Delayed Tetracycline Initiation Increases Mortality Risk in Patients With Japanese Spotted Fever: Retrospective Analysis Using a National Inpatient Database

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Background. This study aimed to determine the relationship between time to tetracycline therapy initiation and disease outcome in patients hospitalized with Japanese spotted fever (JSF).

Methods. Patients with JSF enrolled in the Japanese Diagnosis Procedure Combination database from July 2010 to March 2021 were included in the analysis. Patients who received tetracycline on the day of admission were compared with those who received tetracycline later during their hospital stay using inverse probability of treatment weighting. The primary outcome was in-hospital mortality. Secondary outcomes were total hospitalization cost and length of hospital stay.

Results. A total of 1360 patients were included, of whom 1060 (78%) received tetracycline on the day of admission (early tetracycline group), and 300 (22%) received tetracycline later (delayed tetracycline group). Patients in the delayed tetracycline group had significantly higher in-hospital mortality than those in the early tetracycline group (3.9% vs 1.4%; odds ratio, 2.94; 95% CI, 1.34–6.47), significantly higher hospitalization costs, and longer hospital stays than those in the early tetracycline group.

Conclusions. The prognosis of patients with JSF is worse if tetracycline administration is delayed; therefore, physicians should initiate tetracycline on admission if JSF is suspected as a possible diagnosis.

Keywords. Japanese spotted fever; delayed treatment; tetracycline antibiotics; treatment outcomes.

Japanese spotted fever (JSF) is a rickettsial disease caused by Rickettsia japonica that was first reported in Japan in 1984 [1]. Cases have been reported not only in Japan but also in South Korea [2], China [3], and Thailand [4]. JSF is a tick-borne disease, and several species of Dermacentor, Haemaphysalis, and Ixodes ticks have been shown to transmit R. japonica [5]. The clinical presentation of JSF is characterized by fever, skin rash, eschar, and liver dysfunction (Figure 1). As JSF is uncommon in Japan, with only a few hundred cases per year, diagnosis is sometimes delayed.

The case fatality rate of JSF is unknown because deaths are reported only at the time of case notification by public health centers. Another rickettsiosis, tsutsugamushi disease, is also prevalent in East Asia, but the prognosis of JSF is worse than that of tsutsugamushi disease [6]. Several fatal cases of JSF have been reported in Japan [7, 8]. Tetracyclines are the first-line agents used for the treatment of JSF [9]. Although there have been reports of more deaths in cases of JSF where treatment was delayed [10], no studies have quantitatively evaluated the association between delayed treatment and mortality. Therefore, we conducted an analysis using a nationwide inpatient database to determine the relationship between delayed tetracycline administration and mortality in Japan.

METHODS

Data Source
This retrospective cohort study used the Japanese Diagnosis Procedure Combination (DPC) inpatient database, which contains discharge abstracts and administrative claims data from >1200 acute care hospitals in Japan, which contribute data voluntarily [11]. This database includes the following patient-level data for all hospitalizations: age; sex; diagnoses recorded with International Classification of Diseases, Tenth Revision (ICD-10), codes; daily procedures recorded using Japanese medical procedure codes; daily drug administration; admission status; and discharge abstract. A previous validation study for this database showed high specificity and moderate sensitivity for diagnoses and high specificity and sensitivity for procedures [12].
Study Population
Using the Japanese DPC inpatient database, we identified patients aged ≥18 years who were hospitalized with JSF from July 2010 to March 2021, defined by primary diagnosis with the ICD-10 code A778a. We did not include patients with unconfirmed diagnoses of JSF.

Treatment
Patients who received intravenous or oral tetracycline on the day of admission were assigned to the early tetracycline group. Patients who did not receive tetracycline on the day of admission were assigned to the delayed tetracycline group.

Outcomes and Covariates
The primary outcome was in-hospital mortality. Secondary outcomes were total hospitalization costs (with 1 US dollar equivalent to 115 Japanese yen) and length of hospital stay. Covariates included age; sex; smoking history; body mass index; physical function measured by the Barthel Index (BI) [13], Japan Coma Scale [14], and Charlson comorbidity index [15] on admission; fiscal year; admission on a weekend (Saturday or Sunday); ambulance use; organ support therapy on the day of admission (including intensive care unit [ICU]/high-dependency care unit admission; supplemental oxygen use, mechanical ventilation, catecholamine therapy, renal replacement therapy, and transfusion); and whether the patient was admitted to a teaching hospital. Body mass index was categorized as <18.5, 18.5–24.9, 25.0–29.9, and ≥30.0 kg/m². Physical function on admission was categorized as total/severe dependence (BI: 0–60), slight/moderate dependence (BI: 61–99), and independent (BI: 100). The Japan Coma Scale is well correlated with the Glasgow Coma Scale and was categorized as alert consciousness, confusion, somnolence, and coma [14]. The Charlson comorbidity index was scored using the diagnosis for each patient and categorized as 0, 1, 2, and ≥3 [15].

