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Clinical significance of methicillin-resistant coagulase-negative staphylococci obtained from sterile specimens

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Abstract

Distinguishing true coagulase-negative staphylococci bacteremia from contamination remains a challenge. We conducted a retrospective analysis of 183 patients with methicillin-resistant coagulase-negative staphylococci (MR-CoNS)–positive and methicillin-resistant *Staphylococcus aureus*–positive cultures obtained from sterile sites such as blood, synovial fluid, ascitic fluid, and cerebrospinal fluid. Of the 209 MR-CoNS isolates, 83 (39.7%) were considered infection associated and 126 (60.3%) were considered contamination. MR-CoNS isolates cultured from synovial fluid were more likely to be infection associated (P = 0.009). The median interval from insertion of a central venous catheter to onset of infection tended to be longer in MR-CoNS infection cases than in methicillin-resistant *S. aureus* infection cases (41 days versus 14 days, P = 0.055). In conclusion, our results suggest that the proportion of cases of true MR-CoNS infection may be higher than previously reported.

Keywords: Methicillin-resistant coagulase-negative staphylococci, Methicillin-resistant *Staphylococcus aureus*, Contamination, Sterile specimen

Abbreviations: CoNS, coagulase-negative staphylococci; CRBSI, catheter-related bloodstream infection; MR-CoNS, methicillin-resistant coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*.

1. Introduction

Some coagulase-negative staphylococci (CoNS) species are among the main species of the normal resident skin flora (Roth and James, 1988). Therefore, CoNS isolates from clinical specimens are often considered contaminants, especially when the specimens are obtained from sterile sites. However, some reports have indicated the importance of CoNS, which account for more than 30% of blood culture isolates (Gaynes, et al., 1996; Richards, et al., 1999a, 1999b; Wisplinghoff, et al., 2004). Most CoNS infections occur in patients with indwelling medical devices (Otto, 2009). Additionally, the central venous catheterization procedure rate is increasing (Glickman, et al., 2010), suggesting that the number of CoNS infections may also be increasing.

It remains difficult and challenging to distinguish true CoNS bacteremia from contamination (Hall and Lyman, 2006). Although several investigators have proposed methods to determine the clinical significance of CoNS isolates from blood cultures, multiple positive blood culture results are not sufficient to determine true bacteremia (Beekmann, et al., 2005; Mirrett, et al., 2001; Seo, et al., 2000; Seybold, et al., 2009). Accordingly, the rate of true CoNS bacteremia has been reported to range from 10% to 30% in published reports (Beekmann, et al., 2005; Finkelstein, et al., 2002; Herwaldt, et al., 1996; Mirrett, et al., 2001; Souvenir, et al., 1998; Weinstein, et al., 1997).

Many studies of contamination rates only involve blood cultures. Additionally, most of these studies were conducted more than 10 years ago. Therefore, we conducted a retrospective analysis of 183 patients with methicillin-resistant CoNS (MR-CoNS)–positive and methicillin-resistant *Staphylococcus aureus* (MRSA)-positive cultures that were obtained from sterile sites such as synovial fluid, ascitic fluid, and cerebrospinal fluid as well as blood. In this study, we focused on methicillin-resistant isolates, which are important drug-resistant pathogens. MRSA was also included to compare clinical aspects with MR-CoNS.

2. Materials and methods

2.1 Study setting

This study was conducted at Toyama University Hospital (Japan), a 612-bed tertiary care and teaching hospital with an annual average of 180,000 patient discharges. Between January 2009 and December 2012, all cultures obtained from sterile sites in adult patients (older than 18 years of age) that yielded MRSA and MR-CoNS were identified through a review of the electronic microbiology records. The sterile sites from which specimens were collected included blood, pleural fluid, ascitic fluid, cerebrospinal fluid, synovial fluid, subcutaneous wounds, and closed abscesses. If more

than 3 types of bacteria or fungi were isolated from an ascitic fluid specimen, the result was excluded from the analysis because of the high possibility of contamination with gut flora. Isolate identification and antimicrobial susceptibility testing were assessed by using the MicroScan WalkAway 96 SI (Siemens Healthcare, Erlangen, Germany) according to the manufacturer's instructions. The panels used were MicroScan Dried Pos ID 2 (PID2), MicroScan Dried Gram Pos Combo 6.1J, and MicroScan Dried Gram Pos MIC 6.3J (Siemens Healthcare, Erlangen, Germany).

