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Major Article

Effect of methicillin-resistant *Staphylococcus aureus* in Japan

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Key Words:
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Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most common antimicrobial-resistant organism identified in Japanese health care facilities. This study analyzed the clinical and economic burdens attributable to methicillin resistance in *S aureus* in Japanese hospitals.

Methods: We retrospectively investigated data from 14,905 inpatients of 57 hospitals combined with data from nosocomial infection surveillance and administrative claim databases. The participants were inpatients with admission from April 1, 2014, to discharge on March 31, 2016. The outcomes were evaluated according to length of stay, hospital charges, and in-hospital mortality. We compared the disease burden of MRSA infections with methicillin-susceptible *S aureus* (MSSA) infections based on patients' characteristics and onset periods.

Results: We categorized 7,188 and 7,717 patients into MRSA and MSSA groups, respectively. The adjusted effects of the MRSA group were 1.03-fold (95% confidence interval [CI] 1.01-1.05) and 1.04-fold (95% CI, 1.01-1.06), respectively, with an odds ratio of 1.14 (95% CI, 1.02-1.27).

Conclusions: The results of this study found that patient severity and onset delays were positively associated with both MRSA and burden and that the effect of methicillin resistance remained significant after adjustment.

BACKGROUND

Antimicrobial-resistant (AMR) infections have become a serious threat to global health security[1] and could soon be a leading cause of death that requires excessive consumption of health care resources.[2,3] In Japan, the most common AMR organism is methicillin-resistant *Staphylococcus aureus* (MRSA).[4] The Japan Nosocomial Infections Surveillance program reported that MRSA was detected in almost all of the participating 1,653 hospitals and that the number of patients with MRSA was 177,768, which accounted for approximately half of the total number of patients with *S aureus* (N = 372,787) in 2016.[5] MRSA infections are therefore considered a major concern in AMR infections in Japan.

To address the independent effect of the presence of methicillin resistance in *S aureus*,[3] previous studies have analyzed the effect of MRSA on in-hospital mortality compared with that of methicillin-susceptible *S aureus* (MSSA).[6-13] They concluded that MRSA is associated with increased mortality and length of stay (LOS) or hospital charges; however, some investigators have found no difference in increased mortality.[10] A common limitation in the previous studies was that their investigations are of the burden in single or a limited number of hospitals, which leads to a lack of generalizability.[13] Considering that structure, process, and patient characteristics often vary across facilities,[14] it is necessary to estimate the disease burden of MRSA in as many facilities as possible. Another limitation was that most studies focused only on bacteremia to estimate the disease burden. Considering that bacteremia represents only a fraction of the total burden of antimicrobial resistance,[15] it is more suitable to grasp the burden of all cases of MRSA.

Controlling for hospital LOS before the onset of infection to examine the outcomes of antimicrobial resistance is important for appropriate estimation in study design because these periods are directly correlated with costs, hospital LOS, and mortality.[16] However, a number of previous studies did not consider the infection timing when estimating the burden,[17] and major methodologic pitfalls were considered to have led to biased estimates of burden. To overcome

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this limitation, it is crucial to adjust for this period for more appropriate comparisons.

Using a national administrative claims database might be useful for solving the lack of external validity because this large secondary database can supply multicenter data to strengthen the generalizability of the study findings.[18] Because the database often lacks clinical data, such as microbiologic information, researchers face an additional limitation if they use only this database to estimate the burden of antimicrobial resistance.[18] However, the combination of the microbiologic database and administrative data may be a solution to ensure the credibility of the study findings.

Therefore, the present study aimed to quantify the clinical and economic burdens of inpatients infected with MRSA compared with those of patients infected with MSSA in multiple hospitals using the national administrative claims database linked to microbiologic data.

MATERIALS AND METHODS

Design and data sources

We conducted a retrospective database analysis of administrative claims and microbiologic data obtained from the quality indicator-improvement project that was managed by our laboratory at Kyoto University. The project periodically collects the 2 kinds of data from voluntarily participating acute care hospitals in Japan for the subsequent analysis of medical care quality, such as patient outcomes and health care processes.[19] The administrative database was obtained according to the Japanese Diagnosis Procedure Combination (DPC) system format, whereas the microbiologic database was obtained according to the Japanese Nosocomial Infection Surveillance (JANIS) format.

