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Treatment procedures and associated medical costs of methicillin-resistant *Staphylococcus aureus* infection in Japan: A retrospective analysis using a database of Japanese employment-based health insurance

Akira Yuasa[1,2], Tatsunori Murata[3], Keiji Imai[1], Yuji Yamamoto[4] and Yoko Fujimoto[1]

Abstract

Objectives: This study aimed to determine the patient characteristics, treatment procedures, and medical costs of methicillin-resistant *Staphylococcus aureus* infections in clinical practice in Japan.

Methods: Using the MinaCare database of healthcare information covering nearly 3 million individuals, of which 90% were aged 20–59 years, we extracted and analyzed data of patients who were aged ⩾15 years and diagnosed with methicillin-resistant *S. aureus* during hospitalization between April 2010 and August 2015.

Results: A total of 684 patients with methicillin-resistant *S. aureus* infection were listed in the database, of which 365 were eligible to be included in this study. Mean patient age was 52.9 years, and 31.5% of the patients were females. Methicillin-resistant *S. aureus* bacteremia was the most common methicillin-resistant *S. aureus* infection (32.9%) with a mean age of 48.5 years, followed by pneumonia (24.1%) with a mean age of 61.0 years and methicillin-resistant *S. aureus* surgical site infection (6.3%) with a mean age of 49.7 years. Vancomycin was the most frequently prescribed anti–methicillin-resistant *S. aureus* drug used as the first-line therapy (68.5%), followed by teicoplanin (14.2%), linezolid (7.9%), arbekacin (5.8%), and daptomycin (3.6%). The mortality rate was 11.0%, and the mean treatment duration was 13.3 days. The median total medical cost per patient was US$5083. The median treatment cost for methicillin-resistant *S. aureus* bacteremia was the highest among the methicillin-resistant *S. aureus* infections at US$9099, followed by methicillin-resistant *S. aureus* pneumonia at US$3676 and surgery site infections at US$2084.

Conclusion: Although the proportion of patients with methicillin-resistant *S. aureus* is very small in the employment-based health insurance database, methicillin-resistant *S. aureus* bacteremia is the most common methicillin-resistant *S. aureus* infection in the working-age population and requires the highest medical cost. Methicillin-resistant *S. aureus* pneumonia is more common in the elderly and is a cause of high mortality.

Keywords

Claims database, methicillin-resistant *Staphylococcus aureus*, medical cost, mortality rate, real-world data

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Introduction

Refractory infections caused by the emergence of drug-resistant bacteria have become a serious global concern.[1–3] In Japan, the spread of healthcare-associated drug-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin (VCM)-resistant *Enterococci*, multidrug-resistant *Pseudomonas aeruginosa*, and

[1]Medical Affairs, Pfizer Japan Inc., Tokyo, Japan
[2]Graduate School of Medicine, International University of Health and Welfare, Tokyo, Japan
[3]CRECON Medical Assessment, Inc., Tokyo, Japan
[4]MinaCare Co., Ltd, Tokyo, Japan

Corresponding author:
Akira Yuasa, Corporate Affairs, Health & Value, Pfizer Japan Inc., Shinjuku Bunka Quint Building, 3-22-7 Yoyogi, Shibuya-ku, Tokyo 151-8589, Japan.
Email: akira.yuasa@pfizer.com

multidrug-resistant *Acinetobacter* spp., occurs quite often, and the prevalence of community-acquired infections with drug-resistant bacteria has also increased.[1,4] In particular, MRSA is the most frequently encountered refractory infection in hospitals at present. The national surveillance program—Japan Nosocomial Infections Surveillance (JANIS)—indicated that the prevalence of MRSA infections was 10.46% in 2008, which despite gradual decrease to 6.64% in 2015, remains far too high.[4,5]

Despite the high prevalence of refractory infections, the development of new antimicrobial drugs has remained virtually stagnant over the past decade. The management of infectious diseases is facing a critical situation due to few treatment options against constantly evolving drug-resistant bacterial infections. The resulting prolonged hospitalizations and high mortality among patients with MRSA infections have substantially increased the medical costs, which in turn is a significant social issue. This increasing burden of medical expenses due to MRSA infections has been widely reported in Japan and overseas.[6–12] However, calculating the total costs reported in previous studies is challenging because the estimated medical expenses vary greatly depending on the materials and methods used to treat patients. In addition, healthcare systems, number of medical institutions studying this problem, types of infection, MRSA severity, underlying diseases, and analytical methods vary across countries.[13,14]

