Editorial

Understanding and Controlling Methicillin-Resistant *Staphylococcus aureus* Infections

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During the past four decades, methicillin-resistant *Staphylococcus aureus* (MRSA) has spread throughout the world and has become highly endemic in many geographic areas. Recent studies of methicillin-sensitive *S. aureus* (MSSA) and MRSA isolates collected over many years and analyzed by multilocus sequence typing (MLST), staphylococcal cassette chromosome *mec* (SCC*mec*) typing, and use of a computerized algorithm based on related sequence types (BURST) have revealed that the evolution and spread of MRSA occurred because of the introduction of the mobile SCC*mec* element into several different clones of MSSA.[1] Early MRSA strains appear to have developed from a MSSA strain (ST250-MSSA) that was prevalent in European countries, including Denmark, in the 1950s.[1,2] Of interest, this MSSA ancestor to early MRSA strains is no longer prevalent among disease-associated isolates. More recent epidemic strains of MRSA (EMRSA-2, -6, -7, -12, -13, and -14) that spread effectively in hospitals during the 1980s and 1990s are indistinguishable by MLST, suggesting that a relatively small number of MRSA clones have unique qualities that facilitate their transmission over wide geographic areas. For example, EMRSA clones ST8-MRSA-III and ST239-MRSA-III have been recovered from patients in Finland, France, Germany, the Netherlands, Sweden, the United Kingdom, and the United States.[1] One can conclude from the above findings that the occurrence of epidemics or high levels of endemicity observed in a given geographic area can be explained, at least in part, by whether strains with epidemic potential are circulating in healthcare facilities.

In this issue of *Infection Control and Hospital Epidemiology*, Vriens et al.[3] note that although the prevalence of MRSA is still less than 1% in the Netherlands, occasionally strains of MRSA imported from other countries have spread rapidly between patients and healthcare workers in their surgical intensive care unit (ICU). The outbreaks occurred despite the fact that virtually all hospitals in the Netherlands routinely use aggressive measures to control the spread of MRSA. These measures include placing in isolation any patient transferred from a hospital outside the Netherlands, discontinuing isolation of such patients only after screening cultures have revealed that they are not colonized with MRSA, routinely screening all patients and personnel exposed to a patient with MRSA with treatment (decolonization) of any carriers, and wearing a mask, a gown, and gloves whenever entering the room of a patient with MRSA.[3,4] The authors questioned whether the ability of MRSA to spread rapidly in the surgical ICU was unique, or whether similar spread of MSSA strains was going undetected. To examine this issue, a 2-month, prospective, observational study was conducted to determine the frequency of transmission of MSSA in the surgical ICU. The study involved weekly screening cultures of patients and personnel, prospective recording of the number and type of contacts that each healthcare worker had with patients, and pulsed-field gel electrophoresis (PFGE) of MSSA isolates recovered from patients and personnel. The prevalence of MSSA among patients (24%) and healthcare workers (22%) was similar to what has been described in many other publications. Among the more than 4,100 contacts between patients and healthcare workers, in only 21 instances did both the patient and the healthcare worker carry MSSA. PFGE typing revealed that none of the healthcare workers had the same strain of MSSA as the patients with whom they had contact. Furthermore, none of the patients were colonized with the same strain. Concurrent study of nosocomial transmission of MRSA was not performed. Instead, the authors compared their find-

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ings with historical data on MRSA transmission in the surgical ICU during the preceding 10 years. Apparently, antibiotic usage policies and basic infection control measures employed during the 2-month study were comparable to those used during the preceding 10 years. No in vitro studies were conducted to compare potential virulence factors of MSSA isolates recovered during the study with those of MRSA isolates recovered during earlier outbreaks. The authors concluded that multidrug-resistant MRSA strains may have been transmitted more easily due to antibiotic selection pressure, or that MRSA strains responsible for outbreaks in the surgical ICU may have possessed undescribed virulence factors that facilitate nosocomial transmission. On the basis of the MLST studies cited above,[1,2] it seems plausible that the surgical ICU outbreaks were caused by EMRSA that possess unidentified traits that facilitate transmission among patients and healthcare workers. Although attempts have been made to identify special strain characteristics associated with epidemic transmission of *S. aureus*, studies to date have not been revealing.[5]

