American Journal of Infection Control 44 (2016) 1628-33

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

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

Hironori Uematsu MD, MPH [a], Kazuto Yamashita MD, PhD [a], Susumu Kunisawa MD, PhD [a], Kiyohide Fushimi MD, PhD [b], Yuichi Imanaka MD, PhD [a,*]

[a] Department of Healthcare Economics and Quality Management, Graduate School of Medicine, Kyoto University, Kyoto City, Kyoto, Japan
[b] Department of Health Policy and Informatics, Graduate School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan

Key Words:
MRSA
Clinical and economic burden
Propensity score matching
Infection

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.

* Address correspondence to Yuichi Imanaka, MD, PhD, Department of Healthcare Economics and Quality Management, Graduate School of Medicine, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto City, Kyoto 606-8501, Japan.
E-mail address: imanaka-y@umin.net (Y. Imanaka).

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.

This work was supported in part by Health Sciences Research Grants from the Ministry of Health, Labour, and Welfare of Japan (Nos. H27-shinkogyosei-shitei-005 and H27-seisaku-shitei-009), and a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science. (No. [A]25253033).

Conflicts of Interest: None to report.

0196-6553/
http://dx.doi.org/10.1016/j.ajic.2016.05.008

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

use as the dependent variable; based on evidence from existing studies, we explored the following candidate explanatory variables: age, sex, A-DROP pneumonia severity index (a modified version of CURB-65),[15] Charlson comorbidity index (Dartmouth-Manitoba version),[19] Barthel index,[20] ambulance use,[15] hospital type (university or nonuniversity), and hospital case volume.[21] Multicollinearity was evaluated using variance inflation factors.[22] We performed 1-to-1 matching using nearest-neighbor matching without replacement (caliper width was < 0.2 standard deviations of the logit of the propensity score).[23] To measure covariate balance, we used the criterion where a standardized difference of 10% or more represents meaningful imbalance.[24] We compared outcomes in the unadjusted (all patients) and propensity score–matched cohorts (only matched pairs) using Mann-Whitney *U* test and Wilcoxon signed-rank test, where applicable.

To estimate the economic burden in the anti-MRSA drug group relative to the control group, we conducted analyses using simple linear regression models with a gamma distribution. The analyses used anti-MRSA drug use as an explanatory variable in both the unadjusted and propensity score–matched cohorts. In addition, we performed a similar analysis using inverse probability of treatment weighting where each patient was weighted by the inverse of their propensity score to make up for the reduction of sample size that invariably occurs in propensity score matching.[25]

Finally, we performed a sensitivity analysis using alternate cutoff points for the initiation of anti-MRSA drug administration, because the "within 4 days of hospitalization" criteria may be arbitrary for determining whether or not the drug was used to treat community-onset MRSA. The sensitivity analysis was conducted using cutoff points of 1-7 days.

All statistical analyses were performed using R statistical software version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). *P* values < .05 were considered statistically significant. The Ethics Committee of Kyoto University Graduate School of Medicine approved the collection and analysis of DPC data (approval No. E-05). In accordance with the Japanese Ethical Guidelines for Epidemiological Research, our study waived the need for informed consent.

RESULTS

We identified a total of 105,004 candidate subjects using the inclusion criteria. We excluded patients who were not administered antibiotic therapy within the first 2 days of hospitalization, patients whose total antibiotic therapy throughout hospitalization was for 3 days or fewer (n = 15,273), and patients with missing values (except Barthel index) in the A-DROP score and antibiotic costs (n = 1,670). After excluding these patients, the study sample consisted of 88,061 community-onset pneumonia patients admitted to 1,063 hospitals. Among these, 634 patients were categorized into the anti-MRSA drug group, whereas the remaining 87,427 patients were categorized into the control group. There were a total of 1,266 patients in the propensity score-matched cohort, which included 633 patients in each group.

