-hospital mortality rates were 11.0% (1647 of 14 906) and 8.2% (958 of 11 727), respectively. The unadjusted incidences of CDI during hospitalization were 0.6% (89 of 14

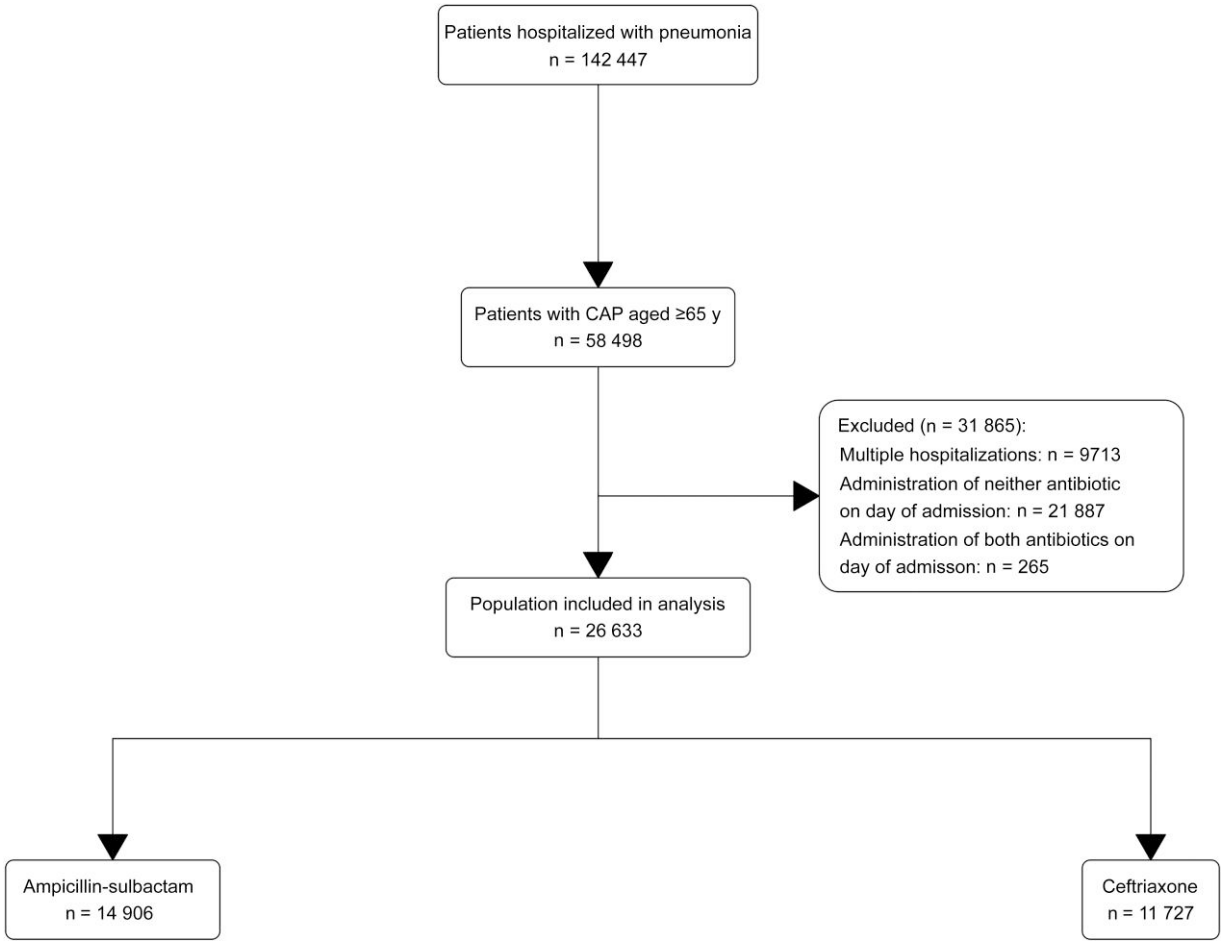


Figure 1. Study flowchart. Abbreviation: CAP, community-acquired pneumonia.

