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ORIGINAL RESEARCH

Epidemiological Study on Case Definition of Methicillin-Resistant *Staphylococcus aureus* Enteritis

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Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) enteritis is a condition in which MRSA grows abnormally in the intestine after administration of antimicrobial agents, resulting in enteritis. Patients with MRSA detected in stool culture tests are often diagnosed with MSRA enteritis. However, uncertainty remains in the diagnostic criteria; therefore, we conducted epidemiological studies to define these cases.

Patients and Methods: Patients who tested positive for MRSA by stool culture using selective media 48 h after admission to Kochi Medical School Hospital between April 1, 2012, and December 31, 2022, and did not meet the exclusion criteria were included. We defined MRSA enteritis (Group A) as cases that were responsive to treatment with vancomycin hydrochloride powder, had a Bristol Stool Scale of ≥ 5, and a stool frequency of at least three times per day; all others were MRSA carriers (Group B). Multivariate analysis was performed to risk factors associated with MRSA enteritis.

Results: Groups A and B included 18 (25.4%) and 53 (74.6%) patients, respectively. Multivariate logistic regression analysis showed that a white blood cell count of > 10000/μL (odds ratio [OR], 5.50; 95% confidence interval [CI], 1.12–26.9), MRSA count of ≥ 2+ in stool cultures (OR, 8.91; 95% CI, 1.79–44.3), and meropenem administration within 1 month of stool specimen submission (OR, 7.47; 95% CI, 1.66–33.6) were risk factors of MRSA enteritis.

Conclusion: The case definitions reviewed for MRSA enteritis may be useful as diagnostic criteria.

Keywords: MRSA enteritis, diagnostic criteria, white blood cell, MRSA counts in stool cultures, meropenem

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most frequently isolated nosocomial antibiotic-resistant bacterium and a problematic organism in healthcare-associated infections.[1] MRSA enteritis is a condition in which MRSA grows abnormally in the intestine after administration of antimicrobial agents, resulting in enteritis. Patients with MRSA detected in stool culture tests are often diagnosed with MRSA enteritis.[2,3] In Japan, MRSA enteritis is characterized by profuse watery diarrhea and has been reported to occur in older individuals, postoperatively in patients who underwent gastrectomy, and immunocompromised patients, and as a bacterial shift phenomenon after the administration of third-generation cephalosporin antibacterial agents.[4] Furthermore, MRSA enteritis was most frequently observed in the late 1980s and the early 1990s,[5,6] and since then, severe cases and deaths due to MRSA enteritis have become rare, and the number of cases has markedly decreased.[7] In addition, while the efficacy of screening for MRSA using chromogenic media has been reported, its diagnostic utility remains uncertain.[8] This is due to the lack of a firm definition of MRSA enteritis, which is caused by a lack of definition of diarrheal symptoms and frequency, inadequate studies on the number of MRSA detected, lack of routine examination of virulence factors and lack of pathological studies.[9] In contrast, *Clostridioides difficile* infection (CDI) is often observed in healthcare facilities,[10] and appropriate diagnostic criteria have been established.[11] Uncertainty remains in the diagnostic criteria of MRSA enteritis; therefore,

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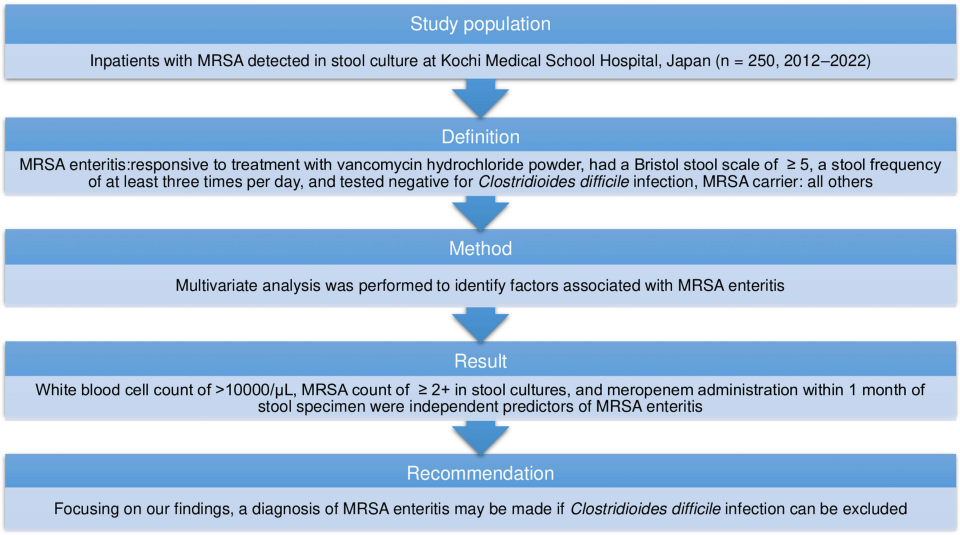
Graphical Abstract



we considered that a case definition for the diagnostic criteria of MRSA enteritis was required. We retrospectively examined the clinical characteristics and associated factors of cases where MRSA was detected in stool culture tests.