Although EMRSA strains similar to those imported into the Netherlands have been introduced into hospitals in other European countries,[1] the prevalence of MRSA varies markedly by country.[4,6] For example, a recent Sentry study revealed that the prevalence of MRSA was low in the Netherlands (< 2.5% in Utrecht University Hospital), 7.5% in Germany, 17% in France, 35% in Belgium, and 50% in southern European countries.[4] In the United States, data from the National Nosocomial Infections Surveillance (NNIS) System of the Centers for Disease Control and Prevention (CDC) suggest that more than 50% of nosocomial *S. aureus* infections acquired in ICUs are caused by MRSA.[7] These data suggest that factors other than strain virulence have a major influence on the prevalence of MRSA in healthcare facilities. The factors most frequently cited for this phenomenon are differences between countries regarding antibiotic use and infection control measures.

Many studies have found that preceding antibiotic therapy is an important risk factor for nosocomial acquisition of MRSA.[8] There is little doubt that widespread use of antibiotics provides multidrug-resistant strains of MRSA with a selective survival advantage. Because many nosocomial MRSA strains are resistant to erythromycin, clindamycin, beta-lactams, and fluoroquinolones, widespread use of many different antibiotics can promote emergence of MRSA. Of interest, overall non-hospital use of antibiotics is significantly lower in the Netherlands, Denmark, and Sweden (areas of low MRSA prevalence) than in France, Spain, and Belgium (areas of high MRSA prevalence).[9] If outpatient use of antibiotics reflects general trends of antibiotic use in hospitals, these data support the assumption that antibiotic use may be responsible for the observed differences in MRSA prevalence in European countries. However, overall non-hospital antibiotic use is similar in Finland (low MRSA prevalence) and the United Kingdom (high MRSA prevalence).[9-11] Furthermore, if restricted antibiotic use was the main factor responsible for a low prevalence of MRSA, one might expect that the incidence of methicillin-resistant *S. epidermis* would also be low in countries where antibiotic use (pressure) is low. However, the prevalence of methicillin-resistant *S. epidermis* is as high in the Netherlands as it is in countries where antibiotic use is much higher.[4] Thus, differences in infection control policies are a more important factor in explaining the marked variation in MRSA prevalence.

There is considerable evidence that the low prevalence of MRSA in northern European countries is due to the prompt implementation of aggressive infection control measures whenever a patient is identified as having MRSA. In Denmark, MRSA strains were highly endemic in the 1960s and early 1970s, but had decreased significantly in prevalence by the mid-1980s and have not increased in recent years despite importation of MRSA from other countries.[12,13] The dramatic decrease in MRSA prevalence has been attributed to reduced use of tetracycline and to routine use of aggressive control measures.[12,13] Control measures have included screening patients admitted from hospitals outside of Denmark to determine whether they are colonized with MRSA, wearing masks, gowns, and gloves when caring for patients, screening patients and personnel for MRSA carriage, and treating those identified as MRSA carriers.[12,13] In the Netherlands, a national MRSA guideline promoting similarly aggressive measures was adopted in 1995, and the prevalence of MRSA has remained low despite importation of epidemic strains of MRSA.[3,4]

In the United States, MRSA continues to be a vexing problem for many healthcare facilities.[7] Although many hospitals have policies (Contact Precautions) requiring the wearing of gloves whenever entering the room of a patient with MRSA, the wearing of gowns if substantial contact with the patient or the environment is anticipated, and the washing or disinfecting of hands after removing gloves, adoption of such policies has not controlled the spread of MRSA in the United States. The inability of many facilities to control the spread of MRSA is most likely due to widespread overuse of antibiotics and to suboptimal implementation of recommended control measures. Poor adherence of healthcare workers to recommended barrier precautions has been documented for patients with vancomycin-resistant enterococci[14] and almost certainly contributes to poor control of MRSA. Poor adherence of personnel to recommended hand washing practices is a widespread problem,[15] and is likely to contribute to poor control of MRSA in many facilities. Both an observational study and a cohort study have suggested that improved hand hygiene can contribute to better control of MRSA,[16,17] although one of these hospitals simultaneously implemented a program of active surveillance cultures, making the relative contribution of the improved hand hygiene unclear.[18]

Because transmission of MRSA occurs significantly more often from patients who are not isolated than from patients who are cared for in Contact Precautions, screening high-risk patients for MRSA and placing colonized patients in isolation is important for effective control.[19,20] A number of studies have provided evidence that the screening of high-risk patients, when performed in conjunction

with other infection control measures, can contribute to better control of MRSA.[18,21,22] Although many hospitals have been reluctant to implement screening programs, several studies have found that such screening programs are cost-effective.[21,23,24] Although effective screening programs have used culture methods generally available to most hospitals, further studies are needed to establish more efficient methods of screening various body sites for the presence of MRSA.[25,26]

