Adverse Events Associated With Methicillin-Resistant *Staphylococcus aureus* in a Nursing Home

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**Background:** Methicillin-resistant *Staphylococcus aureus* (MRSA) generates concern in nursing homes. Restrictive isolation precautions may be applied for indefinite periods. Adverse events driving these concerns include transmission and infection.

**Methods:** The 721-bed Wisconsin Veterans Home in King performs approximately 645 cultures annually. The site, severity, and number of MRSA infections were determined for 69 months. Pulsed-field gel electrophoresis was performed on all initial isolates, followed by a statistical cluster analysis looking for evidence of transmission.

**Results:** Sixty-seven MRSA infections were identified (1.6 per 100 residents per year); many were polymicrobial, and it was difficult to determine the proportionate role of MRSA in morbidity or mortality. There was an episode of rapidly fatal MRSA septicemia in which empiric antibiotic therapy was ineffective. Twenty-one genetic strains were encountered. Statistical analysis identified 13 clusters of genetically identical strains clustered in time and space (*P*<.05).

**Conclusions:** Infections with MRSA were identified at relatively low rates; however, the etiology of many serious nursing home infections is not determined, especially pneumonia. Statistical analysis revealed clustering and evidence of transmission. Nursing home practitioners should consider MRSA when applying empiric treatment to serious infections. We recommend a program including (1) judicious use of antibiotics, including topical agents, to reduce selection of resistant organisms; (2) obtaining and tracking cultures of infectious secretions to diagnose MRSA infections and focus antibiotic therapy; (3) universal standard secretion precautions because any resident could be a carrier; and (4) a detailed assessment and care plan for the carrier that maximizes containment of secretions and independence in activities. However, basic hygiene cannot be maintained in communal areas by some residents without restriction of activities of daily living.

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**METHICILLIN-RESISTANT**

*Methicillin-resistant Staphylococcus aureus* (MRSA) has generated concern and confusion among nursing home practitioners. The potential adverse events driving these concerns include transmission and infection, as well as regulatory deficiencies and malpractice litigation. Methicillin-resistant *S. aureus* might cause outbreaks or infections rendered lethal by misguided empiric antibiotic therapy.1,2 Previously, some nursing homes refused to admit patients with MRSA because the elaborate and restrictive isolation precautions used by hospitals were considered necessary for indefinite periods. The indefinite application of restrictive isolation precautions is labor intensive and might be a personal hardship for the resident. In a longitudinal study, Terpenning et al1 found that gram-negative rods resistant to gentamicin and/or ceftriaxone therapy were less prevalent colonizers than MRSA but posed a greater infection risk to residents. These organisms, however, do not engender the same level of concern. More information is needed to assist nursing home staff in the management of MRSA.

The 4-building, 721-bed Wisconsin Veterans Home in King has an on-site laboratory that performs approximately 645 routine clinical cultures annually and has performed pulsed-field gel electrophoresis (PFGE) on all isolates of MRSA since August 1994. In this article, we present a statistical analysis of the distribution of each isolate type, looking for clustering and evidence of transmission, as well as a description of MRSA infections. This retrospective analysis was undertaken to refocus or possibly redirect our infection control program.
PATIENTS AND METHODS

The Wisconsin Veterans Home, administered by the state of Wisconsin, is a skilled nursing facility that serves veterans and their spouses. During this study, the average daily census was 721. Seventy-nine percent of the residents were men (mean age, 74 ± 10 years); there was an average of 240 hospitalizations per year and average annual mortality of 18%. Ninety percent of hospitalizations were in community hospitals and only 10% were in Veterans Affairs medical centers. Care is provided in 4 separate buildings on 14 floors or nursing units. One unit is a physically separated “wandering unit.” The census on nursing units varies between 50 and 60. The home has an on-site bacteriology laboratory that is open 45 hours per week. Most cultures are performed during those hours. The laboratory enforces strict policies for specimen collection and will not plate a wound or sputum culture unless collected within the previous hour. Urine culture samples are refrigerated immediately. During this study, a mean of 645 cultures were obtained each year for clinical purposes. Beginning in August 1994, any initial isolate from a resident infected or colonized with MRSA underwent PFGE at Marshfield Laboratories, Marshfield, Wis (M.S. and K.R.). Chromosomal DNA was prepared using the method described by Maslow et al.5 Restriction endonuclease digestion of the DNA was done using Smal (Promega Corp, Madison, Wis). Electrophoresis was performed in a 1% gel at 200 V for 20 hours in a CHEF-DRIII system (Bio-Rad Laboratories, Hercules, Calif). Pulse time was increased from an initial time of 5 seconds to a final time of 40 seconds. The PFGE profiles were analyzed using Multi-Analyst Fingerprinting Plus software (Bio-Rad). Interpretation of the patterns was based on guidelines established by Tenover et al.6

