Editorial

James E. Peacock, Jr., MD

Methicillin-Susceptible "Methicillin-Resistant *Staphylococcus aureus*": A Sheep in Wolves' Clothing

As recently reviewed by Sheagren,[1] *Staphylococcus aureus* is a resilient and persistent human pathogen with a remarkable propensity for the development of antibiotic resistance. Following the introduction of penicillin in the 1940s, it was optimistically predicted that the devastating diseases associated with *S. aureus* would soon be controlled and eradicated. This optimism was short-lived as beta-lactamase-producing strains highly resistant to penicillin quickly appeared[2] and rapidly spread across the globe.[3] In keeping with a theme often since repeated in the annals of antimicrobial chemotherapy, the immediate response of the medical community to this threat was to pursue development of newer antibiotics resistant to inactivation by penicillinase. The result of these zealous efforts was the synthesis of methicillin, the prototype semisynthetic penicillinase-resistant penicillin, which was enthusiastically introduced into clinical practice in 1959.[4] Within two short years, strains of *S. aureus* resistant to methicillin were isolated.[5] Although initial reports of outbreaks of disease due to methicillin-resistant *S. aureus* (MRSA) largely originated from Europe,[6,7] the majority of such outbreaks occurring over the past decade have arisen in the US,[8-11] especially in large tertiary referral centers affiliated with medical schools.[12]

Recent national surveys suggest that MRSA have become established endemic and epidemic nosocomial pathogens in many hospitals throughout the US.[12,13] The epidemiological and clinical features of hospital-acquired infections due to MRSA have been well-characterized[12,14,15] as has the pathobiology of the organism.[16] More recently, data supporting the role of vancomycin as optimal therapy for MRSA infections have emerged.[11,17,18] To date, MRSA isolates clearly resistant to vancomycin have not been described.[19] However, concerns about the expense and possible toxicity of vancomycin as well as the specter of emergence of resistance to this agent have led to the evaluation of a plethora of newer antimicrobics for their activity against MRSA.[20,21]

Although recent data demonstrate an ever-increasing prevalence of MRSA isolations,[12] reported rates may in fact underestimate the true extent of the problem. It has been suggested that small community hospitals which lack ongoing infection control programs may frequently underreport the actual numbers of MRSA isolations/infections.[22] An additional cause of underreporting relates to the documented unreliability of various laboratory susceptibility testing procedures, especially newer automated techniques, in detecting methicillin-resistant strains of *S. aureus*.[23-25] As a result, appreciable numbers of cases may go undetected and unreported.

Potential consequences of "underidentification" of MRSA are numerous. Firstly, the cornerstone of controlling the spread of multiple antibiotic resistant nosocomial pathogens is prompt identification of colonized or infected patients and rapid institution of appropriate control measures.[26] Thus, failure to promptly identify and isolate patients harboring MRSA may contribute to more widespread dissemination of this pathogen throughout the hospital environment.[10,12] Once established as an endemic nosocomial pathogen, eradication of MRSA from the environment is virtually impossible[10,12,13] though employment of intensive (and costly) control measures may reduce prevalence rates over

From the Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina.

Address reprint requests to James E. Peacock, Jr., MD, Assistant Professor of Medicine, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, NC 27013.

time.[14] Secondly, MRSA may serve as a reservoir for resistance factors which may be transferred between *S. aureus* and other nosocomial pathogens,[27] thus contributing to the overall burden of antibiotic resistance in the hospital. Lastly, if organisms resistant to methicillin and other semisynthetic penicillinase-resistant penicillins are present but are not recognized as such, failures of therapy due to utilization of ineffective antibiotics may occur,[17-19] with significant adverse impacts upon patient morbidity and mortality. Thus, it is imperative that clinicians and infection control practitioners be aware of the presence of MRSA within their hospitals. As such, it may be necessary to review susceptibility-testing methodology with the microbiology laboratory to insure that appropriate and up-to-date techniques are being utilized to detect MRSA[28] and that "false-negatives" are not occurring.

