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European perspective and update on the management of nosocomial pneumonia due to methicillin-resistant *Staphylococcus aureus* after more than 10 years of experience with linezolid

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important cause of antimicrobial-resistant hospital-acquired infections worldwide and remains a public health priority in Europe. Nosocomial pneumonia (NP) involving MRSA often affects patients in intensive care units with substantial morbidity, mortality and associated costs. A guideline-based approach to empirical treatment with an antibacterial agent active against MRSA can improve the outcome of patients with MRSA NP, including those with ventilator-associated pneumonia. New methods may allow more rapid or sensitive diagnosis of NP or microbiological confirmation in patients with MRSA NP, allowing early de-escalation of treatment once the pathogen is known. In Europe, available antibacterial agents for the treatment of MRSA NP include the glycopeptides (vancomycin and teicoplanin) and linezolid (available as an intravenous or oral treatment). Vancomycin has remained a standard of care in many European hospitals; however, there is evidence that it may be a suboptimal therapeutic option in critically ill patients with NP because of concerns about its limited intrapulmonary penetration, increased nephrotoxicity with higher doses, as well as the emergence of resistant strains that may result in increased clinical failure. Linezolid has demonstrated high penetration into the epithelial lining fluid of patients with ventilator-associated pneumonia and shown statistically superior clinical efficacy versus vancomycin in the treatment of MRSA NP in a phase IV, randomized, controlled study. This review focuses on the disease burden and clinical management of MRSA NP, and the use of linezolid after more than 10 years of clinical experience.

Keywords: Clinical management, Europe, linezolid, methicillin-resistant *Staphylococcus aureus*, nosocomial pneumonia, ventilator-associated pneumonia

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Introduction

Nosocomial pneumonia (NP) is a hospital-acquired infection often affecting patients in intensive care units (ICUs) with substantial morbidity, mortality and costs [1,2]. Methicillin-resistant *Staphylococcus aureus* (MRSA) now accounts for a large proportion of all cases of NP, including ventilator-associated pneumonia (VAP), in hospital patients worldwide [2–4]. International guidelines recommend that empirical therapy for NP should include antibiotics targeting MRSA in patients with late-onset infection and/or when some risk factors are present to provide adequate coverage [5]. The selection of the individual antibiotic agent should be based on local patterns of infection and adjusted according to the microbiology results in

accordance with good antimicrobial stewardship [5]. For NP, the recommended anti-MRSA agents are glycopeptides and linezolid. None of the other new MRSA-effective antibiotics (e.g. daptomycin, tigecycline, telavancin or ceftaroline) are recommended for the treatment of MRSA NP, because they either do not work in the lungs [6,7] or they have restrictions or have not been approved for treatment of NP. This paper gives an update on the management of MRSA NP, with a focus on the use of linezolid after more than 10 years of clinical experience. In particular, we explore current knowledge regarding the epidemiology of MRSA in Europe, the burden of illness, pathogenesis and diagnosis of NP, and new updates on antibacterial management.

Epidemiology of MRSA in Europe

MRSA is the most important cause of antibiotic-resistant healthcare-associated infections worldwide and remains a major health issue in European hospitals [8,9]. Data reported to the European Antimicrobial Resistance Surveillance Network (EARS-Net) indicated that in 2011, 16.7% of *S. aureus* isolates collected from hospital laboratories in 28 countries were found to be MRSA [9]. In ten of the 28 countries (36%), the proportion of MRSA was 10–25% (Fig. 1). Six countries further reported an MRSA proportion of 25–50% and two countries (Portugal and Romania) had rates above 50%. In general, the lowest rates of invasive MRSA isolates were found in the north of Europe (Norway, Sweden, Denmark, Finland, Estonia), whereas the UK and Ireland, and southern and eastern European countries, generally had higher rates [9]. Although there has been a general decline in the rate of MRSA bacteraemia in the UK since 2006 [10] and a sustained decrease in MRSA in Belgium, France, Germany, Ireland, Spain and the UK, the rate of MRSA is still more than 25% in eight of the 28 European countries studied [9]. In 40 Spanish hospitals participating in a nosocomial infection surveillance programme in Catalonia (The VINCat Programme) between 2008 and 2010, the yearly mean rate of resistance to methicillin remained stable for the study period (24–25%), whereas the mean incidence of new cases of MRSA decreased from 0.65 to 0.54 cases per 1000 patient-days (p was not significant) [11].

The recently decreasing or maintained low-level incidence of healthcare-associated MRSA in many European countries is encouraging. In a majority of countries, these successes can be linked to the implementation of multi-faceted preventive interventions (including measures focusing on screening, contact precautions, decolonization, antibiotic stewardship, the update and strengthening of national MRSA guidelines, or bundles of preventive measures and care) [12]. In the UK, a bundle of high impact measures, including the mandatory reporting of all MRSA bacteraemia by the hospital and public benchmarking of MRSA incidence rates, led to an 18-fold reduction in the incidence of MRSA healthcare-associated infections over a 5-year period from 2006 to 2011 [13].

In European countries, MRSA is associated with three main reservoirs: healthcare institutions, the community and livestock [12]. The main burden of MRSA in Europe is within the healthcare system, but community-acquired (CA-) MRSA has been increasingly identified as a cause of hospital-onset and healthcare-associated infections [14,15]. On the other hand, hospital-associated clones have also caused infections in the community [16], suggesting that certain clones have the ability to cross barriers between hospitals and the community.

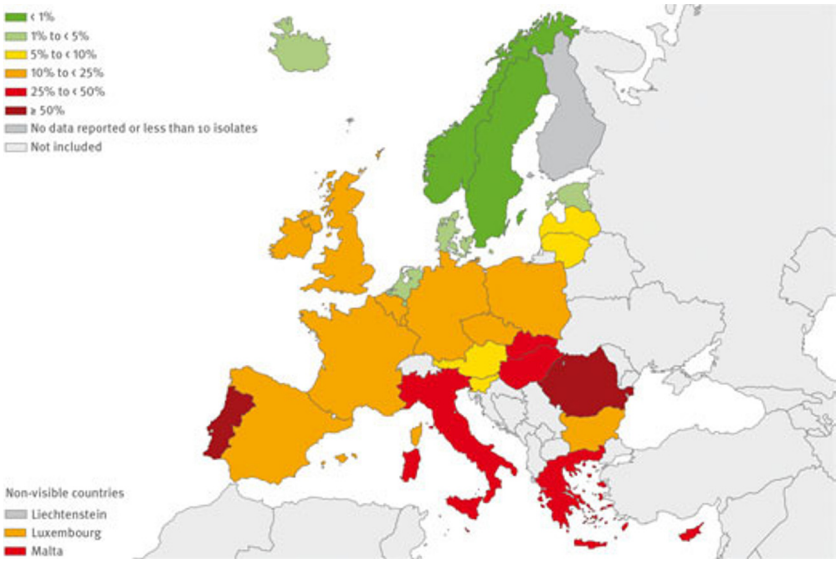

FIG. 1. *Staphylococcus aureus*: percentage of invasive isolates resistant to methicillin (MRSA), by country, European Union/European Economic Area countries, 2008–2011 [9]. Reproduced with permission from the European Centre for Disease Prevention and Control.