Methicillin-resistant \textit{Staphylococcus aureus}: the European landscape

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Pan-European surveillance of bacteraemia caused by methicillin-resistant \textit{Staphylococcus aureus} (MRSA) shows it to be a problem affecting all European countries, although there is marked geographical variation in prevalence. Although the proportion of \textit{S. aureus} bacteraemia due to MRSA is declining in many countries, data from the European Antimicrobial Resistance Surveillance System (EARSS) for 2008 showed that in more than one-third of countries the proportion remained >25%. In contrast to bacteraemia, community-associated MRSA infection in Europe remains relatively uncommon. However, there appears to be an increasing problem involving transmission of MRSA (particularly sequence type 398) from colonized livestock, particularly pigs, to farm workers, abattoir workers and veterinarians who are in contact with such animals. Molecular analysis of isolates of MRSA has shown that there has been spread of only a limited number of MRSA clones in Europe and that many of these clones show geographical clustering due to dissemination through regional healthcare networks. Despite our increasing understanding of the epidemiology of MRSA in Europe, MRSA infections continue to pose a significant public health challenge.

Keywords: MRSA, surveillance, bacteraemia, staphylococcal infections

Introduction

Methicillin, the first semi-synthetic penicillin derivative resistant to hydrolysis by staphylococcal β-lactamase, was introduced into clinical use for the treatment of infections caused by penicillin-resistant \textit{Staphylococcus aureus} in 1960.\textsuperscript{1} Although contemporary isolates of \textit{S. aureus} appeared uniformly susceptible to this new agent, the first isolate of methicillin-resistant \textit{S. aureus} (MRSA) was reported from the UK within a year.\textsuperscript{2} Methicillin is no longer in clinical use, having been superseded by the isoxazolyl penicillins, particularly flucloxacillin in the UK. However, the acronym MRSA has continued to be used.

Following their initial isolation in 1961, MRSA remained uncommon for several years thereafter. However, by the late 1960s the situation was changing with a strain of multiresistant MRSA of phage type 83A being reported from a number of countries.\textsuperscript{3} Although this strain was initially widely disseminated, its prevalence subsequently declined during the late 1970s, for reasons that are not fully understood.\textsuperscript{5} Unfortunately, the disappearance of this strain was soon followed by the emergence of gentamicin-resistant MRSA, which persisted in a number of countries in the early 1980s. Throughout the 1990s there was a marked resurgence in the prevalence of MRSA, often reflecting the emergence of epidemic strains (so-called EMRSA) that spread both within and between hospitals. An example of this was seen in the UK, where the dramatic year-on-year increase in the proportion of \textit{S. aureus} from bacteraemia that were methicillin-resistant was shown to reflect the dissemination of two new EMRSA strains designated EMRSA-15 and EMRSA-16.\textsuperscript{4} Although the factors accounting for the epidemic nature of EMRSA strains are not fully understood, some risk factors for colonization or infection have been identified. Isolates of EMRSA-15 and -16 are commonly resistant to erythromycin and ciprofloxacin in addition to β-lactams, and a study at one affected hospital showed a temporal relationship between the rates of MRSA infection and the use of macrolides, third-generation cephalosporins and fluoroquinolones, suggesting that the use of antimicrobials to which an outbreak strain is resistant is an important contributory factor for the persistence of that strain.\textsuperscript{5}

The remainder of this review will provide an update on the epidemiology of MRSA across Europe with a focus on surveillance and other research undertaken over the last decade.

MRSA bloodstream infections

A major contribution to our knowledge of the occurrence of MRSA infections across Europe followed from the establishment in 1999 of the European Antimicrobial Resistance Surveillance System (EARSS), now known as the European Antimicrobial Resistance Surveillance Network (EARSNet). This is a pan-European surveillance system in which sentinel hospital laboratories report cases of bacteraemia caused by a number of bacterial species including \textit{S. aureus}. Although bacteraemia is less common than other types of infection, EARSS (like many other surveillance systems such as the BSAC Bacteraemia Surveillance Programme)\textsuperscript{16} focuses on bloodstream infections, as they are clinically significant and likely to be investigated...
microbiologically. This in turn reduces the likelihood of selection bias during surveillance based on laboratory reporting.

