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Clinical Characteristics of Invasive Methicillin-Resistant *Staphylococcus aureus* at General Hospital in the Central Region of Japan from July 2014 to June 2015

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Abstract

Methicillin-resistant *Staphylococcus aureus* is crucial pathogen caused severe invasive infection disease. This study was conducted to find out the prevalence and antimicrobial susceptibility pattern of invasive Methicillin-resistant *Staphylococcus aureus* isolates at general hospital in the central region of Japan from July 2014 to June 2015. Methicillin-resistant *Staphylococcus aureus* was identified by standard laboratory procedure. Antimicrobial susceptibility testing was performed by micro dilution assay according to CLSI recommendation. Invasive Methicillin-resistant *Staphylococcus aureus* disease was defined as isolation of bacteria from a normally sterile body site. One hundred seventy-one methicillin-resistant *Staphylococcus aureus* were isolated among which 95 (55.6%) were from inpatient and 76 (44.4%) were from outpatient. The age incidence of (0 - 1) years, (1 - 10) years, (11 - 40) years, (41 - 60) years and >60 years age groups were 18 (10.5%), 41 (24.0%), 15 (8.8%), 5 (2.9%), and 92 (53.8%) respectively. There was significant difference of age distribution between invasive and noninvasive disease in 0 - 1 years group and 11 - 40 years age group. Positive samples were received mostly from the pediatrics (56/32.7%), respiratory medicine (25/14.6%) and general medicine (25/14.6%). We also found the significant differences of department between invasive and noninvasive disease in pediatrics, dermatology, and surgery. Arbekacin, teicoplanin, and vancomycin were the most active antibiotics with 100% susceptible rates in our study. Our study revealed that erythromycin and gentamicin were more antimicrobial effective in invasive disease than in noninvasive disease significantly. Methicillin-resistant *Staphylococcus aureus* infection spreads worldwide easily and inadequate use of antibiotics contributes to uptake of their new antimicrobial resistance. Continuous antimicrobial surveys are need for guiding policy on the adequate use of antibiotics to reduce the morbidity and mortality.

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Keywords

Methicillin-Resistant *Staphylococcus aureus*, Susceptibility, Antimicrobial Resistance, Invasive Disease

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common pathogenic bacteria causing skin and soft tissue infections to life-threatening systemic infection such as toxic shock syndrome (TSS) and necrotizing pneumonia [1]. The mortality rate of severe, invasive MRSA infections is about 20% and it has been estimated that MRSA infections are the leading cause of death by an infectious pathogen in USA [2]. MRSA was first identified in the United Kingdom in 1961, only 2 years after introduction of methicillin [3]. From the 1980s, new strains of MRSA emerged which led to continuous pandemic infections of MRSA around the world. Now many countries report that MRSA strains account for approximately 25% - 50% of infectious *Staphylococcus aureus* in hospitals [4].

MRSA is due to acquisition of altered penicillin-binding protein PBP2a (PBP2'), encoded by the *mecA* gene, which is carried by amobile genetic element called staphylococcal cassette chromosome *mec* [5] [6]. Many MRSA clone have associated resistance to additional antibiotics, such as erythromycin, clindamycin, ciprofloxacin, and tetracycline [7]. Multidrug-resistant strains of *Staphylococcus aureus* are often only susceptible to vancomycin, an antibiotic with considerably lower efficiency compared to beta-lactams. Furthermore, vancomycin-resistant MRSA has been also reported [8].

The present study was conducted to find out the recent clinical characteristics of invasive MRSA isolates at general hospital in the central of Japan. Our result would contribute to more extensive surveillance study.

2. Materials and Methods

2.1. Strains and Clinical Data Collection

A total of 171 MRSA were obtained from various clinical specimens at Daido Hospital from July 2014 to June 2015. Daido Hospital is a 404-bed private general hospital in the central region of Japan. We used medical records appended to clinical species for the analysis of clinical feature at Daido Hospital. We considered several isolates from the same region of the same patient as one isolate per one patient for the analysis in this study. All staphylococcus isolates were identified by standard conventional biochemical methods or the VITEK2 system (bioMérieux, Durham NC, USA). Our experimental design was approved by the ethics committee at Daido hospital.

