Preliminary Communication

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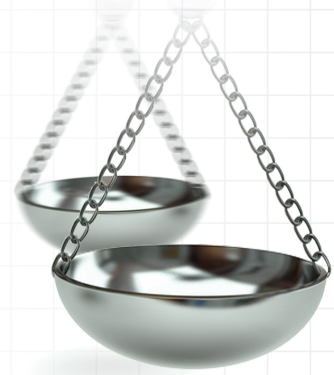

Journal of **Comparative Effectiveness Research**

Ceftriaxone versus ampicillin/sulbactam for the treatment of aspiration-associated pneumonia in adults

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Aim: To compare hospital mortality in patients with aspiration-associated pneumonia treated with ceftriaxone (CTRX) and in those treated with ampicillin/sulbactam (ABPC/SBT). **Methods:** From a Japanese multicentre observational study cohort of patients with pneumonia, those diagnosed with pneumonia and having at least one aspiration-related risk factor were selected. Propensity score-matching analysis was used to balance baseline characteristics of the participants and compare hospital mortality of patients treated with CTRX and those treated with ABPC/SBT. **Results:** Hospital mortality did not significantly differ between patients treated with CTRX and those treated with ABPC/SBT (6.6 vs 10.7%, risk difference -4.0, 95% CI [-9.4, 1.3]; p = 0.143). **Conclusion:** Further studies are needed to compare CTRX and ABPC/SBT treatments in patients with aspiration-associated pneumonia.

First draft submitted: 31 March 2019; Accepted for publication: 27 August 2019; Published online: 18 November 2019

Keywords: ampicillin/sulbactam • aspiration pneumonia • aspiration-associated pneumonia • ceftriaxone • propensity-score analysis

Pneumonia is the fourth leading cause of death worldwide [1]. It has been reported that aspiration pneumonia accounts for 5–15% of community-acquired pneumonia [2] and up to 30% of pneumonia related to stays in long-term care facilities [3]; the reported mortality rate is approximately 10% [4]. In developed countries, the incidence of aspiration pneumonia increases with age [5]. Given its high prevalence, the development of effective treatments for aspiration pneumonia is critical.

Standard antibiotic therapy for aspiration pneumonia is not well established [6–11]. *Streptococcus pneumoniae* and *Haemophilus influenzae* are the two most common aerobic isolates associated with community-acquired aspiration pneumonia [12]. Based on the interpretive criteria of the Clinical and Laboratory Standard Institute (CLSI), the Centers for Disease Control and Prevention (CDC) reported that approximately 4.3% of *S. pneumoniae* isolates were wholly or partially resistant to penicillin in the USA [13], whereas Japanese studies performed in 2012 categorized only 2.7% of *S. pneumoniae* as wholly or partially resistant to penicillin (based on Japan Nosocomial Infections Surveillance [JANIS] database, one of the largest databases maintained by the Japanese Ministry of Health, Labor and Welfare [MHLW]) [14]. However, the percentage of *S. pneumonia* isolates reported as partially or wholly resistant to penicillin could be higher (up to 12.6%) when the interpretive criteria of the European Committee on Antimicrobial Susceptibility Testing were used, showing more severe data [15], although datasets used for analysis in each report are not similar. In 2001, ceftriaxone (CTRX) was reported as being superior to

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ampicillin/sulbactam (ABPC/SBT) for the treatment of penicillin-resistant pneumococci, based on its estimated clinical efficacy and *in vitro* susceptibility [16]. However, the definition of pneumococcal resistance to penicillin was updated in 2008 [17]; to our knowledge, no subsequent studies have compared the effectiveness of these two antibiotics against penicillin-resistant pneumococci either *in vitro* or *in vivo*.

Additionally, *H. influenzae* is the second most common aerobic bacteria detected in cases of aspiration pneumonia. Regarding the treatment of *H. influenzae*-pneumonia, CTRX is superior to ABPC/SBT, particularly when comparing its *in vitro* activity against β-lactamase ampicillin-resistant pneumonias, which are the most common resistant types of pneumonia observed in Japan (40–50% of *H. influenzae*) [14,18,19].

