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What's in a Name? Is Methicillin-Resistant *Staphylococcus aureus* Just Another *S aureus* When Treated With Vancomycin?

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• Methicillin-resistant *Staphylococcus aureus* (MRSA) strains, principally resistant to penicillinase-resistant penicillins and aminoglycosides, are increasingly common hospital isolates. We have examined the significance of MRSA colonization and infection in 1100 consecutively admitted, seriously burned patients in whom vancomycin was used to treat all staphylococcal infections. Colonization with *S aureus* (SA) was identified in 658 patients, in 319 of whom MRSA colonization was identified. Two hundred fifty-three SA infections occurred in 178 patients; of these infections, 58% were pulmonic and 38% were bacteremic. Methicillin-resistant SA infections occurred in 58 of the SA-infected patients. A severity index, based on multiple-regression analysis of mortality as a function of burn size and age in the study population, was used to estimate expected mortality. We demonstrated no measurable increase in mortality attributable to MRSA in this population of burned, SA-infected patients. The results question the clinical and economic value of added control practices, such as closure of units, refusal of transfer or admission, added isolation, treatment of carriers, furlough of colonized staff, and other expensive measures that specifically directed at prevention of MRSA infections in critical care areas.

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Adaptations of β -lactam antibiotics to counter resistance developed by *Staphylococcus aureus* (SA) have never been completely successful. The development of penicillinase-resistant penicillins (PRPs) during the early 1960s attempted to recoup the effectiveness exhibited by native penicillin when it was introduced nearly 20 years earlier, but soon after introduction of these agents to the antibiotic armamentarium, and perhaps even earlier, strains resistant to PRP were documented.^{1,2} Strains resistant to PRP were also found to be resistant to cephalosporins and to other forms of β -lactam antibiotics. Unlike previous experience with strains resistant to native penicillin, which rapidly became common in both the

hospital and the community, infections caused by these new resistant strains appeared to be principally confined to hospitals. This confinement of PRP resistance to hospitals made such strains nosocomial pathogens by definition. The acronym MRSA (methicillin-resistant SA) became a common label for methicillin-resistant strains of SA.

Methicillin-resistant SA strains, because they are readily identifiable and perhaps because they are characterized by a popular acronym, have been treated and reported as if they were distinct pathogens. From the early outbreaks in Europe in the 1960s to the present, the literature has been rife with reports on MRSA. Despite this outpouring of reports, however, the virulence and true pathogenic significance of these strains relative to other SA strains causing infections in the same patient populations are not clear. This difficulty exists because denominators, such as severity of underlying patient disease, frequency of infection, and mortality under the same chemotherapeutic regimens, have not been reported. We have compared the significance of MRSA strains with that of methicillin-sensitive SA (MSSA) strains in causing infections in a population of 1100 burn patient admissions with known individual indexes of severity of injury and the same antimicrobial therapy.

MATERIALS AND METHODS

Occurrences of SA colonization and infection were recorded in 1100 consecutive burned patients admitted between mid-1982 and the first quarter of 1988. Microbial surveillance consisted of admission and three-times-weekly cultures of sputum, urine, and wound surface as well as stool cultures two times weekly for the first 30 days after admission, or more than 30 days if the patient remained in intensive care. Staphylococci species were identified by standard laboratory techniques and rabbit plasma (direct tube) was used for coagulase determinations. In vitro antibiotic testing was performed using agar overlay disk diffusion methods.⁴ Penicillinase-resistant penicillin activity was measured using 1- μ g oxacillin disks with incubation at 35°C.⁵ Methicillin-resistant SA strains were followed by computer, using antibiotic resistance patterns as identifiers. Bacteriophage and plasmid profiles were not performed. Colonization was defined as one or more isolations of a strain from any source. Infections and antibiotic usage were documented using prospective protocols and were

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reviewed by the clinical staff and by the US Army Institute of Surgical Research (San Antonio, Tex) Infection Control Committee. *Staphylococcus aureus* infections were documented by culture and vancomycin was used exclusively for the treatment of documented SA infections. This practice had been initiated several years prior to this review in an attempt to reduce cross-selection for β -lactam resistance in gram-negative organisms. Vancomycin dosage was monitored by measurement of serum levels. When gram-negative infections occurred, the principal regimen was treatment with amikacin sulfate and an ureido-penicillin therapy. Amphotericin B was used for systemic antifungal therapy.

