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CONCISE COMMUNICATION

Increasing Incidence of Sterile-Site Infections Due to Non-Multidrug-Resistant, Oxacillin-Resistant *Staphylococcus aureus* Among Hospitalized Patients

Garrett E. Schramm, PharmD; Jennifer A. Johnson, MD; Joshua A. Doherty, BS; Scott T. Micek, PharmD; Marin H. Kollef, MD

The incidence of community-associated, healthcare-associated, and hospital-acquired sterile-site infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) isolates and the susceptibility of the isolates to non- β -lactam antibiotics were evaluated for 549 hospitalized patients during a 3-year period. The incidence of community-associated MRSA infection increased significantly. The annual percentage of MRSA isolates from cases of healthcare-associated and hospital-acquired infection that were susceptible to 3 or more non- β -lactam antibiotics increased significantly.

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Methicillin-resistant *Staphylococcus aureus* (MRSA) has moved beyond the hospital setting and is emerging as a community-acquired pathogen among patients without established risk factors.¹ Although community-associated MRSA (CA-MRSA) strains are primarily associated with skin and soft tissue infections, they are increasingly the cause of more-invasive infections, including fatal necrotizing pneumonia.^{2,3} The identification of MRSA strains that originated in the community is based on a patient's recent healthcare exposure.⁴ Additionally, CA-MRSA strains have increased susceptibility to non- β -lactam antibiotics, including gentamicin, trimethoprim-sulfamethoxazole, fluoroquinolones, erythromycin, tetracyclines, and clindamycin, compared with healthcare-associated MRSA (HC-MRSA) strains.^{1,5,6}

We performed a retrospective cohort analysis with 3 main goals. The first goal was to determine the incidence of CA-MRSA, HC-MRSA, and hospital-acquired MRSA (HA-MRSA) sterile-site infections (SSIs) in hospitalized patients during a 3-year period. Our second goal was to evaluate the annual susceptibility rates to 5 non- β -lactam antibiotics—gentamicin, trimethoprim-sulfamethoxazole, erythromycin, ciprofloxacin, and clindamycin—for each source of MRSA infection. The third goal was to determine the annual incidence of SSI due to non-multidrug resistant, oxacillin-resistant *S. aureus* isolates, defined as isolates susceptible to 3 or more non- β -lactam antibiotics.⁷

METHODS

This retrospective study was conducted at Barnes-Jewish Hospital at Washington University Medical Center (St. Louis, MO), a university-affiliated, urban teaching hospital (with 1,200 beds). Hospitalized patients with sterile-site specimens culture-positive for MRSA were evaluated during a 3-year period (January 2002 to December 2004). An SSI was defined as bacteremia, bronchoscopically diagnosed pneumonia, peritonitis, or meningitis. All infections were categorized as community associated, healthcare associated, or hospital acquired in origin. CA-MRSA infections were classified in accordance with the criteria established by the Centers for Disease Control and Prevention (CDC).⁴ These criteria included isolation of MRSA within 48 hours after hospitalization for patients who had not been hospitalized, resided in a nursing home or skilled nursing facility, or had a medical procedure (such as dialysis, surgery, or in-dwelling catheterization) in the year preceding isolation of MRSA and who had a medical history that did not include MRSA infection or colonization. Healthcare-associated infections included SSIs that occurred within 48 hours after hospital admission, but with violation of 1 or more of the above-mentioned CDC criteria that define community-associated infection. Hospital-acquired infection was defined by isolation of MRSA after 48 hours or more after hospitalization. At acquisition-type assignment, the MRSA isolate's susceptibility to 5 non- β -lactam antibiotics (gentamicin, trimethoprim-sulfamethoxazole, erythromycin, ciprofloxacin, and clindamycin) was determined, and annual susceptibility rates were compared. The presence of inducible macrolide-lincosamide-streptogramin B resistance was not considered in this analysis. The number of isolates that demonstrated susceptibility to 3 or more non- β -lactam antibiotics was evaluated in an attempt to quantify the incidence of non-multidrug resistant, oxacillin-resistant *S. aureus* infection.⁷

Continuous variables were compared using the Student *t* test, for normally distributed variables, and the Mann-Whitney *U* test, for nonnormally distributed variables. The χ^2 or Fisher's exact test was used to compare categorical variables.

RESULTS

A total of 697 consecutive patients with SSI due to MRSA were evaluated. Of these, 148 (21%) were excluded because of incomplete information regarding healthcare status in the year prior to the positive culture result. The remaining 549 patients comprised the study cohort. Overall, 474 (86.3%) of the 549 isolates were obtained from culture of blood, 51 (9.3%) from culture of bronchoalveolar lavage fluid, 13 (2.4%) from culture of peritoneal fluid, and 10 (1.8%) from culture of cerebrospinal fluid.