Indeed, CTRX therapy has several advantages over ABPC/SBT therapy, including less frequent administration, no requirement for initial dose adjustment in accordance with reduced renal function, and ease of use in an outpatient treatment setting. Furthermore, CTRX can be used as an alternative therapy for patients who are allergic to penicillin [20]. However, CTRX does not target the full spectrum of oral anaerobes that are associated with aspiration pneumonia. In contrast, ABPC/SBT targets almost all of the anaerobes associated with aspiration pneumonia [21], exhibits activity against a narrower spectrum of Gram-negative rods, and is less susceptible to antimicrobial resistance development; thus, ABPC/SBT is usually the preferred treatment for aspiration pneumonia in Japan [22].

Although the role of anaerobic bacteria in aspiration pneumonia may be overemphasized, and CTRX is reported as a treatment option for aspiration pneumonia [3], there has not been a direct comparison of CTRX and ABPC/SBT therapies for treatment of aspiration pneumonia. Moreover, the definition of aspiration pneumonia is not consistent worldwide, and the concept of 'aspiration-associated pneumonia' has been newly defined as pneumonia that exhibits at least one aspiration-related risk factor [23]. To our knowledge, no prior studies have investigated the effectiveness of either CTRX or ABPC/SBT as treatment for aspiration-associated pneumonia.

Against this background, the objective of our study was to compare the effectiveness of CTRX and ABPC/SBT as therapies for aspiration-associated pneumonia, using data from a Japanese multicentre registry. We hypothesized that CTRX would show superiority over ABPC/SBT when treating patients with aspiration-associated pneumonia.

Materials & methods

Study setting

This propensity score-matching study was designed as a substudy of the Adult Pneumonia Study Group-Japan (APSG-J) study to compare the effectiveness of CTRX therapy to that of ABPC/SBT therapy for adult patients with aspiration-associated pneumonia. The APSG-J study adhered to the Guidelines for Ethical Aspects in Epidemiological Study (MHLW, 2008), and was conducted after obtaining approval by the Institutional Review Boards of all five study hospitals, namely the Institute of Tropical Medicine at Nagasaki University, Ebetsu City Hospital, Kameda Medical Center, Chikamori Hospital, and Juzenkai Hospital (Registration No. 11063070). The study was conducted on the four main islands of Japan from September 2011 through August 2014.

The APSG-J study prospectively recruited adult patients with pneumonia to elucidate the burden of community-onset pneumonia and its aetiologies within the world's most aged society [23]. Patients who fulfilled all of the following criteria were enrolled in the APSG-J: patients: aged ≥15 years; exhibiting symptoms compatible with pneumonia (e.g., fever, cough, sputum, pleuritic chest pain and dyspnea); and displaying new pulmonary infiltrates on chest x-ray image or CT scans that were consistent with pneumonia. Patients were enrolled from both in-patient and out-patient services. In our registry, 59% of all patients were male, and the median age was 77 years. The proportion of in-patients was 71.5%, and the in-hospital mortality rate was 11.5% [23].

Patient selection

A previous study defined patients with aspiration-associated pneumonia as those who exhibit at least one of the following aspiration-related risk factors: episodes of aspiration, dysphagia, disturbance of consciousness, neuromuscular diseases, cerebrovascular diseases, tube feeding or bedridden status [23]. This substudy of the larger APSG-J study included all patients with aspiration-associated pneumonia who were initially treated solely with CTRX or ABPC/SBT.

Outcome measures

The primary outcome was defined as in-hospital mortality. Secondary outcomes included the 28-day hospital-free days count. Hospital-free days were defined as the number of days that patients survived and were free from

hospitalization, within 28 days from the initial hospital admission. We used hospital-free days, rather than the length of stay, as an end point, because a recent clinical trial group consensus recommended that the hospital-free days more accurately represent composite measures, as compared with measures, which could be strongly influenced by mortality within a study cohort [24].

Data preparation

All statistical analyses were performed with the R 3.2.3 software for statistical computing (https://www.r-project.org/), using the add-on packages, 'mice' for multiple imputation [25], 'matching' for propensity score matching [26], 'rms' for survival analysis [27] and 'lme4' for the mixed effect model [28]. All tests were two-tailed, and differences were considered significant at p-values ≤ 0.05. The survival of patients was depicted using a Kaplan-Meier survival curve. Because a non-negligible number of missing values was observed (Supplementary Table 1), especially for the respiratory rate and blood sugar variables, we used multiple imputation by employing chained equations to complement all missing values for each study variable, thereby generating 25 datasets with 20 iterations.