A heretofore unrecognized problem in the detection of MRSA relates to "over-identification" of methicillin-susceptible strains as methicillin-resistant. As reported in this issue by Fleming and colleagues,[29] a survey of microbiology laboratories in Oregon in 1981 revealed that 8.3% of all *S. aureus* isolates tested were found to be methicillin-resistant. Identification of isolates as methicillin-resistant correlated inversely with laboratory size (as judged by total number of *S. aureus* isolates tested each year). Interestingly, laboratories which routinely confirmed isolates initially found to be methicillin-resistant by retesting reported significantly fewer MRSA isolates than laboratories which did not perform retesting. Independent retesting of selected isolates by the CDC to confirm the finding of methicillin resistance revealed that only 50% of isolates identified as being MRSA by "small" laboratories (ie <500 isolates tested per year) were in fact methicillin-resistant isolates. In contrast, all isolates identified as MRSA by "large" laboratories were confirmed as such by the CDC. Following a program of instruction and review of laboratory procedures, a repeat survey in 1982 found a significant reduction in numbers of MRSA isolates. The authors inferred that the smaller laboratories with less experience in identifying *S. aureus* and in performing susceptibility studies were probably over-reporting the isolation of MRSA, an hypothesis strongly supported by the available data.

In commenting upon the implications of their observations, Fleming and co-workers alluded to the "potential danger" arising from misidentification of methicillin-susceptible *S. aureus* as methicillin-resistant. The specific adverse consequence envisioned by Fleming et al was that of inappropriate therapy of reported MRSA with cephalosporins, an antibiotic to which these "false MRSA" would be susceptible and to which infections with these organisms might respond. If this "learned behavior" was then applied to true MRSA infections, the response to cephalosporins would be predictably different[17,19] with potentially disastrous consequences for the treated patients.

In addition to the above "danger," other potential sequelae of "over-identification" of susceptible *S. aureus* as MRSA also can be envisioned. In most institutions, identification of a patient harboring MRSA would lead to immediate isolation,[30] with its attendant psychoemotional stress for the patient and his family was well as the impediment to optimal care which isolation measures sometimes impose. An aspect of unwarranted isolation often overlooked relates to the economic consequences of such a decision. In our hospital, the per diem patient charge for "contact isolation" (isolation cart and supplies) approximates $18 per day on the general wards and $50 per day in the intensive care units. In this era of DRGs and cost consciousness, the improper and costly use of unwarranted isolation measures cannot be easily justified. Another potential "cost" of isolation may apply to those patients deemed to be colonized rather than infected. In some institutions, active control programs for MRSA include antibiotic treatment of colonized patients in an attempt to eradicate the organism and eliminate patient reservoirs.[31] Since most such treatment regimens extend for at least 5 days and include rifampin as a component of the therapy, a significant additional patient care cost may accrue, a cost often passed on to the patient or third party payers. A final infection control-related consequence of misidentification of *S. aureus* as methicillin-resistant would pertain to the impact of such information on future patient management and care. A number of reports have now appeared in the medical literature detailing the introduction of MRSA into hospitals via the "patient transfer circuit."[12,32] Although it has been suggested that colonization of patients with MRSA should not be an impediment to indicated transfers to other institutions,[30] in point of fact, many institutions, and particularly chronic care facilities and nursing homes, are reluctant to accept patients who are known to harbor highly antibiotic-resistant organisms. Thus, improperly "labeling" a patient as having MRSA may impair future placement of that patient in other hospitals or nursing homes.

Important clinical consequences of misidentifying methicillin-susceptible *S. aureus* as MRSA also exist. The most obvious consequence relates to the proper therapeutic management of patients who manifest clear-cut infection due to these organisms. Conventional clinical wisdom would dictate that vancomycin be utilized in treating patients with MRSA infections.[11,17-19] Although the therapeutic efficacy of vancomycin would be excellent for these methicillin-susceptible "MRSA" infections, the "cost" of such therapy would be high. Firstly, vancomycin at present is one of the most expensive antimicrobial agents available. If standard dosages of vancomycin (eg 30 mg/kg/day or 2 g/day) are utilized for an average treatment duration of 10 days, the cost for the antibiotic alone in our hospital would be approximately $1,250, an expense far in excess of that for a comparable dose and duration of therapy with nafcillin. Secondly, vancomycin is unquestionably more toxic than the semisynthetic penicillinase-resistant penicillins, with the major adverse effects of therapy including phlebitis, rash, nephrotoxicity and neutropenia.[33] Thirdly, although resistance to vancomycin has not yet been clinically documented in *S. aureus* or other target organisms,[19] concerns about the development of such resistance persist, especially in the setting of extensive use of the drug for "inappropriate" indications. Thus, for these and other reasons, infections due to *S. aureus* which are methicillin-susceptible should