Early data from EARSS showed that bloodstream infection with MRSA was a significant and widespread problem, with MRSA accounting for >25% of S. aureus bacteraemias in many central and southern European countries (Figure 1).7 Although these findings elicited much concern, attempts to reduce the levels of MRSA infection appeared to have little initial impact, with the rates of methicillin resistance among invasive S. aureus remaining high in many countries over the next few years. However, by 2008 the EARSS Annual Report noted that “For the first time more countries showed decreasing MRSA proportions instead of increasing trends”, although the report also noted that “MRSA proportions are still above 25% in one third of countries”.7 Further decreases in the rate of MRSA bacteraemias were subsequently seen, particularly in the UK, where a national surveillance scheme run by the HPA noted that the proportion of S. aureus from blood that were methicillin resistant decreased from 31% in 2007 to 19.3% in 2009.8 This decrease may reflect action by the government in England who, having made the reporting of MRSA bacteraemia mandatory for all hospitals, subsequently set hospitals the target of halving their MRSA rates.9

Data from EARSS have also provided information on the epidemiology of MRSA bacteraemia. In most countries where demographic data have been collected there is an excess of males over females, and infections are seen more commonly in older patients.7 Country-specific data are also available from EARSS regarding the relative frequency of S. aureus bacteraemias in different hospital departments (intensive care, internal medicine, surgery) and the proportions attributable to MRSA.7

Other MRSA infections in hospitalized patients

MRSA are capable of causing a range of infections other than bacteraemia, including skin and soft tissue infections (SSTIs), pneumonia and deep-seated infections such as endocarditis and osteomyelitis. In a recent Europe-wide survey of clinical experience of MRSA the most common infections reported were SSTIs (79%), while for patients with MRSA bacteraemia, the most common underlying foci were intravenous lines (48%) and SSTIs.10 In another study of SSTIs in European medical centres, S. aureus was the most common pathogen (71% of cases), with 22.5% of the isolates being methicillin resistant.11 The proportion of S. aureus resistant to methicillin varied among countries, ranging from 0.4% in Sweden to 48.4% in Belgium (although in the latter country only 31 isolates were tested).

In England, surveillance of surgical site infections has been running since 1997. During the 5 year period between January 2003 and December 2007, at least one causative microorganism was reported for 77% of surgical site infections. The most common organism was S. aureus (accounting for 38% of surgical site infections), of which 64% were MRSA.12 However, between October 2008 and September 2009, the proportion of S. aureus isolates (accounting for 31% of surgical site infections) that were methicillin resistant decreased to 32%.13 This decrease in surgical site infections due to MRSA in England appears to mirror the decline in MRSA bacteraemia.

Community-associated MRSA in Europe

The EARSS programme has focused on surveillance of invasive infections (bacteraemia) caused by MRSA, the majority of

![Figure 1. Proportion of S. aureus isolates from bacteraemia resistant to methicillin in countries participating in EARSS, 2002 (EARSS Annual Reports. Available at http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/Documents.aspx).7](image-url)
which are seen in hospitalized patients. However, MRSA also cause a range of infections of varying clinical severity in the community. In the USA, SSTIs occurring in the community, particularly in groups such as children, athletes, patients presenting at the Emergency Department (ED), military recruits, prison inmates, men who have sex with men and people who are positive for HIV/AIDS, are very common. Molecular characterization of US isolates of community-associated MRSA (CA-MRSA) has indicated that the widespread occurrence of infections in the community, particularly SSTIs, is due in large part to the widespread dissemination of a predominant clone of MRSA designated USA300. The extent of the problem posed by CA-MRSA in the USA and the significant involvement of USA300 is exemplified by a study in 2004 that showed that 59% of patients presenting to an ED with an SSTI yielded cultures positive for MRSA, 97% of which were USA300.

Although isolation of USA300 has been reported from a number of European countries, including Austria, Denmark, Finland, Germany, Italy, the Netherlands, Portugal, Spain, Switzerland, and the UK, the available evidence indicates that the scale of the problem of CA-MRSA is lower than that seen in the USA. Of the reports of USA300 in European countries, some are simply case reports or reports of small outbreaks, while others comprise surveillance studies in which only low numbers of isolates of USA300 or other CA-MRSA were found. In two studies from Denmark and Sweden, which have a low overall incidence of MRSA, patients of non-Scandinavian origin and travellers were overrepresented among cases of CA-MRSA infection, indicating that many such infections reflect the importation of MRSA via colonized patients.

MRSA in animals in Europe

In recent years there has been an increasing awareness of MRSA in animals. Much interest has focused on pigs, as MRSA, particularly isolates belonging to sequence type (ST) 398, have been noted in pigs in a number of countries, including Austria, Belgium, Denmark, France, Germany, Italy, the Netherlands, Poland, Portugal, Spain and Switzerland. From a public health perspective there is accumulating evidence that pigs may serve as a reservoir of MRSA that may transmit to humans. Epidemiological studies have shown significantly higher rates of nasal carriage of MRSA by humans in contact with pigs (farm workers, abattoir workers, veterinarians), with the isolates frequently belonging to ST398. In addition, infections with MRSA ST398 in patients epidemiologically linked to pigs have been reported, including cases of SSTI and joint infection. Arguably more worrying, a case of ventilator-associated pneumonia due to MRSA ST398 in a patient not reporting exposure to animals has also been reported.