Research using claims databases can estimate medical costs based on massive amounts of patient data. Two major types of claims databases are available in Japan: those based in medical institutions and others containing employment-based health insurance (EHI) data. The Diagnosis Procedure Combination (DPC) database is a representative medical institution-based database, which includes data corresponding to approximately half of all the inpatient admissions into acute care hospitals in Japan. DPC is a patient case-mix system primarily used for determining reimbursements for acute care hospitals.[15] Although it encompasses all generations, 80% of the inpatients are over 60 years of age. Remarkably, only one claims database study has been conducted in Japan using the DPC system to date (hereafter, DPC study). Although the DPC study identified overall median and mean medical costs of MRSA infection per patient, patient characteristics and medical expenses for each MRSA infection type remain unclear.

Meanwhile, the EHI databases comprise data of a large working-age population (age 20–59 years). Almost all Japanese people enroll in one of the several national health insurance programs, including EHI, depending on their occupation, age, and status (dependent or not), and they receive medical services accordingly.[16] The claims databases of the Japanese EHI systems are regularly updated with regard to checkups as well as medical and pharmaceutical claims for working individuals and their dependent family members. The advantage of EHI databases is that all medical claims history of all enrollees can be traced via their identifiers regardless of whether they visit hospitals (private or public), primary healthcare clinics, or pharmacies. However, no study has focused on the current clinical scenario of MRSA infection types using an EHI database.

To investigate the current scenario of MRSA infections in Japan, we extensively analyzed the relevant segments of a large-scale EHI database and compared the results with the results of the DPC study. In this study, we assessed detailed patient characteristics, actual treatment, clinical outcomes, and medical costs of each type of MRSA infection.

Methods

Data source

This retrospective analysis was conducted using the MinaCare database (MinaCare Co., Ltd, Tokyo, Japan) covering nearly 3 million individuals, of which 90% were aged 20–59 years, regardless of their health status.[16]

Ethical considerations

Ethical approval of this study was obtained from the Institutional Review Board of the International University of Health and Welfare (IRB Number: 16-Ig-59). The MinaCare database only contains unlinkable anonymized data. We retrospectively used these de-identified data for analysis and the study required no direct patient intervention. The requirement of informed patient consent was waived as the nature of this project was out of the scope of the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" set by the Japanese government.

Subjects

Individuals who met the following inclusion criteria were eligible for the analysis: patients diagnosed with MRSA infection (U80.1 of ICD-10 code or MRSA was indicated as the standard disease name) during hospitalization between April 2010 and August 2015 (hereinafter referred to as the research period) and patients aged ⩾15 years who received an original or a generic anti-MRSA drug containing the active ingredients of VCM, teicoplanin (TEIC), arbekacin (ABK), linezolid (LZD), or daptomycin (DAP), which have all been approved as anti-MRSA drugs in Japan. Exclusion criteria were as follows: patients who were prescribed with anti-MRSA drugs during the baseline period (30 days before the start of follow-up) or whose prescription history of anti-MRSA drugs during the baseline period was not confirmed, patients whose prescription period of anti-MRSA drugs was shorter than 2 days, patients who were diagnosed only with methicillin-resistant coagulase-negative *Staphylococci* infection, or patients only with diagnostic records of an MRSA carrier. In addition, to simply estimate the medical cost per patient with one type of MRSA infection, patients prescribed several anti-MRSA drugs at the initiation of the follow-up period and patients

diagnosed with several types of MRSA infection in the same month were excluded from the analysis.

The date of MRSA infection for each patient was defined as the time of the initial prescription (index date), which was set as the start point of follow-up in this analysis. Patients who were diagnosed with MRSA infection in the previous month were excluded due to multiple infections during the same research period.

Patients were traced using individual identifiers to determine the prognosis, which was categorized as death (in reference to the record at the time of hospital discharge), cure (defined as no prescription of anti-MRSA drugs for 14 days or longer after the final prescription), or unknown (no prescription of anti-MRSA drugs for 14 days or longer after the final prescription could not be confirmed for some reason, patients who were left out of the database, or patients who received a continuous treatment as of July 2015).