Materials and Methods

Study Design and Patients

This retrospective cohort study was conducted at Kochi Medical School Hospital between April 1, 2012, and December 31, 2022.

Patients who tested positive for MRSA after submitting a diarrhea stool specimen were included. If the same patient submitted multiple stool specimens between admission and discharge, only the first submission was considered.

The exclusion criteria were as follows: age < 18 years, patients who submitted a stool specimen within 48 h of admission, patients who received laxatives or intestinal decongestant cleansing agents within 48 h of the date of stool specimen submission, patients who received tube feeding for > 31 days within 1 month of the date of stool specimen submission, and patients with underlying inflammatory bowel disease. The Bristol Stool Scale (BSS) is a diagnostic medical tool used in clinical practice to classify human fecal morphology into seven categories.[12] In this study, after referring to previous reports,[12,13] we defined MRSA enteritis (Group A) as cases that were responsive to treatment with vancomycin hydrochloride powder and had a BSS of at least 5 and a stool frequency of at least 3 times per day, whereas MRSA carriers (Group B) were defined as cases that did not receive vancomycin hydrochloride powder and did not have a BSS of at least 5 or stool frequency of at least 3 times per day.

Data Collection

Clinical data were reviewed from electronic medical records to obtain complete medical records when MRSA was detected in patients' stool samples.

Information obtained from the electronic medical records included age, sex, route of admission, number of days from admission to stool examination, and relevant symptoms (eg, abdominal symptoms and fever) at the time of stool specimen submission. Furthermore, the data included autonomous defecation, underlying or comorbid conditions, biochemical or hematological tests, endoscopic findings, bacteria detected concurrent with MRSA in stool specimens, detection of MRSA in all specimens within 14 days of stool specimen submission. Data on antimicrobials, antacid preparations, intestinal regulating drugs, enteral nutrition, gastrointestinal surgery, cancer chemotherapy and radiation

therapy, vancomycin hydrochloride administration, death within 28 days of stool specimen submission, and death during hospitalization were also collected.

Microbiological Examinations

Within 2 h of receiving the specimens at the hospital, we inoculated approximately 1 g of stool specimen on agar media. The type of media and incubation conditions are as follows: MRSA I-A agar (Nikken Seibutsu Co., Ltd., Japan),[14] BTB lactose agar (Becton Dickinson), CHROMagar™ candida/potato dextrose fractionated medium (Kanto Chemical Co., Inc., Japan), CHROMagar™ STEC/SSV fractionated medium (Kanto Chemical Co., Inc., Japan), Pearlcore® TCBS agar medium "Eiken" (Eiken Chemical Co., Ltd., Japan), Pearlcore® SS agar medium "Eiken" (Eiken Chemical Co., Ltd., Japan) at 37°C for 48 h in an aerobic environment, and Campylobacter 10% sheep blood agar (Becton Dickinson) at 35°C for 48 h in a microaerophilic culture. MRSA I-A agar can concurrently screen clinical specimens for *Staphylococcus aureus* and MRSA using egg yolk reaction for determination.[14] Based on colonies developed on MRSA I-A agar, the number of bacteria was expressed in semiquantitative quantities as 1+, 2+, 3+, and 4+. The number of bacteria by semiquantitative quantification was determined to correspond to the following bacterial abundance: 1+ = 10^3 to 10^4 colony forming units (CFU)/mL, 2+ = 10^4 to 10^5 CFU/mL, 3+ = 10^5 to 10^6 CFU/mL, and 4+ = > 10^6 CFU/mL. Bacterial species were identified based on biochemical properties from April 2012 to July 2022 and using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI Biotyper ver. 9.0.0.0; Bruker Daltonics, Billerica, MA, USA) after August 2022. Antimicrobial susceptibility testing was performed using the microdilution method, and the results were interpreted according to the most recent Clinical and Laboratory Standards Institute Guidelines 2021.[15] Colonies that developed on MRSA I-A agar were subjected to antimicrobial susceptibility tests using the Microscan Pos Series with Combo Panel (Beckman Coulter, Inc., USA). The inoculum was standardized to a density of 0.5 McFarland standard by prompt method. Susceptibility to 15 antimicrobial agents (benzylpenicillin, ampicillin, oxacillin, sulbactam/ampicillin, clavulanic acid/amoxicillin, gentamicin, erythromycin, clarithromycin, minocycline, levofloxacin, vancomycin, daptomycin, sulfamethoxazole-trimethoprim, rifampicin, and linezolid) was assessed. The MRSA strain was used for quality control. The toxin was confirmed to diagnose CDI using a rapid immunoenzyme test for glutamate dehydrogenase and toxin (TECHLAB C. Diff Quik Chek COMPLETE kit, TECHLAB, Inc., USA). For glutamate dehydrogenase (+) and toxin (-) detection, the samples were applied to Accurate™ CCMA medium EX (Shimadzu Diagnostics, Inc., Tokyo, Japan). The strains were then coated with Accurate™ CCMA medium EX (Shimadzu Diagnostics, Inc., Tokyo, Japan) and incubated at 35°C for 48 h under anaerobic conditions. The developed strains were tested using the same kits.

