Commentary

The changing epidemiology of methicillin-resistant *Staphylococcus aureus*: 50 years of a superbug

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The year 2011 marked the 50th anniversary of the methicillin-resistant *Staphylococcus aureus* (MRSA) epidemic—one that has significantly and substantially impacted the nature of health care today. Indeed, the story of MRSA was never a straightforward one; it was one filled with waves of change and surprises. Thus, it is fitting to review the emergence of MRSA and identify important milestones and lessons for infection control professionals, seasoned and novices alike, as we embark on the next era of modern medicine.

RISE OF MRSA IN HEALTH CARE SETTINGS

In 1961, celbenin first became available for the treatment of penicillin-resistant *S. aureus*. Celbenin was the defunct name for what is now methicillin, a drug with high rates of nephrotoxicity and thus rarely used. However, within 6 months of celbenin's availability, celbenin-resistant *S. aureus*, therefore, methicillin-resistant *S. aureus*, was fully characterized in the *British Medical Journal*. The authors of the report eerily foreshadowed the epidemic potential of this resistant organism, stating "if this [sic. methicillin] resistance can be discovered in the laboratory, it is not inconceivable that it will happen in the ward."

MRSA remained quiescent for 20 years until the early 1980s when the incidence and the reaches of MRSA clearly increased and expanded. In the ensuing 3 decades, we witnessed and learned several interesting and important features related to the MRSA epidemic.

MRSA was found to be a perennial phenomenon that affects populations of all types. However, there appears to be an undeniable seasonal pattern to MRSA infections. The incidence of MRSA increases through summer and decreases as the year moves into winter: there is no consensus explanation for this observation.

There have been many hypotheses to explain this observation; some were related to the clothes we wear, the variable amount of sweating from skin, the ambient humidity throughout the year, and the amount of outdoor activity and skin trauma that could predispose to MRSA infections. None of these theories have been proven.

Over time, it became apparent that the outcome of patients infected with MRSA is poor. There is no better demonstration of this fact than with a landmark study published in the *Journal of American Medical Association* in 2007. Investigators found that approximately 1 in 5 patients with an MRSA infection died: a staggering overall mortality of 20%. The authors projected that there were more deaths because of MRSA infections in the year of the study than the cumulative mortality because of HIV/AIDS in the United States.

Moreover, evidence showed that methicillin resistance within *S. aureus* was specifically associated with poorer outcomes; that is patients with MRSA infections fared far worse compared with those infected with methicillin-susceptible *S. aureus*. In one study, patients with MRSA bloodstream infections spent 7 day longer in hospital, fewer were discharged back to home, and the overall mortality of MRSA bloodstream infections was around 35%, despite modern day therapeutic interventions.

There was an important second dimension of the epidemic of MRSA, above and beyond its widespread nature and the poor outcomes of the infections; MRSA was becoming increasingly resistant to existing antibiotics. Data supporting this notion came from 2 perspectives. The first set of clues came from studies reporting the phenomenon of vancomycin “MIC creep” among isolates of MRSA. MIC is the abbreviation for minimum inhibitory concentration, which is the minimum concentration of an antibiotic required to inhibit the growth of MRSA in vitro. Researcher reported that recent isolates of MRSA had proportionally higher vancomycin MICs compared with isolates from the early part of this decade. For example, investigator from New Hanover Regional Medical Center in Wilmington, North Carolina, described that the proportion of MRSA isolates with a vancomycin MIC of 1 mg/L increased from 16% in 2001 to 69% in 2005. Similar observations of vancomycin MIC creep among MRSA isolates were made in other states in the United States, as well as internationally, such as Hong Kong, Malaysia, France, and Germany.
The phenomenon of vancomycin MIC creep turned out to be more than just a microbiologic curiosity: there were important clinical implications. Infections with MRSA isolates with higher vancomycin MICs were associated with higher rate of treatment failure and mortality.14,15 A study of 414 episodes of MRSA bacteremia showed that MRSA isolates with vancomycin MIC of 2 mg/L had 6.4 times the odds of death compared with isolates with vancomycin MIC of 1 mg/L.15

The second set of evidence supporting the notion of expanding antibiotic resistance among MRSA isolates came from increasing reports of vancomycin-intermediate S. aureus16,17 and vancomycin-resistant S. aureus (VRSA). Vancomycin-intermediate S. aureus isolates refer to MRSA isolates that have MIC of 4 to 8 mg/L; such isolates have much thicker cell membranes that impair the penetration, binding, and efficacy of vancomycin.18 VRSA isolates have vancomycin MIC of 16 mg/L or greater, and, fortunately, there have only been a handful of reports around the world.19,20 As of July 2011, there were 11 reports of VRSA from the United States. Eight of these 11 isolates clustered around Detroit, Michigan. Most patients with VRSA had severe and chronic comorbidities, including diabetes, obesity, dialysis, and chronic wounds. The fact that many of these patients with VRSA were concurrently infected or colonized with vancomycin-resistant enterococci (VRE) had given rise to the hypothesis that vancomycin resistance was somehow transferred from VRE to MRSA to result in VRSA.21,22 Interestingly, preliminary evidence showed that the hypothesis is at least partially true because many VRE and MRSA isolates in Michigan were found to have specific genetic machinery that facilitated genetic transfer between VRE and MRSA.23