Propensity score matching

A logistic regression analysis was used to estimate the propensity scores, which were then utilized to predict the use of CTRX over ABPC/SBT. This prediction incorporated 32 pretreatment covariates, including age, sex, pre-existing comorbidities, prescribed drugs prior to admission (specifically oral steroids, benzodiazepines and anti-acid drugs), the above-described aspiration-related risk factors, vital signs (respiratory rate, systolic blood pressure, heart rate, body temperature and oxygen saturation on room air or with some oxygen demand), laboratory data (hematocrit and levels of blood urea nitrogen [BUN], Na and glucose), and findings on a chest x-ray image (pleural effusion). Propensity score matching was carried out in the selected subjects on a pairwise basis after all propensity scores across the imputed datasets had been averaged and logit-transformed. The match calliper was set to ([standard deviation of the propensity score] $\times$ 0.2). We used absolute standardized mean differences (ASMD) of all variables included in the propensity score estimation to assess the match balance; an ASMD of <0.1 was defined as an appropriate match balance.

Primary & secondary analysis

The primary outcome of in-hospital mortality was assessed using the frequency of mortality in each group, the absolute difference between the groups, and the odds ratio. As secondary outcomes, hospital-free days were assessed as a continuous variable and the absolute differences between the groups were determined.

Sensitivity analysis

To assess possible biases associated with multiple imputation, the primary outcome was reassessed using a propensity score-matched analysis of the naive (not imputed) dataset. Since antibiotic selection preferences might differ among the hospitals, we thus included a generalized linear mixed-effect logistic regression analysis as a sensitivity analysis to assess the primary outcome after adjusting for hospital random effects. Furthermore, given that the treatment environment (e.g., in-patient vs out-patient) might influence mortality data, we evaluated the primary outcome only for in-patient cases.

Results

Baseline characteristics of the data before & after propensity score matching

Of the 3817 adult subjects with pneumonia who were registered in the APSG-J study, 1274 met our diagnostic criteria we used for aspiration-associated pneumonia diagnosis. Of these patients, 237 and 400 were initially treated with CTRX and ABPC/SBT, respectively. Propensity score matching was employed to finally extract 218 subjects in each group, who were predicted to use CTRX over ABPC/SBT (Figures 1 & 2, Table 1).

Primary outcome & sensitivity analyses of patients after propensity score matching

Overall, 38 (8.7%) patients died in the hospital over a mean follow-up of 27 days. The in-hospital mortality was 6.6% (95% CI: 3.2–10.0%) in the CTRX group and 10.7% (95% CI: 6.5–14.8%) in the ABPC/SBT group (p = 0.143; Table 2). Survival analysis of the propensity score-matched subjects revealed similar survival time in the two groups. Specifically, the adjusted hazard ratio for death in the CTRX group was 0.80 (95% CI: 0.41–1.58) (p = 0.527; Figure 3). Propensity score-matched analysis of the naive dataset revealed a significantly