All samples were analyzed using quantitative cytomegalovirus real-time polymerase chain reaction on a Cobas 6800 system (Roche Diagnostics, USA).

Variable Definitions

Continuous variables were divided into the following categories: age (</≥ 65 years),[16] Charlson Comorbidity Index (0, 1–2, 3–4, ≥ 5),[17] albumin (</≥ 3.0 g/dL),[18] C-reactive protein (CRP) (</≥ 6.1 mg/dL), creatinine (male: </≥ 1.07, female: </≥ 0.79),[18] estimated glomerular filtration rate (≤/> 60 mL/min/1.73 m^2),[19] white blood cell (WBC) (≤/>10000 /μL),[20] and MRSA counts in stool culture (1+, ≥ 2+).[9,21] The cut-off point for CRP was set to the median value, while age, Charlson Comorbidity Index, albumin level, creatinine level, WBC count, estimated glomerular filtration rate, and MRSA counts in stool culture were set based on the respective guidelines and literature.[15–21]

Statistical Analysis

Categorical variables are reported as percentages and continuous variables are reported as medians and interquartile ranges.[22] All statistical analyses were performed using EZR version 1.29 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[23] Fisher's exact test (two-tailed) was used to compare categorical variables, and the Mann–Whitney *U*-test was used to compare continuous variables. Logistic regression analysis was used to identify independent factors associated with diarrhea in patients with MRSA enteritis. Variables with $P < 0.05$ in univariate

analysis were entered into a multivariate model. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each variable in the multivariate model. Statistical significance was set at $P < 0.05$.

Ethics Statement

This study was approved by the Ethical Review Board of Kochi University School of Medicine (registration number: ERB-109102). All procedures adhered to the tenets of the Declaration of Helsinki. Informed consent was exempted from obtaining because no invasion or intervention on the patients and only medical and other information was used to conduct the study. Information on the conduct of the study was disclosed and patients were given the opportunity to refuse.

Results

Seventy-one patients who tested positive for MRSA using stool culture and did not meet the exclusion criteria were included in the study (Figure 1). The overall patient characteristics are summarized in Table 1. They were older (71.8 years) and predominantly male (64.8%). Stomachache (80.3%) and fever (temperature ≥ 38.0°C) (64.8%) were the most common accompanying symptoms at the time of stool specimen submission. The patient backgrounds of Group A and Group B are shown in Table 1. The results of microbiology examinations, including the MRSA counts in stool culture and details of the bacteria detected along with MRSA, are presented in Table 2. Group A included 18 patients (25.4%), and Group B included 53 patients (74.6%). Group A patient had significantly higher CRP levels ($P = 0.01$), WBC counts ($P = 0.01$), and MRSA counts of ≥2+ in stool cultures (44.4%, $P = 0.02$) than Group B patients. Moreover, a higher number of Group A patients had MRSA detected in sputum within 14 days of stool specimen submission (50.0%, $P < 0.01$) and meropenem administration within 1 month of stool specimen submission than Group B patients (55.6%, $P < 0.01$) (Table 2). The antimicrobial susceptibility profiles of MRSA isolates are shown in Table 3.