2.2. Antimicrobial Susceptibility Analysis

MRSA isolates were examined for 14 antibiotic susceptibilities as follows CEZ, cefazolin; MPIPC, oxacillin; IPM, imipenem; AMK, amikacin; GM, gentamicin; ABK, arbekacin; LVFX, levofloxacin; EM, erythromycin; CLDM, clindamycin; TEIC, teicoplanin; VCM, vancomycin; MINO, minocycline; FOM, fosfomycin; ST, Trimethoprim-sulfamethoxazole. Minimal inhibitory concentrations (MICs) were determined at clinical laboratory in Daido Hospital using broth micro dilution methodology with the VITEK2 system. Evaluation of susceptibilities were calculated based on Clinical Laboratory Standard Institute (CLSI) break point [9].

2.3. Statistical Analysis of the Data

We conducted the statistical analysis with the chi-squared test or Fisher's exact test when appropriate. Differences were considered significant when p was <0.05.

3. Results

First of all, we confirmed that all *Staphylococcus aureus* isolates were resistant to oxacillin in this study. Thus, we defined those isolates as methicillin-resistant *Staphylococcus aureus*. Next, we compared the differences

between invasive and noninvasive disease in this study. Invasive bacterial disease was defined as isolation of bacteria from a normally sterile body site. One hundred seventy-one MRSA were isolated among which 95 (55.6%) were from inpatient and 76 (44.4%) were from outpatient (**Table 1**). There was no significant difference of hospitalization between invasive and noninvasive disease. The age incidence among 0 - 1 years age group was 18 (10.5%) [invasive-0, noninvasive-18] (p = 0.01), among 1 - 10 years age group, 41 (24.0%) [invasive-9, noninvasive-32], among 11 - 40 years age group, 15 (8.8%) [invasive-8, noninvasive-7] ($p = 0.02$), in 41 - 60 years it was 5 (2.9%) [invasive-1, noninvasive-4] and in >60 years age group it was 92 (53.8%) [invasive-28, noninvasive-64] (**Table 1**). Most of the MRSA isolates were from the pediatrics (56/32.7%) [invasive-4, noninvasive-52 ($p < 0.01$) followed by respiratory medicine (25/14.6%) [invasive-6,noninvasive-19], general medicine (20/11.7%) [invasive-4, noninvasive-16] and dermatology (20/11.7%) [invasive-17, noninvasive-3] ($p < 0.01$) (**Table 1**). We also found the significant differences of department between invasive and non-invasive disease in surgery ($p < 0.01$). The results of antimicrobial susceptible patterns of MRSA isolates to various antibiotics tested in this study were shown in **Table 2**. Arbekacin, teicoplanin, and vancomycin were the most active antibiotics with 100% susceptible rates. Two antibiotics; erythromycin ($p = 0.02$) and gentamicin ($p < 0.01$) were more antimicrobial effective in invasive disease than in noninvasive disease significantly. There was no

Table 1. Clinical characteristic of methicillin-resistant *Staphylococcus aureus* isolates.

	Invasive (n = 46)	Noninvasive (n = 125)	*p* value
Hospitalization			
Outpatients	20	75	0.053
Inpatients	26	50	
Gender			
Male	21	71	0.195
Female	25	54	
Age			
0 - 1	0	18	0.015
1 - 10	9	32	0.412
11 - 40	8	7	0.016
4 - 60	1	4	0.874
>60	28	64	0.261
Department			
Cardiology	1	0	0.601
Dental surgery	0	1	0.601
Dermatology	17	3	<0.001
Endocrinology	0	2	0.951
Gastroenterology	2	1	0.363
General medicine	4	16	0.637
Health examination	0	1	0.601
Hematology	0	1	0.601
Nephrology	2	3	0.874
Neurology	0	4	0.511
Neurosurgery	0	5	0.387
Obstetrics and gynecology	0	1	0.601
Ophthalmology	0	1	0.601
Orthopedics	3	4	0.591
Pediatrics	4	52	<0.001
Respiratory medicine	6	19	0.723
Rheumatology	0	1	0.601
Surgery	7	2	0.002
Urology	0	8	0.177

Table 2. Antimicrobial susceptible patterns of methicillin-resistant *Staphylococcus aureus* isolates.