Patient-level characteristics

Table 1 summarizes the patient-level characteristics of the study sample. In all (unadjusted) patients, the mean ages of patients in the anti-MRSA drug group and control group were 76.6 years and 75.6 years, respectively. The proportions of "severe" and "extremely severe" A-DROP scores in the anti-MRSA drug group were 19.2% and 21.8%, respectively, which were significantly higher than the control group (absolute standardized differences were 14.6% and 31.5%, respectively). The proportions of patients with 2 or more comorbidities, poor Barthel index scores (score, 0-65), ambulance

Table 1
Demographic characteristics of 88,061 pneumonia patients

	All patients			Propensity score-matched patients		
	Anti-MRSA drug group*	Control group†	Absolute standardized difference‡ (%)	Anti-MRSA drug group*	Control group†	Absolute standardized difference‡ (%)
Number of hospitals	363	1,063		363	431	
Number of patients	634	87,427		633	633	
Age (y)	76.6 ± 13.1	75.6 ± 14.9	7.9	76.7 ± 13.1	76.3 ± 15.5	2.7
Sex						
Female	227 (35.8)	35,756 (40.9)	10.6	227 (35.9)	246 (38.9)	6.3
Male	407 (64.2)	51,671 (59.1)		406 (64.1)	387 (61.1)	
A-DROP§						
Mild	65 (10.3)	14,577 (16.7)	21.1	65 (10.3)	66 (10.4)	0.5
Moderate	309 (48.7)	53,396 (61.1)	24.7	309 (48.8)	318 (50.2)	2.8
Severe	122 (19.2)	11,802 (13.5)	14.6	122 (19.3)	102 (16.1)	8.0
Extremely severe	138 (21.8)	7,652 (8.8)	31.5	137 (21.6)	147 (23.2)	3.8
Charlson comorbidity index						
0	169 (26.7)	26,726 (30.6)	8.8	169 (26.7)	156 (24.6)	4.6
1	177 (27.9)	29,322 (33.5)	12.5	177 (28.0)	188 (29.7)	3.9
≥ 2	288 (45.4)	31,379 (35.9)	19.1	287 (45.3)	289 (45.7)	0.6
Barthel index						
Fair (70-100)	168 (26.5)	41,307 (47.2)	47.0	168 (26.5)	170 (26.9)	0.7
Poor (0-65)	372 (58.7)	34,133 (39.0)	39.8	371 (58.6)	375 (59.2)	1.3
Data missing	94 (14.8)	11,987 (13.7)	2.6	94 (14.8)	88 (13.9)	2.7
Ambulance use	241 (38.0)	23,333 (26.7)	23.3	241 (38.1)	230 (36.3)	3.6
Hospital type						
University hospital	57 (9.0)	4,614 (5.3)	13.0	56 (8.8)	61 (9.6)	2.8
Nonuniversity hospital	577 (91.0)	82,813 (94.7)		580 (91.2)	575 (90.4)	
Hospital volume mean per year	122 ± 69.8	121 ± 72	1.6	122 ± 72.1	126 ± 76.7	6.4

NOTE. Values are presented as n, n (%), or mean ± standard deviation.
MRSA, methicillin-resistant *Staphylococcus aureus*.
*Patients administered anti-MRSA drugs within 4 days of hospitalization and for 4 consecutive days and more.
†All other patients not included in the anti-MRSA drug group.
‡An index used to measure covariate balance, where a difference of more than 10% indicates imbalance.
§Pneumonia severity scoring system developed by the Japanese Respiratory Society.

Table 2
Outcome comparison for the overall sample and the propensity score-matched cohort

	Anti-MRSA drug group*	Control group†	*P* value	Mean difference
All (unadjusted) patients	634	87,427		
Length of stay (d)	21.0 (14.0-33.0)	12.0 (9.0-20.0)	< .001‡	
Length of stay (d)	30.1 ± 28.7	18.2 ± 23.0	< .001‡	11.8
Total antibiotic costs ($)	757 (436-1,482)	152 (77-347)	< .001‡	
Total antibiotic costs ($)	1,415 ± 1,919	311 ± 674	< .001‡	1,104
Total hospitalization costs ($)	8,751 (6,007-14,598)	4,474 (3,214-6,703)	< .001‡	
Total hospitalization costs ($)	12,772 ± 12,395	6,124 ± 6,621	< .001‡	6,648
In-hospital mortality	143 (22.6)	5,432 (6.2)	< .001§	
Propensity score-matched patients	633	633		
Length of stay (d)	21.0 (14.0-33.0)	14.0 (9.0-23.0)	< .001¶	
Length of stay (d)	30.1 ± 28.8	21.0 ± 25.0	< .001¶	9.0
Total antibiotic costs ($)	756 (436-1,476)	172 (79-412)	< .001¶	
Total antibiotic costs ($)	1,413 ± 1,920	369 ± 754	< .001¶	1,044
Total hospitalization costs ($)	8,741 (6,006-14,559)	5,063 (3,372-8,225)	< .001¶	
Total hospitalization costs ($)	12,755 ± 12,397	7,207 ± 7,352	< .001¶	5,548
In-hospital mortality	143 (22.6)	77 (12.2)	< .001#	

