

Methicillin-Resistant *Staphylococcus aureus* and Community-Acquired Pneumonia: An Evolving Relationship

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(See the Major Article by Moran et al, on pages 1126–33.)

Two entities are considered in this editorial: one is a bacterium and the other a clinical infection, but it is their relationship that is the issue of interest. Originally referred to as micrococcus, *Staphylococcus aureus* has been a recognized problem for well over a century. It is a frequent colonizer of skin and mucosa in animals and humans. In humans, the preferred niche is the anterior nares, although it can also be frequently found in the axillae and perineum. Nasal carriage rates in the general population vary from 10% to 40%.

Staphylococcus aureus is also a highly successful pathogen responsible for a variety of clinical problems ranging from folliculitis to endocarditis, osteomyelitis to pneumonia, and food intoxication to septic shock. A number of structural and secreted virulence factors play a role in

the pathogenesis of these various conditions and the evasion of host defenses.

Penicillinase-resistant semisynthetic penicillins, such as methicillin, became available in the late 1950s. Shortly thereafter, methicillin-resistant strains of *S. aureus* appeared [1]. The development of such strains is likely related to the acquisition of staphylococcal cassette chromosome (SCC)*mec* allotypes. SCC*mec* is an acquired fragment of DNA that carries β -lactam resistance genes and may also carry resistance genes to additional antibiotics. This early appearance of antibiotic resistance was a harbinger of things to come, and methicillin-resistant *S. aureus* (MRSA) has been a growing problem in hospital-acquired infections for some time. More recently, community-associated MRSA (CA-MRSA) infections have been described in patients with skin and soft tissue infections and pneumonia and is a cause of growing concern.

Community-acquired pneumonia (CAP) is not a reportable disease, and therefore accurate figures are not available. Data from the United States suggest that there are >4 million cases per year, resulting in >600 000 hospitalizations, 64 million days of restricted activity, and 50 000 deaths annually [2]. The overall yearly cost associated with CAP in the United States is estimated to be \$9–\$10 billion dollars.

CAP is often misdiagnosed and improperly treated. When confronted with

a patient with possible CAP, there are 2 questions to be answered. First, is the clinical syndrome in fact pneumonia or some other clinical entity? Second, if CAP, what is the etiologic pathogen? The diagnosis of pneumonia itself is based on a compatible history and the presence of select clinical features plus a chest radiographic abnormality.

The lack of rapid, sensitive, and specific methods to determine the etiologic agent in a particular patient means that the attending physician must often initiate antimicrobial treatment without knowing the pathogen with any degree of certainty. Given the large number of potential pathogens including bacteria, atypical bacteria, and viruses, uncertainty regarding etiology represents a significant problem, particularly for patients ill enough to require admission to hospital. For those requiring management in an intensive care unit (ICU) setting, correct initial selection of an antimicrobial regimen assumes critical importance because of the high mortality rates seen in such cases.

Although it was clear that MRSA was becoming an important pathogen in cases of hospital-acquired pneumonia and ventilator-associated pneumonia, it is currently considered to be the etiologic agent in 20%–40% of such cases [3, 4]. As might be expected, the situation seemed to be quite different for

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CAP; *S. aureus* was thought to be quite uncommon, typically occurring as a superinfection in patients with influenza and overall accounting for infection in only 1%–5% of all CAP patients.

A sharp increase in MRSA infection in patients without obvious exposure to the healthcare system led to the recognition of the new clones referred to as CA-MRSA. CA-MRSA with its SCC*mec* type IV, and usually with a gene for Panton-Valentine leukocidin, has been responsible for a variety of infections with the majority of isolates in the United States being pulsed-field type USA300 [5].

The prevalence of CA-MRSA varies between countries and even within national boundaries. The community-associated variant has characteristics that distinguish it somewhat from its hospital-acquired counterpart, including susceptibility to certain antibiotics (eg, clindamycin, trimethoprim/sulfamethoxazole, and doxycycline) and differing epidemiologic risk factors such as occurrence in athletes, gay men, and patients with concurrent skin and soft tissue infections. More recently, CA-MRSA infections have begun to move from the community setting into the healthcare setting and no longer seem to be restricted to certain risk groups or to geographic locales where outbreaks first occur [4, 6].