906) and 0.4% (50 of 11 727). In the IPTW-weighted sample, the ampicillin-sulbactam group was associated with a higher in-hospital mortality rate than the ceftriaxone group (10.5% vs 9.0%, respectively; RD, 1.5% [95% CI, .7%–2.4%]; OR, 1.19 [1.08–1.31]). The incidence of CDI was numerically higher with ampicillin-sulbactam (0.6% vs 0.4%; RD, 0.2% [95% CI, .0%–.4%]; OR, 1.45, [.99–2.11]), but this difference did not reach statistical significance (Table 2).

In a subgroup analysis of patients with ≥1 aspiration risk factor, the SMDs of both groups after IPTW were also well balanced at <0.1 (Supplementary Figure 3). The in-hospital mortality rate after IPTW was higher with ampicillin-sulbactam than with ceftriaxone (14.2% vs 11.5%, respectively; RD, 2.6% [95% CI. 1.5%–3.8%]; OR, 1.27 [1.14–1.40]). CDI was also more common with ampicillin-sulbactam in this subgroup (0.8% vs 0.5%; RD, 0.3% [95% CI, .0%–.6%]; OR, 1.52 [1.00–2.31]).

Sensitivity Analysis

We performed a survival analysis for 90-day all-cause mortality as a sensitivity analysis. Figure 3 illustrates the cumulative incidence of all-cause mortality after IPTW. Furthermore, using the Fine-Gray model after IPTW, we found an adjusted subdistribution hazard ratio for death within 90 days of 1.12 (95% CI, 1.01–1.25) in the ampicillin-sulbactam group compared to the ceftriaxone group. We also computed E-values to assess the potential for unmeasured confounding to explain the association of the main result (OR, 1.19 [95% CI, 1.08–1.31]). The E-value was 1.67 for the point estimate of the OR and 1.37 for the lower limit of the 95% CI. Supplementary Figure 4 presents the observed bias plot.

DISCUSSION

In this target trial emulation study of 26 633 patients, we observed that the initial use of ampicillin-sulbactam was associated with higher in-hospital mortality compared to the initial use of ceftriaxone in older patients admitted with CAP, including those with aspiration risk factors. In the subgroup with ≥1 aspiration risk factor, the use of ampicillin-sulbactam was associated with a higher risk of developing CDI during hospitalization. These findings suggest that ceftriaxone is preferable to

