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Major Article

The economic burden of methicillin-resistant *Staphylococcus aureus* in community-onset pneumonia inpatients

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Background: The quantitative effect of multidrug-resistant bacterial infections on real-world health care resources is not clear. This study aimed to estimate the burden of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in pneumonia inpatients in Japan.

Methods: Using a nationwide administrative claims database, we analyzed pneumonia patients who had been hospitalized in 1,063 acute care hospitals. Patients who received anti-MRSA drugs were categorized into an anti-MRSA drug group, and the remaining patients comprised the control group. We estimated the burden of length of stay, in-hospital mortality, total antibiotic agent costs, and total hospitalization costs. Risk adjustments were conducted using propensity score matching.

Results: The study sample comprised 634 patients administered anti-MRSA drugs and 87,427 control patients. In propensity score-matching analysis (1 to 1), the median length of stay, antibiotic costs, and hospitalization costs of the anti-MRSA drug group were significantly higher than those of the control group (21 days vs 14 days [$P < .001$], \$756 vs \$172 [$P < .001$] and \$8,741 vs \$5,063 [$P < .001$], respectively); the attributable excess of these indicators were 9.0 ± 1.6 days, \$1,044 ± \$101, and \$5,548 ± \$580, respectively.

Conclusions: These findings may serve as a reference to support further research on multidrug-resistant bacterial infections and eventually inform policy formulation.

BACKGROUND

The emergence of drug-resistant bacteria has developed into a major global health issue since the use of antibiotics has become widespread.[1] In addition to having severe effects on patient health, infections by these bacteria can place an extremely heavy burden on health care systems, as well as consume inordinate quantities of resources.[2] The majority of multidrug-resistant bacterial infections in Japan are attributed to methicillin-resistant *Staphylococcus aureus* (MRSA). In an analysis of 551 hospitals conducted by the Japan Nosocomial Infections Surveillance program in 2013,[3] it was found that 93.7% of newly detected multidrug-resistant bacterial infections were caused by MRSA, followed by penicillin-resistant *Streptococcus pneumoniae* (5.11%) and multidrug-resistant *Pseudomonas aeruginosa* (1.17%). In addition, a large proportion of these multidrug-resistant bacterial infections resulted in pneumonia, which accounted for approximately one-third of new infections. Furthermore, pneumonia is also a common infectious disease that has been increasing in incidence in Japan due to an aging population.[4] Thus, MRSA pneumonia can be considered a representative disease for the issue of multidrug-resistant bacterial infections.

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YI had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He also contributed to the study design, data acquisition, interpretation, critical review for important intellectual content, and approval of the final version of the manuscript from the point of view of an infection preventionist. HU contributed to the study conception from the point of view of a pulmonologist, and to the design, data collection, analysis, interpretation, drafting, critical review for important intellectual content, and approval of the final version of the manuscript. KY contributed to the study design, analysis, critical review for important intellectual content, and approval of the final version of the manuscript. SK contributed to the data management, critical review for important intellectual content, and approval of the final version of the manuscript. KF contributed to the data collection, critical review for important intellectual content, and approval of the final version of the manuscript.

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Historically, MRSA has been generally considered a nosocomial pathogen.[5] However, previous studies have reported that in addition to increases in health care-associated MRSA infections, the incidence of community-associated MRSA is also on the rise.[6,7] This phenomenon may have been induced by the proliferation of health care delivery outside of hospitals in addition to the overuse of antibiotics. Furthermore, another study reported that community-associated MRSA infections have a substantial economic burden due to increases in hospitalization and mortality.[8] For this reason, the issue of multidrug-resistant bacterial infections should not be limited to MRSA infections that occur within hospitals, but should also address infections that originate outside hospitals.

Community-onset pneumonia cases, which include the epidemiologic characteristics of both community-acquired pneumonia and health care-associated pneumonia,[9] can pose a serious threat if the patients are infected with MRSA. Without appropriate infection surveillance and prevention, the pathogen can spread throughout hospitals and infect the many immunocompromised and frail patients. Because these infections occur outside the hospital setting, the efforts of hospital staff alone are insufficient to control their occurrence. There is therefore a need for governments to provide support by implementing measures to reduce the incidence and spread of community-onset MRSA pneumonia. Although the frequency and burden of community-onset MRSA pneumonia must first be quantified to support the decision-making process for such measures, there has been a lack of studies that address this issue.

