Epidemiology of Methicillin-Resistant Staphylococcus aureus

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The frequency of methicillin-resistant Staphylococcus aureus (MRSA) infections continues to grow in hospital-associated settings and, more recently, in community settings in the United States and globally. The increase in the incidence of infections due to S. aureus is partially a consequence of advances in patient care and also of the pathogen’s ability to adapt to a changing environment. Infection due to S. aureus imposes a high and increasing burden on health care resources. A growing concern is the emergence of MRSA infections in patients with no apparent risk factors. MRSA infection in community settings involves considerable morbidity and mortality, as does nosocomial MRSA infection. For community-associated MRSA, person-to-person transmission has been reported, and several factors have been shown to predict disease. We examine the trends in both nosocomial and community-associated MRSA infections and explore recent studies of the mechanisms that allow S. aureus to become resistant to currently available drugs.

“Micrococcus, which, when limited in its extent and activity, causes acute suppurative inflammation (phlegmon), produces, when more extensive and intense in its action on the human system, the most virulent forms of septicæmia and pyæmia...” [1]. This quote from Sir Alexander Ogston in 1882 describes several facets of Staphylococcus aureus that continue to plague physicians in modern times. This centuries-old pathogen still causes significant morbidity and mortality despite huge advances in medical care. Indeed, infections due to S. aureus continue to grow in number and complexity as a consequence, ironically, of advances in patient care and of its ability to adapt to a changing environment [2].

Since its first appearance in 1960 [3], methicillin resistance in S. aureus strains has become widespread in hospitals and intensive care units (ICUs) [4]. National Nosocomial Infection Surveillance (NNIS) System data demonstrate a steady increase in the incidence of nosocomial infections caused by methicillin-resistant S. aureus (MRSA) among ICU patients over time. MRSA now accounts for >60% of S. aureus isolates in US hospital ICUs [5].

Of growing concern is the emergence of MRSA in patients with no health care contact or apparent risk factors. Community-associated MRSA infections were initially described in children with bloodstream infections and no prior health care exposure [6] and have been increasingly reported as the cause of skin infections and abscesses among previously healthy adults and as the cause of bloodstream infections among patients in health care settings [7]. We will focus on the increasing frequency of MRSA and the growing problem of community-associated MRSA.

INCREASING FREQUENCY AND COMPLEXITY OF S. AUREUS INFECTIONS

S. aureus infections are increasingly reported around the world [8–10]. In a recent analysis of US inpatients, nearly 400,000 inpatient admissions for S. aureus infection per year were reported in 2003 [11]. In addition, the medical issues of these infected patients have become more complex as a result of our sophisticated medical system [2, 12]. Consequently, treatment of
these infections has become more difficult. Infection due to Staphylococcus aureus also imposes a high and increasing burden on health care resources [13], as well as increasing morbidity and mortality. MRSA infections kill ∼19,000 hospitalized American patients annually; this is similar to the number of deaths due to AIDS, tuberculosis, and viral hepatitis combined (table 1) [14–17]. In a recent study, health care costs for all patients with S. aureus bacteremia in the presence of indwelling devices were high, and they were twice as high among patients with hospital-acquired S. aureus bacteremia [13]. Among these hospitalized patients with medical devices, the 12-week mortality ranged from 17% for patients with long-term indwelling catheters to 35% for patients with cardiac devices [13].

Infective endocarditis is among the most severe complications of S. aureus bacteremia, and its incidence has been increasing [2]. S. aureus infective endocarditis represents nearly 30% of definite cases of infective endocarditis in a recent international cohort accrued from referral hospitals, and S. aureus is now the most common cause of infective endocarditis diagnosed at major medical centers in the developed world [20]. In addition, ∼40% of S. aureus infective endocarditis cases develop in health care settings [2].

HOSPITAL-ASSOCIATED MRSA INFECTION

Although MRSA was identified in 1961, it was not until the mid 1980s that it became a frequent adversary. The increase in MRSA infections most likely reflects the growing impact of medical interventions, devices, older age, and comorbidities of patients [2, 13]. Antibiotic use and overuse probably also contribute to the emergence of resistance.