Statistical Analysis
Our primary approach to compare the outcomes between the early and delayed tetracycline groups was an inverse probability of treatment weighting (IPTW) [16, 17]. A multivariable logistic regression model using the above-mentioned covariates was used to compute the propensity scores for patients who received tetracycline on the day of admission. We used the stabilized average treatment effect weight, which allowed us to maintain the total sample size of the original data and provided a more accurate interval estimate of the variance of the main effect and controls for type I error compared with the nonstabilized IPTW [18]. To assess the performance of the IPTW, we compared all covariates using standardized differences, with absolute standardized differences ≤10% considered to denote negligible imbalances between the 2 groups [19]. Odds ratios and their 95% CIs were calculated for binary outcomes, and risk differences were calculated for continuous outcomes using weighted generalized linear models, with cluster-robust standard errors and individual hospitals treated as clusters. Two-tailed P values <.05 were considered statistically significant.

To assess the robustness of IPTW, we performed a sensitivity analysis with traditional multivariable regression analysis using a generalized linear model with outcomes as the dependent variable and tetracycline use on the day of admission and all covariates as the independent variables. All analyses were performed using Stata/MP 17.0 software (StataCorp LLC, College Station, TX, USA). Continuous variables were reported as medians and interquartile ranges, and categorical variables were reported as frequencies and percentages. All reported P values were 2-sided, and P < .05 was considered statistically significant.

Figure 1. Rash and eschar, characteristic of cases of Japanese spotted fever. A, Rash on the trunk of a case of Japanese erythrocytic fever. B, Eschar found on the neck of the same patient.
Ethics Approval and Consent to Participate
The study was approved by the Institutional Review Board of The University of Tokyo (approval number, 3501-3; December 25, 2017). No information allowing the identification of individual patients, hospitals, or physicians was obtained, and the requirement for informed consent was waived because of the anonymous nature of the data.

RESULTS
Between July 2010 and March 2021, 2789 cases of Japanese spotted fever were reported to the Japanese government [20], and 1386 patients were enrolled in the DPC inpatient database for this study during the same period. After excluding 26 patients aged <18 years, 1360 eligible patients (48.8% of cases notified in the same period) were included in the analysis, of whom 27 died during hospitalization (overall in-hospital mortality, 2.0%) (Supplementary Table). The number of patients stratified by the length of stay from admission to tetracycline initiation is shown in Figure 2. Of the eligible patients, 1060 (78%) who received tetracycline on the day of admission were allocated to the early tetracycline group, and the remaining 300 patients (22%) were allocated to the delayed tetracycline group. During hospitalization, 30 patients (2.2%) did not receive tetracycline.

Patient characteristics before and after IPTW are shown in Table 1. In the original cohort, patients in the delayed tetracycline group tended to have lower body mass index, less independent physical function on admission, lower levels of consciousness on admission, higher Charlson comorbidity index scores, and less requirement for oxygen supplementation and renal replacement therapy; they also tended to be admitted using the ambulance and were less likely to be admitted to a teaching hospital than patients in the early tetracycline group. The distributions of propensity scores before and after IPTW are shown in Supplementary Figures 1 and 2. After IPTW, patient characteristics were well balanced between the 2 groups (Table 1 and Figure 3).

The outcomes before and after IPTW are shown in Table 2. After IPTW, patients in the delayed tetracycline group had significantly higher in-hospital mortality than those in the early tetracycline group (3.9% vs 1.4%; odds ratio, 2.94; 95% CI, 1.34–6.47). Patients in the delayed tetracycline group had significantly higher hospitalization costs and longer hospital stays than those in the early tetracycline group. The results of the sensitivity analysis using traditional multivariable regression were similar to those of the main analysis (Table 3).

DISCUSSION
To the best of our knowledge, this is the first study to quantitatively demonstrate that a delay in tetracycline therapy in cases of JSF is associated with a worse prognosis. Our analysis showed that a delay in tetracycline administration beyond the day of hospitalization resulted in a 2.9-fold increase in the risk of patient death.

