



EDITORIAL

MRSA as a cause of community-acquired pneumonia

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Staphylococcus aureus is a species of bacterium that can cause a broad variety of infections, ranging from minor skin infections to severe pneumonia and sepsis. The genetic adaptation of *S. aureus* has led to a multidrug-resistant pathogen, methicillin-resistant *S. aureus* (MRSA) after the introduction of methicillin (previously methicillin) into clinical practice in the 1960s [1]. MRSA is resistant to β -lactam antibiotics, including penicillin and cephalosporins. Resistance is mediated by penicillin binding protein 2a, a penicillin binding protein encoded by the *mecA* gene that permits growth in the presence of methicillin. The *mecA* gene is situated in the staphylococcal cassette chromosome SCCmec. Initially, MRSA was only a nosocomial pathogen, *i.e.* healthcare-associated MRSA. It is associated with severe invasive disease [2] and tends to have multidrug resistance. It carries SCC chromosome type II (SCCmec type II) [3].

In the mid 1990s, MRSA began to be detected in the community, *i.e.* community-acquired MRSA (CA-MRSA). It is the leading cause of identifiable skin and soft tissue infections seen in USA emergency rooms [4]. CA-MRSA (and methicillin-susceptible *S. aureus* (MSSA)) may be associated with the presence of Panton Valentine leukocidin (PVL), a two-component staphylococcal membrane toxin that targets leucocytes [5] and frequently carries SCC *mec* type V or IV. PVL isolates have been linked to severe infections and necrotising pneumonia [6].

Published data has suggested that MRSA was not a frequent cause of community-acquired pneumonia (CAP), although with increasing incidence over the past few years the situation is now less clear. Now, a systematic study of both case series and case reports of CA-MRSA pneumonia, published in the present issue of the *European Respiratory Journal*, has estimated the incidence at 0.51–0.64 cases per 100,000 population [7]. Since the CAP incidence is between 100 and 1,000 per 100,000 [8], the frequency of CA-MRSA CAP can be estimated to be between one in 200 and one in 2,000 cases of CAP.

MRSA CAP appears to be a severe disease, with multilobar shadowing in three quarters of patients, 75–85% reaching the intensive care unit (ICU) and death occurring in between 20% and 60% in the article by VARDAKAS *et al.* [7]. However, the resistance profile of the pathogen does not necessarily determine the severity of disease caused by that organism.

Although the majority of CA-MRSA infections involving skin and soft tissue most likely occur independent of PVL toxin production [9], PVL is required for lung tissue necrosis and inflammation, as present in the rare, but frequently fatal, cases of necrotising pneumonia [10]. Change to the initial empirical antibiotic regimen was deemed to be appropriate in most cases from the published articles.

The frequency in the more severely ill admitted to the hospital and ICU is much more difficult to assess. The frequency of *S. aureus* CAP in the ICU averages ~10%, and ~10% of adults admitted with CAP are managed in the ICU, but rates of both vary enormously from country to country.

Compared with nosocomial MRSA, CA-MRSA isolates are commonly sensitive to antibiotics such as clindamycin, fluoroquinolones, trimethoprim–sulfamethoxazole, tetracyclines and rifampicin, although some resistant isolates are emerging [11]. There is evidence of increasing prevalence of asymptomatic colonisation among children and adults in the community [12, 13]. The strain most often isolated in the community outbreaks was USA300 [14], which is typically resistant to β -lactam and macrolide antimicrobial agents and contains genes for PVL toxin [15]. USA300 isolate has also been described among “men who have sex with men” [16]. Although CA-MRSA is sensitive to several antibiotics (clindamycin, trimethoprim–sulphamethoxazole and tetracyclines) the optimal treatment is not yet established. The 2007 Infectious Diseases Society of America/American Thoracic Society guidelines recommend vancomycin or linezolid [17]. Linezolid, an agent from the oxazolidinone family, is active against all CA-MRSA isolates but prolonged administration increases the likelihood of resistance through the accumulation of mutations in multiple copies of the 23s ribosomal RNA *S. aureus* gene [18]. Vancomycin is still considered first-line treatment for patients with invasive infection. Strains of MRSA with high levels of resistance to vancomycin are evolving [4]. Observational reports have used these antibiotics (vancomycin or linezolid) in combination with clindamycin. Owing to the increasing importance of CA-MRSA, animal studies and human randomised trials are needed to find the best antibiotic treatment. The currently recommended empirical therapy for CAP, which consists of a β -lactam with a macrolide or fluoroquinolone for severe CAP, may not provide adequate protection against MRSA. The frequency of CA-MRSA CAP overall should have no influence on guideline antibiotic recommendations; however, if the above projections are correct the frequency in those reaching the ICU could be enough to impact on guideline recommendations. The many excellent studies of the microbial aetiology of CAP in hospitals

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and the ICU must be supplemented by new studies to bridge this knowledge gap.

Post-influenza staphylococcal pneumonia has been reported during influenza pandemics and epidemics for the past century. There is evidence of mechanisms indicating influenza interaction with *S. aureus*: an influenza-induced increase in *S. aureus*-specific adhesion throughout the respiratory tract and *S. aureus*-specific proteases, which may increase influenza viral replication [19, 20]. During the 2003–2004 influenza season, 15 cases of pneumonia caused by *S. aureus*. MSSA and MRSA were reported to the Centers for Disease Control and Prevention (CDC) [21]. In 2007, the CDC received reports of 10 cases of MRSA CAP, including six deaths among previously healthy individuals [22]. In the present series of MRSA CAP, 38% had documented evidence of influenza infection and 57% had symptoms consistent with influenza [7]. MRSA should remain in the differential diagnosis of severe CAP occurring during the influenza season, especially in those with cavitary infiltrates and in those with a history of MRSA infection. This could be of great importance in the ongoing pandemic of swine-related H1N1 influenza virus infection.

As the incidence of CA-MRSA rises, either as a cause of skin and soft tissue infection or as a cause of CAP, physicians should take into consideration traditional risk factors for MRSA infections, especially if resistant clones are involved and in severe CAP cases: recent hospitalisation, surgery, dialysis, residence in a long-term care facility in the 12 months preceding the culture, invasive device, and history of MRSA infection or colonisation. In addition, evidence of skin and soft tissue infection should now be sought. Rapid tests for confirmation of *S. aureus* infection need to be supplemented by rapid tests for toxin-producing strains.

The rarity of such infections and the practical difficulties of such trials mean that comparative randomised antibiotic trials in CA MRSA CAP will probably never be carried out. Additional data from animal studies and trials in skin and soft tissue infection are required to guide antibiotic recommendations and therapy for this difficult infection. A review series on MRSA and the lung is launched in this issue of the *European Respiratory Journal* [23] and will develop these topics further as the series continues.

STATEMENT OF INTEREST

Statements of interest for M. Woodhead and A. Torres can be found at www.erj.ersjournals.com/misc/statements.dtl

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