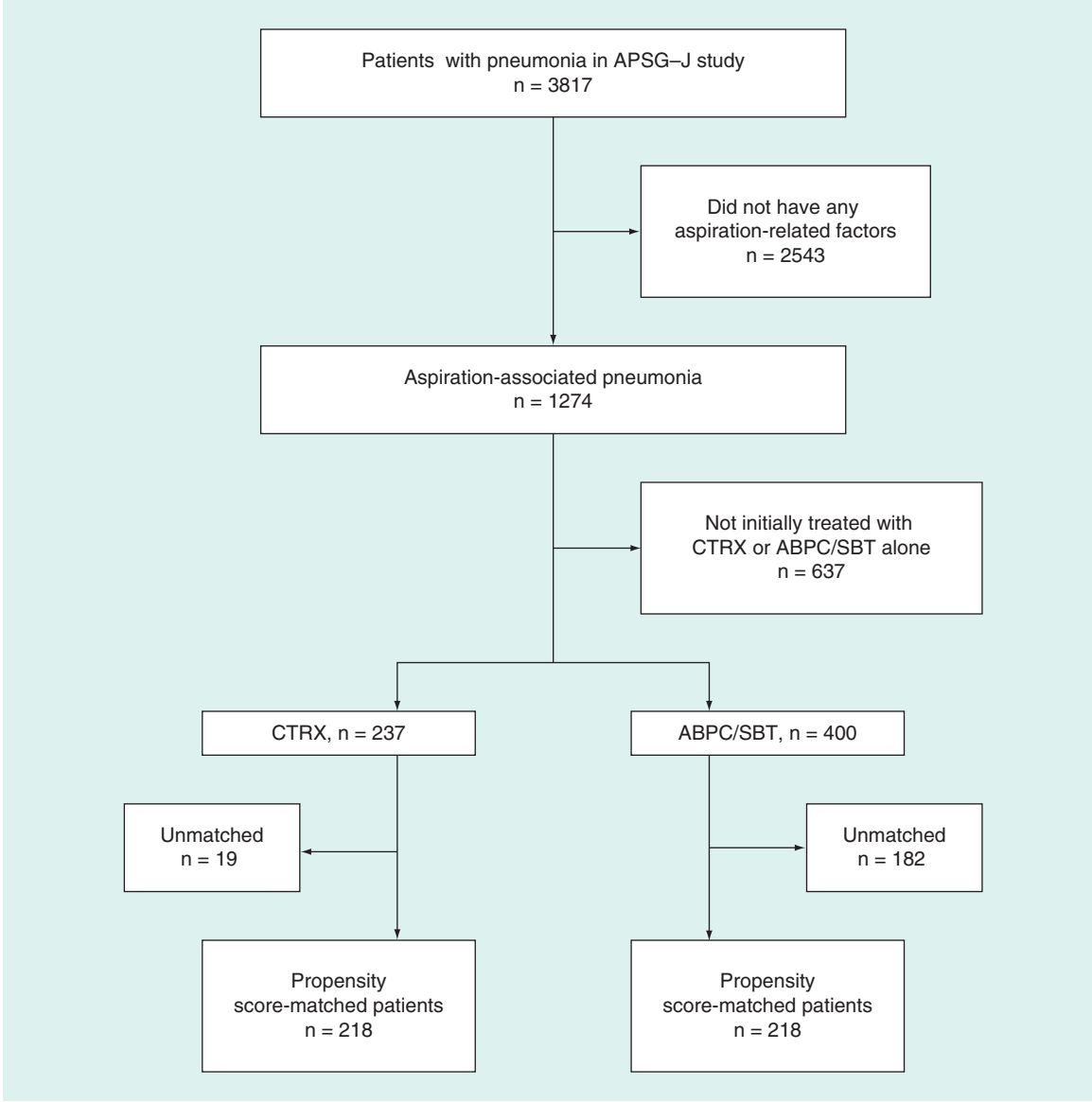

Figure 1. Selection of participants for the study.
ABPC: Ampicillin; APSG-J: Adult Pneumonia Study Group-Japan; CTRX: Ceftriaxone; SBT: Sulbactam.

lower in-hospital mortality rate in patients treated with CTRX (3.7% [95% CI: 0.80–6.6%]) than in patients treated with ABPC/SBT group (11.7% [95% CI: 6.8–16.7%]; p = 0.011). Importantly, an analysis using the hospital random effect as a sensitivity measure supported the above finding (odds ratio, 0.60 [95% CI: 0.28–1.28]; p = 0.189). Analysis using only in-patient cases produced the same results (odds ratio, 0.72 [95% CI: 0.35–1.49]; p = 0.379).

Secondary outcomes of patients after propensity score matching

When considering all of the propensity score-matched subjects, the number of hospital-free days in the CTRX group was significantly greater than that in the ABPC/SBT group (CTRX: 11 days [95% CI: 10–13 days] vs ABPC/SBT: 9 days [8–10 days]; p = 0.005; Table 2).

Discussion

In this study, the mortality observed in the group of patients with aspiration-associated pneumonia who was treated with CTRX was comparable to that for patients with aspiration-associated pneumonia who were treated with