	Invasive (n = 46)	Noninvasive (n = 125)	*p* value
EM	21	34	0.002
CLDM	36	88	0.307
MINO	37	99	0.859
LVFX	16	51	0.475
AMK	42	74	0.777
GM	37	114	0.01
FOM	34	81	0.260
ST	45	123	0.687
CEZ	32	91	0.676
IPM	37	101	0.957

significant difference of antimicrobial effect between invasive and noninvasive disease in other antibiotics. Surprisingly, our results showed that 123 (72%) cefazoline- and 138 (81%) imipenem-susceptible MRSA isolates by *in vitro* analysis.

4. Discussion

In this study, we described the characteristics of invasive MRSA isolates from July 2014 to June 2015 at general hospital in the central region of Japan. With respect to hospitalized group, MRSA was isolated more from outpatients than inpatients. Our study showed the outpatient to inpatient ratio was about 1.25 times and there were no significant differences among gender. We clarified MRSA with age distribution. The present study reveals the prevalence of MRSA as seen in 0 - 1 years age group, it is 11%, increasing to 24% in 1 - 10 years age group, diminishing to 8.8% in 11 - 40 years age group and to 3% in 41%-60 years age group, and finally increasing to 53.8% in more than 60 years age group. Although young patients under 10 years frequently caused MRSA infection, the about half of MRSA were isolated from over 60 years age patients in our study. It is suggested to decrease immunity in the extremes of age groups.

In the analysis of clinical departments, we found that department where most patients with MRSA were detected was pediatrics. However, most MRSA were isolated from noninvasive disease in pediatrics. We presume that those isolates may colonize in patient. On the contrary, we found most MRSA caused invasive disease in surgery and dermatology. Staphylococcal skin disease frequently caused severe invasive disease such as TSS, Neonatal TSS-like exanthematous disease, and Staphylococcal scalded skin syndrome [1]. We may pay attention to infection-control management still more.

In the analysis of antimicrobial susceptibility, we did not find any vancomycin and teicoplanin-resistant MRSA in our study. A significant problem associated with MRSA is the subpopulation of MRSA with reduced vancomycin susceptibility in Japan [10]. However, the prevalence of MRSA with reduced vancomycin is low in Asian countries [11]. The recent trend of vancomycin-susceptible pattern of MRSA in Japan may be similar with that in Asian countries.

Furthermore arbekacin was effective antibacterial agent against all MRSA in our study. Arbekacin is classified as a kanamycin family aminoglycoside [12]. Arbekacin causes membrane damage and binds both to the 50s and 30S ribosomal subunits, resulting in codon misreading and inhibition of translation [13]. Arbekacin is not inactivated by aminoglycoside-inactivating enzymes [14]. Arbekacin shows the most potent antibacterial effect against clinically isolated MRSA strains among the aminoglycosides such as gentamicin, tobramycin, and amikacin [15], and the antibacterial effect of arbekacin is equivalent to that of vancomycin [15]. When MRSA is treated either with arbekacin or vancomycin with the same concentration, the post antibiotic effect of vancomycin was shorter compared with arbekacin [16]. Our results also suggested that arbekacin is potential first choice of anti-MRSA drug.