The first 115 patients were cared for in an open-bed intensive care ward; thereafter, a single-bed isolation intensive care unit was used for acute care. As we have previously described, following the cohort admission to the new single-bed isolation unit with its added physical isolation, our standard infection control practices were enhanced. A marked decrease in gram-negative infections and, in particular, *Pseudomonas aeruginosa* infections was correlated with a demonstrable improvement in survival, and this improvement has continued.^{6,8} To date, our standard infection control practices have continued to prevent the reemergence of multiply resistant gram-negative strains that we have reported to influence mortality significantly.⁹ In contrast, SA strains have not been responsive to the same infection control practices. In this report, the significance of SA infections in relation to patient outcome adjusted for burn size and age is documented. The severity index used for adjustment was based on multiple logistic regression analysis of mortality in patients admitted after 1980.

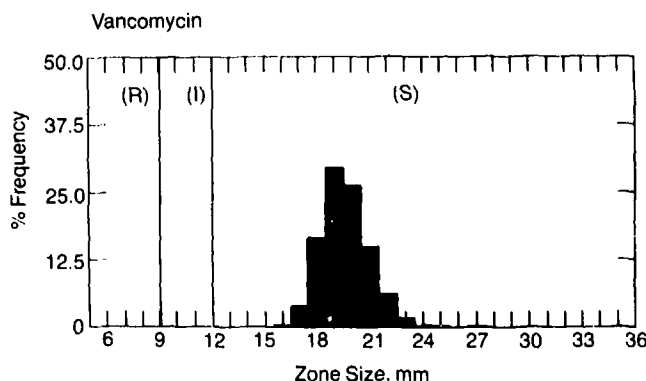
RESULTS

Staphylococcus aureus was isolated from 658 patients; a total of 6602 strains were examined for in vitro antibiotic sensitivity. Methicillin-resistant SA strains were isolated from 319 of the colonized patients. A comparison of the antibiotic sensitivities of the isolated MRSA and MSSA strains is presented in Table 1. The MRSA sensitivities clearly show why such strains are sometimes called multiply resistant SA. Increased resistance to older drugs such as the sulfonamides, streptomycin, erythromycin, and gentamicin is obvious. In contrast, vancomycin and amikacin sulfate were active against both oxacillin-resistant and oxacillin-sensitive strains. The distribution of zones of inhibition by vancomycin (30- μ g disk) for the tested SA strains is presented in the Figure. Even with prolonged exclusive use of this agent for SA infections, no resistant strains or shifts in sensitivity distribution have been observed at this institute.

One hundred seventy-eight of the 1100 patients had one or more SA infections during the hospitalization period. The demographic characteristics of the total population, the SA organisms colonized, and the respective patients are presented in Table 2. As can be seen, the colonized patients

differed little from the total population. *Staphylococcus aureus*-infected patients, however, had larger burns and, as indicated by their severity indexes, were a subset of patients with nearly twice the predicted injury-related mortality of the other groups.

The SA-infected group was partitioned on the basis of the sensitivity of the infecting strains to PRP. Methicillin-sensitive SA caused 157 infections in 120 patients, MRSA caused 58 infections in 43 patients, and a group of 15 patients with infection by both sensitive and resistant strains experienced 38 infections. The characteristics of the three groups are presented in Table 3. The MSSA and MRSA groups appear similar; the mixed group had slightly more severe injuries and longer hospital stays. The types and frequencies of infection



Distribution of zones of growth inhibition for 6602 *Staphylococcus aureus* strains using 30- μ g vancomycin disks for the period July 1, 1982, to July 1, 1988. R indicates resistant; I, intermediate; and S, sensitive.