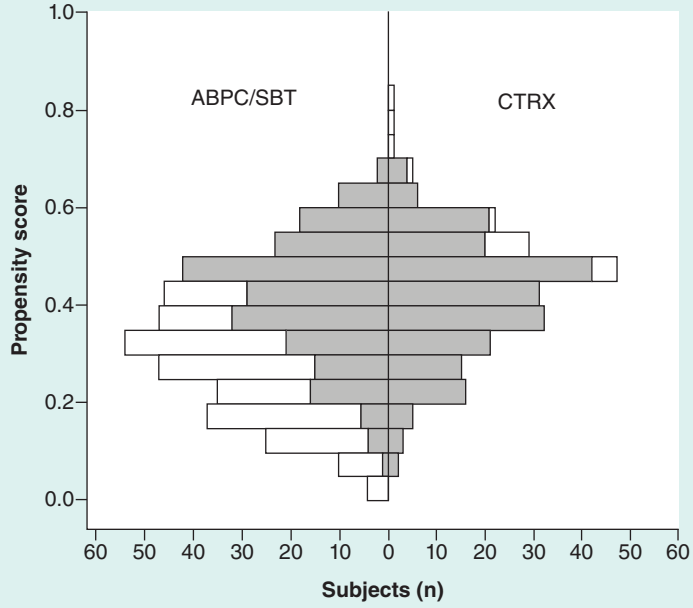

Figure 2. Distributions of the propensity scores before and after matching.
This histogram is based on 5% steps in propensity score. White bars, before matching; gray bars, after matching.
ABPC: Ampicillin; CTRX: Ceftriaxone; SBT: Sulbactam.

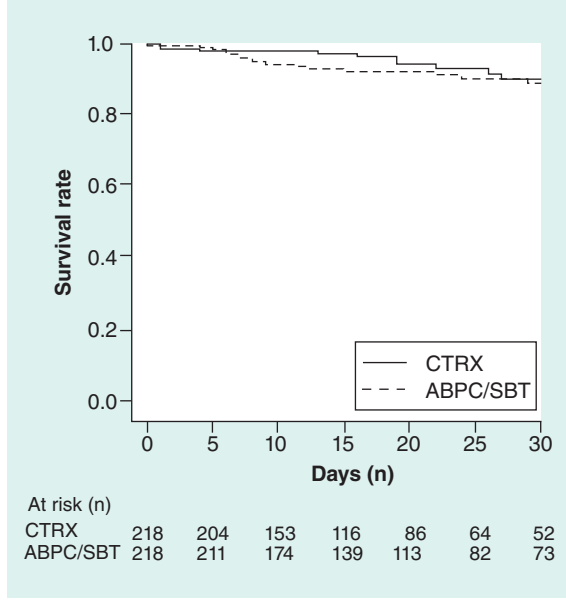

Figure 3. Survival curves for propensity score-matched subjects with aspiration-associated pneumonia initially treated with ceftriaxone and ampicillin/sulbactam.
ABPC: Ampicillin; CTRX: Ceftriaxone; SBT: Sulbactam.

ABPC/SBT. We thus failed to show the superiority of CTRX over ABPC/SBT for treating aspiration-associated pneumonia. To our knowledge, this is the first study to compare the effectiveness of CTRX to that of ABPC/SBT for the treatment of aspiration-associated pneumonia.

Many of the previous studies on treatments for aspiration pneumonia have focused on antibiotics that specifically target anaerobic bacteria [6–11]. However, the bacterial etiology of aspiration pneumonia is controversial. In the 1970s, aspiration pneumonia was thought to be caused by both anaerobes and aerobes based on studies wherein

Table 1. Pretreatment variables of patients with aspiration-associated pneumonia included in the propensity score estimation before and after matching.