Recent studies demonstrate a continuing increase in MRSA infections in hospitals [4, 9, 12, 21, 22]. CDC investigators found an estimated 125,969 hospitalizations annually for S. aureus infections in 1999–2000, including bloodstream infections and pneumonia [21]. Of the isolates associated with these hospitalizations, 43.2% were methicillin resistant [21]. A large surveillance program of nosocomial bloodstream infections in the United States showed that among all S. aureus isolates, the percentage of MRSA isolates increased from 22% in 1995 to 57% in 2001 [12]. Similarly, among NNIS hospitals in 2003, 64.4% of health care–associated S. aureus infections occurring in ICUs were caused by MRSA, compared with 35.9% in 1992, representing a 3.1% increase per year (P < .001) [5, 22]. More recently, Klevens et al. [14] reported an increase in hospital-onset MRSA bacteremia cases, with an estimated 18,900 cases in 2005.

Geographic variation in the United States has been observed, with more MRSA infections seen in the South [21, 23]. Similarly, in Europe, considerable variation exists in the incidence of MRSA, with only 0.5% in Iceland but 44% in Greece from 1999 to 2002 [23].

Importantly, hospital-associated MRSA infections involve notable morbidity and mortality [24, 25]. Two well-conducted meta-analyses showed that mortality due to MRSA infection was greater than that due to methicillin-susceptible S. aureus (MSSA) infection from the 1980s to 2000 and from 1990 to 2000 [24, 25]. Although many agree with these findings, considerable debate continues regarding the reason for this difference. Some argue that factors such as the virulence of the MRSA organism itself contributes to this difference, whereas others suggest that patient differences account for the variation in mortality, because a greater number of older patients with severe underlying diseases contract infections due to MRSA [2, 24]. Still others believe that ineffective antibiotics play a large role in the suboptimal response to therapy [26–28]. Studies comparing vancomycin with β-lactam antibiotics for the treatment of invasive MSSA infections have demonstrated more microbiological failure, persistent bacteremia, and clinical relapse with vancomycin therapy, suggesting that β-lactam antibiotics are superior for treatment of these infections [26, 27].

COMMUNITY-ASSOCIATED MRSA INFECTION

A growing concern is the emergence of MRSA infections in patients with no apparent risk factors. In 1993, MRSA isolates with unique genetic elements were reported among infected western Australian aborigines who never had contact with the health care system [29]. In the United States, 4 cases of rapidly fatal MRSA infections in children were reported by the Centers for Disease Control and Prevention (CDC) in 1997–1999 [30]. The causative bacteria was the MW2 strain of community-associated MRSA, which appears to have acquired staphylococcal cassette chromosome (SCC) mec type IV, the S. aureus pathogenicity island SaPI3, and the bacteriophage Sa2 in its evolution from MSSA476 [31]. Gillet et al. [32] described a series of children in France from 1986 to 1998 with pneumonia caused by S. aureus strains positive for Panton-Valentine leukocidin (PVL). Of 16 children, 12 (75%) presented with an influenza-like illness, and 37.5% died within 48 h after hospital admission [32]. Hageman et al. [33] described 17 young patients from 9 US states with S. aureus community-acquired pneumonia during the 2003–2004 influenza season. Of the 17 patients, 15 (88%) had infection due to MRSA, 12 (71%) had associated influenza, 4 (24%) had MRSA risk factors, and 5 (29%) died. All MRSA isolates had toxin genes and SCCmec type IVa, and 11 (85%) were positive for PVL [33]. In the same year, Francis et al. [34] identified 4 adults with necrotizing pneumonia in Baltimore during the winter of 2003–2004. All lacked risk factors for hospital-associated MRSA and had isolates positive for PVL toxin and SCCmec IVa that belonged to the pulsed-field type USA300 [34]. Retrospective reports subsequently showed that MRSA infections occurred among children with no risk factors who
received treatment at the University of Chicago Children’s Hospital between 1988 and 1995 [30, 35]. In this series, a significant proportion of MRSA isolates were susceptible to non–β-lactam antibiotics and caused clinical disease. Most children presented with skin infections, including cellulitis or abscess [35].

Several investigators have demonstrated that community-associated MRSA may have evolved from established community-associated MSSA clones that possessed the genes for PVL toxin [36–38] (figure 1). By inserting the smaller, mobile SCCmec type IV into PVL-positive MSSA, the community-associated MRSA would possess resistance determinants and enhanced toxins, potentially gaining a fitness advantage [31, 39–41]. Resulting characteristics of community-associated MRSA infections include a lack of hospital-associated risk factors, susceptibility to many non–β-lactam antibiotics, distinct genotypes, and distinct genetic determinants of virulence (e.g., PVL toxin) [6, 42–44]. Gordon and Lowy [45] discuss the molecular epidemiology and virulence associated with community-associated MRSA in this supplement.