ideally be treated with semisynthetic penicillinase-resistant penicillins, not vancomycin.

Identification of multiple-antibiotic-resistant pathogens such as MRSA is obviously an appropriate goal for both clinicians and infection control practitioners. Recent problems with increasing antibiotic resistance among nosocomial bacteria[26] and the difficulties associated with the treatment of infections due to such organisms suggest that we must be prepared to respond appropriately to this challenge.[30] Nevertheless, as the experience of Fleming and colleagues attests, we should be aware that misidentification of susceptible organisms as resistant occasionally occurs.[29] As such, a certain degree of healthy scepticism is probably warranted in these circumstances, especially if such organisms have never been encountered, or very infrequently encountered, in one's institution. In such a setting, it is entirely proper for the clinician to critically review the associated epidemiology and to request clarification of microbiology laboratory practices involved in the identification and susceptibility testing of the organism in question. In addition, retesting of isolates to confirm resistance patterns may be indicated in selected circumstances or with certain organisms such as MRSA. Only with a carefully considered and rational approach to the problem of resistant microbes can we be expected to recognize the "sheep in wolves' clothing" described by Fleming and co-workers.

REFERENCES

1. Sheagren JN: *Staphylococcus aureus*. The persistent pathogen. *N Engl J Med* 1984; 310:1368-1373, 1437-1442.
2. Barber M: Staphylococcal infection due to penicillin-resistant strains. *Br Med J* 1947; 2:863-865.
3. Plorde JJ, Sherris JC: Staphylococcal resistance to antibiotics: Origin, measurement, and epidemiology. *Ann NY Acad Sci* 1974; 236:413-434.
4. Editorial: A new penicillin. *Br Med J* 1960; 2:720-721.
5. Jevons MP: "Celbenin"-resistant staphylococci. *Br Med J* 1961; 1:124-125.
6. Parker MT, Jevons MP: A survey of methicillin resistance in *Staphylococcus aureus*. *Postgrad Med J* 1964; 40(suppl):170-178.
7. Benner EJ, Kayser FH: Growing clinical significance of methicillin-resistant *Staphylococcus aureus*. *Lancet* 1968; 2:741-744.
8. Klimek JJ, Marsik FJ, Bartlett RC, et al: Clinical, epidemiologic and bacteriologic observations of an outbreak of methicillin-resistant *Staphylococcus aureus* at a large community hospital. *Am J Med* 1976; 61:340-345.
9. Crossley K, Loesch D, Landesman B, et al: An outbreak of infections caused by strains of *Staphylococcus aureus* resistant to methicillin and aminoglycosides. I. Clinical studies. *J Infect Dis* 1979; 138:273-279.
10. Peacock JE Jr, Marsik FJ, Wenzel RP: Methicillin-resistant *Staphylococcus aureus:* Introduction and spread within a hospital. *Ann Intern Med* 1980; 93:526-532.
11. Craven DE, Reed C, Kollisch N, et al: A large outbreak of infections caused by a strain of *Staphylococcus aureus* resistant to oxacillin and aminoglycosides. *Am J Med* 1981; 71:53-58.
12. Haley RW, Hightower AW, Khabbaz RF, et al: The emergence of methicillin-resistant *Staphylococcus aureus* infections in United States hospitals. Possible role of the housestaff-patient transfer circuit. *Ann Intern Med* 1982; 97:297-308.
13. Boyce JM: Nosocomial staphylococcal infections (letter). *Ann Intern Med* 1981; 95:241-242.
14. Thompson RL, Cabezudo I, Wenzel RP: Epidemiology of nosocomial infections caused by methicillin-resistant *Staphylococcus aureus*. *Ann Intern Med* 1982; 97:309-317.