NOTE. Values are presented as median (interquartile range), mean ± standard deviation, n (%), or n.
MRSA, methicillin-resistant *Staphylococcus aureus*.
*Patients administered anti-MRSA drugs within 4 days of hospitalization and for 4 consecutive days and longer.
†All other patients not included in the anti-MRSA drug group.
‡*P* values by Mann-Whitney *U* test.
§*P* values by χ^2 test.
¶*P* values by Wilcoxon signed-rank test.
#*P* values by McNemar test.

use, and admission to university hospital were significantly higher in the anti-MRSA drug group than in the control group. Although the proportions of most variables were imbalanced between the groups in the unadjusted cohort, the proportions of all variables were balanced between the groups in the propensity score–matched cohort (where balance was assessed with an absolute standardized difference that was < 10%). The variance inflation factors were lower than 2 in the logistic regression model used to develop the propensity score, indicating a low risk of multicollinearity.

Outcome comparisons

Table 2 shows the outcome comparisons of LOS, total antibiotic costs, total hospitalization costs, and in-hospital mortality between the groups. In the anti-MRSA drug group (in the unadjusted cohort), the median values of LOS, total antibiotic costs, and total hospitalization costs were significantly higher than those in the control group. In the propensity score-–matched patients cohort, the mean differences in LOS, total antibiotic costs, and total hospitalization costs were 9.0 days, $1,044 and $5,548, respectively, whereas the anti-MRSA drug group demonstrated consistently higher values than the control group; thus, the anti-MRSA drug group had incremental outcomes of 42.9%, 354%, and 77.0%, respectively, relative to the control group. In-hospital mortality was also significantly higher in the anti-MRSA drug group for both the unadjusted and matched cohorts.

Burden estimation of community-onset MRSA pneumonia

Table 3 shows the attributable excess estimates of LOS, total antibiotic costs, and total hospitalization costs of the anti-MRSA drug group relative to the control group using simple linear regression models. In the propensity score-matched cohort, the estimate ± standard error of LOS, total antibiotic costs, and total hospitalization costs were 9 ± 1.6 days, $1,044 ± $101 and $5,548 ± $580, respectively; when using the inverse probability of treatment weighting method, the corresponding values were 10.4 ± 1.2 days, $1,056 ± $85.90 and $5,169 ± $479, respectively. Thus, the 2 different methods did not produce substantially different results.

Table 3
Attributable excess estimated from univariate regression analysis of the anti-methicillin-resistant *Staphylococcus aureus* drug group relative to the control group

	Unadjusted (n = 88,061)	Propensity score-matched (n = 1,266)	Inverse probability of treatment weighting (n = 88,061)
Length of stay (d)	11.8 ± 1.5*	9.0 ± 1.6*	10.4 ± 1.2*
Total antibiotic costs ($)	1,104 ± 121*	1,044 ± 101*	1,056 ± 85.9*
Total hospitalization costs ($)	6,648 ± 548*	5,548 ± 580*	5,169 ± 479*

NOTE. Values are presented as estimate ± standard error.
**P* < .001 (Null hypothesis: Estimate is zero).

Sensitivity analysis

Figure 1 shows the results of the sensitivity analysis with differing cutoff points (1-7 days) for initiation of anti-MRSA drug administration. The results shown in the middle positions of each bar graph indicate the primary cut-off point (4 days after hospitalization). Each bar represents the attributable excess cost estimates of the anti-MRSA drug group relative to the control group in the propensity score-matched cohorts. The estimates for all 3 indicators were highest (LOS: 13.4 days, total antibiotic costs: $1,180, and total hospitalization costs: $6,473) when the cutoff was set at 7 days; the estimates were lowest (LOS: 8.1 days, total antibiotic costs: $1,030, and total hospitalization costs: $5,045) when the cutoff was set at 2 days. Total antibiotic costs did not vary substantially among the various cutoff points. In contrast, the cutoff points of 5, 6, and 7 days produced higher average estimates than the cutoff points of 2, 3, and 4 days for LOS and total hospitalization costs.