Outcomes

In this study, we examined a considerable array of patient characteristics, including the types of MRSA infections, age, sex, comorbidities and complications, use of each anti-MRSA drug prescribed at the start of the follow-up period, use of prescribed medications other than anti-MRSA drugs during the baseline period, clinical outcomes, treatment duration, and medical costs during the treatment period.

Medical costs are shown in US dollars (US$), using the Bank of Japan's official exchange rate of 103 Yen/US$, which was the mean exchange rate in 2014, a year included in the present research period and that used in the DPC study.

Statistical analysis

Because our goal here was to clarify how MRSA infections were actually treated using the large claims database, we did not calculate and justify a sample size in advance or compared variables, including outcomes, among the patient groups we studied. We used descriptive statistics for summarizing the data, and all analyses were performed using SAS 9.4 (Cary, NC, USA).

Results

Based on the inclusion criteria mentioned above, 684 patients with MRSA infections were extracted from the MinaCare database. Among these, 319 were eliminated based on our exclusion criteria, and the remaining 365 patients were included (Supplementary Figure 1).

Patient characteristics, treatment with anti-MRSA drugs, and clinical outcomes of patients with MRSA infection in the database are presented in Table 1. Mean patient age was 52.9 years, and 31.5% of the patients were females. MRSA bacteremia (32.9%) was the most common MRSA infection, followed by MRSA pneumonia (24.1%) and MRSA surgical site infection (6.3%). Diabetes mellitus (50.7%), cancer (46.6%), and cerebrovascular disease (19.7%) were frequent comorbidities across all patients. VCM was the most frequently prescribed anti-MRSA drug at the start of the follow-up period (68.5%), followed by TEIC, LZD, ABK, and DAP. Mean duration of the anti-MRSA drug treatment was 13.3 days across all patients, 15.5 days for those with MRSA bacteremia, 12.5 days for those with MRSA pneumonia, and 10.6 days for those with MRSA surgical site infections. The median treatment period was 10 days across all patients.

The mortality rate was the highest among patients with MRSA pneumonia (17.0%), followed by those with MRSA bacteremia (11.7%). Cure was confirmed in 82.5% of the patients with MRSA bacteremia and 77.3% of the patients with MRSA pneumonia.

Table 2 summarizes the backgrounds of deceased patients according to each infection site. Mean age of deceased patients was 60 years, which was 7.1 years older than the mean age of all patients included in the study (52.9 years). However, there was only a small difference in mean age between surviving and deceased patients with MRSA bacteremia (48.5 vs 51.7 years). Diabetes mellitus (70.0%) and cancer (60.0%) were the common comorbidities among deceased patients. Mean treatment durations for deceased patients with MRSA bacteremia and pneumonia were 17.8 and 15.9 days, respectively, whereas durations for those patients cured of MRSA bacteremia and pneumonia were 13.9 and 11.6 days, respectively.

Median medical cost per patient during the treatment period was US$5083. The costs based on the type of MRSA infection varied substantially, being US$9099 for MRSA bacteremia, US$3676 for MRSA pneumonia, and US$2084 for MRSA surgical site infections (Table 3). Median drug cost per patient was US$1695, which included medications for treating MRSA, cancer, and fungal infections as well as immunosuppressants and products for blood transfusions. The drug cost for MRSA bacteremia was the highest among different types of MRSA infections (US$5098), followed by MRSA pneumonia (US$1395) and MRSA surgical site infections (US$512). Median cost for anti-MRSA drugs per patient was US$394, which was similar across all types of MRSA infections. However, the cost per patient for blood products for transfusion to treat MRSA bacteremia was very high at US$2216, accounting for a large portion of the total drug costs. Furthermore, patients with MRSA bacteremia also spent US$386 on antifungal drugs.

Other significant costs were for tests (US$219 per patient), medical treatments (US$152 per patient), and room costs (US$1694 per patient). These costs were higher in patients with MRSA bacteremia than in those with other types of MRSA infections. Mean costs are listed in Supplementary Table 1.

Discussion

This retrospective observational study using the EHI MinaCare database analyzed the actual treatments and

Table 1. Patient characteristics, treatments, and clinical outcomes of patients with MRSA infection.