Table 1. Baseline Characteristics of Eligible Patients in Target Trial Emulation

Characteristic	Patients, No. (%)[a]		SMD
	Ampicillin-Sulbactam (n = 14 906)	Ceftriaxone (n = 11 727)	
Age group, y			
65–70	1178 (7.9)	1303 (11.1)	0.03
71–80	3993 (26.8)	3489 (29.8)	0.03
81–90	7298 (49.0)	5300 (45.2)	0.04
≥91	2437 (16.3)	1635 (13.9)	0.02
Female sex	6336 (42.5)	4878 (41.6)	0.02
Admission year			
2010–2014	992 (6.7)	604 (5.2)	0.02
2015	1580 (10.6)	1100 (9.4)	0.01
2016	1998 (13.4)	1484 (12.7)	0.01
2017	2245 (15.1)	1548 (13.2)	0.19
2018	2279 (15.3)	1828 (15.6)	0.00
2019	2232 (15.0)	2193 (18.7)	0.04
2020	1486 (10.0)	1457 (12.4)	0.02
2021	1109 (7.4)	851 (7.3)	0.00
2022	805 (5.4)	547 (4.7)	0.01
2023	180 (1.2)	115 (1.0)	0.00
Admission department			
Internal medicine	6611 (44.4)	5600 (47.8)	0.03
Respiratory	3834 (25.7)	2378 (20.3)	0.05
Cardiology	1493 (10.0)	1490 (12.7)	0.03
Other	2968 (19.9)	2259 (19.3)	0.01
BI, median (IQR)	35 (0–90)	50 (5–100)	0.19
BMI, median (IQR)[b]	20.0 (17.9–23.2)	20.9 (18.3–23.6)	0.11
BMI missing	1705 (11.4)	1203 (10.3)	…
NHCAP	4486 (30.1)	3053 (26.0)	0.09
Aspiration pneumonia	1543 (10.4)	407 (3.5)	0.27
Myocardial infarction	310 (2.1)	253 (2.2)	0.01
Congestive heart failure	3134 (21.0)	2709 (23.1)	0.05
Peripheral vascular disease	272 (1.8)	250 (2.1)	0.02
Cerebrovascular disease	1900 (12.7)	1218 (10.4)	0.07
Dementia	2508 (16.8)	1623 (13.8)	0.08
Chronic pulmonary disease	2598 (17.4)	2451 (20.9)	0.09
Rheumatic disease	296 (2.0)	321 (2.7)	0.05
Peptic ulcer disease	507 (3.4)	326 (2.8)	0.04
Mild liver disease	375 (2.5)	313 (2.7)	0.01
Diabetes without chronic complication	2242 (15.0)	1882 (16.0)	0.03
Diabetes with chronic complication	344 (2.3)	476 (4.1)	0.1
Hemiplegia or paraplegia	35 (0.2)	24 (0.2)	0.01
Renal disease	564 (3.8)	814 (6.9)	0.14
Any cancer (excluding skin)	555 (3.7)	344 (2.9)	0.04
Moderate or severe liver disease	18 (0.1)	8 (0.1)	0.02
Metastatic solid tumor	271 (1.8)	169 (1.4)	0.03
CCI, median (IQR)	1 (0–2)	1 (0–2)	0.06
Dehydration	6590 (44.2)	5466 (46.6)	0.05
Data missing	7 (0.0)	12 (0.1)	…
Hypoxia	6134 (41.2)	4859 (41.4)	0.01
Data missing	16 (0.1)	14 (0.1)	…