The paper by Moran et al in this issue of *Clinical Infectious Diseases* provides important information regarding CA-MRSA CAP [7]. This prospective observational study was designed to determine the properties of adults with MRSA-related CAP who were hospitalized through the emergency department and to identify factors associated with such infections. Until very recently, most data on CAP caused by MRSA were provided by case series. According to one paper, “clinical presentation is usually that of a severe pneumonia with high fever, hypotension, and hemoptysis followed by rapid progression to septic shock and requirement for ventilator support”

[6]. Papers from the United States and Europe have reported mortality rates >50% [8–10].

A 2010 paper by Lobo et al, however, disputed such findings [11]. In contrast to prior studies, they found (1) significantly lower mortality rates (13.3%), (2) medical care required for only approximately half of patients, (3) an absence of findings previously attributable to CA-MRSA including hemoptysis and neutropenia, and (4) no relationship to influenza.

The Moran study adds to the Lobo data by finding that mortality rates (14%) were lower than expected and that clinical and epidemiologic factors thought to be associated with MRSA infection did not help in deciding initial empirical antibiotic therapy.

The Moran study appears carefully planned and executed and has a number of positive features. It was carried out in 12 different cities around the United States, which hopefully mitigates regional variations in incidence of MRSA. Most important, by providing both numerator and denominator, they put the frequency of MRSA as a CAP pathogen into perspective by reporting it in only 2.4% of patients and 5% of patients admitted to the ICU. They did note, however, that, in general, patients with infection caused by MRSA tended to be sicker at the time of presentation and were more likely to require intubation or pressors or to die in the emergency department.

The few weaknesses of the paper are relatively minor. It would have been nice to know the results of urine antigen or serologic testing for atypical pathogens and nasopharyngeal viral molecular testing to get an idea of their prevalence and to determine if MRSA can be a copathogen with them. The incidence may be slightly underestimated; only the peak pneumonia season was included, and CA-MRSA infections appear to have no seasonal variation [12]. Also, the authors failed to provide a definition of severe CAP used for ICU admission. Are they

using the CURB criteria or the Pneumonia Severity Index score or a functional definition based on requirements for mechanical ventilation and/or vasopressors [13–15]? Finally, the fact that all 12 sites were university-affiliated centers may make their data and conclusions less generalizable than if both community-based and academic centers been involved.

In the end, however, we still have a problem. The good news seems to be that MRSA CAP may not be as common or severe as previously thought—but how does the average physician decide when to treat with anti-MRSA drugs? Certainly, the risk is higher for those ill enough to require ICU admission; however, should all severe CAP cases be treated for MRSA for an average of only slightly >1 patient per hospital per season? What about those patients who are not as sick? If not treated appropriately initially, will patients who actually have CA-MRSA CAP do significantly worse?

In selecting a particular antibiotic regimen, what is the best agent? Because part of the pathogenesis of *S. aureus* infections is dependent upon exotoxins, then perhaps drugs that suppress toxin production may be important for serious CA-MRSA infections. Lobo et al mention both linezolid and clindamycin because both can inhibit exotoxin production [11]. We are certainly in favor of linezolid for treatment of CAP caused by MRSA. As for clindamycin, however, Moran et al found that 18% of their isolates were clindamycin resistant. While this rate is certainly disconcerting, 49%–76% of such isolates were clindamycin resistant in a Boston healthcare facility [16]. Whether antibiotic sensitivity testing correlates with toxin-suppression activity is also unclear.

Only prospective interventional trials will answer the questions of optimal treatment. However, the study of Moran et al presents data critical to the design and powering of such trials. The authors

have therefore performed an important service for patients, clinicians, and clinical researchers.

Note

Potential conflicts of interest. R. W. has received honorarium and consulting fees from Pfizer. L. M. reports no potential conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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