2.2 Definition of infection

Most infections, including bloodstream infections, were defined according to the standard definitions of the US Centers for Disease Control and Prevention (Horan, et al., 2008). Catheter-related bloodstream infection (CRBSI) was diagnosed when the same organism grew from at least one percutaneous blood culture and from a catheter tip culture (Mermel, et al., 2009). Decisions regarding contamination in all specimen types were made after the following factors were considered: the patient's clinical history, physical findings, body temperature at the time of culture, leukocyte count, C-reactive protein level, number of positive blood cultures, culture results of specimens from other sites, imaging results, clinical course, and response to therapy (Weinstein, et al., 1997).

Briefly, the absence of specific physical and laboratory findings or an improvement in the response to treatment with ineffective antibiotics such as β-lactams indicated contamination. Episodes that could only be effectively treated with anti-MRSA antibiotics were considered infections. If both MRSA and MR-CoNS were cultured from the same specimen, the specimen was considered MRSA infected but not MR-CoNS infected because MRSA is a more invasive pathogen than MR-CoNS. Culture positive results reported for a given specimen within 1 month were counted as a single episode. The criteria for hospital-acquired infection were as follows: the causative agent was cultured more than 48 h after admission; the patient had a history of hospitalization, surgery, dialysis, or residence in a long-term health care facility within 6 months before the culture was obtained; and the patient had an indwelling intravenous line, catheter, or any other percutaneous medical device when the culture was obtained (Huang, et al., 2006).

2.3 Data collection

The following data for patients with bloodstream infections (including CRBSIs) were extracted from the clinical records: age; sex; risk factors such as underlying conditions (e.g., diabetes mellitus, neoplasm, and immunosuppressive therapy), the presence of

intravascular devices, and previous surgeries; clinical signs; results of laboratory studies; antibiotic therapies; and death within 30 days. The duration of hospital stay, interval from admission to onset, and interval from insertion of a central venous catheter to onset were also examined. For patients transferred from other facilities, the duration of hospital stay included the duration of hospitalization at both institutions.

2.4 Statistical analysis

Differences in the group proportions were assessed by using the chi-square or Fisher exact test. Continuous variables were compared by using the Mann-Whitney test. Statistical analyses were performed by using Prism version 5.0 (GraphPad, Inc., San Diego, CA, USA). Differences were considered significant at a P value <0.05.

3. Results

During the study period, 284 cultures obtained from sterile sites in 183 patients were MRSA or MR-CoNS positive; these yielded 335 microorganisms, including 126 MRSA and 209 MR-CoNS isolates. Ninety-four patients had 106 infection episodes: 58 were MRSA infections and 48 were MR-CoNS infections.

3.1 Rate of contamination

Of the 126 MRSA isolates, 115 (91.3%) were considered infection associated and 11 (8.7%) were considered contamination. Of the 11 latter isolates, 9 were cultured from blood and 2 were cultured from a closed abscess; the most common reason for considering contamination was that the clinical symptoms and laboratory data improved after treatment with an antimicrobial agent known to be ineffective against MRSA infection, such as a β-lactam. Of the 209 MR-CoNS isolates, 83 (39.7%) were considered infection associated and 126 (60.3%) were considered contamination. The proportions of infection-associated or contaminant isolates for each specimen are shown in Table 1. These proportions remained the same even if the type of specimen was limited to blood (39.6%). If only the initially cultured isolates from the blood of each patient were evaluated, the proportion of infection decreased to 33.3%. MR-CoNS isolates cultured from synovial fluid were significantly more likely to be infection associated than isolates cultured from other specimens (5/83 vs. 0/126, $P = 0.009$).