	Total	Type of MRSA infection				
		Bacteremia	Pneumonia	SSI	Others	Unknown
N	365	120	88	23	32	102
Age, mean (SD)	52.9 (15.7)	48.5 (15.5)	61.0 (13.8)	49.7 (15.0)	48.6 (16.3)	53.0 (14.9)
Female, n (%)	115 (31.5)	40 (33.3)	32 (36.4)	6 (26.1)	11 (34.4)	26 (25.5)
Comorbidity						
Diabetes mellitus, n (%)	185 (50.7)	68 (56.7)	50 (56.8)	10 (43.5)	12 (37.5)	45 (44.1)
Cancer, n (%)	170 (46.6)	67 (55.8)	46 (52.3)	6 (26.1)	13 (40.6)	38 (37.3)
Cerebrovascular disease, n (%)	72 (19.7)	17 (14.2)	25 (28.4)	4 (17.4)	4 (12.5)	22 (21.6)
Bone fracture/bone disorder, n (%)	55 (15.1)	12 (10.0)	11 (12.5)	5 (21.7)	5 (15.6)	22 (21.6)
Rheumatoid arthritis, n (%)	15 (4.1)	3 (2.5)	5 (5.7)	1 (4.3)	2 (6.3)	4 (3.9)
Drugs prescribed in baseline period						
Systemic steroid, n (%)	114 (31.2)	51 (42.5)	28 (31.8)	4 (17.4)	8 (25.0)	23 (22.5)
Immunosuppressant, n (%)	35 (9.6)	24 (20.0)	7 (8.0)	0 (0.0)	2 (6.3)	2 (2.0)
Antibacterial, n (%)	212 (58.1)	78 (65.0)	61 (69.3)	8 (34.8)	12 (37.5)	53 (52.0)
Conducting blood culture test, n (%)	267 (73.2)	75 (62.5)	80 (90.9)	14 (60.9)	21 (65.6)	77 (75.5)
Anti–MRSA drug as a first-line therapy						
Vancomycin, n (%)	250 (68.5)	69 (57.5)	64 (72.7)	18 (78.3)	26 (81.3)	73 (71.6)
Teicoplanin, n (%)	52 (14.2)	28 (23.3)	9 (10.2)	3 (12.0)	1 (3.1)	11 (10.8)
Linezolid, n (%)	29 (7.9)	12 (10.0)	8 (9.1)	0 (0.0)	0 (0.0)	9 (8.8)
Arbekacin, n (%)	21 (5.8)	5 (4.2)	7 (8.0)	0 (0.0)	1 (3.1)	8 (7.8)
Daptomycin, n (%)	13 (3.6)	6 (5.0)	0 (0.0)	2 (8.7)	4 (12.5)	1 (1.0)
Treatment duration (days), mean (SD)	13.3 (11.8)	15.5 (15.3)	12.5 (9.1)	10.6 (8.6)	10.0 (6.8)	12.9 (10.7)
Treatment duration (days), median (Q1, Q3)	10.0 (6.0, 16.0)	10.0 (7.0, 18.0)	10.0 (6.0, 16.5)	6.0 (4.0, 16.0)	9.0 (5.0, 13.0)	9.0 (6.0, 16.0)
Clinical outcome of MRSA treatment						
Death, n (%)	40 (11.0)	14 (11.7)	15 (17.0)	0 (0.0)	3 (9.4)	8 (7.8)
Cure, n (%)	305 (83.6)	99 (82.5)	68 (77.3)	23 (100.0)	29 (90.6)	86 (84.3)
Unknown, n (%)	20 (5.5)	7 (5.8)	5 (5.7)	0 (0.0)	0 (0.0)	8 (7.8)

MRSA: methicillin-resistant *Staphylococcus aureus*; SD: standard deviation; SSI: surgical site infections.

medical costs of MRSA infections. The database mainly covers the working-age population (aged 20–59 years). The working-age population is approximately 60 million people in Japan, which has a total population of 130 million. The MinaCare database comprises data of nearly 3 million people, accounting for approximately 5% of the total working-age population in Japan. However, only 365 patients (2.2 per 100,000 person-year) with MRSA infection were identified to be eligible over the study period of 5 years. Mean patient age was 52.9 years, and 31.5% of the patients were females. The mean MRSA treatment duration was 13.3 days, the in-hospital mortality rate was 11.0%, and the median total cost was US$5083 per patient. In contrast, in the DPC study, using an inpatient database comprising 7.8 million Japanese inpatients, 93,838 patients (1207 per 100,000 person-year) were categorized as being MRSA-infected, with a mean age of 66.8 years, a female proportion of 37.9%, a median hospitalization period of 51 days, an in-hospital mortality rate of 22.9%, and a median total hospitalization cost of US$21,399 per patient in 2015.[15]

Evidently, there are considerable differences in the results between the two databases. First, the proportion of patients with MRSA infections identified in this study based on the MinaCare database was substantially smaller than identified in the DPC study (2.2 vs 1207 per 100,000 person-year). This difference can be explained by the fact that the MinaCare database covers 3 million people, regardless of their health status. In addition, this study excluded patients with multiple types of MRSA infection.

