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Risk of Methicillin-Resistant *Staphylococcus aureus* Infection after Previous Infection or Colonization

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Studies evaluating the risk of methicillin-resistant *Staphylococcus aureus* (MRSA)-associated sequelae in colonized or infected inpatients have not extended follow-up into the period after discharge from the hospital. We determined the 18-month risk of MRSA infection among 209 adult patients newly identified as harboring MRSA. Twenty-nine percent of patients (60 patients) developed subsequent MRSA infections (90 infections). These infections were often severe. Twenty-eight percent of infections (25 of 90) involved bacteremia, and 56% (50 of 90) involved pneumonia, soft tissue infection, osteomyelitis, or septic arthritis. Eighty percent of patients (48 of 60) with subsequent MRSA infection developed the infection at a new site, and 49% of new MRSA infections (44 of 90) first became manifest after discharge from the hospital. Accurate assessment of the risk of MRSA-associated sequelae requires prolonged follow-up after discharge.

Staphylococcus aureus is a human commensal organism carried in the nares of 30% of healthy adults [1]. In hospitalized patients, it can colonize skin, vascular catheters, and wound sites, as well as the nasopharynx [2–4]. Emergence of methicillin-resistant *S. aureus* (MRSA) has made treatment less effective and more costly [5]. Among colonizing *S. aureus* strains, methicillin-resistant strains are more likely to cause subsequent hospital infections, which incur longer hospital stays and higher costs because of therapy and infection control requirements [5]. Eradication regimens exist but have not been widely implemented [6], possibly because of their cost, the risk of side effects, and the lack of compelling evidence of efficacy.

Much is known about risk factors for MRSA colonization and infection in the hospital setting. We also know MRSA colonization predisposes to MRSA infection during the same hospitalization [4, 7–9]. The risk of colonization is higher for patients who have been recently hospitalized, are admitted to an intensive care unit (ICU), require invasive procedures, have long hospital stays, or enter the hospital during an outbreak of MRSA infection [1, 10–12]. Risk factors for infection after colonization include recent antibiotic therapy, an ICU stay, undergoing intravenous catheterization, presence of soft tissue wounds, and prior colonization with MRSA [4, 7–9].

Although much is known about MRSA-associated morbidity, little is known about the impact of MRSA colonization on patients after hospital discharge. There are no studies describing the risk of infection or re-hospitalization for patients who leave the hospital after being identified as harboring MRSA. Nevertheless, we know that MRSA can be carried in the nares for >1 year [13]. One study estimated the half-life of MRSA colonization to be 40 months [13]. Thus, it is reasonable to suspect that colonized patients who are dis-

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charged remain at substantial risk of MRSA infection. This may be particularly true of debilitated patients who required surgery or ICU care. Furthermore, it is reasonable to assume that patients who have recovered from invasive MRSA disease may be more susceptible to reinfection. We therefore determined whether MRSA colonization predisposes patients to long-term risk of MRSA-associated morbidity, particularly in the post-discharge period.

PATIENTS AND METHODS

We retrospectively identified a cohort of adult patients from Brigham and Women's Hospital (BWH), a 700-bed hospital in Boston, Massachusetts, who had MRSA-positive cultures that represented newly detected colonization or infection. We then conducted an observational study to determine the frequency of subsequent MRSA infection in these patients during the 18 months after the initial detection of MRSA. BWH had no records (results of testing of clinical specimens, transfer records, or medical histories) indicating that these patients had been previously colonized or infected with MRSA.

Using infection control records, we identified all patients for whom MRSA-related infection control precautions had been newly initiated during April–June or during October–December 2000. If the first known instance of MRSA colonization or infection occurred during a hospitalization, then that hospitalization was classified as the index hospitalization. We obtained information on age, sex, and hemodialysis status for all patients and obtained information on dates of admission, occurrence of an ICU stay, and discharge disposition for all inpatients. One infectious diseases physician (S.S.H.) reviewed the BWH medical records (which included admission and progress notes, discharge summaries, medication orders, laboratory and microbiologic data, and radiographic studies) of patients newly identified as MRSA-positive to identify the source of the initial MRSA isolate and whether it represented infection or colonization. Subsequent MRSA infections were determined for the 18-month period after the initial MRSA-positive culture.