Table 2.—Demographic Data for Total Admissions and *Staphylococcus aureus*-Colonized and *S aureus*-Infected Patients

Variable	Admissions (n = 1100)	Colonized (n = 658)	Infected (n = 178)
Mean age, y	30	31	38
Total burn size, mean %	28	34	48
3° burn size, mean %	14	18	29
Sex, M/F	908/192	558/100	146/32
Mean No. of d in hospital	39	50	58
Mean severity index	0.1888	0.235	0.4406

Table 1.—Percentage of Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Methicillin-Sensitive *S aureus* (MSSA) Isolates Resistant to Selected Antibiotics

Antibiotic	MRSA, % (n = 2484)	MSSA, % (n = 4118)
Oxacillin	100.0	0.0
Gentamicin	50.9	8.0
Streptomycin	49.4	7.8
Erythromycin	23.2	8.2
Tetracycline	6.7	6.4
Sulfonamides	39.2	8.9
Penicillin	90.2	83.2
Amikacin	0.5	0.5
Vancomycin	0.0	0.0

Table 3.—Demographic Data for Groups of *Staphylococcus aureus*-Infected Patients*

Variable	MSSA (n = 120)	MRSA (n = 43)	MSSA and MRSA (n = 15)
Mean age, y	39	37	38
Total burn size, mean %	47	46	52
3° Burn size, mean %	30	23	34
Sex, M/F	96/24	35/8	15/0
Mean No. of d in hospital	57	56	76
Mean severity index	0.4397	0.4194	0.5089

*MSSA indicates methicillin-sensitive *S aureus*; MRSA, methicillin-resistant *S aureus*.

Table 4.—Sites of Occurrence of *Staphylococcus aureus* Infections*

Site	MSSA Infections			MRSA Infections			MRSA/MSSA Infections		
	No. of Cases	No. of Patients (n = 120)	PBD	No. of Cases	No. of Patients (n = 43)	PBD	No. of Cases	No. of Patients (n = 15)	PBD
Pneumonia	105	96	16	23	22	18	19	13	21
Bacteremia	49	46	17	33	25	36	15	13	59
Other	3	3	48	2	2	77	4	4	31

*MSSA indicates methicillin-sensitive *S aureus*; MRSA, methicillin-resistant *S aureus*; and PBD, mean postburn day of infection.

Table 5.—Summary of Infection for *Staphylococcus aureus* (SA)—Infected Patients*

Variable	No. (%) of Patients		
	MSSA (n = 120)	MRSA (n = 43)	MSSA and MRSA (n = 15)
SA alone	54 (45.0)	18 (41.8)	2 (13.3)
SA and gram-negative	51 (42.5)	19 (44.2)	10 (66.0)
SA and fungi	37 (30.8)	18 (41.9)	9 (60.0)

*MSSA indicates methicillin-sensitive *S aureus*; MRSA, methicillin-resistant *S aureus*.

Table 6.—Outcome Analysis of Patients With *Staphylococcus aureus* Infections*

Variable	n	No. of Patients		P (Confidence Limits)
		Observed Mortality	Predicted Mortality	
Total cohort	178	79	78	.05 (68-89)
MSSA-infected	120	59	53	.05 (44-62)
MRSA-infected	43	16	18	.05 (12-24)
MSSA- and MRSA-infected	15	4	8	.05 (3-12)

*MSSA indicates methicillin-sensitive *S aureus*; MRSA, methicillin-resistant *S aureus*.

in the MSSA, MRSA, and mixed groups are presented in Table 4. As can be seen, frequencies of infection were similar between the groups; bacteremia was more common with MRSA. In the MRSA group, the postburn day of bacteremia was also later. These longer hospital stays may have offered more opportunity for colonization or for procedure-related introductions of organisms to the bloodstream in these patients. The distributions within the three groups of patients with infections due only to SA or with infections attributed to SA and other organisms are shown in Table 5. *Staphylococcus aureus* infections without infection attributable to any other species occurred in 74 (42%) of the 178 patients. Patients with MSSA infections and patients with MRSA infections had similar frequencies of other infections. Patients with both MRSA and MSSA infections, perhaps as a result of their longer hospitalizations and more severe injuries, had proportionately more infections with gram-negative and fungal pathogens.