Variables	Before matching			After matching		
	CTRX (n = 237)	ABPC/SBT (n = 400)	ASMD	CTRX (n = 218)	ABPC/SBT (n = 218)	ASMD
Median age (years)	83 (76–88.25)	82 (75–89)	0.117	82 (76–88)	82 (75–88)	0.086
Male sex	145 (61.2)	241 (60.3)	0.021	129 (59.2)	134 (61.5)	0.044
Pre-existing comorbidity						
– Diabetes mellitus	57 (24.1)	77 (19.2)	0.117	51 (23.4)	54 (24.8)	0.032
– Malignancy	44 (18.6)	80 (20.0)	0.036	41 (18.8)	37 (17.0)	0.048
– Bronchial asthma	16 (6.8)	30 (7.5)	0.029	13 (6.0)	15 (6.9)	0.037
– COPD or bronchiectasis	42 (17.7)	72 (18.0)	0.007	35 (16.1)	39 (17.9)	0.049
– Heart failure	55 (23.2)	81 (20.2)	0.072	50 (22.9)	42 (19.3)	0.090
– Liver disease	15 (6.3)	24 (6.0)	0.014	9 (4.1)	13 (6.0)	0.084
– Kidney disease	34 (14.3)	47 (11.8)	0.077	25 (11.5)	31 (14.2)	0.082
– Dementia	56 (23.6)	124 (31.0)	0.166	54 (24.8)	52 (23.9)	0.021
Medication						
– Prednisolone	8 (3.4)	22 (5.5)	0.103	8 (3.7)	7 (3.2)	0.025
– Anti-acid drug	85 (35.9)	132 (33.0)	0.060	73 (33.5)	79 (36.2)	0.058
– Sleeping drug	40 (16.9)	69 (17.3)	0.010	34 (15.6)	39 (17.9)	0.061
Community-acquired pneumonia	111 (47.0)	206 (51.5)	0.089	110 (50.5)	113 (51.8)	0.025
Aspiration-associated risk factors						
– Overt aspiration	66 (27.8)	121 (30.2)	0.053	63 (28.9)	63 (28.9)	<0.001
– Vomiting	11 (4.6)	53 (13.2)	0.305	11 (5.0)	8 (3.7)	0.067
– Dysphagia	50 (21.1)	82 (20.5)	0.015	45 (20.6)	42 (19.3)	0.034
– Disturbance of consciousness	22 (9.3)	63 (15.8)	0.196	22 (10.1)	24 (11.0)	0.030
– Neuromuscular diseases	27 (11.4)	56 (14.0)	0.078	26 (11.9)	26 (11.9)	<0.001
– Cerebrovascular diseases	8 (3.4)	17 (4.2)	0.046	8 (3.7)	11 (5.0)	0.067
– Tube feeding	134 (56.5)	222 (55.5)	0.021	120 (55.0)	129 (59.2)	0.083
– Bedridden status	37 (15.6)	84 (21.0)	0.14	36 (16.5)	35 (16.1)	0.012
Vital signs upon arrival at hospital						
– Median RR	22 (18–26)	22 (18–25)	0.087	22 (18–26)	22 (20–27)	0.067
– Median SBP	132 (119–153)	126 (112–147)	0.197	132 (118–150)	130 (117–151)	0.018
– Median PR	92 (83–107)	96 (81–110)	0.084	91 (83–106)	97 (82–110)	0.091
– Median BT	37.5 (36.8–38.3)	37.4 (36.8–38.2)	0.052	37.5 (36.8–38.2)	37.5 (36.8–38.4)	0.036
– Median SpO_2	95 (93–97)	95 (92–97)	0.176	95 (92–97)	95 (92–97)	0.058
Laboratory data at admission						
– Median Hct	36.6 (33.3–40.5)	35.9 (32.3–39.4)	0.132	36.5 (33.2–40.6)	36.6 (33.8–40.1)	0.043
– Median BUN	19.9 (15.0–27.8)	19.9 (14.5–27.0)	0.076	19.7 (15.0–25.5)	19.9 (14.5–28.0)	0.046
– Median serum Na	138 (136–140)	138 (135–140)	0.101	138 (136–141)	138 (135–141)	0.009
– Median Glu	125 (105–160)	124 (106–153)	0.081	126 (105–162)	124 (107–158)	0.008
– Pleural effusion on CXR	19 (8.0)	44 (11.0)	0.102	19 (8.7)	19 (8.7)	<0.001

Data presented as No. (%) or median (25th–75th percentiles).
ABPC: Ampicillin; ASMD: Absolute standardized mean difference; BT: Body temperature (°C); BUN: Blood urea nitrogen (mg/dl); COPD: Chronic obstructive pulmonary disease; CXR: Chest x-ray image; CTRX: Ceftriaxone; Glu: Glucose (mg/dl); Hct: Hematocrit (%); Na: Sodium (mEq/l); PR: Pulse rate (beats/min); RR: Respiratory rate (breaths/min); SBP: Systolic blood pressure (mmHg); SBT: Sulbactam; SpO_2: Oxygen saturation (%).

sputum samples were obtained from patients with a variety of ethnic backgrounds [29–34]. In the 1990s, sputum cultures were obtained from the lower respiratory tract of patients using careful sequential blind protected specimen brush sampling and minibronchoalveolar lavage. Importantly, these cultures were found to contain primarily aerobic bacteria. Therefore, anaerobes were not thought to be involved in the pathophysiology of aspiration pneumonia [35]. In 2010, a Japanese group reported that anaerobes are also common within lung abscesses [36]. Taken together, it is not clear whether treatments for aspiration pneumonia should target aerobes, anaerobes or both. Indeed, the existing data do not provide conclusive evidence. For example, *Prevotella* (previously known as *Bacteroides melaninogenicus*)

Table 2. Comparisons of primary and secondary outcomes for the treatment of patients with aspiration-associated pneumonia between the ceftriaxone and ampicillin/sulbactam groups.