MRSA was identified in cultures of clinical specimens performed at the direction of the patient's physician, or according to the hospital infection control policy, which calls for screening of nares specimens from all patients in a hospital unit when ≥ 3 newly colonized or infected patients are identified within a 2-week period in a given hospital unit. Accordingly, all non-nares specimens were clinical specimens, and all nares specimens were obtained for surveillance purposes. Patients were classified in 1 of 2 groups on the basis of whether the initial MRSA isolate indicated colonization or disease. All isolates from normally sterile sites were considered to indicate infection. Evidence of infection from nonsterile sources (sputum or wound specimens) was based upon National Nosocomial In-

fections Surveillance criteria [14–17]. All subsequent MRSA infections were described according to the number of days between the onset of infection and the first isolation of MRSA, the source of infection, and whether the infection occurred during the same hospital visit as the initial isolation of MRSA. Each infection was categorized according to the source of primary infection: either primary bacteremia [17] (unknown source and catheter-related [18]), pneumonia, soft-tissue infection, bone infection, or other, as described elsewhere [12].

Study group characteristics described included the mean patient age and the mean length of hospital stay (for inpatients), as well as the proportion of patients who were male, who were receiving chronic hemodialysis, and who were inpatients at the time of MRSA detection. Inpatients were further described according to their discharge disposition and the proportion treated in the ICU. We determined the proportion of patients developing any subsequent MRSA infection, and we determined the proportion of MRSA infections according to the source. Proportions were compared by Fisher's exact test.

The risk of subsequent MRSA infection among patients with newly detected colonization or infection was determined by a 2-sample test of proportions (a χ^2 test) that evaluated the season that infection occurred, patient sex, patient history of chronic hemodialysis, whether the initial MRSA-positive culture represented colonization or infection, and whether the patient was discharged to a rehabilitation center or a skilled nursing facility. The same test was also used to determine whether there were differences in the sources of infection between predischARGE and postdischarge MRSA infections. A 2-tailed, 2-sample *t* test was used to evaluate patient age and length of hospital stay as predictors for subsequent MRSA infection (all infections and postdischarge infections alone). All tests were performed with STATA statistical software (Stata).

RESULTS

We identified 435 adult patients for whom MRSA-related infection control precautions were initiated during the two 3-month study periods. Of these, 209 patients were newly identified as being colonized or infected with MRSA, and 201 were inpatients at the time of identification. For 75 (37%) of the 201 inpatients (including transferred patients), MRSA was detected in culture within 3 days after admission. Demographic and clinical characteristics of the 209 patients with newly identified MRSA infection or colonization are summarized in table 1. Men more frequently tested positive for MRSA than did women. Inpatients had an average length of hospital stay of 24 days (SD, ± 22.5 days; median, 17 days; interquartile range, 8–35 days), and less than one-third of inpatients returned home when discharged from the hospital.

Ninety-seven patients (46%) had MRSA-positive cultures

Table 1. Demographic and clinical characteristics of patients at Brigham and Women's Hospital with newly identified methicillin-resistant *Staphylococcus aureus* (MRSA) colonization or infection.

Characteristic	Value
Total no. of patients	209
Season infection identified	
Spring (Apr–Jun)	97 (46)
Fall (Oct–Dec)	112 (54)
Sex	
Male	120 (57)
Female	89 (43)
Age, years	
Mean	68
Median	71
ICU stay	126 (60)
Chronic hemodialysis	9 (4)
Outpatient	8 (4)
Inpatient	201 (96)
Average length of hospital stay, days	24
Discharge disposition of inpatients ^a	
Home	58 (29)
Rehabilitation center	83 (41)
Skilled nursing facility	25 (12)
Other hospital	2 (1)
Hospice	2 (1)
Died	31 (15)

NOTE. Data are no. (%) of patients, unless indicated otherwise.

^a Hospitalization during which initial MRSA was first isolated.

representing colonization, and 112 (54%) had cultures representing infection (table 2). The respiratory tract was the most common source of newly identified MRSA isolates for cases of both colonization and infection. For the 201 inpatients, the mean time to the initial MRSA-positive culture was 9 days (median, 6 days). There was no significant difference in the mean time to the initial MRSA-positive culture between patients whose culture result represented colonization (10 days) and those whose culture result represented infection (9 days).