Altered mental status	2396 (16.1)	1370 (11.7)	0.14
Data missing	52 (0.3)	12 (0.1)	…
Hypotension	913 (6.3)	630 (5.4)	0.04
Data missing	9 (0.1)	7 (0.1)	…
Immunocompromise	2138 (14.3)	1728 (14.7)	0.02
Data missing	44 (0.3)	23 (0.2)	…

Table 1. Continued

Characteristic	Patients, No. (%)[a] Ampicillin-Sulbactam (n = 14 906)	Ceftriaxone (n = 11 727)	SMD
Severe pneumonia	2921 (19.6)	2380 (20.3)	0.03
Data missing	45 (0.3)	24 (0.2)	…
Serum sodium, median (IQR), mEq/L	140 (135–140)	137.4 (135–140)	0.02
Data missing	752 (5.0)	396 (3.4)	…
SUN, median (IQR), mg/dL	19.0 (14.3–27.0)	20.0 (14.7–28.9)	0.11
Data missing	615 (4.1)	321 (2.7)	…
Serum creatinine, median (IQR), mg/dL	0.8 (0.6–1.1)	0.9 (0.7–1.3)	0.2
Data missing	605 (4.1)	312 (2.7)	…
Serum albumin, median (IQR), g/L	3.2 (2.8–3.6)	3.3 (2.9–3.6)	0.15
Data missing	3032 (20.3)	2224 (19.0)	…
Hematocrit, median (IQR), %	36.0 (31.9–39.2)	35.8 (32.0–39.5)	0.03
Data missing	494 (3.3)	239 (2.0)	…
WBC count, median (IQR), cells/μL	10 000 (7300–13 585)	9900 (7100–13 300)	0.05
Data missing	655 (4.4)	914 (7.8)	…
Arterial pH, median (IQR)	7.40 (7.40–7.50)	7.40 (7.40–7.50))	0.05
Data missing	9057 (60.8)	7363 (62.8	…
Arterial CO_2, median (IQR), mm Hg	36.0 (32.3–42.0)	36.4 (32.3–41.8)	0.03
Data missing	9071 (60.9)	7368 (62.8)	…
Arterial O_2, median (IQR), mm Hg	68.0 (56.1–83.7)	67.0 (54.7–82.1)	0.07
Data missing	9342 (62.7)	7737 (66.0)	…
Blood glucose, median (IQR), mg/dL	130 (107–157)	127 (108–160)	0.03
Data missing	3457 (23.2)	2648 (22.6)	…
Total bilirubin, median (IQR), mg/dL	0.7 (0.5–1.0)	0.7 (0.5–1.0)	0.03
Data missing	1135 (7.6)	842 (7.2)	…
No. of aspiration risk factors			
0	5190 (34.8)	5020 (42.8)	0.2
1	4672 (31.3)	3646 (31.1)	
2	2742 (18.4)	1772 (15.1)	
3	1508 (10.1)	845 (7.2)	
4	618 (4.1)	354 (3.0)	
5	155 (1.0)	81 (0.7)	
6	20 (0.1)	9 (0.1)	
7	1 (0.0)	0 (0.0)	
High-flow nasal cannula	54 (0.4)	39 (0.3)	0.01
Mechanical ventilation	264 (1.8)	178 (1.5)	0.02
Macrolide use	881 (5.9)	1111 (9.5)	0.13
Fluoroquinolone use	418 (2.8)	446 (3.8)	0.06
Tetracycline use	152 (1.0)	317 (2.7)	0.12
Clindamycin use	16 (0.1)	146 (1.2)	0.14
Metronidazole use	3 (0.0)	6 (0.1)	0.02