ERA OF COMMUNITY-ASSOCIATED MRSA

Community-associated MRSA (CA-MRSA) represented another dimension within the epidemic of MRSA. The first report of CA-MRSA came from indigenous population in Western Australia.24 These patients were remotely located in rural Australia and had no recent contact with health care facilities located hundreds of miles away. Subsequently, scores of similar infections because of CA-MRSA rapidly emerged, and a set of uniform epidemiologic criteria for defining CA-MRSA was formally published by the Centers for Disease Control and Prevention (CDC).25 Specifically, the CDC defined CA-MRSA as the diagnosis of MRSA in the outpatient setting or within 48 hours after admission to the hospital. The patient must not have had any medical history of MRSA infection or colonization, no recent medical history within the past year of hospitalization, admission to a nursing home, dialysis, or having had surgical procedures. The patient also should not have a permanent indwelling catheter or medical device through the skin into the body.

The publication and adoption of standard criteria for CA-MRSA allowed researchers to study the epidemiology of this organism and its associated disease, determining that CA-MRSA only emerged around 1993, before which CA-MRSA was almost undetected in the wild.4 In the ensuing years, CA-MRSA became widespread in the community setting. The extent of this spread was not well appreciated until another landmark study found that CA-MRSA was clearly the most common cause of skin and soft tissue infections among patients presenting to emergency rooms in the United States. Additionally, CA-MRSA gained notoriety through other high-profile outbreaks involving previously healthy individuals, including outbreaks among college athletes, incarcerated individuals, school children, intravenous drug users, pregnant women, and those with HIV infection.26-29 A widely publicized outbreak of CA-MRSA occurred among professional football players on the St Louis Ram’s National Football League team during the 2003 football season.30 Several players developed recurrent infections that limited their playing time and required medical and surgical treatment.

Advances in molecular technologies allowed investigators to determine that there were numerous distinct types of MRSA that could cause infections that are categorized as CA-MRSA. They discovered that CA-MRSA isolates were usually genetically distinct compared with hospital-acquired MRSA. For example, CA-MRSA isolates usually belonged to USA 300 pulse field type, often carried an extra toxin known as the Panton-Valentine Leucocidin protein, and often remained susceptible to a wide range of oral antibiotics such as trimethoprim-sulfamethoxazole, clindamycin, and tetracyclines.

CA-MRSA isolates also demonstrate fascinating geographic diversity around the globe. In the United States, the predominant type of CA-MRSA is known as sequence type 8 (ST8); Australia has 2 major strains: ST93, the “Queensland” strain, and ST1, the Western Australia strain. Europe is characterized by cocirculation of several different types of CA-MRSA: ST80, ST5, and ST8.

Finally, CA-MRSA, despite its name, has infiltrated hospitalized populations and has caused frequent infections in the typical health care setting, such as central line-associated bloodstream infection, ventilator-associated pneumonia, and wound infection.31 The intermixing of CA-MRSA and hospital-acquired MRSA is increasing and will surely continue to complicate the detection and specific management of MRSA infections.

NOVEL TRENDS WITH MRSA

The epidemiology of MRSA continues to surprise researchers and clinicians alike. For the first time since 1960, the incidence of MRSA-related infections has started to decline. A study of health care-associated infections (HAI) data submitted from intensive care units (ICU) around the United States showed that the incidence of MRSA- and methicillin-susceptible S. aureus-associated central line-associated bloodstream infections decreased from 2001 to 2009.32 A similar pattern of decrease in the incidence of MRSA-related HAI was noted in a study from a network of community hospitals in the Southeastern region of the United States.33

On this 50th year anniversary of MRSA, it is fitting to examine the aims and the effectiveness of strategies we currently employ against the superbug. Active surveillance and contact precautions are commonly deployed in the acute care settings for patients colonized and infected with MRSA. The effectiveness of these interventions was examined in 2 high-profile studies published in 2011. The first study examined the effectiveness of the MRSA directive implemented in 2007 in all acute care facilities in the Veterans Affairs system.34 The study used a straightforward design and compared incidence of MRSA infections before and after the implementation of a bundle of interventions, which included active surveillance for nasal colonization, contact precautions for colonized or infected patients, hand hygiene, and change in the institutional culture with positive deviance. Approximately 2 million patient admissions and transfers in more than 196 ICUs and 420 wards were studied. The study found that the incidence of MRSA infections declined significantly (from 1.64 to 0.62 per 1,000 patient-days) and that the transmission of MRSA decreased by 17%. In the same issue of the New England Journal of Medicine, conflicting results came from a different study showing that active surveillance and barrier precautions were not effective in reducing MRSA-related infections.35 Specifically, this second study used a more robust study (cluster-randomized) design and enrolled 9,000 patient admissions in 18 participating ICUs. Intervention was limited to active surveillance and contact isolations; hand hygiene was practiced as per usual institutional policies. During the
6-month intervention, the incidence of MRSA colonization or infection did not significantly decrease compared with the baseline and to control units. How should the reader interpret these 2 similar studies with opposing results? Most experts suggest that the answer might be somewhere in the middle and that an institutional practice change, bundled with intensified hand hygiene and improved culture of safety, could still help reduce the incidence and burden of MRSA infections.

