

## New insights concerning methicillin-resistant *Staphylococcus aureus* disease

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Methicillin-resistant *Staphylococcus aureus* (MRSA) has been a common nosocomial pathogen since the 1960s, and has been a major problem in hospitals worldwide. In 2006, the European Antimicrobial Surveillance System (EARSS), a free network that connects more than 600 laboratories in 28 European countries, recorded one incidence of MRSA per 100 000 patient-days, ranging from 0.2 in Denmark to 26.9 in Portugal (<http://www.rivm.nl/earss/>). In 2005, data from The Surveillance Network-USA (TSN), an electronic surveillance network that collects microbiology data from 300 clinical microbiology laboratories across the USA, reported that MRSA rates were 59%, 55% and 48% for strains from non-intensive-care unit (ICU) inpatients, ICU patients, and outpatients, respectively [1]. Two meta-analyses showed that bloodstream infections (BSIs) due to MRSA are associated with almost two-fold higher mortality rates than those due to methicillin-susceptible *S. aureus* [2,3]. Costs were significantly higher for MRSA BSIs than for methicillin-susceptible *S. aureus* BSIs [4].

Risk factors include: degree of compliance with hand disinfection procedures, use of antimicrobials, underlying diseases, prior hospitalization, surgery, duration of hospitalization, central venous catheterization and endotracheal intubation, enteral feeding, admission to the ICU, and nursing staff workload [5–8]. A 1-year study, carried out at an ICU, showed that urgent admission, values of APACHE II score at 24 h, bronchoscopy and days of staff deficit were all independent risk factors for acquisition of nosocomial MRSA. When a simple stochastic model was fitted, staff deficit was the only factor that was significantly associated with cross-transmission. It was predicted that a 12% improvement in adherence to hand hygiene might have compensated for staff shortage and prevented transmission during periods of overcrowding, shared care, and high workload [6]. British and US guidelines recommend that patients should be screened

routinely before ICU admission in a hospital where MRSA is endemic [9,10].

A systematic review of isolation policies in the hospital management of MRSA demonstrated that intensive concerted interventions, which include isolation policies, can substantially reduce MRSA infections, even in settings with a high level of endemic MRSA [11]. Recently, MRSA infections have been diagnosed with increasing frequency upon hospital admission. In a cohort study of 127 patients with MRSA bacteraemia, diagnosed upon hospital admission, independent risk factors included a history of MRSA colonization or infection within 90 days, presence of a central venous catheter, and skin ulcers or cellulitis [12,13]. A meta-analysis of MRSA infections identified within 24–72 h of hospitalization documented a prevalence of community-acquired MRSA infections, defined as infections in patients without any known risk factors for MRSA, of  $\leq 0.24\%$  [14,15]. These 'community-acquired' MRSA strains arise from two different patient populations: those with true community-acquired infections due to MRSA strains that have emerged *de novo* from community-based *S. aureus* strains, and those with infections due to healthcare-associated MRSA strains that have been acquired in hospital or during a previous exposure to a healthcare setting or intervention.

Increased adherence to hand-washing guidelines and controlled use of antibiotics may be two of the few modifiable factors offering a potential for primary prevention of MRSA infection in the hospital setting. The efficacy of a multimodal, centrally coordinated, multisite hand hygiene culture-change programme for reducing rates of MRSA was assessed in Victorian hospitals. Increased compliance with hand hygiene recommendations was associated with a significant reduction of MRSA BSIs [16,17].

The importance of a dose–effect association, supporting a causal relationship between MRSA and antimicrobial drug

use, has been demonstrated [13,18]. A meta-analysis including 24 230 patients showed a clear association between exposure to antibiotics and MRSA colonization and infection. Subjects who have been exposed to antibiotic therapy have an almost two-fold greater chance of acquiring MRSA as opposed to non-exposed subjects. This risk is almost three times greater after the use of quinolones and glycopeptides [16].

For several years, conventional culture methods have been considered the reference standard for detection of MRSA colonization, but these can take at least 48–72 h to obtain a result. In the absence of pre-emptive room isolation, this delay might allow the spread of bacteria among hospitalized patients. Recently, rapid methods for molecular detection of MRSA-colonized patients have been developed. However, studies on the impact of these new tests on the rate of MRSA acquisition are extremely heterogeneous and showed discordant results [17,18]. Therefore, for the moment, definitive recommendations cannot be made. As informed use of hospital resources for detection of MRSA is important, studies to analyse the cost-effectiveness of molecular tests in different epidemiological situations are needed.

Therapy for MRSA infections has to be decided individually, taking into consideration the susceptibility patterns, source of infection, presence of metastatic sites of infection, comorbidities, and history of allergy. However, a number of questions remain unsolved in the treatment of MRSA infections. Although glycopeptides are still the drugs of choice, several concerns remain: reports of clinical failure with vancomycin treatment, regardless of *in vitro* susceptibility; increasing reports of MRSA strains with reduced vancomycin susceptibility; difficulty in dosage monitoring of teicoplanin; and lack of evidence of the efficacy of combination therapy. The increase in multidrug resistance, not only among nosocomial but also among healthcare-associated and community-acquired MRSA strains, is particularly worrisome. Combination therapy may be considered in severe cases, as for endocarditis unresponsive to standard monotherapy. However, new trials are needed to define the role of combination therapy in reducing mortality due to severe MRSA infections. Among the newly developed antimicrobials, linezolid may be the most versatile, as it can also be administered orally. Daptomycin is the only drug among the newly developed antimicrobials that has been approved for MRSA BSI. Dalbavancin, telavancin and tigecycline look promising. However, in order to update existing guidelines, new trials are needed. At the moment, use of these drugs should be carefully monitored, to assess their efficacy and the risk of development of resistance.

To address the impact and clinical relevance of new diagnostic and therapeutic approaches, the European Society of

Clinical Microbiology and Infectious Diseases sponsored a consensus conference. The following reviews summarize the consensus of opinion on that occasion.

National guidelines for the control and prevention of MRSA do exist. These are increasingly evidence-based, although not all guidelines involve a rigorous assessment of the literature to determine the strength of the recommendations [19]. Few recommendations have acquired the highest rating on the strength of evidence, and well-designed studies of the many aspects of MRSA management and control are lacking. Consensus among experts is thus important when evidence is tenuous or well-performed studies are lacking.

Although it should be clearly stated that expert reports and consensus based on clinical experience should be explicitly labelled as low-quality evidence, there remains a role for expert opinion while better systems for rating the quality of evidence and the strength of existing recommendations are developed and adopted.

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