DISCUSSION

In an analysis of 1,063 acute-care hospitals in Japan, we estimated the incidence of community-onset MRSA pneumonia to be approximately 0.7% among general community-onset pneumonia patients, with an associated in-hospital mortality rate of 22.6%. When compared with the control group, the attributable excess costs of

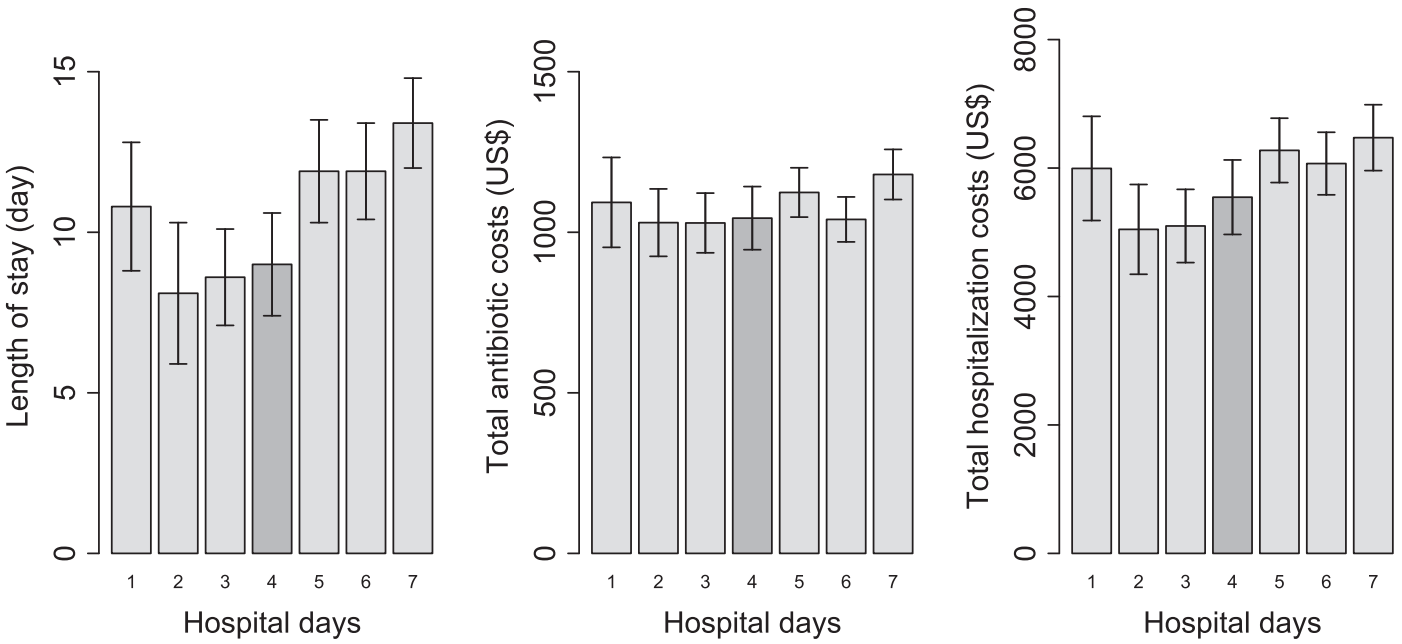

Fig 1. Bars indicate the attributable excess cost estimates in the propensity score-matched cohort. Bins indicate the mean ± standard error of the mean. The *x*-axes of the graphs indicate the cutoff point of hospital days (1-7 days) after admission for the initiation of anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drug administration to treat community-onset MRSA pneumonia. The primary cutoff point used in this study was the administration of anti-MRSA drugs within 4 days of hospitalization.

the anti-MRSA drug group were 9.0 ± 1.6 days for LOS, $1,044 ± $101 for total antibiotic costs, and $5,548 ± $580 for total hospitalization costs after risk adjustments using propensity score matching. Patients with community-onset MRSA pneumonia had considerably higher in-hospital mortality than patients with non-MRSA pneumonia.

Two previous studies have conducted investigations of the economic burden of community-onset MRSA pneumonia. However, the control groups of those studies did not consist of community-onset pneumonia patients, but instead comprised patients infected with methicillin-sensitive *Staphylococcus aureus*.[10,11] Taneja et al[10] reported that the in-hospital mortality of community-acquired MRSA pneumonia patients in a US hospital was 21.8%, which was congruent with our results. However, the median LOS was 13.0 days and the median total hospitalization costs were $71,868, which differed substantially from our sample. In a study of health care-associated pneumonia patients in a US hospital, Shorr et al[11] reported similar outcomes in LOS and total hospitalization costs as those of Taneja et al.[10] A possible reason for the differences in our findings and those of these previous studies is the large difference in medical fee schedules between Japan and the United States. In the United States, hospitalizations tend to be relatively short in duration, but more expensive.[12] In contrast, LOS tends to be longer in Japan, with a health expenditure per gross domestic product that is similar to the Organisation for Economic Co-operation and Development average.[26] For this reason, the burden estimation presented here (excluding in-hospital mortality) would be expected to differ from that of the United States.