Multivariate logistic regression analysis showed that WBC counts of >10000 /μL (OR, 5.50; 95% CI, 1.12–26.9; $P = 0.04$), MRSA counts of ≥ 2+ in stool cultures (OR, 8.91; 95% CI, 1.79–44.3; $P < 0.01$), and meropenem administration

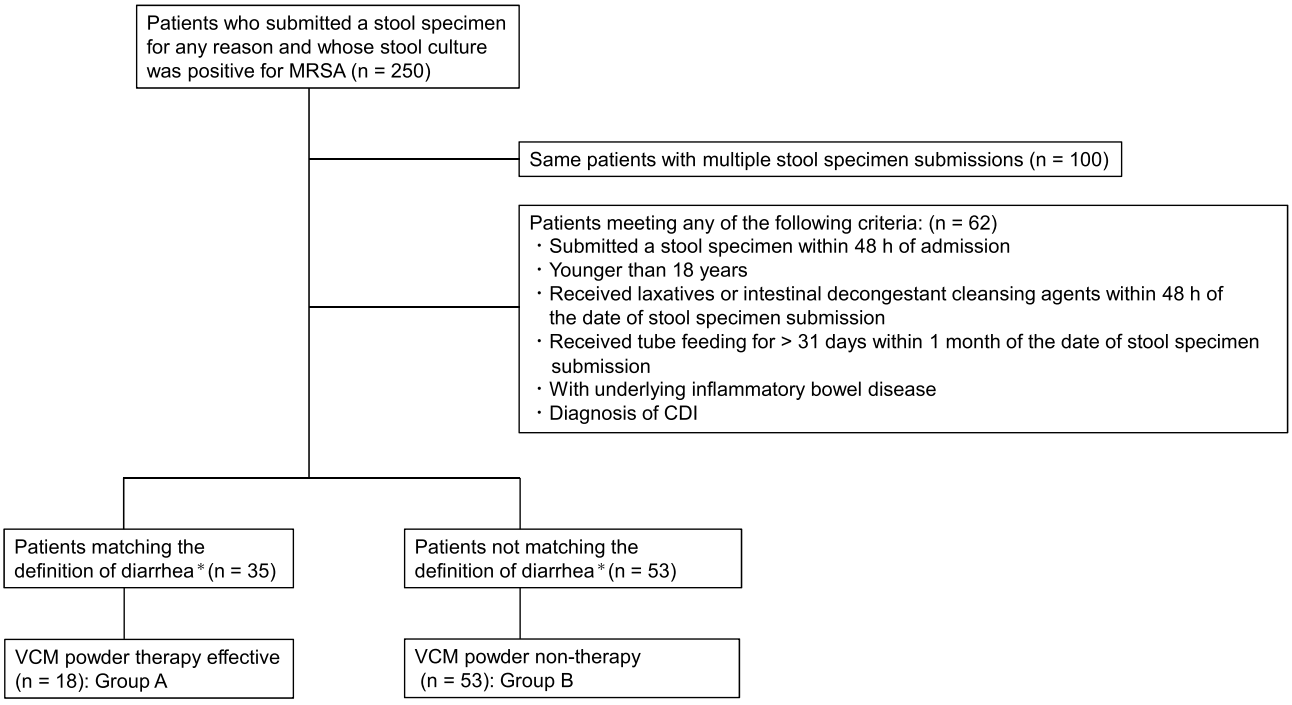


Figure 1 Study design.
Notes: *Bristol Stool Scale of ≥ 5 and a stool frequency of ≥ 3 times per day.
Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*, CDI, *Clostridioides difficile* infection, VCM, vancomycin.