15. Locksley RM, Cohen ML, Quinn TC, et al: Multiply-antibiotic resistant *Staphylococcus aureus*: Introduction, transmission, and evolution of nosocomial infection. *Ann Intern Med* 1982; 97:317-324.
16. Peacock JE Jr, Moorman DR, Wenzel RP, et al: Methicillin-resistant *Staphylococcus aureus*: Microbiologic characteristics, antimicrobial susceptibilities, and assessment of virulence of an epidemic strain. *J Infect Dis* 1981; 144:575-582.
17. Sorrell TC, Packham DR, Shanker S, et al: Vancomycin therapy for methicillin-resistant *Staphylococcus aureus*. *Ann Intern Med* 1982; 97:344-350.
18. Cafferkey MT, Hone R, Keane CT: Antimicrobial chemotherapy of septicemia due to methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 1985; 28:819-823.
19. Watanakunakorn C: Treatment of infections due to methicillin-resistant *Staphylococcus aureus*. *Ann Intern Med* 1982; 97:376-378.
20. Thompson RL, Fisher KA, Wenzel RP: In-vitro activity of N-formimidoyl thienamycin and other beta-lactam antibiotics against methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 1982; 21:341-343.
21. Aldridge KE, Janney A, Sanders CV: Comparison of the activities of coumermycin, ciprofloxacin, teicoplanin, and other non-β-lactam antibiotics against clinical isolates of methicillin-resistant *Staphylococcus aureus* from various geographical locations. *Antimicrob Agents Chemother* 1985; 28:634-638.
22. Boyce JM, Causey WA: Increasing occurrence of methicillin-resistant *Staphylococcus aureus* in the United States. *Infect Control* 1982; 3:377-383.
23. Barry AL, Badal RE: Reliability of the microdilution technique for detection of methicillin-resistant strains of *Staphylococcus aureus*. *Am J Clin Pathol* 1977; 67:489-495.
24. Boyce M, White RL, Bonner MC, et al: Reliability of the MS-2 system in detecting methicillin-resistant *Staphylococcus aureus*. *J Clin Microbiol* 1982; 15:220-225.
25. Aldridge KE, Janney A, Sanders CV, et al: Interlaboratory variation of antibiograms of methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* strains with conventional and commercial testing systems. *J Clin Microbiol* 1983; 18:1226-1236.
26. Weinstein RA, Kabins SA: Strategies for prevention and control of multiple drug-resistant nosocomial infection. *Am J Med* 1981; 70:449-454.
27. Jaffe HW, Sweeney HM, Nathan C, et al: Identity and interspecific transfer of gentamicin-resistance plasmids in *Staphylococcus aureus* and *Staphylococcus epidermidis*. *J Infect Dis* 1980; 141:738-747.
28. Aldridge KE: Methicillin-resistant *Staphylococcus aureus*: Clinical and laboratory features. *Infect Control* 1985; 6:461-465.
29. Fleming DW, Helgerson SD, Mallery BL, et al: Methicillin-resistant *Staphylococcus aureus*. How reliable is laboratory reporting? *Infect Control* 1986; 7:164-167.
30. Wenzel RP: The emergence of methicillin-resistant *Staphylococcus aureus*. *Ann Intern Med* 1982; 97:440-441.
31. Ward TT, Winn RE, Hartstein AI, et al: Observations relating to an interhospital outbreak of methicillin-resistant *Staphylococcus aureus*: Role of antimicrobial therapy in infection control. *Infect Control* 1981; 2:453-459.
32. Saroglou G, Cromer M, Bisno AL: Methicillin-resistant *Staphylococcus aureus*: Interstate spread of nosocomial infections with emergence of gentamicin-methicillin resistant strains. *Infect Control* 1980; 1:81-89.
33. Farber BF, Moellering RC Jr: Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. *Antimicrob Agents Chemother* 1983; 23:138-141.