Although there are no established risk factors for community-associated MRSA infection [42], person-to-person transmission has been reported [46], and several factors have been shown to predict disease (table 2). Outbreaks have been reported among men having sex with men, medically underserved individuals, military recruits, prison inmates, athletes, postpartum women, individuals who use intravenous drugs, and heterosexual couples (razors were implicated in 2 of 3 cases of heterosexually transmitted community-associated MRSA [51]) [35, 44–55]. CDC investigators reported an outbreak among members of the St. Louis Rams football team during the 2003 season [54]. They investigated 8 MRSA infections after turf abrasions and found a greater risk of infection in individuals who played the linebacker position and those with a higher body mass index. Further studies showed that trainers lacked regular access to hand hygiene and that players often shared towels and did not shower before entering the communal whirlpool. Additionally, players received an average of 2.6 courses of antibiotics per year, a rate that is 10 times the adjusted rate for the general age-matched population [54].

As is the case with hospital-associated MRSA, colonization with community-associated MRSA poses increased risks to the host. In a prospective observational study of US Army soldiers, Ellis et al. [44] showed that colonization with PVL-positive strains of community-associated MRSA was associated with a significant risk of developing pyogenic soft-tissue infection. The isolates obtained from infected individuals were all positive for PVL, and most belonged to the USA300 genotype [44].

Several studies have shown that the prevalence of community-associated MRSA varies geographically. Global outbreaks have been reported from the United States to Saudi Arabia to New Zealand [56] (figure 2). In a population-based surveillance study of 3 communities in 2001–2002, CDC investigators reported on 1647 cases of community-associated MRSA infection from Atlanta, Minnesota, and Baltimore. They found that community-associated MRSA composed 8%–20% of all MRSA isolates, for an annual disease incidence of 25.7/100,000 persons in the general population in Atlanta versus 18/100,000 persons in the general population in Baltimore. Of note, the incidence was higher among children <2 years old [46]. King et al. [47] also demonstrated that approximately two-thirds of all community-associated S. aureus skin infections in Atlanta were due to MRSA.

Clinically, community-associated MRSA infection often presents as pyogenic skin and soft-tissue infections in previously healthy individuals [47]. In a recent multicenter study, community-associated MRSA was the most common (59%) identifiable cause of such infections among patients who presented to US emergency rooms. Of these isolates, 97% were pulsed-
Figure 1. Established community-associated methicillin-susceptible Staphylococcus aureus (MSSA) clones that possess genes for the Panton-Valentine leukocidin (PVL) toxin. One postulated means of evolution of MSSA into methicillin-resistant S. aureus (MRSA) (both hospital-acquired and community-acquired strains) involves the horizontal transfer of virulence genes, such as PVL genes, and the acquisition of staphylococcal cassette chromosome (SCC) mec allotypes. ST, sequence type; SWP, southwest Pacific clone. Reprinted from [38], with permission from Elsevier.

Figure 2. Global outbreaks of community-associated methicillin-resistant Staphylococcus aureus infection, 1997–2000.
trimethoprim-sulfamethoxazole, as well as a significant increase in the number of infections due to MRSA with PFGE-type USA300 and USA400 (4.0% vs. 14.7%; \(P = .003\)), reflecting the appearance of community-associated MRSA strains in the hospital [22]. Most recently, CDC investigators reported the increase in MRSA infections in the United States in 2005. They noted the presence of USA300 PFGE type in 22.2% of isolates from health care–associated, community-onset cases and in 15.7% of health care–associated, hospital-onset cases [14].

**CONCLUSION**

Over the past 2 decades, we have seen the gradual increase in MRSA infections in our health care facilities. Recently, MRSA infections have been the most frequent and often the most invasive pathogens associated with our most vulnerable patient populations. Unfortunately, health care–associated MRSA is also causing a growing number of infections in the community.

More than a decade ago, a new pathogen—community-associated MRSA—was first recognized. Its rapid spread has been characterized by outbreaks of cutaneous infections in healthy individuals. This organism, containing new virulence factors, can also cause necrotizing, frequently lethal pneumonia, especially after influenza infection. Now this organism is moving into the health care setting. Although more susceptible to non–β-lactam antibiotics, community-associated MRSA strains that cause infection often are quite destructive despite “appropriate” therapy, making it imperative that we increase our understanding of these pathogens.

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