Opposing results from studies and differences in expert opinion have led to a renewed interest in non-pathogen-specific approaches to infection prevention. These non-specific interventions include the following: enhancing hand hygiene performance, improved cleanliness of health care environment, adherence to practices and bundles that reduce device-related infections, and optimal measures to reduce surgical site infections. Furthermore, there are modeling studies that indicate that non-pathogen-specific infection prevention measures could effectively reduce more HAIs with less cost compared with traditional pathogen-specific interventions.36

The main premise of non-pathogen-specific infection prevention is to reduce pathogens to their most basic and common mechanism of transmission; for MRSA, person-to-person transmission is almost universally through contact. Contaminated hands of health care workers are believed to play a major role in organism transmission in the health care setting. However, the role of MRSA transmission via contaminated environmental or non-human surfaces is becoming better appreciated. A recent study examined presence of MRSA on common surfaces in the home and in the community. Fifteen percent of surfaces in homes were contaminated with MRSA, including microwave keypad, couch, television remote control, and even the washing machine. Approximately 12% of sampled surfaces of a college campus showed MRSA on ATM keypads, elevator buttons, bathroom door knobs, water fountain buttons, and locker handles.

The concept of contaminated environment can apply to animals and non-human vectors. There is increasing evidence to suggest that domestic and farm animals act as vectors or reservoirs of MRSA and may even harbor zoonotic isolates of MRSA. For instance, an unusual cluster of skin and soft tissue infections among Dutch children living on pig farms led to the detection of a new strain of porcine-origin MRSA, known as ST398.38 Another strain of cattle-derived MRSA was recently discovered, and it was notable for a novel type of MecA resistance gene it carries, known as MecALGA251. This gene confers the same resistance phenotype as other MRSA, but the novel gene is not detectable by the current polymerase chain reaction methods.39 Fortunately, these MecALGA251 MRSA isolates were thought to be still very uncommon and had only been reported in parts of the United Kingdom.

Novel strains and new resistance patterns of MRSA should be expected, and such phenomenon is due to ongoing biologic diversity and genetic adaptation of bacteria in general. In other words, antibiotic resistance is an ongoing process for bacteria and cannot be stopped by drugs. S aureus has been in existence for millions of years, surviving different conditions and has continued to proliferate in parallel with the human race. Antibiotics have only been available for approximately 60 years, and staphylococci are clearly adapting and thriving in the face of that antibiotic selection pressure. Perhaps then, it is not surprising that resistance to many chemical disinfects is also being reported in MRSA isolates. Decreased susceptibility has been reported in MRSA isolates against chlorhexidine, mupirocin, and quaternary ammonium.30,41 Molecular studies have identified specific genes that confer resistance to disinfectants that we trust (eg, chlorhexidine resistance is mediated through QAC genes, mupirocin resistance through MUP genes, and resistance to quaternary ammonium from SMR and QAC genes).42,43 Even though antibiotics will not stop the ongoing evolution of antimicrobial resistance, antimicrobial stewardship and judicious use of antibiotics could help prolong the usefulness of existing antimicrobial agents.

**NOVEL TECHNOLOGIES TO REDUCE ENVIRONMENTAL ACQUISITION OF MRSA**

New technologies that can reduce the burden of MRSA and other nosocomial pathogens have gained a lot of attention and interest recently. Two such technologies have been adapted for health care applications, and each has its advantages and disadvantages. First is ultraviolet-C (UVC) irradiation, which has been used in the food and beverage industry for many years to reduce the microbial burden of consumer goods products. UVC was recently adapted to the health care setting for disinfection of patient rooms and other environmental surfaces. UVC achieves rapid disinfection of vegetative bacteria within 15 to 25 minutes and can kill *Clostridium difficile* spores within 45 to 50 minutes.44 It also has the ability to disinfect surfaces that are not in direct line of sight of the UVC emitter, such as under-surfaces of the over-bed table. Finally, UVC machines have the added benefit of being portable and do not require modifications to the room or its ventilation and air ducts. Another maturing technology is hydrogen peroxide vapor. This technology requires a good seal to the entrances to the room and minor modifications to room ventilation. However, hydrogen peroxide vapor is highly effective and was used to effectively control an outbreak of *C difficile* infection occurring on 5 different wards.45

In summary, MRSA has made a tremendous impact in the landscape of modern health care. MRSA remains the dominate pathogen in health care and is establishing itself within the community setting. MRSA will continue to develop resistance to antibiotics as well as disinfectants. At the same time, we will better understand the role the environment plays in the transmission of MRSA. Although antibiotic resistance will continue, we can look toward nonantibiotic measures to control the problem of MRSA infections, such as antibiotic stewardship and improved technologies for cleaning and disinfecting patient rooms. Perhaps MRSA surprised us the last 50 years, and, now, we are much better prepared and equipped for the fight for the next 50 years.

**References**


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