This study was strengthened by the large sample size across multiple facilities and the extensive adjustments for patient severity, which were relatively limited in previous studies. The large sample size helps to reduce random error in the estimated outcomes, and the multicenter sample can increase the external generalizability of these findings. In addition, it is essential to adjust for patient baseline characteristics when we evaluate the burden of MRSA pneumonia on health care resources relative to non-MRSA pneumonia, because infections caused by MRSA can occur more frequently in fragile and immunocompromised patients.[27] Due to these aspects of the study design, we believe that our estimates are likely to be indicative of true values.

Our estimation models for risk-adjusted attributable excess costs were robust because 2 different propensity score methods (propensity score matching and inverse probability of treatment weighting) did not produce significantly different results. A major flaw of the propensity score-matching method is the inevitable reduction of sample size, which can lead to selection bias and reduce external validity. Despite this, the similar results produced in the inverse probability of treatment weighting analysis (which used the entire sample) indicated that our propensity score-matching model was reliable. However, there is still the possibility of unmeasured confounding bias, which is not removed in propensity score analysis.[28]

The sensitivity analysis indicated that our models were stable because changes to the cutoff points for initiating anti-MRSA drug administration did not have a large influence on total antibiotic costs and total hospitalization costs. Although we observed slightly higher estimates in all 3 indicators when the cutoff points were set at 5 days or more, these results may have reflected the inclusion of hospital-acquired MRSA pneumonia cases. The estimates for the cutoff point of 1 day of hospitalization had larger standard error, which may have reflected the instability arising from the smaller sample size.

The contributions of these findings include confirmation of the incidence of community-onset MRSA pneumonia and quantification of risk-adjusted attributable excess costs using a multicenter sample. By combining these findings with epidemiologic data (such as the total annual number of community-onset pneumonia inpatients) in future research, we can obtain nationwide estimates of the economic burden of community-onset MRSA pneumonia inpatients. This can provide basic descriptive statistics to serve as a

reference for supporting further research on multidrug-resistant bacterial infections, and inform policy formulation to reduce the burden of these infections.

Limitations

Our study has several limitations. First, the DPC database does not provide microscopy or laboratory-based information on the infecting pathogens. Thus, the results may include a degree of selection bias as MRSA cases were identified through the use of anti-MRSA drugs. If patients demonstrate sensitivity to anti-MRSA drugs, they may be administered trimethoprim/sulfamethoxazole or minocycline as an alternative treatment.[6] This could lead to an underestimation of the attributable costs in this study. On the other hand, anti-MRSA drugs are used not only to treat MRSA, but also to treat penicillin-resistant *Streptococcus pneumoniae*.[29] In this case, this could lead an overestimation of the frequency of MRSA infections. However, this is unlikely to heavily influence the results due to the low incidence of these infections. Second, our samples may not be representative of all severe community-onset pneumonia patients, because we did not include those whose major diagnosis was either sepsis or respiratory failure with a secondary diagnosis of pneumonia. The underestimation of severe pneumonia patients could therefore result in an underestimation of medical costs. Third, the control group included other multidrug-resistant bacteria, which may have resulted in an underestimation of the costs due to MRSA infections alone. In consideration of these limitations, it is possible that these findings may have underestimated the burden of MRSA.

CONCLUSIONS

This study quantified the burden of MRSA infections in community-onset pneumonia patients in Japan. Our findings suggest that these infections induce substantial clinical and economic burden through longer LOS and higher in-hospital mortality rate, antibiotic medication costs, and total hospitalization costs. These estimates can support further studies on multidrug-resistant bacterial infections, and eventually can be used to inform policymakers when examining measures to reduce the burden of these infections.