Two previous studies have reported the burden of community-onset MRSA pneumonia,[10,11] but both were conducted using data from single health care institutions in the United States. Because the length of stay (LOS) and medical costs in the United States are markedly different from those of other countries in the Organisation for Economic Co-operation and Development, it is difficult for policymakers in other countries to use these studies as references.[12] In addition, we must also first ascertain the incidence of community-onset MRSA pneumonia among general community-onset pneumonia patients to quantify the influence of this disease.

The aims of this study were to estimate the frequency of community-onset MRSA pneumonia using a Japanese national administrative claims database comprising data from 1,063 hospitals, and to quantify the clinical and economic burden of these patients.

METHODS

Data source

We obtained patient data from the Diagnosis Procedure Combination (DPC) database, which periodically collects administrative claims data from voluntarily participating hospitals.[13] These data encompass approximately half of all inpatient admissions to acute care hospitals in Japan. Electronic data on all discharged patients from the participating hospitals are submitted to the DPC Research Group, which is funded by Japan's Ministry of Health, Labour, and Welfare; these data have been applied to disease management analyses and the formulation of health policies.[14] DPC data contain summaries of clinical information, including trigger diagnoses, major diagnoses, comorbidities at admission, A-DROP pneumonia severity index at admission,[15] Barthel index score at admission, and discharge status.[4,15] The A-DROP score, which is a modified version of the CURB-65 score for predicting severity in patients with community-acquired pneumonia, ranges from 0-5 points.[16] These points determine the following 4 levels of pneumonia severity: mild (level 0), moderate (level 1 or 2), severe (level 3), and extremely severe (level 4 or 5).

Diseases are identified in the DPC database through ICD-10 codes. In addition, the database also includes detailed processes of care, such as procedures and drug administration, with their specific dates of implementation and corresponding costs.

Study inclusion and exclusion criteria

We selected patients for inclusion in the study if they fulfilled the following criteria: record of pneumonia (ICD-10 codes J10.0, J11.0, J12–J18, A48.1, B01.2, B05.2, B37.1, or B59) in both the trigger and major diagnoses during discharge from the participant hospitals between April 1, 2013, and March 31, 2014; age 18 years or older; and presented with community-onset pneumonia (not hospital-acquired pneumonia) on admission.

To increase the accuracy of identifying community-onset pneumonia cases in the administrative data, we excluded patients if they did not begin antibiotic therapy within 2 days of hospitalization, were not administered antibiotic therapy for 4 consecutive days or more, or had missing values in the A-DROP score and antibiotic costs.

Identification of MRSA pneumonia cases

Due to limitations of the DPC database, we could not obtain microscopy or laboratory-based information on the etiologic agent that caused pneumonia in each patient. We therefore attempted to identify patients with community-onset MRSA pneumonia by examining the use of 5 anti-MRSA drugs (vancomycin, teicoplanin, daptomycin, linezolid, and arbekacin) that are approved for use in Japan.[17] To distinguish between patients who had community-onset MRSA pneumonia and patients with hospital-acquired MRSA pneumonia, we considered patients who were administered anti-MRSA drugs within the first 4 days of hospitalization as having acquired the infection before admission. In addition, to account for the possibility of non-MRSA pneumonia patients being administered anti-MRSA drugs as empirical therapy, we only considered patients who were administered anti-MRSA drugs for 4 days and more as MRSA pneumonia cases.

Cost estimation

Total antibiotic costs were calculated as the summary of all charges for antibiotic medications incurred during hospitalization. Total hospitalization costs were calculated as the summary of all charges for medical services provided during hospitalization, as previously described.[4,18] These services include basic and specialized inpatient care, initial consultation and examination, imaging services, pharmacy, injections, treatments, invasive procedures, and predischarge consultation. The fees were summarized in Japanese yen and converted to US dollars (US$1 = ¥104) using the mean purchasing power parity in 2013.

Statistical analysis

As indicators of the clinical and economic burden of MRSA, the primary outcome measures were LOS, total antibiotic costs during hospitalization, and total hospitalization costs; the secondary outcome measure was in-hospital mortality.

The study sample was first divided into an anti-MRSA drug group and a control group. Patients were included in the anti-MRSA drug group if they had been administered any of the 5 stipulated anti-MRSA drugs within 4 days of hospitalization, and if the drugs were administered for 4 consecutive days or more. To reduce the possibility of selection bias due to different characteristics between the 2 groups, we used propensity score matching. We estimated the propensity score using a logistic regression model with anti-MRSA drug