Given the lack of criteria regarding clinical signs or symptoms in the definition of CRBSI, we also confirmed clinical characteristics in patients with CRBSI to avoid overestimating the incidence of infection. Of the 44 CRBSI-associated MR-CoNS isolates in this study, 38 were obtained from patients with fever (≥38°C), 4 were

obtained from patients with hypotension (<90 mm Hg), and 3 were obtained from patients with neutropenia (<500 cells/μL). Some patients had more than one of these 3 factors.

We also examined the possibility that the study population comprised patients with a potentially higher risk of infection than the general hospital population. Of the 83 infection-associated MR-CoNS isolates, only 3 were obtained from patients in the intensive care unit; 77 isolates were from patients in the general ward, and 3 isolates were obtained from patients of the outpatient clinic. None of the study participants were bone marrow transplant recipients. Twelve MR-CoNS isolates were obtained from patients with hematologic malignancies.

3.2 MR-CoNS species

The proportions of each MR-CoNS species obtained from sterile sites are shown in Table 2 and are classified as infection or contamination. *Staphylococcus epidermidis* was the dominant species, responsible for 75.9% of all MR-CoNS infections. Of the 154 MR-CoNS blood culture isolates, 101 (65.6%) were of *S. epidermidis*; of these, 45 (44.6%) were infection-associated isolates. Among the cases of infection, *S. epidermis* was followed in prevalence by *Staphylococcus hominis* (9.6%), *Staphylococcus capitis*

(8.4%), *Staphylococcus warneri* (2.4%), and *Staphylococcus schleiferi* (2.4%). However, among the cases of contamination, *S. epidermidis* accounted for only 60.3% of cases, followed by *S. hominis* (14.0%), *Staphylococcus haemolyticus* (8.1%), *S. capitis* (6.6%), and *Staphylococcus simulans* (5.0%). *S. epidermidis* was more prevalent among the cases of infection (P = 0.025); however; *S. haemolyticus* and *S. simulans* were more prevalent among the cases of contamination (P = 0.007 and 0.041, respectively). *Staphylococcus saprophyticus*, which usually causes urinary tract infections, was not detected in this study.

3.3 Community-acquired or hospital-acquired organisms

Of the 335 MRSA- and MR-CoNS–positive cultures, 297 isolates were obtained more than 48 h after admission and 38 were cultured within 48 h of admission; the latter included 12 MRSA isolates (32%) and 26 MR-CoNS isolates (68%). Of the 38 isolates cultured within 48 h, 36 were considered hospital-acquired organisms according to the clinical definition; therefore, 333 isolates were hospital acquired. Only 2 *S. simulans* isolates were considered community-acquired isolates.

3.4 Difference between MRSA and MR-CoNS infection

We next compared the clinical features between the 58 MRSA and 48 MR-CoNS cases of infection. The types of infection are shown in Table 3. The proportion of CRBSIs was higher among MR-CoNS infections than among MRSA infections (62.5% versus 24.1%, $P < 0.001$). In contrast, among bone and joint infections, the proportion of MRSA infections was higher than that of MR-CoNS infections ($P = 0.021$). No single *Staphylococcus* species was isolated among prosthetic joint infections.

A comparison between MRSA and MR-CoNS infections with respect to the clinical characteristics of bloodstream infections (including CRBSIs) is summarized in Table 4. The MRSA-infected patients were older than the MR-CoNS–infected patients (68.8 years versus 59.7 years, $P = 0.016$). The median interval from insertion of a central venous catheter to the onset of infection tended to be longer in the cases of MR-CoNS infection than in the cases of MRSA infection (41 days versus 14 days, $P = 0.055$). The mortality rate with MRSA infection was 25%, which was higher than that with MR-CoNS infection (2.9%, $P = 0.016$). Vital signs on the day of the positive blood culture were similar. However, leukocyte counts and C-reactive protein levels tended to be higher in the cases of MRSA infection than in the cases of MR-CoNS infection ($P = 0.082$ and $P = 0.023$, respectively). Regarding underlying conditions, the rates of use of a central venous catheter exceeded 80% for both infection groups, especially among

cases of MR-CoNS infection, for which 33 of 34 episodes involved central venous catheters. The most commonly used initial drugs for the treatment of both MRSA and MR-CoNS infections were vancomycin and teicoplanin. In some cases, removal of a central venous catheter resulted in clinical improvement without antibiotics. In other cases not treated with anti-MRSA drugs, the patients died before the culture results became available.