JSF is a notifiable disease in Japan, and physicians are required to notify the government within 7 days of diagnosing a patient with JSF. The study included 49% of JSF cases reported to the Japanese government during the 10-year period covered, with a roughly consistent percentage of males and median age [20]; thus, our results are likely to reflect the actual situation of JSF patients in Japan. According to reports from the National Institute of Infectious Diseases in Japan, the case fatality rate of JSF is 0.91% [6]. In this study, 27 of the 1360 patients died during hospitalization, resulting in an in-hospital mortality rate of 2.0%. This difference may be because some patients die after notification to public health centers, so the National Institute of Infectious Diseases in Japan figures are likely to underestimate the case fatality rate. On the other hand, mild cases in patients who were not hospitalized were not included in this study, as cases treated in an outpatient setting are not included in the Japanese DPC inpatient database. Our figures may therefore overestimate the case fatality rate.

In general, JSF is diagnosed based on positive test results on serological testing of whole blood or tissue samples. This includes an increase in the immunoglobulin (Ig)M antibody titer to ≥80 or a ≥4-fold increase in the specific IgG antibody titer in convalescent serum compared with specimens obtained during the acute phase. As few hospitals in Japan have the capacity to perform these tests and tests must be performed by centralized laboratories in each prefecture, it usually takes several days to weeks to confirm the diagnosis of JSF. Therefore, clinicians must decide whether treatment is warranted before JSF diagnosis can be confirmed.
In other infectious diseases, such as sepsis, several studies have shown that delays in antimicrobial therapy initiation are associated with a worse prognosis [21]. Another rickettsiosis, tsutsugamushi disease, typically resolves within 48 hours with appropriate antimicrobial therapy [22]. Because tsutsugamushi disease often resolves spontaneously without antimicrobial therapy [23], it is difficult to assess the association between delayed antimicrobial therapy and mortality risk, although reports suggest that delayed antimicrobial therapy is associated with an increased incidence of complications [24]. Several reports have shown that the case fatality rate of Rocky Mountain spotted fever, which is in the same spotted fever group as JSF, is higher if antimicrobial treatment is delayed [25–28], so the results of our study are not unexpected. Based
Figure 3. Balance of covariates before and after inverse probability of treatment weighting. Abbreviations: HCU, high-dependency care unit; ICU, intensive care unit.

Table 2. Outcomes Before and After Inverse Probability of Treatment Weighting

| Outcome                        | Before IPTW                  | After IPTW                 | Odds Ratio or Risk Difference (95% CI) | P Value |
|--------------------------------|-----------------------------|----------------------------|----------------------------------------|---------|
| In-hospital mortality, No. (%) | Delayed TC (n = 300) 12 (4.0) Early TC (n = 1060) 15 (1.4) | Delayed TC (n = 296) 11 (3.9) Early TC (n = 1064) 14 (1.4) | 2.94 (1.34–6.47) | .007    |
| Median total hospitalization cost (IQR), USD | 4989 (3358–8591) 3327 (2541–5047) | 4927 (3298–8359) 3346 (2549–5098) | 2997 (1810–4185) | <.001   |
| Median length of hospital stay (IQR), d | 14 (9–20) 10 (8–14) | 14 (9–19) 10 (8–14) | 5.7 (3.7–7.6) | <.001   |

Abbreviations: IPTW, inverse probability of treatment weighting; IQR, interquartile range; TC, tetracycline.
on these results, physicians should administer tetracyclines on the day of admission if JSF is considered a possible diagnosis on admission. It is also important for clinicians to be aware of the local epidemic situation in order to suspect JSF.

This study had some limitations. First, we used a multicenter, real-world database in Japan. We attempted to control for measured confounders using IPTW; however, there may be some residual confounding due to unmeasured confounders. Second, although we included cases registered as JSF in the DPC database in this study, we did not have data on the diagnosis method. As testing for JSF is only available in regional health laboratories in each Japanese prefecture, it is generally assumed that disease registration in the DPC database is based on these test results. In addition, the DPC inpatient database can determine when tetracycline was administered, but not when JSF was diagnosed, so this study cannot determine the relationship between the timing of diagnosis and delay in treatment initiation. Third, because we evaluated the effectiveness of all tetracyclines, we could not examine differences in effectiveness between different doses or types of tetracyclines. In addition, the effectiveness of nontetracycline antimicrobial agents such as quinolones could not be evaluated because almost all patients in this study were treated with tetracyclines.

CONCLUSIONS

This study found that the prognosis of patients with JSF was worse if tetracyclines were not administered on the first day of hospitalization. Physicians should administer tetracyclines immediately on admission if JSF is suspected.

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.

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Author contributions. S.K. coordinated this study and drafted the final manuscript. H.O. contributed to the data collection and was responsible for data analysis. H.M. and H.Y. supervised this study. All authors reviewed the results and approved the final version of the manuscript.

Data availability. The data sets analyzed in the current study are not publicly available because of contracts with the hospitals providing data to the database.

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