Abbreviations: BI, Barthel Index; BMI, body mass index; CCI, Charlson Comorbidity Index; CO_2, carbon dioxide; IQR, interquartile range; NHCAP, nursing and healthcare-associated pneumonia; O_2, oxygen; SMD, standardized mean difference; SUN, serum urea nitrogen; WBC, white blood cell.

[a]Data represent no. (%) of patients unless otherwise specified.

[b]BMI calculated as weight in kilograms divided by height in meters squared.

ampicillin-sulbactam for the initial treatment of older patients with CAP.

Our results differ from those of previous studies on aspiration pneumonia, in which neither extended anaerobic coverage nor limited anaerobic coverage demonstrated a significant advantage [7, 13, 41]. One potential explanation for this discrepancy is that the previous studies, including the 2 meta-analyses, had insufficient sample sizes, with <1000 patients across both analyses. This likely resulted in a lack of statistical power to detect significant differences. In contrast, the absolute RD for mortality during hospitalization in our study was 1.5% (95% CI, .7%–2.4%), and we were able to detect this difference because of the large sample size. This difference corresponds to the number needed to treat 67 (42–143).

In the United States, the incidence of hospitalizations for CAP per 100 000 population is 1507 for those aged 65–74 years,

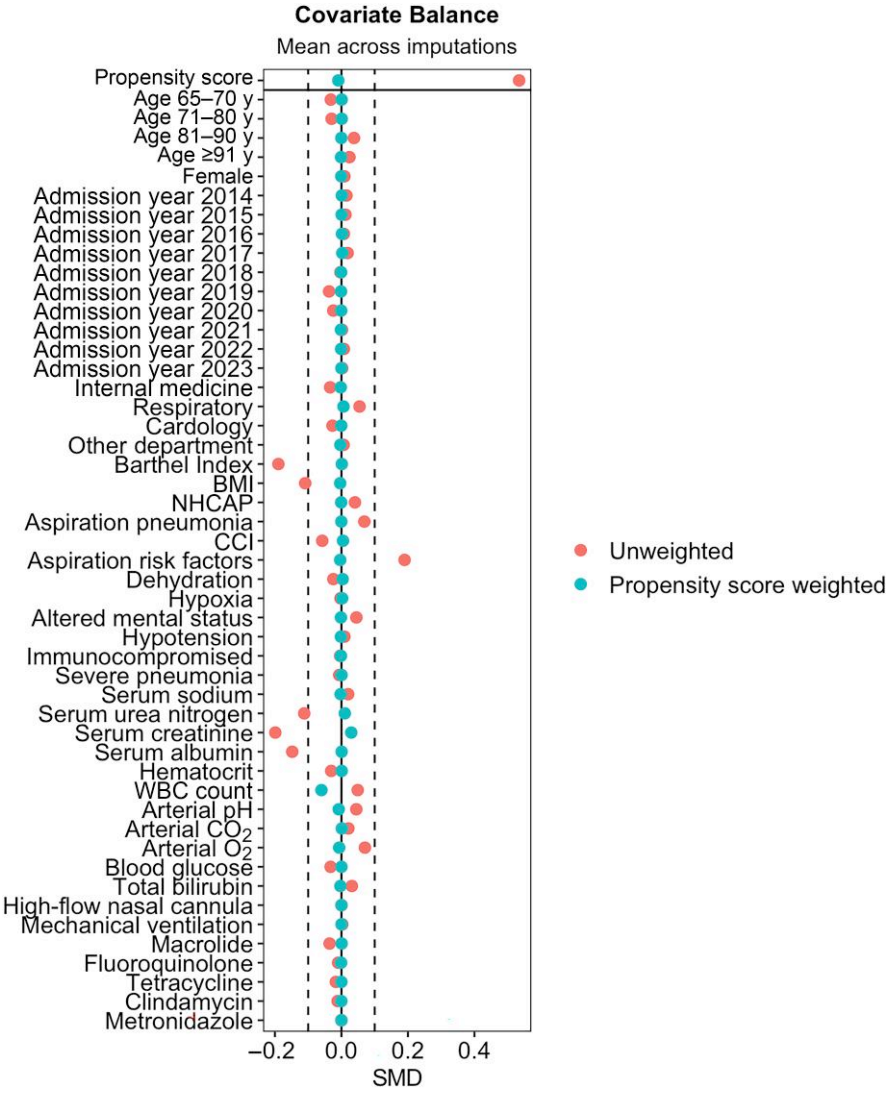


Figure 2. Love plot depicting standardized mean differences (SMDs) before and after inverse probability of treatment weighting (IPTW) of the whole cohort. Circlular dots indicate SMDs for each variable; dots located closer to the center line represent better balance. The dots representing propensity score weighted (after-IPTW) SMDs are <0.1 for all variables, suggesting that both groups are well balanced. Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CO_2, carbon dioxide; NHCAP, nursing and healthcare-associated pneumonia; O_2, oxygen; WBC, white blood cell.

Table 2. Main Results and Subgroup Analysis After Multiple Imputation

	Before Adjustment		After IPTW (95% CI)			
Main Result	Ampicillin-Sulbactam (n = 14 906)	Ceftriaxone (n = 11 727)	Ampicillin-Sulbactam (n = 13 506.32)	Ceftriaxone (n = 10 305.76)	Adjusted RD (95% CI), %	Adjusted OR (95% CI)
In-hospital mortality rate, %	11.0	8.2	10.5 (10.0–11.0)	9.0 (8.3–9.6)	1.5 (.7–2.4)	1.19 (1.08–1.31)
CDI, %	0.6	0.4	0.6 (0.5–0.8)	0.4 (0.3–0.5)	0.2 (.0–.4)	1.45 (.99–2.11)
Subgroup analysis[a]						
≥1 Aspiration risk factor	n = 9716	n = 6707	n = 8802.31	n = 5959.29	…	…
In-hospital mortality rate, %	14.4	11.2	14.2 (13.4–14.9) %	11.5 (10.7–12.3)	2.6 (1.5–3.8)	1.27 (1.14–1.40)
CDI, %	0.8	0.6	0.8 (0.6–1.0)	0.5 (0.4–0.7)	0.3 (.0–.6)	1.52 (1.00–2.31)

Abbreviations; CDI, *Clostridioides difficile* infection; CI, confidence interval; IPTW, inverse probability of treatment weighting; OR, odds ratio; RD, risk difference.

[a]The same analysis used in the main analysis was performed in patients with ≥1 risk factor for aspiration.