The 124 MRSA isolates were susceptible to clindamycin. Community-associated MRSA is known to be susceptible to clindamycin [17]. If the definition of this research was adapted to our results, about 72.5% of MRSA were considered as community associated MRSA. Community-associated MRSA contains SCC *mec* type IV or

V [18]. Other researcher reported that SCC *mec* type IV strains are susceptible to imipenem [19]. If the definition of this research was adapted to our results, about 80.7% of MRSA were considered as SCC mec type IV strain. From these two definitions, at least 70% of MRSA may be community-associated MRSA. In contrast to most healthcare-associated MRSA, community-associated MRSA is susceptible to non-beta lactam antibiotics, and therefore, is not multidrug resistant [20]. We found that many MRSA isolates had not only imipenem but also cefazolin susceptible activity. Those MRSA may be community-associated MRSA. The susceptible pattern of MRSA in Japan may gradually change. Asian countries have shown over 50% rate of MRSA, which is the most important cause of healthcare-associated infections [11]. MRSA accounts for 25.5% of community-associated Staphylococcus infections and 67.4% of healthcare-associated infections in Asia [11]. The result of our study was opposite to this Asian studies. As this previous Asian studies did not include in Japan, the prevalence of community-associated *Staphylococcu*s infections may be different from other Asian country. We suggest that community-associated MRSA spreads widely, in Japan, instead of healthcare-associated MRSA. Further molecular analysis is needed for the clarification of epidemiology of community-associated MRSA in Asian countries.

5. Conclusions

Incidence of MRSA infection is increasing worldwide and may lead to severe invasive infection by dissemination to other organs of the body if not treated adequately. The indiscriminate use of antibiotics has led to the emergence of multidrug resistance among commonly used antibiotics.

Our investigation aims to guide medical staffs on appropriate use of antibiotics. This aim is not only to reduce the morbidity and mortality in the patients but also to control the emergence and spread of resistance among MRSA. Continuous surveillance of the use of antibiotics helps in preserving the effectiveness of antibiotics. The results from our study strongly emphasize the need for continuous epidemiological monitoring of antibiotic resistant.

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References

[1] Iwamoto, M., Mu, Y., Lynfield, R., Bulens, S.N., Nadle, J., Aragon, D., *et al.* (2013) Trends in Invasive Methicillin-Resistant *Staphylococcus aureus* Infections. *Pediatrics*, **132**, e817-e824. http://dx.doi.org/10.1542/peds.2013-1112

[2] Klevens, R.M., Morrison, M.A., Nadle, J., Petit, S., Gershman, K., Ray, S., *et al.*, Active Bacterial Core surveillance (ABCs) MRSA Investigators (2007) Invasive Methicillin-Resistant *Staphylococcus aureus* Infections in the United States. *JAMA*, **298**, 1763-1771. http://dx.doi.org/10.1001/jama.298.15.1763

[3] Barber, M. (1961) Methicillin-Resistant *Staphylococci. Journal of Clinical Pathology*, **14**, 385-393. http://dx.doi.org/10.1136/jcp.14.4.385

[4] Diekema, D.J., Pfaller, M.A., Schmitz, F.J., Smayevsky, J., Bell, J., Jones, R.N., *et al.*, SENTRY Partcipants Group (2001) Survey of Infections Due to Staphylococcus Species: Frequency of Occurrence and Antimicrobial Susceptibility of Isolates Collected in the United States, Canada, Latin America, Europe, and the Western Pacific Region for the SENTRY Antimicrobial Surveillance Program, 1997-1999. *Clinical Infectious Disease*, **32**, S114-S132. http://dx.doi.org/10.1086/320184

[5] Hartman, B. and Tomasz, A. (1981) Altered Penicillin-Binding Proteins in Methicillin-Resistant Strains of *Staphylococcus aureus*. *Antimicrobial Agents and Chemotherapy*, **19**, 726-735. http://dx.doi.org/10.1128/AAC.19.5.726

[6] Katayama, Y., Ito, T. and Hiramatsu, K. (2000) A New Class of Genetic Element, Staphylococcus Cassette Chromosome Mec, Encodes Methicillin Resistance in *Staphylococcus aureus*. *Antimicrobial Agents and Chemotherapy*, **44**, 1549-1555. http://dx.doi.org/10.1128/AAC.44.6.1549-1555.2000

[7] Shorr, A.F. (2007) Epidemiology of Staphylococcal Resistance. *Clinical Infectious Disease*, **45**, S171-S176. http://dx.doi.org/10.1086/519473

[8] Otto, M. (2012) MRSA Virulence and Spread. *Cellular Microbiology*, **14**, 1513-1521. http://dx.doi.org/10.1111/j.1462-5822.2012.01832.x

[9] Clinical and Laboratory Standards Institute (CLSI) (2014) Performance Standards for Antimicrobial Susceptibility

Testing: 24st Informational Supplement. Clinical and Laboratory Standards Institute M100-S24, Wayne.