References

1. Magiorakos A, Srinivasan A, Carey R, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268-81.
2. Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. Clin Infect Dis 2003;36:1433-7.
3. Ministry of Health, Labour and Welfare. Japanese Nosocomial Infectious Surveillance 2013, Available from: https://www.nih-janis.jp/report/open_report/2013/3/2/zen_Open_Report_201300.pdf, Published July 9, 2014, Accessed September 29, 2015.
4. Uematsu H, Kunisawa S, Yamashita K, Imanaka Y. The impact of patient profiles and procedures on hospitalization costs through length of stay in community-acquired pneumonia patients based on a Japanese administrative database. PLoS ONE 2015;10:e0125284.
5. Graffunder EM, Venezia RA. Risk factors associated with nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection including previous use of antimicrobials. J Antimicrob Chemother 2002;49:999-1005.
6. Naimi TS, LeDell KH, Como-Sabetti K, Borchardt SM, Boxrud DJ, Etienne J, et al. Comparison of community-and health care–associated methicillin-resistant *Staphylococcus aureus* infection. JAMA 2003;290:2976-84.
7. Gould I. The clinical significance of methicillin-resistant *Staphylococcus aureus*. J Hosp Infect 2005;61:277-82.
8. Lee BY, Singh A, David MZ, Bartsch SM, Slayton RB, Huang SS, et al. The economic burden of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA). Clin Microbiol Infect 2013;19:528-36.
9. Falcone M, Russo A, Cangemi R, Farcomeni A, Calvieri C, Barillà F, et al. Lower mortality rate in elderly patients with community-onset pneumonia on treatment with aspirin. J Am Heart Assoc 2015;4:e001595.
10. Taneja C, Haque N, Oster G, Shorr AF, Zilber S, Kyan PO, et al. Clinical and economic outcomes in patients with community-acquired *Staphylococcus aureus* pneumonia. J Hosp Med 2010;5:528-34.
11. Shorr AF, Haque N, Taneja C, Zervos M, Lamerato L, Kothari S, et al. Clinical and economic outcomes for patients with health care-associated *Staphylococcus aureus* pneumonia. J Clin Microbiol 2010;48:3258-62.
12. Anderson GF, Squires DA. Measuring the U.S. health care system: a cross-national comparison. Issue Brief (Commonw Fund) 2010;90:1-10.
13. Uematsu H, Hashimoto H, Iwamoto T, Horiguchi H, Yasunaga H. Impact of guideline-concordant microbiological testing on outcomes of pneumonia. Int J Qual Health Care 2014;26:100-7.
14. Hamada T, Yasunaga H, Nakai Y, Isayama H, Horiguchi H, Fushimi K, et al. Impact of hospital volume on outcomes in acute pancreatitis: a study using a nationwide administrative database. J Gastroenterol 2014;49:148-55.
15. Uematsu H, Kunisawa S, Sasaki N, Ikai H, Imanaka Y. Development of a risk-adjusted in-hospital mortality prediction model for community-acquired pneumonia: a retrospective analysis using a Japanese administrative database. BMC Pulm Med 2014;14:203.
16. Shindo Y, Sato S, Maruyama E, Ohashi T, Ogawa M, Imaizumi K,et al. Comparison of severity scoring systems A-DROP and CURB-65 for community-acquired pneumonia. Respirology 2008;13:731-5.
17. Aikawa N, Kusachi S, Mikamo H, Takesue Y, Watanabe S, Tanaka Y, et al. Efficacy and safety of intravenous daptomycin in Japanese patients with skin and soft tissue infections. J Infect Chemother 2013;19:447-55.
18. Park S, Lee J, Ikai H, Otsubo T, Ukawa N, Imanaka Y. Quality of care and in-hospital resource use in acute myocardial infarction: evidence from Japan. Health Policy (New York) 2013;111:264-72.
19. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004;57:1288-94.
20. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963;185:914-9.
21. Kumamaru H, Tsugawa Y, Horiguchi H, Kumamaru KK, Hashimoto H, Yasunaga H. Association between hospital case volume and mortality in non-elderly pneumonia patients stratified by severity: a retrospective cohort study. BMC Health Serv Res 2014;14:302-6963-14-302.
22. O'Brien RM. A caution regarding rules of thumb for variance inflation factors. Qual Quan 2007;41:673-90.
23. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011;10:150-61.
24. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. J Thorac Cardiovasc Surg 2007;134:1128-35, e3.
25. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399-424.
26. Sasaki T, Izawa M, Okada Y. Current trends in health insurance systems: OECD countries vs. Japan. Neurol Med Chir (Tokyo) 2015;55:267-75.
27. Shindo Y, Ito R, Kobayashi D, Ando M, Ichikawa M, Shiraki A, et al. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. Am J Respir Crit Care Med 2013;188:985-95.
28. Austin PC, Mamdani MM, Stukel TA, Anderson GM, Tu JV. The use of the propensity score for estimating treatment effects: administrative versus clinical data. Stat Med 2005;24:1563-78.
29. Heffelfinger JD, Dowell SF, Jorgensen JH, Klugman KP, Mabry LR, Musher DM, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance: a report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. Arch Intern Med 2000;160:1399-408.