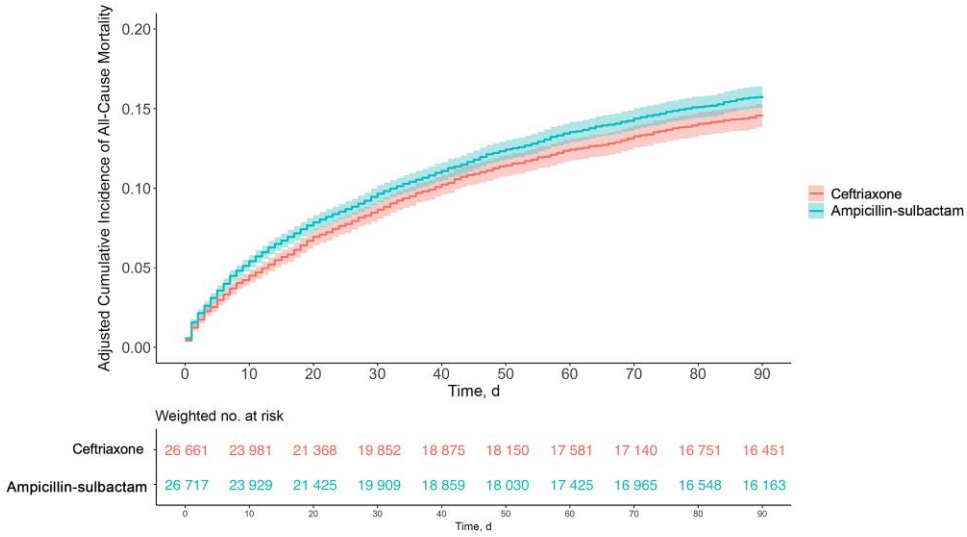


Figure 3. Ninety-day adjusted cumulative incidence of all-cause mortality after inverse probability of treatment weighting. Shaded areas represent 95% confidence intervals.

2205 for those aged 75–84 years, and 3951 for those aged ≥85 years [1]. Considering the disease burden of pneumonia in the older population, this difference cannot be ignored. Patients considered to have aspiration pneumonia in the past often had risk factors for macroaspiration, such as alcohol misuse disorder, illicit drug use, and seizure disorder. They were often associated with abscesses and lung necrosis. In contrast, patients with modern aspiration pneumonia include residents of long-term care facilities and older patients with cognitive dysfunction, tube feeding, and dysphagia [10]. The spectrum of patients may differ between the past and present. Physicians should avoid extensive anaerobic coverage when treating CAP in older adults unless there is clear involvement of anaerobic bacteria.

The pathophysiology of the higher mortality rates observed in the ampicillin-sulbactam group compared with the ceftriaxone group can be attributed to several factors. First, the results could be explained by the adverse effects of antimicrobials with broad anaerobic coverage on the microbiota in the respiratory and intestinal tracts. Previous reports have shown that administering antimicrobial agents with broad anaerobic coverage to critically ill patients or patients with sepsis not indicated for anaerobic coverage is associated with worse clinical outcomes [42–44]. Second, ceftriaxone is more potent activity against penicillin-resistant *Streptococcus pneumoniae,* β-lactamase–nonproducing ampicillin-resistant *Haemophilus influenzae*, and *Klebsiella pneumoniae* than ampicillin-sulbactam [12, 45]. In our study, approximately 30% of cases were classified as NHCAP, and there is a report indicating that *K pneumoniae* was detected in about 16% of NHCAP cases [45]. The difference in activity against gram-negative bacteria may partially explain the results of this study.

Third, in the subgroup with ≥1 risk factor for aspiration, the ampicillin-sulbactam group was associated with an increased risk of CDI compared with the ceftriaxone group. Although CDI may be unlikely to be the direct cause of death in most cases, it is plausible that the development of CDI led to a deterioration in overall condition, which may have partially and indirectly contributed to the increased mortality rate [46]. Fourth, according to a report by Teshome et al, de-escalation to β-lactam antibiotics with a lower spectrum score was associated with a reduced risk of acquiring new drug-resistant gram-negative bacteria in hospitalized patients with sepsis [47]. In this context, the spectrum score of ampicillin-sulbactam is 7, while that of ceftriaxone is 5, indicating that the risk of acquiring drug-resistant bacteria may have indirectly contributed to the observed increase in mortality rate in the ampicillin-sulbactam group.

Strengths and Limitations

Our study has several strengths. First, this large sample size of 26 633 patients provides robust statistical power, allowing for precise estimates. Second, a wide range of confounders were adjusted using rigorous epidemiological methods, ensuring that all covariates were well balanced between the 2 groups. Third, previous studies have focused on aspiration pneumonia [41], whereas this study focuses not only on aspiration pneumonia but also on pneumonia in the older population, which provides higher generalizability. Aspiration pneumonia accounts for approximately 60% of CAP cases requiring hospitalization and approximately 80% in patients aged >70 years [48]. Particularly, aspiration is involved in approximately 70% of older patients with pneumonia in, even in the absence of an obvious aspiration event [49]. Pneumonia in older adults is assumed to include an element of aspiration.