Table 1 Comparison of Patient Characteristics Between Group A and Group B

Variables	No. of patients in Group A (%) (n = 18)	No. of patients in Group B (%) (n = 53)	P-value
Age (mean ± SD)	71.1 ± 7.7	72.1 ± 12.9	0.25
Sex			
Male	11/18 (61.1)	35/53 (66.0)	0.78
Female	7/18 (38.9)	18/53 (34.0)	0.71
Department			
Gastroenterology	4/18 (22.2)	13/53 (24.5)	1.00
Gastroenterological Surgery	5/18 (27.8)	10/53 (18.9)	0.51
Cardiovascular Surgery	2/18 (11.1)	5/53 (9.4)	1.00
Nephrology	1/18 (5.6)	7/53 (13.2)	0.67
Respiratory and Allergy Medicine	2/18 (11.1)	6/53 (11.3)	1.00
Hematology	1/18 (5.6)	4/53 (7.5)	1.00
Urology	1/18 (5.6)	3/53 (5.7)	1.00
Neurosurgery	2/18 (11.1)	1/53 (1.9)	0.16
Psychiatry	0/18 (0)	1/53 (1.9)	0.45
Breast Surgery	0/18 (0)	1/53 (1.9)	0.45
Obstetrics and Gynecology	0/18 (0)	1/53 (1.9)	0.45
Otorhinolaryngology	0/18 (0)	1/53 (1.9)	0.45
Hospitalization route			
From home	5/18 (27.8)	15/53 (28.3)	0.97
From medical institutions	10/18 (55.6)	33/53 (62.3)	0.61
From long-term care medical facilities	3/18 (16.6)	5/53 (9.4)	0.40
Median days from admission to stool specimen submission (range)	10.5 (6–37)	12 (4–36)	0.68
Associated symptoms at the time of stool specimen submission			
Stomachache	16/18 (88.9)	41/53 (77.4)	0.49
Fever (temperature ≥ 38.0 °C)	14/18 (77.8)	32/53 (60.4)	0.26
With autonomous defecation	8/18 (44.4)	28/53 (52.8)	0.59
Underlying disease			
Peptic ulcer	12/18 (66.7)	32/53 (60.4)	0.78
Diabetes	4/18 (22.2)	24/53 (45.3)	0.10
Heart failure	5/18 (27.8)	22/53 (41.5)	0.40
Myocardial infarction	3/18 (16.7)	5/53 (9.4)	0.41
Solid cancer	11/18 (61.1)	20/53 (37.7)	0.10
Blood cancer	0/18 (0)	3/53 (5.7)	1.00
Cerebrovascular disease	2/18 (11.1)	15/53 (28.3)	0.20
Renal dysfunction	4/18 (22.2)	11/53 (20.8)	1.00
Dialysis	0/18 (0)	0/53 (0)	N/A
Chronic lung disease	4/18 (22.2)	10/53 (18.9)	0.74
Liver dysfunction	6/18 (33.3)	7/53 (13.2)	0.08
Autoimmune disease	0/18 (0)	2/53 (3.8)	1.00
Dementia	2/18 (11.1)	1/53 (1.9)	0.16
Hemiplegia	1/18 (5.6)	2/53 (3.8)	1.00
Charlson Comorbidity Index			
0	0/18 (0)	0/53 (0)	N/A
1–2	0/18 (0)	5/53 (9.4)	1.00
3–4	7/18 (38.9)	16/53 (30.2)	0.56
≥ 5	11/18 (61.1)	32/53 (60.4)	1.00

(*Continued*)

Table 1 (Continued).

Variables	No. of patients in Group A (%) (n = 18)	No. of patients in Group B (%) (n = 53)	P-value
Biochemical tests (range)			
Serum albumin (g/dL)	2.3 (1.5–5.6)	2.6 (1.6–4.4)	0.27
CRP (mg/dL)	4.3 (0.02–21.9)	3.5 (0.05–22.4)	0.01
Serum creatinine (mg/dL)	1.08 (0.34–11.0)	0.95 (0.28–6.4)	0.91
e-GFR (mL/min/1.73 m^2)	40.5 (11.8–91.3)	52.8 (5.8–279)	0.63
Hematological test (range)			
Red blood cell count (10^4/μL)	405 (267–475)	433 (251–526)	0.88
Hemoglobin (g/dL)	13.5 (5.1–16.8)	14.1 (5.9–16.4)	0.71
White blood cell count (10^3/μL)	8.1 (0.2–23.2)	5.7 (0.7–31.4)	0.01
Platelet count (10^4/μL)	19.1 (6.2–31.0)	22.3 (8.9–40.2)	0.52
With endoscopic findings	0/18 (0)	2/53 (3.8)	1.00
Factors of inpatient treatment within 1 month of the date of stool specimen submission			
Antibacterial agents	17/18 (94.4)	43/53 (81.1)	0.18
Antacid preparations	15/18 (83.3)	45/53 (84.9)	1.00
Intestinal regulating drugs	12/18 (66.7)	23/53 (43.4)	0.11
Enteral feedings	3/18 (16.7)	10/53 (18.9)	1.00
Gastrointestinal surgery	5/18 (27.8)	9/53 (17.0)	0.32
Cancer chemotherapy	6/18 (33.3)	14/53 (26.4)	0.56
Radiotherapy	0/18 (0)	0/53 (0)	N/A
Type of antimicrobial administered within 1 month of the date of stool specimen submission			
Penicillins	1/18 (5.6)	3/53 (5.7)	1.00
Penicillin-based with beta-lactamase inhibitor	4/18 (22.2)	11/53 (20.8)	1.00
First-generation cephalosporins	5/18 (27.8)	12/53 (22.6)	0.75
Second-generation cephalosporins	2/18 (11.1)	5/53 (9.4)	1.00
Third-generation cephalosporins	2/18 (11.1)	4/53 (7.5)	0.64
Fourth-generation cephalosporins	1/18 (5.6)	6/53 (11.3)	0.67
Carbapenems	10/18 (55.6)	6/53 (11.3)	< 0.01
Glycopeptides	2/18 (11.1)	6/53 (11.3)	1.00
New quinolones	4/18 (22.2)	5/53 (9.4)	0.22
Death within 28 days	1/18 (5.6)	0/53 (0)	0.45
Death during hospitalization	3/18 (16.7)	4/53 (7.5)	0.36