Insufficient epidemiologic analysis of endemic MRSA colonization and infection may also be a cause of continued spread of MRSA. In some instances, thorough epidemiologic investigations of outbreaks have established a colonized or infected healthcare worker as the source of transmission.[27-29] In such situations, even a high degree of adherence of healthcare workers with recommended barrier precautions and hand hygiene will not interrupt this type of transmission.

Finally, despite years of studying endemic and epidemic MRSA in healthcare facilities, we may not have elucidated all factors that can influence transmission. In this issue of *Infection Control and Hospital Epidemiology,* Squier et al.[30] have identified rectal carriage of *S. aureus* as a risk factor for staphylococcal infection among high-risk surgical patients. Prospective screening cultures of patients in a surgical ICU and a liver transplant unit revealed a high prevalence of rectal colonization with MSSA or MRSA. Patients with rectal colonization experienced a significantly higher incidence of staphylococcal infections when compared with similar patients who had nasal carriage only or with non-carriers. A recent study from France revealed that a substantial proportion of patients who had antibiotic-associated diarrhea and whose gastrointestinal tract was heavily colonized with MRSA had an accompanying bacteremia by the same strain.[31] Both of these studies suggest that there are further lessons to learn regarding the epidemiology and control of MRSA in healthcare facilities.

REFERENCES

1. Enright MC, Robinson DA, Randle G, Feil DJ, Grundmann H, Spratt BG. The evolutionary history of methicillin-resistant *Staphylococcus aureus* (MRSA). *Proc Natl Acad Sci U S A* 2002;99:7687-7692.
2. Crisostomo MI, Westh H, Tomasz A, Chung M, Oliveira DC, de Lencastre H. The evolution of methicillin resistance in *Staphylococcus aureus*: similarity of genetic backgrounds in historically early methicillin-susceptible and -resistant and contemporary epidemic clones. *Proc Natl Acad Sci U S A* 2001;98:9865-9870.
3. Vriens MR, Fluit AC, Troelstra A, Verhoef J, van der Werken C. Is methicillin-resistant *Staphylococcus aureus* more contagious than methicillin-susceptible *S. aureus* in a surgical intensive care unit? *Infect Control Hosp Epidemiol* 2002;23:491-494.
4. Verhoef J, Beaujean D, Blok H, et al. A Dutch approach to methicillin-resistant *Staphylococcus aureus. Eur J Clin Microbiol Infect Dis* 1999;18:461-466.
5. Aathithan S, Dybowski R, French GL. Highly epidemic strains of methicillin-resistant *Staphylococcus aureus* not distinguished by capsule formation, protein A content or adherence to Hep-2 cells. *Eur J Clin Microbiol Infect Dis* 2001;20:27-32.
6. Voss A, Milatovic D, Wallrauch-Schwarz C, Rosdahl VT, Braveny I. Methicillin-resistant *Staphylococcus aureus* (MRSA) in Europe. *Eur J Clin Microbiol Infect Dis* 1994;13:50-55.
7. Centers for Disease Control and Prevention. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1992-June 2001. *Am J Infect Control* 2001;29:404-421.
8. Boyce JM. Methicillin-resistant *Staphylococcus aureus*: detection, epidemiology and control measures. *Infect Dis Clin North Am* 1989;3:901-913.
9. Cars O, Molstad S, Melander A. Variation in antibiotic use in the European Union. *Lancet* 2001;357:1851-1853.
10. Salmenlinna S, Lyytikainen O, Kotilainen P, Scotford R, Siren E, Vuopio-Varkila J. Molecular epidemiology of methicillin-resistant *Staphylococcus aureus* in Finland. *Eur J Clin Microbiol Infect Dis* 2000;19:101-107.
11. Fluit AC, Wielders CLC, Verhoef J, Schmitz FJ. Epidemiology and susceptibility of 3,051 *Staphylococcus aureus* isolates from 25 university hospitals participating in the European SENTRY study. *J Clin Microbiol* 2001;39:3727-3732.