Our study has some potential limitations. First, as this is not an RCT, the influence of unmeasured confounding factors, especially confounding by indication, is unavoidable. The E-value measures the minimum strength of association that an unmeasured confounder would need to have with the exposure and outcome to explain the observed association. In this case, an E-value of 1.67 for the OR of 1.19 means that an unmeasured confounder must be associated with the exposure and outcome by a risk ratio of 1.67 each to explain the observed OR thoroughly. For the lower CI (1.08), an unmeasured confounder would require an risk ratio of 1.37 each to nullify the results. Based on the observed bias plot, the observed covariates have a smaller impact on the effect size than the hypothetical unmeasured confounder needed to explain the observed association (Supplementary Figure 4). Therefore, although unmeasured confounders may exist, their influence must be unusually large to invalidate the study findings [34–36]. Even if such unmeasured confounding eliminates the association, it neither indicates the superiority of ampicillin-sulbactam nor supports its continued use as the first choice for CAP in older adults. In the absence of an RCT demonstrating the benefit of anaerobic coverage, routine anaerobic coverage should be avoided in this population, according to current practice guidelines.

Second, the median LOS was 13 days in the ampicillin-sulbactam group and 11 days in the ceftriaxone group in our study, which is longer than the reported LOS of 6–10 days for hospitalized CAP in the United States [50], potentially affecting the generalizability of our findings. In Japan, a study on CAP and NHCAP documented median LOSs of 8 (IQR 6–14) days and 12 (IQR 9–21) days, respectively [51]. Another study reported a median LOS of 9 (IQR 7–15.5) days for CAP and 16 (IQR 10–35) days for NHCAP [52]. Since these reports were not limited to elderly populations, it is not surprising that the LOS in our study was somewhat longer. Differences in LOS across countries may reflect variations in healthcare systems. To account for this and address potential issues with generalizability, we conducted a sensitivity analysis using survival analysis, in addition to evaluating hospital-based mortality outcomes, to confirm the robustness of our findings.

Third, we were unable to include microbiological susceptibility data for the analysis. The proportion of gram-negative bacteria, such as *Escherichia coli* and *K pneumoniae*, among the causative pathogens could potentially influence the observed results.

Fourth, misclassification of disease codes might occur because the database is derived from administrative claims data. However, a validation study confirmed the high specificity of diagnosis of bacterial pneumonia in the DPC database [20]. On the other hand, the moderate sensitivity may affect the representativeness of the population. Finally, the study detected the incidence of CDI only during hospitalization, which may be an underestimate because CDI often occurs within 3 months after antimicrobial therapy [53].

In conclusion, our study revealed that ampicillin-sulbactam was associated with a higher in-hospital mortality rate than ceftriaxone in older patients with CAP, even in those with risk factors for aspiration. As recommended in current guidelines, antimicrobials with broad anaerobic coverage should be avoided as initial treatment for CAP in older adults unless anaerobic bacteria are involved, as in cases of empyema or lung abscess.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. This work was conducted as part of the Nippon Foundation–Osaka University Project for Infectious Disease Prevention. We thank Editage (www.editage.jp) for English-language editing.

Author contributions. S. Y., A. S., and Y. K. conceived and designed the study and drafted the manuscript. A.S. managed the database. S. Y. performed the data analysis. All authors confirmed the validity of the data analysis and interpreted the data; critically revised and approved the final version of the manuscript; consented to be accountable for all aspects of this study; and read and agreed to the published version of the manuscript.

Disclaimer. The funders played no role in the study design, execution, analyses, interpretation, or decision to submit the results.

Financial support. This work was supported by the Pfizer Health Research Foundation, which supported the cost of data acquisition.

Generative AI and AI-assisted technologies in the writing process. During the preparation of this work, the authors used ChatGPT (GPT-4o, by OpenAI) to enhance readability, proofread the English text, and assist in writing R code. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Data sharing statement. The datasets generated and/or analyzed during the current study are not publicly available due to the restrictions of Real World Data, but they are available from the corresponding author on reasonable request.

Potential conflicts of interest. A. S. received funding from the Pfizer Health Research Foundation. All other authors report no potential conflicts.

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