Abbreviations: CRP, C-reactive protein; MRSA, methicillin-resistant *Staphylococcus aureus*; e-GFR, estimated glomerular filtration rate; SD, standard deviation.

Table 2 Microbiological Examinations Between Groups A and B

Variables	No. of patients in Group A (%) (n = 18)	No. of patients in Group B (%) (n = 53)	P-value
MRSA counts in stool culture			
1+	7/18 (38.9)	40/53 (75.4)	< 0.01
2+	8/18 (44.4)	10/53 (18.9)	0.02
3+	2/18 (11.1)	1/53 (1.9)	0.16
4+	1/18 (5.6)	2/53 (3.8)	1.00

(*Continued*)

Table 2 (Continued).

Variables	No. of patients in Group A (%) (n = 18)	No. of patients in Group B (%) (n = 53)	P-value
Bacteria detected concurrently with MRSA in stool specimens	17/18 (94.4)	53/53 (100)	0.44
Details of bacteria detected concurrently with MRSA in stool specimens			
Staphylococcus epidermidis	2/18 (11.1)	2/53 (3.8)	0.26
Enterococcus species	11/18 (61.1)	35/53 (66.0)	0.46
Corynebacterium species	1/18 (5.6)	0/53 (0)	0.44
Clostridioides difficile	3/18 (16.7)	5/53 (9.4)	0.33
Lactobacillus species	0/18 (0)	2/53 (3.8)	0.61
Escherichia coli	4/18 (22.2)	19/53 (35.8)	0.22
Klebsiella pneumoniae	5/18 (27.8)	13/53 (24.5)	0.51
Klebsiella oxytoca	2/18 (11.1)	3/53 (5.7)	0.37
Klebsiella aerogenes	0/18 (0)	2/53 (3.8)	0.61
Serratia marcescens	1/18 (5.6)	0/53 (0)	0.44
Proteus mirabilis	1/18 (5.6)	1/53 (1.9)	0.45
Citrobacter freundii	2/18 (11.1)	3/53 (5.7)	0.37
Citrobacter koseri	0/18 (0)	3/53 (5.7)	0.72
Enterobacter cloacae	2/18 (11.1)	6/53 (11.3)	0.67
Pseudomonas aeruginosa	2/18 (11.1)	3/53 (5.7)	0.37
Acinetobacter baumannii	1/18 (5.6)	0/53 (0)	0.44
Stenotrophomonas maltophilia	0/18 (0)	1/53 (1.9)	0.46
Candida albicans	9/18 (50.0)	29/53 (54.7)	0.47
Candida glabrata	4/18 (22.2)	8/53 (15.1)	0.36
Candida parapsilosis	1/18 (5.6)	4/53 (7.5)	0.63
Retrospective MRSA detection in other specimens within 14 days of the date of stool specimen submission			
Sputum	9/18 (50.0)	6/53 (11.3)	< 0.01
Urine	2/18 (11.1)	3/53 (5.7)	0.60
Blood (2 sets)	1/18 (5.6)	4/53 (7.5)	1.00
Indwelling urinary catheter	1/18 (5.6)	2/53 (3.8)	1.00
Establishing a division	0/18 (0)	1/53 (1.9)	0.45

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

within 1 month of stool specimen submission (OR, 7.47; 95% CI, 1.66–33.6; P < 0.01) remained risk factors for diarrhea development (Table 4). In contrast, CRP > 6.1 mg/dL and retrospective detection of MRSA in sputum within 14 days from the date of stool culture submission were not associated with diarrhea (Table 4).