Molecular epidemiology of MRSA in Europe

Resistance to methicillin is mediated by production of a novel penicillin-binding protein (PBP) with low binding affinity not only for methicillin, but for all licensed β-lactams. This novel PBP, known as PBP2’ (or PBP2x) is encoded by the mecA structural gene that is part of a larger mobile genetic element called the staphylococcal chromosomal cassette mec (SCCmec). MRSA evolved from methicillin-susceptible S. aureus (MSSA), which lack the mecA gene, by acquisition of the gene, probably from coagulase-negative staphylococci.

The application of molecular techniques, particularly multilocus sequence typing (MLST), based on divergence in the DNA sequence of seven housekeeping genes, and spa typing, based on polymorphism in the spa gene that encodes staphylococcal protein A, has shown that the population structure of S. aureus is clonal, and that MRSA lineages have evolved from MSSA on a limited number of occasions. Much of the public health problem posed by MRSA is due to the dissemination of a small number of MRSA clones. An example of this is the situation referred to above, where the steep increase in MRSA seen in the UK largely reflected the emergence and spread of EMRSA-15 (ST22-IV) and EMRSA-16 (ST36-III). By 1999–2000, EMRSA-15 and EMRSA-16 accounted for 95.6% of all UK MRSA bacteremias, the two strains comprising, respectively, 60.2% and 35.4% of MRSA isolated from blood. Subsequently, however, the proportion of EMRSA-16 declined to 21.4% in 2001 and 9% in 2007, while the proportion of EMRSA-15 rose commensurately, accounting for 85% of MRSA in 2007.

More recently, Grundmann and colleagues initiated a Europe-wide surveillance study with the goal of determining the clonal composition of MRSA isolates found across Europe. In each country, national reference laboratories collected the first five MRSA and the first five MSSA from a panel of laboratories that regularly participated in the EARSS programme. Isolates were then characterized by spa typing in each reference laboratory using a standard protocol, and the results were uploaded to a central database. Over a 6 month period (September 2006–February 2007) 2890 isolates were collected from 357 laboratories in 26 countries. A total of 660 spa types were found, of which 505 were seen exclusively in MSSA, 95 were only seen in MRSA and 60 were seen in both. Thus the MSSA and MRSA isolates comprised 565 and 155 spa types, respectively. There was marked inter-country variation among the spa types of MRSA, with dominant types often forming distinct geographical clusters (Figure 2), indicating that invasive MRSA clones in Europe have a predominantly regional distribution. Conversely, spa types seen in MSSA often showed wide geographical distribution, with only 5 of the 27 major MSSA spa types showing geographical clustering. Grundmann and colleagues concluded from this study that, in contrast to the wide genetic and geographic diversity of MSSA, only a limited number of MRSA clones have spread in Europe. Moreover, the geographical clustering of MRSA clones indicated that rather than spreading freely in the community, these clones disseminate through regional healthcare networks. Further support for the concept of MRSA spread via national healthcare networks (i.e. inter-hospital transfer of colonized patients) came from a study in the Netherlands in which mathematical modelling was applied to national data on patterns of patient referral. Although the spread of successful clones of MRSA has been the subject of intense investigation, the factors that contribute to the success of individual clones remain to be elucidated.
Discussion

While there is evidence that the prevalence of MRSA is declining in some European countries, MRSA still remains a significant public health problem. Measures to control the spread of MRSA have focused on trying to break the chain of transmission (e.g. the isolation of colonized or infected patients, hand washing, screening of patients for colonization, decolonization) or trying to reduce the selective pressure for emergence and persistence of MRSA associated with overuse of antibiotics by improving antibiotic prescribing. However, there appears to be variation in the extent to which control measures are applied, with Scandinavian countries and the Netherlands, which have low rates of MRSA infection, applying a ‘search-and-destroy’ policy when cases of MRSA are detected. In addition, there is marked inter-country variation in antibiotic usage. Clearly attempts to control MRSA must not only be sustained in those countries where rates are declining, but must be more widely applied. Surveillance is regarded as a means of generating ‘information for action’. In terms of MRSA, coordinated surveillance across Europe is providing information. It is hoped that the required levels of action will follow.

Transparency declarations

This article is part of a Supplement sponsored by the BSAC and supported by an unrestricted educational grant from Pfizer. The author received an honorarium from the BSAC for writing this article. The author is Editor-in-Chief of the Journal of Antimicrobial Chemotherapy but took no part in and did not influence the editing of this manuscript. The author has no other conflicts of interest to declare.

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