Moreover, elderly people, particularly those with comorbidities, are more susceptible to MRSA. According to the JANIS data, patients are at an increased risk of acquiring MRSA infection with advanced age. In 2015, the incidence of MRSA infection was 3.9% in children, 12.2% in individuals in

Table 2. Baseline characteristics of deceased patients with MRSA infection.

	Total	Type of MRSA infection				
		Bacteremia	Pneumonia	SSI	Others	Unknown
N	40	14	15	0	3	8
Age, mean (SD)	60.0 (12.6)	51.7 (15.2)	66.8 (6.1)	0 (0.0)	63.0 (6.1)	60.8 (11.4)
Female, n (%)	13 (32.5)	3 (21.4)	6 (40.0)	0 (0.0)	2 (66.7)	2 (25.0)
Comorbidity						
Diabetes mellitus, n (%)	28 (70.0)	10 (71.4)	12 (80.0)	0 (0.0)	1 (33.3)	5 (62.5)
Cancer, n (%)	24 (60.0)	11 (78.6)	9 (60.0)	0 (0.0)	1 (33.3)	3 (37.5)
Cerebrovascular disease, n (%)	13 (32.5)	2 (14.3)	7 (46.7)	0 (0.0)	2 (66.7)	2 (25.0)
Bone fracture/bone disorder, n (%)	5 (12.5)	3 (21.4)	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)
Rheumatoid arthritis, n (%)	4 (10.0)	0 (0.0)	2 (13.3)	0 (0.0)	0 (0.0)	2 (25.0)
Drugs prescribed in baseline period						
Systemic steroid, n (%)	12 (30.0)	3 (21.4)	5 (33.3)	0 (0.0)	2 (66.7)	2 (25.0)
Immunosuppressant, n (%)	2 (5.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
Antibacterial, n (%)	24 (60.0)	9 (64.3)	8 (53.3)	0 (0.0)	1 (33.3)	6 (75.0)
Conducting blood culture test, n (%)	34 (85.0)	11 (78.6)	14 (93.3)	0 (0.0)	2 (66.7)	7 (87.5)
Anti-MRSA drug as a first-line therapy						
Vancomycin, n (%)	23 (57.5)	5 (35.7)	10 (66.7)	0 (0.0)	2 (66.7)	6 (75.0)
Teicoplanin, n (%)	5 (12.5)	2 (14.3)	2 (13.3)	0 (0.0)	0 (0.0)	1 (12.5)
Linezolid, n (%)	6 (15.0)	4 (28.6)	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)
Arbekacin, n (%)	4 (10.0)	1 (7.1)	1 (6.7)	0 (0.0)	1 (33.3)	1 (12.5)
Daptomycin, n (%)	2 (5.0)	2 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment duration (days), mean (SD)	15.4 (9.8)	17.8 (12.4)	15.9 (9.7)	0 (0.0)	10.0 (1.0)	12.4 (5.1)
Treatment duration (days), median (Q1, Q3)	12.5 (9.0, 21.0)	12.5 (10.0, 29.0)	13.0 (10.0, 23.0)	0 (0.0, 0.0)	10.0 (9.0, 11.0)	11.0 (8.5, 15.5)

MRSA: methicillin-resistant *Staphylococcus aureus*; SD: standard deviation; SSI: surgical site infections.