During this study, the Wisconsin Veterans Home had policies and procedures that required modified “contact precautions” for residents colonized or infected with MRSA, with the addition of “droplet precautions” in the presence of an active respiratory tract infection with splatter into the environment.7 Precautions also included use of dedicated equipment and hand hygiene with chlorhexidine gluconate. The care plan for MRSA carriers was individualized to take into account mobility, hygiene, ability to contain potentially infectious secretions, and any infection tracking reports suggesting that the individual might be transmitting MRSA. The Centers for Disease Control and Prevention guidelines for contact and droplet precautions were modified for each individual based on this assessment, with resident quality of life given strong consideration. When a resident was newly discovered to be infected with MRSA, small numbers of focused surveillance culture specimens were sometimes obtained to determine whether that individual might be part of a cluster of transmission. These culture specimens could include wounds, Foley catheters, tracheostomies, and gastrostomies of those on the same nursing unit, as well as cultures of respiratory secretions (chronic cough or rhinorrhea), hand dermatitis, or the anterior nares of roommates or close social contacts (tight circle). If this system suggested that transmission was occurring, infection control procedures were upgraded.

RESULTS

CLINICAL STUDY

In July 2000, we used our bacteriology database to generate a listing of all individuals with MRSA isolates and all subsequent cultures on those individuals. We reviewed the medical charts of affected residents until June 30, 2000, to determine the proportion of patients with MRSA who had infections and to characterize the site and severity of infections (vancomycin use, hospitalization, or death).

STATISTICAL ANALYSIS

We identified 71 individuals with MRSA isolates in 69 months (August 1, 1994, to June 30, 2000). There were 21 PFGE strains. Tenover et al8 proposed that a 3-band difference or less between epidemiologically related strains probably indicates a common source, whereas a 4- to 6-band difference possibly indicates a common source. Three-band differences typically result from a single genetic event. This criterion is recommended for outbreaks of 1 to 3 months.9 More genetic variability between related bacteria is anticipated during longer durations. Combining the 21 PFGE types for this analysis was not attempted because of the existence of more than 200 comparisons between strains. We hypothesized that if transmission was not occurring within our facility, each of the 10 PFGE strains with more than 1 isolate should be distributed randomly in time among 14 nursing units. A model that captures only clustering of organisms with no band differences is robust and, if anything, will underestimate the degree of transmission within the facility. We performed a cluster analysis that included 3 characteristics: PFGE type, unit location, and date of first isolate from all initial MRSA events. We used a single linkage method and a euclidean distance measure to determine how the distance between 2 clusters would be defined. The final partition was determined by specifying a similarity level of 95%. The level of similarity (S) between 2 clusters (j) was given by the equation $S=100(1−d_{ij}/d_{max})$, where $d_{ij}$ is a distance measure calculated between all observations in cluster i against all observations in cluster j and $d_{max}$ is the maximum distance measure computed in the original distance matrix. Methicillin-resistant *S aureus* events that share a greater than 95% similarity among their 3 common characteristics were identified as a single cluster.8

Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>PFGE Type</td>
<td>Type of genetic fingerprint</td>
</tr>
<tr>
<td>Unit Location</td>
<td>Location of isolate</td>
</tr>
<tr>
<td>Date of First Isolate</td>
<td>Date of first detection</td>
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(Continued)
there were 7 cases in which MRSA was isolated after abnormal findings on screening urinalysis. Some individuals had more than 1 episode of infection. During the 69 months of study, 67 clinical infections were identified in which MRSA was isolated, including 19 hospitalizations, including 5 amputations. Methicillin-resistant S. aureus was also associated with 3 deaths from pneumonia in which MRSA had been isolated, 1 from septicemia, and 1 from transitional bladder carcinoma with polymicrobial urinary tract infection. Two of 3 bacteremias occurred among the 4 A10 isolates. The third bacteremic isolate, an A2 strain, varied by 4 bands from A10. There were 2 deaths related to peripheral vascular disease in which MRSA had been isolated in mixed culture. It was difficult to determine how much of the burden of hospitalization and mortality associated with MRSA isolation was specifically related to MRSA rather than severe underlying disease or polymicrobial flora. There were also 4 deaths from pneumonia or lung cancer in residents unable to produce sputum with current MRSA colonization at other sites.

Fourteen isolates were discovered during screening in a tight circle around an index case (10 residents and 4 staff) (see the “Patients and Methods” section). In 9 isolates the secondary cases were genetically identical, in 1 there was 3 bands of difference, and in 4 they were unrelated (>7 bands of difference) (patients 13, 38, 58, and 69). Patient 38 developed a wound infection, with MRSA isolated 20 months after the initial nasal isolate.

In 2 situations, nasal cultures of roommates yielded MRSA:

(continued)
one was of an identical PFGE profile (patient 37) and the second was unrelated (patient 69).

**CLUSTER ANALYSIS**

Pulsed-field gel electrophoresis was performed on all 71 MRSA isolates initially isolated between August 1, 1994, and June 30, 2000. Two of the 14 nursing units had no isolates, including the physically isolated “Alzheimer” unit. Twenty-seven of the PFGE profiles were of an identical type noted as “A” (Table). Patients are numbered in the temporal order of isolation in the facility. Twenty-three additional isolates had PFGE patterns that differed by no more than 6 bands from the main A profile, designated A1 through A12. There were 10 additional PFGE strains that included 53% of the 71 initial isolates. The clusters involved 2 to 10 individuals clustered in time (1-9 months) and space. Most (n=10) involved a single nursing unit and 3 involved 2 or 3 units in a single building. Hospitalizations within 1 year of the initial isolate were examined for each cluster. No pattern emerged except that both individuals in cluster 12 had been admitted to the hospital that accepts 80% of our admissions within 3 months of the first isolate.

There were additional examples of clustering within nursing units including cases that varied by 3 or fewer bands from prevailing strains. Patient 59 had profile K isolated on December 24, 1999, which varied by 3 bands from the endemic A10 strain. Finally, only 2 of 14 units had any A1, A2, and L isolates. A1 differs from A2 by 2 bands and from L by 3 bands. These genetically related strains were clustered on 2 nursing units. In other cases, unusual PFGE types were encountered on separate nursing units clustered in time. For example, during the 69 months of study, only 4 individuals with profile F were identified. Three were identi-
tified from 3 separate buildings between December 22, 1997, and March 19, 1998 (patients 38, 39, and 41). We did not identify an epidemiologic link, although the clustering of this unusual PFGE type in time suggests a common source.

The total number of individuals who had MRSA isolated during a given year (initial or repeated) remained stable at 13 to 15 from 1995 through 1999. The rate of MRSA infection also remained stable at approximately 1 per month. Throughout the study, we viewed the 50- to 60-bed nursing unit as the most likely site of transmission and therefore primarily looked for transmission within nursing units. There were 7 clusters in which genetically identical MRSA infections were noted on the same unit within 30 days.