Table 3 Antimicrobial Susceptibility of MRSA Strains Between Groups A and B

Antimicrobial types	Antimicrobial agents	No. of sensitive isolates	No. of sensitive isolates	P-value
		In Group A (%)	In Group B (%)	
Penicillin	PCG	0/18 (0)	0/46 (0)	N/A
Penicillin	ABPC	0/18 (0)	0/46 (0)	N/A
Penicillin	MPIPC	0/18 (0)	0/46 (0)	N/A
Penicillin	SBT/ABPC	0/18 (0)	0/46 (0)	N/A
Penicillin	CVA/AMPC	0/9 (0)	0/29 (0)	N/A
Aminoglycoside	GM	12/18 (66.7)	29/46 (63.0)	0.51
Macrolide	EM	0/18 (0)	2/46 (4.3)	0.65
Lincomycin	CLDM	0/9 (0)	2/29 (6.9)	0.60
Tetracycline	MINO	11/18 (61.1)	28/46 (60.9)	0.61
Quinolone	LVFX	0/18 (0)	3/46 (6.5)	0.67
Glycopeptide	VCM	18/18 (100)	46/46 (100)	1.00
Lipopeptide	DAP	9/9 (100)	17/17 (100)	1.00
Sulfonamide	ST	17/18 (94.4)	46/46 (100)	0.48
Rifamycin	RFP	18/18 (100)	46/46 (100)	1.00
Oxazolidinone	LZD	18/18 (100)	46/46 (100)	1.00

Notes: Susceptibility to 15 antimicrobial agents. PCG benzylpenicillin, ABPC ampicillin, MPIPC oxacillin, SBT/ABPC sulbactam - ABPC, CVA/AMPC clavulanic acid - amoxicillin, GM gentamicin, EM erythromycin, CLDM clindamycin, MINO minocycline, LVFX levofloxacin, VCM vancomycin, DAP daptomycin, ST sulfamethoxazole-trimethoprim, RFP rifampicin, LZD linezolid.

Table 4 Multivariate Analysis of Patients' Background Risk Factors

Risk factors	Odds ratio	95% CI	P-value
C-reactive protein > 6.1 (mg/dL)	3.03	0.72–12.7	0.13
White blood cell counts >10000 (/μL)	5.50	1.12–26.9	0.04
MRSA counts ≥ 2+ in stool culture	8.91	1.79–44.3	< 0.01
Retrospective detection of MRSA in sputum within 14 days of the date of stool specimen submission	3.54	0.80–15.6	0.10
Meropenem administration within 1 month of stool specimen submission	7.47	1.66–33.6	< 0.01

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; CI, confidence interval.

Discussion

MRSA enteritis was reported as a postoperative complication with a high mortality rate in Japan in the 1990s.[5,6] Diarrhea and fever were the main symptoms, and most cases occurred after gastrectomy or colorectal resection.[2–4] In Japan, there have been no reports of MRSA enteritis since 2002.[18] The exclusion of CDI is important for the diagnosis of MRSA enteritis because of its history, which suggests that culture-positive *C. difficile* for MRSA may have been misidentified as antibiotic-associated enterocolitis due to MRSA.[24] *C. difficile*-positive patients were excluded from this study.

In this study, 27.8% of patients in Group A underwent gastrectomy or colorectal resection. The disease was thought to be caused by early postoperative immune compromise of host-side antibodies due to exotoxins, such as enterotoxin and toxic shock syndrome toxin 1.

In previous reports, the mean age ranged from 51 to 72 years, and the patients we reviewed were older, with similar results.[2,3,25,26] The background of patients diagnosed with MRSA enteritis included sex differences and reported history of

gastrointestinal surgery.[2,3] The results were similar for groups that fit the case definition of MRSA enteritis in our study, which was more common in males (71.4%) than in females. The results were not statistically significant in terms of surgical history. Men and women have different immunocompetencies,[27] men have a lower humoral immune response than women due to lower antibody production by B cells,[28] and androgens and sex steroid hormones are thought to be involved.[29]

Diarrheal stools due to MRSA enteritis have been reported to be watery; however, there have been no reports on the frequency of stools. Simultaneous evaluation of diarrheal appearance and frequency of stools, as defined in this study, would be a useful diagnostic tool for MRSA enteritis. In case reports of MRSA enteritis, endoscopic findings indicate that the small intestine is the primary site of the lesion.[30] Therefore, MRSA enteritis is considered a non-inflammatory small intestinal type of enteritis, and it has been inferred that fecal leukocytes are not as significant as those in colonic enteritis. In the present study, we were unable to examine the fecal leukocytes. However, in previous reports, MRSA enteritis was diagnosed when the blood leukocyte count exceeded 10000 /μL or decreased below 3100 /μL.[26,27] In our study, MRSA enteritis was associated with a blood leukocyte count exceeding 10000 /μL. This leukocytosis may be related to granulocyte colony-stimulating factor production from stromal cells and monocytes due to MRSA-derived enterotoxin.[31] Granulocyte colony-stimulating factor was found in 3 (16.7%) of the 18 MRSA enteritis cases.