their 20s to 50s, 14.3% in those in their 60s, 26.3% in those in their 70s, 32.7% in those in their 80s, and 10.5% in those in their 90s or older;[17] almost similar rates were reported in 2018.[18] The mean age of patients in the DPC study was consistent with the above trend (66.8 years),[15] whereas the mean age in this study (52.9 years) was relatively young, indicating that the estimated incidence rate obtained using an EHI database would be low. This risk becomes clearer when incidences are compared based on the types of MRSA infections. In this study, MRSA bacteremia (mean age of 48.5 years) was the most common type of MRSA infection, accounting for 32.9% of all the patients, followed by MRSA pneumonia (mean age 61.0 years; 24.1%). On the contrary, according to the annual report released by JANIS, MRSA pneumonia (39.4%) was the most common type of MRSA infection among new cases of nosocomial MRSA, followed by MRSA bacteremia (16.6%) in 2015.[17] These differences in incidence rates can be attributed to different age distributions involved in each study. Elderly inpatients are more vulnerable to MRSA pneumonia because they spend most of their daily lives in a healthcare setting and present with a considerable number of specific risk factors, including recent hospitalization, recent use of intravenous antibiotics, long-term residence in a care facility, extended hospital stay, dialysis, or use of indwelling percutaneous catheters.[19–22] Meanwhile, certain proportions of patients in all age groups, including young ones, who undergo surgeries are systemically infected with MRSA. Therefore, it is important to consider that patients with MRSA pneumonia were identified in the MinaCare database, which largely comprises the working-age population. Therefore, the EHI databases appear to be inappropriate for estimating the total medical costs of diseases that show an age-dependent prevalence.

Furthermore, treatment periods and medical costs per patient for each type of MRSA infection may be similar regardless of age because the standard administration period of antibiotics has been established for each type of MRSA infection in the guidelines for the treatment of MRSA.[23] For example, depending on the extent of infection, adults with uncomplicated MRSA bacteremia are administered antibiotics for at least 2 weeks, and those with complicated MRSA bacteremia (defined as patients with positive blood culture results that do not meet the criteria for uncomplicated bacteremia) are administered 4–6 weeks of therapy. In addition, 7 days and 3

Table 3. Median costs during the treatment period for patients with MRSA infection (US dollars/patient).

	Total		Type of MRSA infection									
			Bacteremia		Pneumonia		SSI		Others		Unknown	
	n = 365		n = 120		n = 88		n = 23		n = 32		n = 102	
	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3
Total costs	5083	2319, 11,616	9099	4188, 20,178	3676	1931, 11,360	2084	1215, 5843	3701	1797, 6109	4712	8126, 2224
Costs of drugs	1695	576, 5790	5098	1728, 12,470	1395	547, 4820	512	242, 1196	975	407, 2817	1193	2638, 395
Anti-MRSA drugs	394	156, 873	528	307, 1356	320	137, 849	279	137, 933	389	132, 664	254	754, 151
Antifungal drugs	0	0, 456	386	0, 1938	0	0, 293	0	0, 0	0	0, 0	0	0, 0
Anticancer drugs	0	0, 0	0	0, 0	0	0, 0	0	0, 0	0	0, 0	0	0, 0
Immunosuppressants	0	0, 0	0	0, 149	0	0, 0	0	0, 0	0	0, 0	0	0, 0
Blood products for transfusion	0	0, 1723	2216	0, 6009	0	0, 901	0	0, 0	0	0, 0	0	163, 0
Costs of tests	219	88, 456	283	138, 660	202	96, 479	85	25, 189	169	78, 288	217	350, 88
Costs of medical treatments	152	24, 662	271	40, 759	164	38, 619	27	0, 199	106	13, 548	170	708, 19
Plasmapheresis	0	0, 0	0	0, 0	0	0, 0	0	0, 0	0	0, 0	0	0, 0
Total body irradiation	0	0, 0	0	0, 0	0	0, 0	0	0, 0	0	0, 0	0	0, 0
HSCT	0	0, 0	0	0, 0	0	0, 0	0	0, 0	0	0, 0	0	0, 0
Room costs	1694	807, 3235	2356	1078, 4691	1148	663, 2875	1072	533, 3235	1389	872, 1971	1456	2918, 881
Isolation room fee	0	0, 0	0	0, 2080	0	0, 0	0	0, 0	0	0, 0	0	0, 0
Specific ICU costs	0	0, 0	0	0, 0	0	0, 0	0	0, 0	0	0, 0	0	0, 0
High care unit costs	0	0, 0	0	0, 0	0	0, 0	0	0, 0	0	0, 0	0	0, 0
Management costs for specific drugs	0	0, 73	46	0, 91	0	0, 73	23	0, 73	0	0, 59	0	73, 0
Blood irradiation	0	0, 0	0	0, 11	0	0, 0	0	0, 0	0	0, 0	0	0, 0

HSCT: Hematopoietic stem cell transplantation; MRSA: methicillin-resistant *Staphylococcus aureus*; SSI: surgical site infections.

weeks of antibiotic administration is recommended for in-hospital and necrotizing MRSA pneumonia, respectively. However, there are no established guidelines for the treatment of multiple or recurrent infections in immunocompromised patients or patients receiving immunosuppressive therapies, especially the elderly. The DPC study included patients with multiple types of MRSA infections with a median length of hospital stay of 51 (IQR: 30–88) days. However, we excluded patients with multiple and recurrent MRSA infections in the same month to better estimate medical costs for each type of MRSA infection. Thus, the great difference in medical costs between the present and DPC studies can be attributed to rather different patient selection criteria.