Of the 209 patients who were newly identified as being MRSA positive, 60 patients (29%) developed 90 subsequent infections due to MRSA (table 3). Nineteen patients (9%) had >1 episode of subsequent MRSA infection. On average, infections occurred 102 days (median, 29 days; 95% CI, 71–134) after the initial MRSA-positive culture. Risk of subsequent MRSA infection differed according to the source of the initial MRSA isolate. Patients had a 20%–30% risk of future MRSA-associated morbidity if the initial MRSA isolates were from respiratory and soft tissue sources, but a 40%–50% risk if the initial sources were bone, joint fluid, or the nares (i.e., as detected by a screening nares culture for MRSA surveillance) (table 2).

Of 60 patients with subsequent MRSA infection, 48 patients (80%) had 67 infections that were localized to a site different than the site from which MRSA was initially isolated. These episodes were most commonly bacteremia (22 [33%] of 67 infections) or soft tissue infection (16 [24%] of 67). Twenty-two (37%) of 60 patients had infections localized to the site from which MRSA was initially isolated. The majority of same-site infections (13 of 22) were pneumonia. Seven patients had both same-site and different-site infections during the 18-month period after initial MRSA isolation. Only bone and joint infections were more likely to result in recurrent infections at the same site (OR, 5.6; $P = .02$, Fisher's exact test). Three bone infections (2 sternal and 1 foot infection) recurred despite surgical debridement. In one case, a prosthetic hip infection was followed by infection of the cement spacer after prosthesis removal and by subsequent infection of the femur and pelvis despite radical surgery. One case of subsequent osteomyelitis occurred at a site distinct from the original bone infection.

Risk of subsequent MRSA infection did not differ significantly according to sex, age, whether the initial MRSA-positive culture represented colonization or infection, the quarter of year during which infection occurred, or history of chronic hemodialysis. It also did not differ significantly among inpatients according to discharge disposition (i.e., discharge to home, a rehabilitation center, or a skilled nursing facility) or the occurrence of an ICU stay. Not surprisingly, inpatients who had subsequent MRSA infections were more likely to have had a longer hospital stay (mean, 33 days), compared with those who did not (mean, 22 days) ($P < .001$).

Notably, one-half of the patients (31 [52%] of 60) developed 44 subsequent MRSA infections that first became manifest after discharge from the index hospitalization. There were no significant predictors for development of predischARGE versus postdischarge MRSA infections. However, predischARGE infections were more likely to be related to the presence of a vascular catheter (OR, >7; $P < .01$) or to involve the bloodstream (OR, 2.6; $P < .05$) (table 3).

DISCUSSION

Approximately one-third of patients newly identified as being MRSA positive developed subsequent infection, regardless of whether the initial MRSA-positive culture represented colonization or infection. Moreover, the vast majority of patients (80%) developed infections at a site unrelated to the initial site from which MRSA was isolated. These MRSA infections following initial detection of MRSA colonization (or infection) were substantially more common than previously reported, largely because previous studies did not evaluate postdischarge events, which accounted for one-half of MRSA-associated morbidity in our study population. Published reports have noted

Table 2. Risk of subsequent methicillin-resistant *Staphylococcus aureus* (MRSA) infection, according to the sources of the initial and subsequent MRSA isolates.

Class and source of initial isolate	No. (%) of patients with initial MRSA isolates	No. (%) of patients with subsequent MRSA infection		
		At any site	At the same site ^a	At a different site ^a
Colonization				
Nares	22 (23)	11 (50)	5 (45) ^b	8 (73)
Sputum	60 (62)	16 (27)	7 (44)	12 (75)
Soft tissue	15 (15)	5 (33)	0	5 (100)
Other ^c	1 (1)	0	0	0
Total ^d	97 (100)	30 (31)	12 (40)	23 (77)
Infection				
Pneumonia	47 (42)	12 (26)	2 (17)	12 (100)
Soft tissue	22 (20)	5 (23)	1 (20)	4 (80)
Bone/joint	20 (18)	9 (45)	6 (67)	4 (44)
Catheter ^e	2 (2)	0	0	0
Blood	22 (20)	7 (32)	2 (29)	5 (71)
Other ^f	15 (13)	3 (20)	1 (33)	2 (67)
Total ^d	112 (100)	30 (27)	10 (33)	25 (83)
Overall				
Nares/respiratory tract	129 (62)	39 (30)	14 (36)	32 (82)
Soft tissue	38 (18)	10 (26)	1 (10)	9 (90)
Bone/joint	20 (10)	9 (45)	6 (67)	4 (44)
Catheter	2 (1)	0	0	0
Blood	22 (11)	7 (32)	2 (29)	5 (71)
Other	16 (8)	3 (19)	1 (33)	2 (67)
Total ^d	209 (100)	60 (29)	22 (37)	48 (80)

NOTE. Data are % or % (no.) of patients with the indicated class(es) of isolate.