4. Discussion

In this study, we analyzed and compared various aspects of cases involving MRSA and MR-CoNS cultures. Initially, we evaluated each positive culture obtained from sterile sites to distinguish true infection from contamination because some CoNS species are among the main species of normal resident skin flora (Roth and James, 1988). In this study, the percentage of MRSA contamination among blood cultures was similar to that in a previous report (6.4%) (Weinstein, et al., 1997).

On the other hand, 39.7% of the MR-CoNS–positive cultures were considered true infections, which is a higher proportion than previously reported (5%–30%) (Beekmann, et al., 2005; Finkelstein, et al., 2002; Hall and Lyman, 2006; Herwaldt, et al., 1996; Natoli, et al., 2009; Souvenir, et al., 1998; Weinstein, et al., 1997). There were some differences in the settings of our study and those previously reported. First, various

specimen types were included in our study, whereas previously published studies only evaluated blood cultures. Even so, our results limited to blood cultures showed higher infection rates compared with the results of previous studies. Second, the scope of our study was limited to methicillin-resistant species. We chose to study methicillin-resistant isolates only because this would enable precise decisions regarding the presence or absence of a true infection, according to the requirement for anti-MRSA drugs. Third, we adopted a definitive diagnosis of CRBSI that only required the growth of the same organism from at least one percutaneous blood culture and a catheter tip culture. However, we confirmed that most determinations of true infection-associated CRBSI in this study met the requirements defined in previous studies, with regard to, for example, clinical signs. Fourth, multiple samples may have been taken from the same patient over a short interval. However, the proportion of cases of infection among the initially cultured isolates from blood only in each patient remained higher than the proportions reported in previous studies. Fifth, there was no evidence to indicate the possibility that this study population might comprise patients at a potentially higher risk of infection than the general hospital population, such as bone marrow transplant recipients, patients with hematologic malignancies, and patients in intensive care units (Herwaldt, et al., 1996). These results indicated the possibility that the incidence of

CoNS infection may have increased in recent years compared with the rate in the 1990s. This is not surprising because patient populations and treatment modes have changed over time and, in particular, the rate of central venous catheterization has increased (Glickman, et al., 2010).

One of the objectives of this study was to examine differences in the clinical significance of MR-CoNS infection in blood and other sterile specimens. Most specimens from sterile sites are normally collected via percutaneous puncture, and therefore, microbes from the normal skin flora could likely contaminate those specimens. We therefore expected that the infection-associated rates for each type of specimen would be nearly identical. Indeed, most rates of contamination for other types of specimens were similar to that in blood. However, an MR-CoNS–positive culture from synovial fluid was more likely to be associated with infection. The pretest probability for synovial fluid collection may be higher than that for other sterile specimens (e.g., blood); however, the number of isolates in this study was small, and a larger number of cases would have to be studied to confirm this hypothesis.

S. epidermidis was the dominant MR-CoNS species in this study and was more likely to be infection associated than contamination, as previously reported (Chu, et al., 2008; Finkelstein, et al., 2002; Herwaldt, et al., 1996; Kloos and Bannerman, 1994).

Conversely, *S. haemolyticus* and *S. simulans* were less likely to be infection associated and were always considered contamination in this study. Herwaldt et al. indicated that non-*S. epidermidis* species blood culture isolates were less likely to be infection associated. Another potential concern in this study was the false identification of *Staphylococcus* species. MicroScan WalkAway, which was used for identification, has been reported to have poor reliability for some uncommon CoNS strains (Olendzki, et al., 2014). Unlike other species, the identification of *S. epidermidis*, *S. haemolyticus*, and *S. hominis* was reported to be sufficiently reliable in the same study. The authors also reported that the automated system showed 100% specificity and 90% sensitivity for the detection of oxacillin resistance. Our results indicate the need for careful evaluation, especially for uncommon CoNS strains.