Retrospective observational studies have reported low cure and high mortality rates of MRSA pneumonia.[24,25] We observed a similar trend in this study: the mortality rate of patients with MRSA pneumonia (17.0%) was higher than that of patients with bacteremia (11.7%). In this study, deceased patients with MRSA pneumonia were older, although there was no significant difference in age between deceased patients with MRSA pneumonia and MRSA bacteremia. The DPC study reported a higher mortality rate (22.9%) due to a higher proportion of elderly patients. According to the guidelines,[23] it takes 2–3 weeks to treat MRSA bacteremia and MRSA pneumonia accompanied by MRSA bacteremia or necrotizing MRSA pneumonia, resulting in high medical costs. Indeed, mean treatment periods for MRSA pneumonia, MRSA bacteremia, and MRSA surgical site infections were 12.5, 15.5, and 10.6 days, respectively, although the median treatment period for each type of MRSA infection was 6–10 days. Accordingly, the total treatment cost (US$3676) for MRSA pneumonia was higher than that for MRSA surgical site infection (US$2084). However, the total cost for MRSA bacteremia (US$9099) was twofold higher than the total cost for MRSA pneumonia, although the treatment period for MRSA bacteremia was only several days longer than that for MRSA pneumonia. The higher cost for MRSA bacteremia was due to the cost for products for blood transfusion (US$2216) in most cases and requirement of isolation room admission in some cases. Meanwhile, costs for anti-MRSA drugs (US$528 for bacteremia) accounted for quite a small portion of the total medical costs (5%), and there were no major differences in these costs among different types of MRSA infections. In addition, VCM was the most frequently prescribed drug (about 70%) regardless of the type of MRSA infection, and it was also the anti-MRSA drug used for the longest period.

We believe that estimating the treatment periods, medical costs, and mortality rates for each type of MRSA infection in the actual clinical situation is essential. Periodic monitoring using this approach would help promote appropriate treatment for MRSA infections in the future. The Government of Japan has developed a National Action Plan on Antimicrobial Resistance (AMR) (2016–2020)[26] in accordance with the Global Action Plan on AMR produced by the World Health Organization.[27] Based on this plan, antibiotics should be prescribed only when necessary and appropriate. Our study demonstrated that the treatment periods being used in practice are close to those recommended in the guidelines. Nonetheless, new drug-resistant bacteria are emerging, and we need to keep the action plan evolving appropriately and substantially to encourage the development of new antibiotics.

Studies using claims databases have several limitations, which may affect the validity and reproducibility of their results. For example, this study has no controls and was not designed to compare medical costs of MRSA infection with those of other illnesses. Furthermore, there is no guarantee that all the disease names are recorded correctly in the claims database because no definitive diagnostic criteria for MRSA pneumonia are presently available. Moreover, even though healthcare data are corrected or copied, these might include errors regarding the number of treatments and dosages, and general disease classification errors can lead to the underestimation of numerous metrics, including incidence rates. Furthermore, since this investigation involves retrospective analysis using a claims database, we did not calculate and justify the sample size of this study in advance. Therefore, the limited sample size may also affect the validity and reproducibility of our results.

Conclusion

We investigated the current status of MRSA infection, the actual treatment histories of using anti-MRSA drugs, and the outcomes of patients with MRSA infections in Japan using a claims database of the Japanese EHI, which largely comprises working-age individuals. The incidence and medical costs of MRSA infections in such a population are considerably lower than those in inpatients populations, suggesting that an EHI database study is not helpful for understanding the total burden of an age-dependent disease. However, with this approach, disease costs per patient may be estimated and the state of drug prescription rates in the real-world setting may evaluated, including the safety and effectiveness of the prescribed drugs.

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ORCID iD

Akira Yuasa https://orcid.org/0000-0002-3699-7231

Supplemental material

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