^a Describing infections as arising from a source identical to or different than the source of the initial MRSA isolate.

^b Infection occurred in the respiratory tract (pneumonia).

^c Stool ($n = 1$).

^d For some patients, MRSA isolates came from multiple sources.

^e Without bacteremia.

^f Urine ($n = 11$), bronchitis ($n = 1$), sinusitis ($n = 1$), peritonitis ($n = 1$), and mediastinitis ($n = 1$).

that the risk of subsequent MRSA infection exceeds 30% in colonized ICU patients [19, 20]. With the inclusion of post-discharge records, our data suggest that at least 29% of all patients newly identified as MRSA positive, regardless of ICU status, developed an average of 1.5 subsequent MRSA infections. Additionally, we found that 36% of episodes of MRSA bacteremia (8 of 25) in previously colonized or infected individuals were detected after discharge. Colonized patients appear to be at risk for MRSA infection over many months and can potentially place caretakers and family members at risk of becoming colonized [21, 22].

The 29% risk of subsequent MRSA infection among patients who are newly identified as being MRSA positive is probably an underestimate of the actual risk, because our study was limited

to the 18 months after initial MRSA detection. In addition, we could not account for other cases detected and treated at other medical facilities. Complete postdischarge follow-up would have likely revealed additional cases of MRSA-associated morbidity. Of the 178 patients who either had initial MRSA-positive cultures as outpatients or survived to discharge in their index hospitalization, only 63% had some form of follow-up records available for us to assess; 82 patients (46%) were rehospitalized, and an additional 30 (17%) had at least 1 outpatient visit during the 18 months of observation. To our knowledge, at least 51 patients died during the period of observation (29%), including 31 who died during the index hospitalization.

These results reflect the carriage and infection rates at a single hospital and may not be generalizable to other centers because

Table 3. Sources of subsequent infection with methicillin-resistant *Staphylococcus aureus* (MRSA).

Source	Patients, no. (%) (n = 60)	MRSA infections, no. (%) ^a		
		Total (n = 90)	Predischarge (n = 46)	Postdischarge (n = 44)
Pneumonia	14 (23)	18 (20)	9 (20)	9 (20)
Soft tissue	16 (27)	18 (20)	9 (20)	9 (20)
Bone/joint	11 (18)	14 (16)	2 (4)	12 (27)
Catheter ^b	5 (8)	7 (8)	7 (15)	0
Blood	23 (38)	25 (28)	17 (37)	8 (18)
Other ^c	8 (13)	8 (9)	2 (4)	6 (14)

^a For some patients, MRSA isolates came from multiple sources.

^b With or without associated bacteremia.

^c Urine (n = 6), mediastinitis (n = 1), and sinusitis (n = 1).

of variations in patient characteristics, physician practice, and different hospital transmission dynamics. In addition, because strain typing was not performed, it is impossible to know whether subsequent infections were due to the same strain as the initial infection or colonization or due to a newly acquired strain. Nevertheless, the finding of a substantial number of postdischarge infections due to MRSA is noteworthy. Risk factors associated with subsequent MRSA infection were longer hospital stays, for inpatients, and the initial involvement of a bone or joint.

Although future studies that include strain typing are needed, our finding that more than one-half of patients with MRSA infections had episodes of infection that occurred after discharge is consistent with previous findings that MRSA colonization can persist for prolonged periods and places patients at higher risk of infection. This high risk of infection increases the attractiveness of eradicating MRSA carriage, particularly in view of the recent emergence of strains of *S. aureus* fully resistant to vancomycin [23]. Eradication measures, which may include treatment with topical mupirocin or with a combination of active systemic agents, such as rifampin, doxycycline, or trimethoprim-sulfamethoxazole, have not been widely studied or implemented in the United States. Even if instituted only at the time of hospital discharge, an eradication measure with 50% efficacy over several months could reduce the overall burden of subsequent MRSA infection by 25%. Further studies of MRSA-associated sequelae after colonization are needed and should take into account postdischarge events.

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