[10] Jean, S.S. and Hsueh, P.R. (2011) High Burden of Antimicrobial Resistance in Asia. *International Journal of Antimicrobial Agents*, **37**, 291-295. http://dx.doi.org/10.1016/j.ijantimicag.2011.01.009

[11] Song, J.H., Hsueh, P.R., Chung, D.R., Ko, K.S., Kang, C.I. and Peck, K.R., *et al.*, ANSORP Study Group (2011) Spread of Methicillin-Resistant *Staphylococcus aureus* between the Community and the Hospitals in Asian Countries: An ANSORP Study. *Journal of Antimicrobial Chemotherapy*, **66**, 1061-1069. http://dx.doi.org/10.1093/jac/dkr024

[12] Kondo, S. (1994) Development of Arbekacin and Synthesis of New Derivatives Stable to Enzymatic Modifications by Methicillin-Resistant *Staphylococcus aureus*. *Japanese Journal of Antibiotics*, **47**, 561-574.

[13] Tanaka, N., Matsunaga, K., Hirata, A., Matsuhisa, Y. and Nishimura T. (1983) Mechanism of Action of Habekacin, a Novel Amino Acid Containing Aminoglycoside Antibiotic. *Antimicrobial Agents and Chemotherapy*, **24**, 797-802. http://dx.doi.org/10.1128/AAC.24.5.797

[14] Matsumoto, T. (2014) Arbekacin: Another Novel agent for Treating Infections Due to Methicillin-Resistant *Staphylococcus aureus* and Multidrug-Resistant Gram-Negative Pathogens. *Clinical Pharmacology*, **6**, 139-148. http://dx.doi.org/10.2147/cpaa.s44377

[15] Watanabe, T., Ohashi, K., Matsui, K. and Kubota, T. (1997) Comparative Studies of the Bactericidal, Morphological and Post-Antibiotic Effects of Arbekacin and Vancomycin against Methicillin-Resistant *Staphylococcus aureus*. *Journal of Antimicrobial Chemotherapy*, **39**, 471-476. http://dx.doi.org/10.1093/jac/39.4.471

[16] Maltezou, H.C. and Giamarellou, H. (2006) Community-associated methicillin-resistant *Staphylococcus aureus* infections.*International Journal of Antimicrobial Agents*, **27**, 87-96. http://dx.doi.org/10.1016/j.ijantimicag.2005.11.004

[17] Kluytmans-Vandenbergh, M.F. and Kluytmans, J.A. (2006) Community-Associated Methicillin-Resistant *Staphylococcus aureus*: Current Perspectives. *Clinical Microbiology and Infection*, **12**, 9-15. http://dx.doi.org/10.1111/j.1469-0691.2006.01341.x

[18] Motoshima, M., Yanagihara, K., Morinaga, Y., Matsuda, J., Sugahara, K, Yamada, Y., *et al.* (2010) Genetic Diagnosis of Community-Associated MRSA: A Multiplex Real-Time PCR Method for Staphylococcal Cassette Chromosome Mec Typing and Detecting Toxin Genes. *Tohoku Journal of Experimental Medicine*, **220**, 165-170. http://dx.doi.org/10.1620/tjem.220.165

[19] Yamaguchi, T., Nakamura, I., Chiba, K. and Matsumoto, T. (2012) Epidemiological and Microbiological Analysis of Community-Associated Methicillin-Resistant *Staphylococcus aureus* Strains Isolated from a Japanese Hospital. *Japanese Journal of Infectious Disease*, **65**, 175-178.

[20] Kang, C.I. and Song, J.H. (2013) Antimicrobial Resistance in Asia: Current Epidemiology and Clinical Implications. *Infection & Chemotherapy*, **45**, 22-31. http://dx.doi.org/10.3947/ic.2013.45.1.22