The DPC system is a patient case-mix system used for the determination of acute care hospital reimbursements under the public medical insurance scheme.[20,21] The DPC data include clinical information, such as patient age, sex, comorbidities, information to evaluate the Barthel Index, major diagnoses, admission and discharge dates, and outcomes at discharge. The database also includes information on the detailed processes of care, such as drug administration, and all surgical and intensive care with their specific dates of implementation and corresponding costs.

The JANIS was established by Japan's Ministry of Health, Labour and Welfare to enhance the source of information on the epidemiology of nosocomial infections in Japanese hospitals, the details of which are described elsewhere.[22,23] The data include detailed bacteria information such as clinical material, species, and drug susceptibility test findings used to determine the presence of antimicrobial resistance.

This study merged the data from the DPC system administrative and JANIS microbiologic databases.

Study inclusion and exclusion criteria

This study included inpatients who (1) were admitted on or after April 1, 2014, and discharged on or before March 31, 2016; (2) were administered antibiotics; and (3) were positive for *S aureus* based on microbiology test results. We excluded inpatients for (1) receiving sequential antibiotic administration for ≤3 days, including the specimen submission day of the first positive culture; (2) hospital discharge outcome of exacerbation; (3) missing costs data; and (4) hospital LOS >90 days.

Collection of antimicrobial susceptibility testing data

S aureus resistance was determined by drug susceptibility tests using oxacillin according to the 2012 Clinical & Laboratory Standards Institute guidelines.[24] Only the first cases were enrolled in instances of multiple episodes of *S aureus* infection during hospitalization. Both MRSA and MSSA from several specimens submitted on the same day were classified as MRSA.

Infection onset time

Because of limitations of the DPC and JANIS databases, we could not obtain accurate data regarding the onset of the *S aureus* infections. We therefore considered the first *S aureus* culture result submission date as a proxy for the onset timing of the infection. We only considered patients administered antibiotics for ≥4 days from this time as having acquired the infection, as described in our previous study.[25]

Cost calculations

To assess the economic burden, we measured the hospital charges from the hospital perspective. The total hospital charges were calculated as the sum of the following fees for medical services provided during hospitalization, as previously described.[4] The hospital charges consisted of basic and specialized inpatient care, initial consultations and examinations, imaging services, pharmacy, injections, treatments, invasive procedures, and predischarge consultations. The fees were summed in Japanese yen and converted to U.S. dollars (US$1 = ¥102.5) using the mean purchasing power parities in 2014 and 2015.

Statistical analysis

The outcomes included hospital LOS, hospital charges, and (all-cause) in-hospital mortality as indicators of the clinical and economic burden of MRSA. The study sample was first divided into MRSA and MSSA groups. The baseline characteristics and outcomes of the 2 groups were compared using *t* tests or Mann-Whitney *U* tests, as appropriate. We calculated the number of MSSA and MRSA infections, the proportion of MRSA cases, and the mean outcomes according to each onset date to determine the relationship between onset dates and outcomes. To examine the effects of disease burden considering that the observations in the same hospital tend to be correlated, we performed a hierarchical generalized regression analysis using the selected cohorts.[26] We used a gamma regression analysis with a log link for outcomes including hospital LOS and total hospital charges and used a logistic regression analysis for the outcome of in-hospital mortality. We used a random-intercept model with hospitals and patients as random effects. We explored the following confounders as fixed effects to develop an adjusted model (adjusted model 1): patient age, sex, Charlson Comorbidity Index (Dartmouth-Manitoba version[27]), Barthel Index, nosocomial infection at admission (infected patients transferred from other hospitals or wards where they were first infected), surgery, bloodstream infection, and use of intensive care unit. We included the hospital day when cultures were submitted in another adjusted model (adjusted model 2). The cutoff points to stratify Barthel Index were determined based on interquartile range. When using the gamma regression analysis, we showed the multiplicative effects to indicate how each outcome was multiplied when the MSSA infection changed to an MRSA infection. Subgroup analysis was also performed of bloodstream infection cases to reduce the possibility of potential carrier cases with *S aureus*. An additional subgroup analysis was also performed to assess the attributable burden of MRSA by categorizing patients as those with hospital-acquired infections (those with cultures positive for *S aureus* on day 3 or later) or others (those with cultures positive on days 1-2).