TABLE 1. Non- β -Lactam Susceptibility Among Methicillin-Resistant *Staphylococcus aureus* (MRSA) Isolates Obtained from Hospitalized Patients

Antimicrobial	No. (%) of MRSA isolates, by class of infection			P
	Community-associated (n = 35)	Healthcare-associated (n = 266)	Hospital-acquired (n = 248)	
Gentamicin	35 (100)	234 (88.0)	203 (81.9)	.006
Trimethoprim-sulfamethoxazole	34 (97.1)	239 (90.2)	221 (89.1)	.328
Erythromycin	4 (11.4)	18 (6.8)	15 (6.0)	.493
Ciprofloxacin	14 (40.0)	21 (7.9)	8 (3.2)	<.001
Clindamycin	28 (80.0)	84 (31.6)	49 (19.8)	<.001

During the 3-year period evaluated, there were 35 (6.4%) CA-MRSA SSIs, 266 (48.5%) HC-MRSA SSIs, and 248 (45.1%) HA-MRSA SSIs. The number of CA-MRSA SSIs significantly increased from 2002 (5%) and 2003 (5%) to 2004 (10%) ($P < .05$). Patients with CA-MRSA infection were statistically younger ($P < .001$), were more likely to be African American ($P < .001$), and were more likely to have a concomitant skin and/or soft tissue infection ($P < .001$). MRSA isolates from cases of community-associated infection were statistically more likely to be susceptible to gentamicin ($P = .006$), ciprofloxacin ($P < .001$), and clindamycin ($P < .001$) than were isolates from cases of healthcare-associated and hospital-acquired infections (Table 1). The susceptibility of isolates from cases of CA-MRSA infection did not differ statistically among the antibiotics evaluated from 2002 to 2004. In contrast, isolates from cases of healthcare-associated infection demonstrated a significant increase in susceptibility to clindamycin from 2002 to 2004 ($P < .001$). Isolates from cases of hospital-acquired infection demonstrated significant increases in susceptibility to ciprofloxacin ($P = .031$) and clindamycin ($P = .011$) from 2002 to 2004. A significant increase in the number of non-multidrug resistant, oxacillin-resistant *S. aureus* isolates from sterile sites (susceptible to 3 or more non- β -lactam antibiotics) was also observed from 2002 to 2004 ($P < .001$). A statistically significant increase in the number of non-multidrug resistant, oxacillin-resistant *S. aureus* isolates was not observed among isolates from cases of community associated infection but was observed among isolates from cases of healthcare-associated ($P = .001$) and hospital-acquired ($P = .039$) infection (Table 2).

DISCUSSION

Our study demonstrated that the incidence of CA-MRSA SSIs that required hospitalization increased significantly during the 3-year study period. Additionally, the number of isolates from cases of HC-MRSA and HA-MRSA infection with susceptibility to 3 or more non- β -lactam antibiotics (ie, non-multidrug resistant, oxacillin-resistant *S. aureus* isolates) significantly increased, generally as a result of improved sensitivity to clindamycin and ciprofloxacin from 2002 to 2004.

Consistent with our findings, isolates from cases of CA-

MRSA infection have been found to have increased susceptibility to non- β -lactam antibiotics, including ciprofloxacin, clindamycin, gentamicin, and trimethoprim-sulfamethoxazole, compared with that of isolates from cases of HC-MRSA infection.^{1,5,6} Simultaneous susceptibility to these non- β -lactam antibiotics has been found to be an independent predictor of being infected with a CA-MRSA strain.⁵ Additionally, the trend of non-multidrug resistant, oxacillin resistant *S. aureus* isolates as an increasing cause of healthcare-associated or hospital-acquired infections and, specifically in our study, SSIs has been recently reported.⁸

Our study has several important limitations. First is the study's retrospective design. As such, included and excluded patients could have been misclassified because of a lack of documented information. It is possible that patients classified as having CA-MRSA infected could actually have had HC-MRSA infection, and vice versa. However, more than 90% of the isolates from cases of CA-MRSA infection in the study demonstrated susceptibility to non- β -lactam antibiotics, making false-positive results unlikely. Second, our microbiology laboratory did not test tetracycline susceptibility or test for inducible macrolide-lincosamide-streptogramin B resistance. The susceptibility rates for clindamycin in our study may have been falsely elevated in the clinical sense.^{9,10} Third, we did not perform genetic staphylococcal chromosomal cassette (SCC) *mec* typing or test for genes that encode virulence factors, such as Panton-Valentine leukocidin. However, trials

TABLE 2. Annual Incidence of Sterile-Site Infection Due to Non-Multidrug Resistant, Oxacillin-Resistant Strains of Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Type(s) of MRSA infection	Proportion of MRSA isolates ^a			P
	2002	2003	2004	
All (n = 549)	25/166	55/194	69/189	<.001
Community-associated (n = 35)	8/8	8/8	17/19	NS
Healthcare-associated (n = 266)	10/73	29/101	36/92	.001
Hospital-acquired (n = 248)	7/85	18/85	16/78	.039

NOTE. NS, not significant ($P > .05$).

^a No. of isolates with the specified resistance profile (see Methods) as a proportion of isolates recovered from infections of the specified class.

that have performed molecular typing of non-multidrug resistant, oxacillin-resistant *S. aureus* isolates have found the strains to be predominately SCCmec type IV.^{7,11-14} Consequently, an antimicrobial profile with susceptibility to multiple non- β -lactam antibiotics could be used as a phenotypic marker for community-type strains and the possibility that the organism produces potentially lethal toxins.^{2,3,15}

Despite these limitations of our study, the larger point is to reinforce the evidence that incidence of CA-MRSA SSIs that require hospitalization is increasing, as well as to recognize that there are HC-MRSA isolates that are susceptible to multiple non- β -lactam antibiotics. Clinicians should be cognizant of a susceptibility profile that indicates a non-multidrug resistant, oxacillin-resistant *S. aureus* isolate when they are selecting antimicrobial therapy for healthcare-associated infections.

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