In our study, rates of hospital-acquired infection were higher than those in previous studies (Beekmann, et al., 2005; Finkelstein, et al., 2002; Herwaldt, et al., 1996; Weinstein, et al., 1997). The main reason for this difference is that we used the timing criterion of “not only 48 h after admission” as well as other detailed criteria such as a history of hospitalization. Second, we investigated only methicillin-resistant species. Indeed, Cherifi et al. found that *S. epidermidis* CRBSI, which was considered hospital acquired, was significantly resistant to more antibiotics when compared with *S.*

epidermidis isolates obtained from healthy volunteers (Cherifi, et al., 2013).

The clinical features and outcomes differ between *S. aureus* and CoNS infections. *S. aureus* is an aggressive pathogen that causes various invasive and fatal infections. In contrast, *S. epidermidis* is usually associated with infections of implanted medical devices such as central venous catheters (Pfaller and Herwaldt, 1988). We confirmed that MR-CoNS caused CRBSI more frequently than MRSA. This finding is compatible with the fact that *S. epidermidis* is responsible for 50% to 70% of catheter-related infections (von Eiff, et al., 2002). Interestingly, the proportion of bone and joint infections was higher among MRSA infections than among MR-CoNS infections. This might have been due to differences in *S. aureus* pathogenicity, including the production of enterotoxins, exotoxins, leukocidins, and leukotoxins that is not observed in *S. epidermidis* infection (Gill, et al., 2005).

In conclusion, our results suggest that the proportion of true cases of MR-CoNS infection is higher than previously reported. The MR-CoNS contamination rates in blood and other sterile site specimens, excluding synovial fluid, were similar. Because patient populations and treatment modes change over time, we urge the continued monitoring of both *S. aureus* and CoNS infections.

ETHICAL APPROVAL

This study was performed in conformity with the Declaration of Helsinki after approval by the Ethics Committee of University of Toyama. The patients' privacy was fully protected, and personal information was handled such that patients could not be identified.

CONFLICT OF INTEREST

Yoshihiro Yamamoto has received lecture fees from Pfizer Inc. Koichi Izumikawa has received honoraria from Pfizer Japan, Inc., Astellas Pharma Inc., and Merck & Co., Inc. No other authors declare any conflicts of interest.

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Table 1. Sterile specimens with isolated methicillin-resistant coagulase-negative staphylococci

Specimens (n)	No. (%) of isolates		*P* value
	Infection-associated isolates	Contaminants	
Blood (154)	61 (39.6)	93 (60.4)	0.960
Subcutaneous wound (13)	8 (61.5)	5 (38.5)	0.097
Synovial fluid (5)	5 (100.0)	0 (0.0)	0.009
Ascitic fluid (18)	4 (22.2)	14 (77.8)	0.113
Closed abscess (13)	3 (23.1)	10 (76.9)	0.379
Cerebrospinal fluid (4)	2 (50.0)	2 (50.0)	0.650
Pleural fluid (2)	0 (0.0)	2 (100.0)	0.519
All (209)	83 (39.7)	126 (60.3)	

Table 2. Methicillin-resistant coagulase-negative staphylococci isolated from sterile sites[a]

Microorganism	Total (n = 209)	No. (%) of isolates per indicated category		*P* value
		Infection (n = 83)	Contamination (n = 126)	
Staphylococcus epidermidis	139 (66.5)	63 (75.9)	76 (60.3)	0.019
Staphylococcus hominis	25 (12.0)	8 (9.6)	17 (14.0)	0.401
Staphylococcus capitis	15 (7.2)	7 (8.4)	8 (6.6)	0.568
Staphylococcus haemolyticus	10 (4.8)	0 (0.0)	10 (8.1)	0.007
Staphylococcus lugdunensis	6 (2.9)	1 (1.2)	5 (4.1)	0.406
Staphylococcus simulans	6 (2.9)	0 (0.0)	6 (5.0)	0.083
Staphylococcus warneri	4 (1.9)	2 (2.4)	2 (1.7)	0.650
Staphylococcus schleiferi	2 (1.0)	2 (2.4)	0 (0.0)	0.157
Staphylococcus sciuri	1 (0.5)	0 (0.0)	1 (0.8)	1.000
Staphylococcus intermedius	1 (0.5)	0 (0.0)	1 (0.8)	1.000