Fecal specimens from patients with diarrhea that developed after 3 days of hospitalization had a low yield when tested for standard bacterial pathogens.[32,33] Based on this finding, several groups have suggested that unless overriding circumstances prevail, fecal specimens from patients hospitalized for > 3 days should not be subjected to routine stool culture.[34,35] However, in our study, only patients who submitted stool cultures > 3 days after admission were selected and tested using MRSA selective media for rapid detection of infected patients.

The detection of MRSA and the number of MRSA bacteria in the stool culture are important for diagnosing MRSA enteritis, given the possibility that a stool culture would be necessary. The criterion for bacterial abundance was $\geq 10^4$ to 10^5 CFU/mL, that is, high bacterial abundance. Ogawa et al diagnosed MRSA enteritis when the amount of MRSA bacteria in the stool culture was 10^4 CFU/mL.[9] Our study finding was similar, concluding that an MRSA bacterial level of 10^4 to 10^5 CFU/mL or higher was required.

In all but one case, other bacteria detected concurrently with MRSA in stool specimens were commensal intestinal bacteria. A small number of *C. difficile* were detected in Groups A and B. Based on the results of rapid immunoenzyme tests, these organisms were considered carriers. No pathogenic enterohemorrhagic *Escherichia coli, Salmonella* species, or cytomegalovirus was detected. The antimicrobial susceptibility results of MRSA revealed that all strains were completely resistant to oxacillin. Conversely, several strains were found to be sensitive to erythromycin, clarithromycin, clindamycin, and levofloxacin only in Group B. The susceptibility pattern suggested community-acquired MRSA.[36]

Antimicrobial exposure is a risk factor for diarrhea, especially with broad-spectrum antimicrobials.[37] In our study, previously reported third-generation cephalosporins were not identified as associated factors.[4] When tested retrospectively for 1 month from the date of diarrhea onset as an exposure history, meropenem was found to cause significant diarrhea. Thus, past exposure history can be a risk factor, and we emphasize the importance of reviewing dosing history. A broad-spectrum antimicrobial agent, such as meropenem, which has antimicrobial activity against an entire range of aerobic and anaerobic bacteria in the intestinal tract, can cause bacterial turnover in the intestinal tract, resulting in MRSA enteritis.[38]

This study has several limitations. First, this was a retrospective study with a relatively small number of patients. Therefore, it was impossible to corroborate the histological findings. Endoscopic findings were obtained in one case and were not abnormal. Pseudomembrane formation in the small intestine may be a hallmark of MRSA enteritis, and endoscopy and case series are required for its diagnosis.[39,40] Second, we were unable to examine MRSA-derived toxins that may cause enterocolitis; enterotoxin A and toxic shock syndrome toxin 1 involvement are thought to be responsible for the severity of MRSA enterocolitis.[7,41] Molecular genetic studies are required to examine these diagnostic criteria. Despite these limitations, this is the first study to evaluate the factors involved in defining MRSA enteritis aimed at confirming its existence in hospitals.

Conclusion

MRSA enteritis may be diagnosed when diarrhea occurs, WBC count is >10000 /μL, and MRSA count in stool cultures is ≥ 2+. The history of meropenem use in the past 1 month should also be considered. These diagnostic criteria would

allow clinicians to identify patients with diarrhea-onset disease likely to develop MRSA enteritis. A multicenter study will be conducted in the future to increase the number of cases studied and to evaluate the diagnostic ability of the risk factors identified in our study. Moreover, whenever possible, we will examine the causes of pathogenicity and pathologic underpinnings in MRSA enteritis.

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Author Contributions

All authors made significant contributions in the conception, study design, implementation, data acquisition, analysis, interpretation, or all of these areas; drafted or wrote the article or performed critical peer review; reviewed and agreed to any significant changes made in the final version approved for publication and in the proofreading stage; agreed to the journal to which they submitted the paper; and accepted responsibility for all aspects of the research.

Disclosure

The authors report no conflicts of interest in this work.

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