Patient outcome was also analyzed (Table 6). When the cohort of SA-infected patients was examined, the mean severity index was 0.4406. Multiplying this value by the 178 patients in the cohort yielded a predicted number of 78 deaths; 95% confidence limits for this value are shown. The MSSA, MRSA, and mixed infection subgroups were similarly exam-

ined. In each subgroup and in the entire cohort, the observed mortality fell within the confidence limits calculated on the basis of burn size and age.

COMMENT

We have previously reviewed the lethality attributable to specific groups of organisms that cause bacteremia in burned patients and demonstrated that a significant increase in the risk of death, beyond that attributable to severity of injury, was associated with gram-negative bacteremia.⁹ In a 5800-patient sample, *P aeruginosa* and enteric gram-negative rods were associated with as much as a 50% increase in observed mortality. Using the same analytical system, the present study identifies no differences of consequence between infections caused by MRSA and those caused by MSSA. These infections occurred in similar patients, were seen in conjunction with other infections with the same frequencies, and, when treated with vancomycin, had the same outcome.

These results seriously question the need for unique concern about MRSA, above and beyond concern for staphylococcal infection in general, in burned or immunosuppressed patients. The frequency of MRSA in medical centers and the often necessary transfer of patients between institutions providing either greater or lesser levels of clinical care make the likelihood of preventing colonization with MRSA for any appreciable period quite small.¹⁰ The costs of temporarily closing care facilities or restricting patient movement among levels of care because of concern about MRSA must be weighed, both in terms of cost and impairment of patient care, against some realistic assessment of the risks unique to MRSA. The uniform effectiveness of vancomycin against these organisms and the rarity of reactions to modern preparations of the antibiotic¹¹ argue strongly that staphylococcal infection is staphylococcal infection and that the title MRSA makes no difference. For a difference to be a difference, it has to make a difference.

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Discussion

TIMOTHY L. PRUETT, MD, Charlottesville, Va: You demonstrate that in a hospital setting that has a very high prevalence of MRSA, prompt recognition and treatment with appropriate antibiotics make MRSA no different from any other staphylococcus. However, the question we have to raise is whether we can indeed expand the information that you have given us to cover the general tertiary care hospital that most of us represent. You are in a bit of a unique situation in that you have a very large burn unit and you can easily focus on your particular arena, whereas the majority of us have patients in the intensive care unit, patients undergoing general surgery, and a smattering of others. How can we make a correlation between what you say and what we have?

We currently put patients in reverse isolation and wound protection settings. It costs a great deal, but our colleagues in epidemiology nonetheless assure us that it is important. The mortality and morbidity is not different between patients with MRSA and MSSA strains when they are treated appropriately with vancomycin. However, if patients are inappropriately treated, the literature is replete with examples of the fatal consequences.

Does MRSA colonize staphylococcus more frequently than its MSSA counterpart?

A recent report from the Parkland Memorial Hospital's Burn Unit (Dallas, Tex) gave the suggestion that MRSA was a more colonizing kind of staphylococcus than MSSA. In a reply in the *Journal of Infectious Diseases* in 1983, Boyce noted that when MRSA was introduced into a hospital, an increased number of staphylococcal infections followed.

If indeed we accept MRSA as a normal nosocomial pathogen and do not try to eradicate it from our hospitals, are we going to increase the propensity for staphylococcal infections and have you noticed this phenomenon?

You noted that for there to be a difference in staphylococcal infection, there must be a difference in form. You did show one difference between the two kinds of staphylococci, which was in the incidence of bacteremia.

At my institution, there is someone who believes very strongly in protracted therapy of staphylococcal infections and that they are different from other kinds of infections. Indeed, there is a large group of authors in the infectious disease literature who feel that staphylococcal bacteremia should be treated with 4 to 6 weeks of appropriate antimicrobial therapy.

If we increase our staphylococcal infection, there will also be longer treatment and increased morbidity and hospital-associated costs.