[a]Specimens were collected from sterile sites, including blood, pleural fluid, ascitic fluid, cerebrospinal fluid, synovial fluid, subcutaneous wounds, and closed abscesseStaphylococcus

Table 3. Comparison of types of infection between MRSA and MR-CoNS infections

Type of infection	No. (%) of episodes per indicated category		*P* value
	MRSA (n = 58)	MR-CoNS (n = 48)	
Surgical site	16 (27.6)	10 (20.8)	0.421
Catheter-related bloodstream	14 (24.1)	30 (62.5)	<0.001
Bloodstream	10 (17.2)	4 (8.3)	0.177
Bone and joint	9 (15.5)	1 (2.1)	0.021
Skin and soft tissue	4 (6.9)	1 (2.1)	0.374
Lower respiratory tract	3 (5.2)	0 (0.0)	0.250
Gastrointestinal system	1 (1.7)	1 (2.1)	1.000
Cardiovascular system	1 (1.7)	1 (2.1)	1.000

MRSA, methicillin-resistant *Staphylococcus aureus*; MR-CoNS, methicillin-resistant coagulase-negative staphylococci.

Table 4. Comparison of clinical characteristics of bloodstream infections[a]

Variable	Causative microorganism		*P* value
	MRSA (n = 24)	MR-CoNS (n = 34)	
Age (years)	68.8± 9.5	59.7±15.5	0.016
Male sex	15(62.5)	21(61.8)	0.954
Length of hospital stay (days)	97(20-407)	102(29-525)	0.468
Length from admission to onset (days)	41(0-294)	45(0-437)	0.554
Length from CVC insertion to onset (days)	14(1-537)	41(6-970)	0.055
Duration of antibiotic therapy (days)	15(0-45)	8(0-70)	0.099
Death within 30 days	6(25.0)	1(2.9)	0.016
Vital signs and laboratory data			
Body temperature (°C)	38.6±0.6	38.9±0.8	0.050
Systolic blood pressure (mm Hg)	111.6±19.1	115.7±22.6	0.770
Leukocyte (/μL)	12,033.3±8797.7	7850.6±5290.2	0.082
Hemoglobin (g/dL)	9.2±2.3	9.6±2.2	0.517
Platelet ($\times 10^3$/μL)	16.8±12.2	21.4±15.3	0.280
C-reactive protein (mg/dL)	10.2±7.4	6.3±5.8	0.023
Albumin (g/dL)	2.8±0.6	2.8±0.6	0.521
Creatinine (mg/dL)	1.0±0.7	1.0±0.7	0.818
Sodium (mEq/L)	136.0±6.0	136.4±4.8	0.652
Underlying condition			
Recent surgery (previous 30 days)	7(29.2)	9(26.5)	0.820
CVC	20(83.3)	33(97.1)	0.149
Diabetes mellitus	5(20.8)	6(17.6)	1.000
Neoplasm	13(54.2)	19(55.9)	0.897
Immunosuppressive therapy	12(50.0)	11(32.4)	0.176
Initial drug of choice			
Vancomycin	14(58.3)	13(38.2)	
Teicoplanin	5(20.8)	2(5.9)	
Arbekacin	1(4.2)	0(0.0)	

Values are mean ± SD, n (%), and median (minimum to maximum).

[a]Bloodstream infections in this table include catheter-related bloodstream infection

MRSA, methicillin-resistant *Staphylococcus aureus*; MR-CoNS, methicillin-resistant coagulase-negative staphylococci; CVC, central venous catheter; SD, standard deviation.

Table 4. Tashiro et al.