Outcomes	CTRX (n = 218)	ABPC/SBT (n = 218)	Absolute difference	p-value	Odds ratio
Primary outcome					
– In-hospital mortality	6.6	10.7	-4.0 (-9.4, 1.3)	0.143	0.59 (0.30, 1.19)
Secondary outcome					
– 28-day hospital-free days	11	9	2 (1, 4)	0.005	

In-hospital mortality (%); 28-day hospital-free days (days).
ABPC: Ampicillin; CTRX: Ceftriaxone; SBT: Sulbactam.

is reportedly a primary oral anaerobe associated with aspiration pneumonia [37]. The proportion of human clinical isolates of *Prevotella* with β-lactamase activity was approximately 58% in a prior study, and that study showed that *Prevotella* demonstrated greater susceptibility to a β-lactamase inhibitor combined with penicillin, than it did to third-generation cephalosporins [38]. However, it has not been possible to determine whether the specific bacteria that are the aetiologic agents of aspiration pneumonia are aerobic or anaerobic, owing to the difficulty of cultivating anaerobic bacteria and the challenges associated with the funding and staffing of a bacteriology laboratory. Based on our study, we suspect that it may not be necessary to target all anaerobic bacteria when treating patients with aspiration-associated pneumonia.

Here, we found that there were a greater number of hospital-free days in the CTRX group than in the ABPC/SBT group. This result requires careful interpretation, as the duration of hospitalization often depends on socioeconomic factors (e.g., poverty status, availability of nursing caregivers and the existence of additional aging family members), which were not measured in this study and therefore could not be used as covariates for the propensity score matching analysis. Additional studies are needed to further investigate the feasibility of this outcome.

Our study has several notable strengths. To our knowledge, this study is the first to examine the effectiveness of CTRX for the treatment of aspiration-associated pneumonia. Moreover, we used a prospectively collected multicentre registry, aided by multiple imputation and propensity score matching, to increase the robustness of the analysis. Additionally, many covariates were analyzed to increase the consistency of the results. We also used the concept of aspiration-associated pneumonia, which is a newly defined term denoting pneumonia with at least one aspiration-related risk factor. To date, there is no consensus regarding the definition of aspiration pneumonia, as previous international study groups have not been able to establish a consistent definition. Notably, as many as 30% of the patients in our study had aspiration-associated pneumonia. The presence of these patients in our cohort may have led to an overestimation of the number of patients with aspiration pneumonia. Although it is very difficult to establish a uniform definition for aspiration pneumonia because of the varied nature of the disease, clinicians should attempt to develop matching opinions. We believe that using the term aspiration-associated pneumonia is one possible solution that may unify the diverse definitions of aspiration pneumonia.

This study also has several limitations. First, this was an observational study. Therefore, important covariates, such as socioeconomic factors, were not measured, and as such, were not included as pretreatment covariates or associated outcomes. Second, we were unable to identify the bacteriological origins of the disease precisely. The variation in our results may be associated with differences in bacterial etiology, although we were unable to include culture results as pretreatment variables, as these results were obtained after the commencement of treatment and approximately 3 days are required for the pathogens to be identified. However, both the naive dataset and the complete-case analysis revealed that the aerobic bacteria present in the two treatment groups were similar, that is, *S. pneumoniae* was the most likely pathogen and *H. influenzae* was the second most likely pathogen in both groups. At last, the sample size was small. This may have led to insufficient power in our study. We would have needed 1356 samples in each group if we had assumed that the mortality rates of the CTRX and ABPC/SBT groups were 7 and 10%, respectively ($\alpha = 0.05$; $\beta = 0.20$).

In conclusion, in this retrospective propensity score-matched analysis of prospectively collected multicentre cohort data, we failed to show the superiority of CTRX over ABPC/SBT for the treatment of aspiration-associated pneumonia. Regardless, this study provides meaningful insights into the treatment of aspiration-associated pneumonia. Further studies with larger sample sizes are needed, as a lack of power may have contributed to our findings.