Civilian hospitals have a larger pediatric and elderly population. Is MRSA of more importance in these groups? There are reported smatterings in the literature from pediatric and geriatric centers that try to say the problem exists, but at the same time they say that there is no purported difference in the strains.

More importantly for those of us who also deal with problems other than burns, what about the incidence of prosthetic infections? We have a fairly active trauma center and use a large number of prosthetic devices, particularly orthopedic. Is vancomycin as effective as the typical cephalosporins for the prevention of prosthetic-device infections?

I do not think anybody really knows the answers to all these questions, but the point is that there are a lot of gray areas. The fact that we do not understand them potentially means that we should not totally do away with all the ancillary measures of containment of bacteria such as MRSA.

Do you have morbidity with vancomycin? Two studies using prophylactic vancomycin were stopped because of adverse hemodynamic

effects. Can you assess the question of cost—vancomycin currently being expensive—as well as the length of therapy for staphylococcal infection? In your patients, do you have a notion as to whether vancomycin is an effective prophylactic agent for MRSA?

DAVID N. HERNDON, MD, Galveston, Tex: You have shown that MRSA is not more virulent than staphylococcus alone. There is a difference, of course. Vancomycin is more expensive. It has potential autotoxicity and nephrotoxicity. I would be interested in your data on that subject.

I think, perhaps, the more germane issue is whether staphylococcus makes a difference. The incidence of staphylococcal infection in your patient population is high; it is high in most burn patients.

Should we create a cohort for burn patients with MRSA infections? You have alluded to the fact that in 1982 you changed the method of isolation of your patients, and as it had no effect on staphylococcal infection, you suggest that the cohort is ineffective. I think that is an inappropriate inference for which data are lacking. I would like your comment on that. It does make a difference.

EDWIN A. DEITCH, MD, Shreveport, La: You had a high incidence of bacteremia. Where did the bacteria come from? You had a very high incidence of pneumonia. Were these patients intubated? Was pneumonia a secondary infection due to contamination of the lower airways of these intubated patients or was it primary pneumonia?

DR A. MC MANUS: To start with Dr Pruett's comments and perhaps one of the other comments about isolation, I did not want to give the impression that we do not practice infection control. What I tried to show you is that the infection control practices that we have implemented are controlling gram-negative infections that we previously could not control and our survival has increased.

Many of the staphylococcal infections that I have shown you are occurring in patients who, perhaps, would not have been in the hospital several years ago, because they would have died of gram-negative infections. As far as colonization of these strains, I think this is the universally accepted identification of MRSA. These strains are classic colonizers, which is why they tend to be found in hospitals, unlike penicillin- or β -lactamase-resistant staphylococci, which tend to be more community based. There is no question that one of their attributes is an increased colonization frequency.

As far as infections go, I do not know if MRSA strains cause more infections or more serious infections than sensitive strains. As I mentioned, most often people treat these as if they are a distinct pathogen. They do not give you the overall infection rate for SA, and you have to have that to predict or to infer whether they are more infective.

As far as prophylaxis and prosthesis complications, the standard regimens for perioperative coverage in our unit are vancomycin and amikacin sulfate. The incidence of thrombophlebitis and endocarditis is very low and is at the lowest level we have recorded over the past 35 years.

As far as complications go, I know of no serious complication or death as a result. Histamine responses like "red man" syndrome have occurred, but they are controllable. I do not think there has been any outstanding difficulty with the toxicity of vancomycin. We do monitor levels routinely, and I think it is a general impression of our clinicians that this drug is no more toxic than any other drug with which they work.

As far as a cohort of burn patients with MRSA infections, hospitals that have patients with MRSA infections frequently close down a section for 2 or 3 weeks and then a month later they are back in the same position. I think it is important to know whether it really makes a difference in outcome to base the risk vs the cost of creating a cohort.

I throw this out from a burn standpoint, but I think that it should be investigated in every situation: can you document a truly adverse or a specifically adverse complication or outcome difference with MRSA? If you can, then you should go through the extra precautions above what is necessary to prevent cross-contamination with gram-negative organisms. If you cannot, then you should not.