The data demonstrate that apparent endemic MRSA isolates, indistinguishable by PFGE, were clustered in defined areas over discrete periods. The plausible mechanism for the clusters is transmission within a common living space with shared caregivers. Our findings blur the distinction between “outbreak” strain (which includes incidence higher than the baseline and linkage in time and space with a plausible common source) and “endemic” strain.6 Endemic strains can also be statistically linked in time and space with a plausible common source. It is no surprise that MRSA can be slowly transmitted within a nursing home and slowly discovered by culturing infected secretions. Our large study includes 4146 resident-years of surveillance. Smaller facilities that seldom perform cultures and track MRSA isolates over a short period could be experiencing similar infection rates without drawing attention (ie, 1.6 infections per year in a 100-bed facility). A number of Veterans Affairs and community investigators studied MRSA colonization and performed time-sequenced surveillance cultures in nursing homes. Transmission of MRSA might be inferred by the acquisition of colonization within the nursing home. The rate of acquisition partially depends on background colonization rates (“colonization pressure”).1 Bradley et al9 reported that 10% of 341 individuals acquired new colonization (multiple sites sampled) in a study with mean follow-up of 3.6 months and background colonization rates of 23%. New colonization has also been reported1,2,10-12 at rates of 2% to 9% per year. Without subtyping, the relationship of new cases to specific pre-existing cases is tenuous. In general, MRSA does not seem to be highly contagious, but acquisition does occur within the nursing home.

Many individuals carry S aureus in their nose for long periods and never develop infections. Infection might subsequently develop after an aspiration event, a break in the skin, or a bladder obstruction. An MRSA surveillance system that completely depends on cultures of infected secretions would be expected to allow considerable transmission to occur before detection. Infection control experts who advise nursing homes might have no idea how few routine cultures are performed in nursing homes compared with hospitals. Because of the slow and uncertain relationship between transmission and infection, we often performed surveillance cultures in a tight circle around index cases, followed by PFGE, and determined that transmission was occurring. Not all MRSA isolates from the tight circle were genetically related. Surveillance cultures might be especially helpful if the index case is independently mobile and if restriction of activities of daily living is being considered. Theoretically, this practice offers the infection control practitioner an earlier indication of transmission than would be provided by routine cultures of infected secretions. The efficacy and cost-effectiveness of this procedure are unknown.

We identified 67 MRSA infections in 69 months (1.6 per 100 residents per year) and determined adverse associations (ie, vancomycin therapy in 21, hospitalization in 19, and death). We do not know what proportions of outcomes were related to methicillin resistance vs underlying disease. We did not find high rates of MRSA infection, although the bacterial cause of many serious nursing home infections is not determined.3 Sputum specimens are not obtained during many episodes of terminal pneumonia. (Pneumonia is noted as a factor on 32% of death certificates at the Wisconsin Veterans Home.) Rahimi10 reported no deaths or hospitalizations attributed to MRSA infection in 1 year in 87 nursing home patients. Feingold et al11 reported a similar experience in a 60-bed nursing home. It is unlikely that any intervention could improve on the results of these small nonintervention studies (infection rates, <1.1 per 100 residents per year). Similar prospective studies,1,2,9,10,12-14 however, have demonstrated MRSA infection–related deaths or hospitalizations. Diabetes mellitus, dialysis, and peripheral vascular disease have been identified as risk factors for MRSA infection.9,13 Methicillin-resistant S aureus infection rates (infections per bed per year) have been reported to be 0% to 6.3%,9,10,12-14 with higher rates in known carriers.1,9,12-14 Muder et al13 reported an infection rate of 15% in 32 known carriers in 100 days, with dialysis as a significant risk factor. Prospective surveillance to identify carriers will not identify some individuals who subsequently develop MRSA infections.1,2,12-14 Methicillin-resistant S aureus bacteremia can be lethal, especially if initial antibiotic therapy is misguided.1,9 Individuals known to carry MRSA who present with serious infection syndromes should be covered for MRSA until appropriate cultures return. Infections with MRSA might be associated with lethal outcomes in nursing home residents.

Staphylococcus aureus is a common cause of skin infections, pneumonia, and bacteremia in hospitals. At any given time, it colonizes the nose of approximately 30% of humans, and it is one of the heartiest non–spore-forming bacteria and can survive in the environment.15 During this study, 24% of S aureus isolates at the Wisconsin Veterans Home were resistant to methicillin therapy, a percentage similar to that in hospitals throughout the United States.16 During the relatively brief period humans have been using antibiotics, Staphylococcus has adapted with the emergence of antibiotic resistance. Nursing home residents are frequently hos-
pitalized and frequently treated with antibiotics. At any given point, 6% to 8% of residents are being subjected to antibiotic treatment within close quarters, where mobility, socialization, and group activities are encouraged. The scene is set for the introduction, selection, and transmission of MRSA. As stated at the beginning of this article, our purpose was to determine the burden of transmission and infection and to refocus or redirect our infection control program. We recommend that MRSA be dealt with in the context of an infection control program with 4 components:

1. The judicious use of all antibiotics, including topical agents, to reduce the emergence of resistant bacteria.

2. Implementation of a system that encourages performing cultures of infected secretions. As long as MRSA infection is recognized, recovery should not be compromised, except in severe infections in which effective antibiotic choice is limited. The importance of this point cannot be overemphasized. Severe MRSA infections must be identified by culture. Culture and sensitivity data also have many institutional benefits: (a) They allow determination of the proportion of MRSA isolates from various sites. Clinicians should be aware of the relative probability of MRSA at their institution and include it in the early differential diagnosis of serious clinical infections so that proper antibiotic therapy is not delayed. This latter circumstance is the reason we fear MRSA. (b) They allow identification of outbreaks. (c) They might allow clinicians to substitute narrow-spectrum antibiotics such as amoxicillin for broad-spectrum antibiotics such as cephalosporins or quinolones that give MRSA a selective advantage (ie, prevention of MRSA). The Infectious Disease Society of America recommends “pathogen-directed therapy based on in vitro susceptibility test results” for the treatment of community-acquired pneumonia because of concerns that empirical selection of drugs will drive microbial resistance.

3. Implementation of universal standard secretion precautions. It is likely that when transmission occurs, it is because of lapses in basic standard secretion precautions. In the absence of screening, there are probably many unrecognized carriers of antibiotic-resistant bacteria. These unrecognized carriers probably pose a greater risk of transmission than the resident with “MRSA” emblazoned on his chart. Staff must be reminded that any resident could be a carrier. This is analogous to bloodborne pathogens.

4. Performance of an individual assessment of residents with MRSA that includes mobility, comprehension, hygiene, ability to contain colonized secretions, and any bacteriologic data implicating the resident in transmission. This will allow formulation of an individual care plan to isolate colonized secretions and maximize activities of daily living. The MRSA carrier state creates a conflict between 2 powerful principles of nursing home practice, ie, maintaining a safe environment and maximizing independence in activities of daily living. This conflict is greatest in a colonized resident with poor hygiene who is independently mobile. Control measures used in hospitals should not automatically be extrapolated into nursing homes. Contact secretion precautions should be applied, especially if secretions were poorly contained and close contact was required. A SHEA position paper on antimicrobial resistance in long-term care recommended that residents colonized with resistant pathogens not be restricted from group activities unless they are shedding large numbers of organisms and the resident was epidemiologically linked to infection in other residents. Unfortunately, there may be a delay between transmission and the discovery of transmission by culturing infected secretions. In addition, some mobile carriers not implicated in transmission are observed to be contaminating the common environment during independent activity. Nursing home staff have great difficulty reconciling this observation with their own efforts to contain secretions. We, therefore, believe that physical separation that is well tolerated should be implemented without evidence of transmission. If the resident leaves his or her room, colonized sites should be secured and covered and assisted hand washing and possibly clean clothes provided. Personal items and equipment could be left behind, with regular decontamination of surfaces frequently touched by the resident. The care plan must be individualized and will be limited by the facility resources. Unfortunately, basic hygiene in common areas cannot be maintained in some residents without some restriction of activities of daily living. This step requires significant attention to the resident’s psychosocial adaption. If antibiotic treatment of MRSA is administered because of infection or transmission, the sites of colonization should be fully characterized to optimize therapy. Consider the presence of such things as foreign bodies, devitalized tissue, ischemia, sinuses, bronchicetasis, elevated postvoid residua, and osteomyelitis. If an underlying substrate is not addressed mechanically, decolonization is especially unlikely. Management recommendations for known carriers will continue to evolve. Perhaps residents, surrogates, and the public should be informed that nursing homes, like child day care facilities, care for individuals who have received multiple courses of antibiotics and might carry antibiotic-resistant bacteria. Residents socialize and interact with one another and can exchange bacteria during social interactions.

The fear of MRSA should be harnessed to improve universal standard secretion precautions and to obtain culture specimens for targeting antibiotic treatment.

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