12. Espersen F, Nielsen PB, Lund K, Sylvest B, Jensen K. Hospital-acquired infections in a burns unit caused by an imported strain of *Staphylococcus aureus* with unusual multi-resistance. *Journal of Hygiene* 1982;88:535-541.
13. Rosdahl VT, Knudsen AM. The decline of methicillin resistance among Danish *Staphylococcus aureus* strains. *Infect Control Hosp Epidemiol* 1991;12:83-88.
14. Boyce JM. Consequences of inaction: importance of infection control practices. *Clin Infect Dis* 2001;33(suppl 3):S133-S137.
15. Pittet D, Mourouga P, Perneger TV, Members of the Infection Control Program. Compliance with handwashing in a teaching hospital. *Ann Intern Med* 1999;130:126-130.
16. Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. *Lancet* 2000;356:1307-1312.
17. Grundmann H, Hori S, Winter B, Tami A, Austin DJ. Risk factors for the transmission of methicillin-resistant *Staphylococcus aureus* in an adult intensive care unit: fitting a model to the data. *J Infect Dis* 2002;185:481-488.
18. Harbarth S, Martin Y, Rohner P, Henry N, Auckenthaler R, Pittet D. Effect of delayed infection control measures on a hospital outbreak of methicillin-resistant *Staphylococcus aureus. J Hosp Infect* 2000;46:43-49.
19. Jernigan JA, Titus MG, Groschel DH, Getchell-White S, Farr BM. Effectiveness of contact isolation during a hospital outbreak of methicillin-resistant *Staphylococcus aureus. Am J Epidemiol* 1996;143:496-504.
20. Herwaldt LA. Control of methicillin-resistant *Staphylococcus aureus* in the hospital setting. *Am J Med* 1999;106(5A):11S-18S.
21. Papia G, Louie M, Tralla A, Johnson C, Collins V, Simor AE. Screening high-risk patients for methicillin-resistant *Staphylococcus aureus* on admission to the hospital: is it cost effective? *Infect Control Hosp Epidemiol* 1999;20:473-477.
22. Girou E, Pujade G, Legrand P, Cizeau F, Brun-Buisson C. Selective screening of carriers for control of methicillin-resistant *Staphylococcus aureus* (MRSA) in high-risk areas with a high level of endemic MRSA. *Clin Infect Dis* 1998;27:543-550.
23. Chaix C, Durand-Zaleski I, Alberti C, Brun-Buisson C. Control of endemic methicillin-resistant *Staphylococcus aureus*: a cost-benefit analysis in an intensive care unit. *JAMA* 1999;282:1745-1751.
24. Karchmer TB, Durbin LJ, Simonton BM, Farr BM. Cost-effectiveness of active surveillance cultures and contact/droplet precautions for control of methicillin-resistant *Staphylococcus aureus. J Hosp Infect* 2002;51:126-132.
25. Kunori T, Cookson B, Roberts JA, Stone S, Kibbler C. Cost-effectiveness of different MRSA screening methods. *J Hosp Infect* 2002;51:189-200.
26. Kluytmans J, Van Griethuysen A, Willemse P, Van Keulen P. Performance of CHROMagar selective medium and oxacillin resistance screening agar base for identifying *Staphylococcus aureus* and detecting methicillin resistance. *J Clin Microbiol* 2002;40:2480-2482.
27. Gaynes R, Marosok R, Mowry-Hanley J, et al. Mediastinitis following coronary artery bypass surgery: a 3-year review. *J Infect Dis* 1991;163:117-121.
28. Boyce JM, Opal SM, Potter-Bynoe G, Medeiros AA. Spread of methicillin-resistant *Staphylococcus aureus* in a hospital after exposure to a health care worker with chronic sinusitis. *Clin Infect Dis* 1993:17:496-504.
29. Sherertz RJ, Reagan DR, Hampton KD, et al. A cloud adult: the *Staphylococcus aureus*-virus interaction revisited. *Ann Intern Med* 1996;124:539-547.
30. Squier C, Rihs JD, Risa K, et al. *Staphylococcus aureus* rectal carriage and its association with infections in patients in a surgical intensive care unit and a liver transplant unit. *Infect Control Hosp Epidemiol* 2002;23:495-501.
31. Gravet A, Rondeau M, Harf-Monteil C, et al. Predominant *Staphylococcus aureus* isolated from antibiotic-associated diarrhea is clinically relevant and produces enterotoxin A and the bicomponent toxin LukE-LukD. *J Clin Microbiol* 1999;37:4012-4019.