Future perspective

In the future, the duration of antibiotic therapy for aspiration-associated pneumonia can be shortened, perhaps even rendered unnecessary, thanks to antimicrobial stewardship.

Summary points

- We compared the effectiveness of ceftriaxone to that of ampicillin/sulbactam in the treatment of aspiration-associated pneumonia.
- We selected the subjects in the Adult Pneumonia Study Group-Japan (APSG-J) study with aspiration-associated pneumonia initially treated with only ceftriaxone or ampicillin/sulbactam, which were used empirically. The APSG-J study prospectively recruited adult patients with pneumonia to elucidate the burden of community-onset pneumonia and its aetiologies.
- A propensity score for the selection of ceftriaxone therapy utilizing 32 pretreatment covariates was used for matching of subjects on a pairwise basis.
- Of the 3817 subjects with pneumonia in the APSG-J study, 1274 met our criteria for aspiration-associated pneumonia. Of these patients, 273 and 400 were initially treated with ceftriaxone and ampicillin/sulbactam, respectively.
- The in-hospital mortality was 6.6% (95% CI: 3.2–10.0%) and 10.7% (95% CI: 6.5–14.8%) in the ceftriaxone and ampicillin/sulbactam groups, respectively ($p = 0.143$). Sensitivity analyses supported this result.
- The number of hospital-free days in the ceftriaxone group was significantly greater than that in the ampicillin/sulbactam group (ceftriaxon: 11 days [95% CI: 10–13 days] vs ampicillin/sulbactam: 9 days [8–10 days]; $p = 0.005$).
- In conclusion, the mortality observed in the group of patients with aspiration-associated pneumonia who were treated with ceftriaxone was comparable to that for patients with aspiration-associated pneumonia who were treated with ampicillin/sulbactam.
- Further studies with larger sample sizes are needed, as a lack of power may have contributed to our findings.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2019-0041

Author contributions

Literature search performed by S Hasegawa. Data collection was done by K Morimoto. Study design and manuscript preparation performed by S Hasegawa, A Shiraishi and T Mori. Analysis of data performed by S Hasegawa and A Shiraishi. Review of manuscript was done by S Hasegawa, A Shiraishi, M Yaegashi, N Hosokawa, K Morimoto and T Mori.

Acknowledgments

The Adult Pneumonia Study Group-Japan (APSG-J) comprises Masahiko Abe[1], Takao Wakabayashi[1], Masahiro Aoshima[2], Naoto Hosokawa[3], Norihiro Kaneko[2], Naoko Katsurada[2], Kei Nakashima[2], Yoshihito Otsuka[4], Eiichiro Sando[5], Kaori Shibui[5], Daisuke Suzuki[3], Kenzo Tanaka[6], Kentaro Tochitani[3], Makito Yaegashi[5], Masayuki Chikamori[7], Naohisa Hamashige[7], Masayuki Ishida[7], Hiroshi Nakaoka[7], Norichika Aso[8], Hiroyuki Ito[8], Kei Matsuki[8], Yoshiko Tsuchihashi[8], Koya Ariyoshi[9], Bhim G. Dhoubhadel[9], Akitsugu Furumoto[9], Sugihiro Hamaguchi[1,9], Tomoko Ishifuji[9], Shungo Katoh[1,9], Satoshi Kakiuchi[9], Emi Kitashoji[9], Takaharu Shimazaki[9], Motoi Suzuki[9], Masahiro Takaki[9], Konosuke Morimoto[9], Kiwao Watanabe[9] and Lay-Myint Yoshida[10].

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Financial & competing interests disclosure

The data source (The Adult Pneumonia Study Group, Japan) of the current study was in part supported by Pfizer, Inc. K Morimoto reports grants from Pfizer, speaking fees from MSD and Pfizer. A Shiraishi has received consulting and speaker's fees from Nobelpharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing assistance was provided by Editage.

Ethical conduct of research

This study was of non-interventional nature and did not include primary data collection (i.e., was based on published secondary data only). Therefore, ethic committee or institutional review board approval was not required. Data used were taken from published cohort trials, which were conducted according to the principles of the Declaration of Helsinki and with informed consent from participants.

Data sharing statement

The datasets analyzed in the current study are available from the corresponding author on reasonable request.

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