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MRSA bacteraemia

Ian M. Gould *

Department of Medical Microbiology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, UK

Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been pandemic for over a decade and is causing a major increase in serious staphylococcal infections. This is reflected in large increases in *S. aureus* bacteraemia with over 50% in many countries being caused by MRSA. Moreover, in some countries it also seems as though methicillin-susceptible *S. aureus* (MSSA) bacteraemia is also increasing. MRSA certainly has not replaced MSSA but is an additional burden with significantly higher mortality. Standard treatment of MRSA bacteraemia with glycopeptides is probably suboptimal in the presence of increasing resistance, MIC drift, uncertainties about laboratory susceptibility testing and fears of toxicity. New antibiotics look set to replace glycopeptides as the gold standard for treatment of MRSA bacteraemia, but whether the underlying causes of MRSA bacteraemia can be addressed successfully in order to control this pandemic disease is less certain.

Keywords: MRSA; Bacteraemia; *Staphylococcus aureus*; Glycopeptides; MIC; Treatment; Prevention; Bactericidal; Epidemiology

1. Introduction

With the epidemic of MRSA that most hospitals have experienced in the past 10–20 years, proportionate rises in *Staphylococcus aureus* bacteraemia (SAB) have occurred. Many of the MRSA clones are virulent, causing at least a doubling in numbers of SAB cases seen in the past 20 years in both the UK and USA [1]. As with other types of *S. aureus* infection, methicillin-susceptible *S. aureus* (MSSA) bacteraemia has not been replaced by MRSA bacteraemia, which is now seen as an additional major infectious burden. During this period MSSA bacteraemia has, if anything, also increased, although not to anything like the same extent as MRSA bacteraemia. Some areas needing clarification are: (1) why inroads have not been made into the numbers of MSSA bacteraemia by programmes to address the underlying causes such as intravascular (IV) access, IV drug use and urinary catheters [2]; (2) whether MRSA bacteraemia has the same causes; and (3) if not, what are the reasons for such an increase in numbers of MRSA bacteraemia?

2. Mortality rates

One thing is certain; the mortality from MRSA bacteraemia is higher than that from MSSA bacteraemia with two meta-analyses showing an approximate doubling [3,4]. The reasons for this are complex and not entirely clear (Table 1). The most obvious reasons are the well-known poor performance of glycopeptides (the standard therapy for MRSA bacteraemia) compared with semi-synthetic penicillins when prescribed for MSSA bacteraemia [5,6] and the likely common delay in their administration. It is well known that delay in starting appropriate therapy leads to increased mortality in bacteraemia. Whether these issues can be addressed satisfactorily by more common use of glycopeptides as empiric therapy and the use of increased doses remains to be clarified. It is unlikely that any method of risk assessment would be specific enough not to result in patients with MSSA bacteraemia getting sub-standard empiric therapy with glycopeptides. Similarly, even increased dosing of glycopeptides to ensure trough levels of around 20 mg/L may still be associated with sub-optimal outcome due to the poor PK/PD of these agents and the raised MICs of many strains. Furthermore, toxicity of such high-dose regimens of glycopeptides gives cause for concern [7].

* Tel.: +44 1224 554954; fax: +44 1224 550632.
E-mail address: i.m.gould@abdn.ac.uk.

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Table 1

MRSA versus MSSA bacteraemia Why is MRSA mortality higher?
Older age
Delayed appropriate empiric therapy
Previous antibiotic (4FQ in particular)
Strain
Pneumonia
Standard therapy is sub-optimal

In the pre-antibiotic era, mortality from SAB was probably in excess of 70% although, as in today's practice, one must expect that cases due to readily treatable or removable sources must have had a lower mortality rate [8]. With the advent of penicillin treatment, case series mortality decreased significantly to around 30% but soon penicillinase-producing multi-resistant strains become endemic in hospitals. By the 1950s mortality was again high, perhaps 50–60%. At this time LP Garrod wrote that there were few curses to a hospital as great as the problem of antibiotic-resistant staphylococci [9]. With the discovery of 6 amino-penicillanic acid, by Rolinson and co-workers at Beecham Research Laboratories, a solution to the β-lactamase problem in *S. aureus* was found. Methicillin was the first of the semi-synthetic penicillins that resulted from the newfound ability to synthesise β-lactams rather than rely on fermentation and its introduction saw a fall in fatality rates for SAB back to around 30%. Nowadays for MRSA bacteraemia, mortality rates as high as those in the pre-antibiotic era have been reported after mono-therapy with a glycopeptide although recent series report rates nearer 30–40% (and 20% for MSSA bacteraemia) with attributable mortality perhaps around 20%. Complicated course in SAB is well predicted by community onset, acute systemic illness, persistent fever at 72 h and continued positive blood cultures at 48–96 h [10]. Death is associated with treatment duration less than 14 days, an un-eradicated focus, septic shock, age >60 years and total daily dose of flucloxacillin <4 g for MSSA bacteraemia (Table 2) [11].

3. Epidemiology

Robust European-wide data on incidence have been published for several years now and indicate wide variations both between countries and also between hospitals within specific countries [12]. Holland and the Scandinavian countries retain very low rates of MRSA bacteraemia (<5%), no doubt due to their well-publicised search and destroy policies which have kept the rate of all MRSA infections low. It is probable that bacteraemia rates are a surrogate marker for the prevalence of MRSA in any particular country or institution although one can expect variations depending on control strategies and case mix in hospitals. Historically in the UK tertiary referral centres have had higher bacteraemia rates than district general hospitals although with some successes at control, rates seem to be equating. Hospitals with large dialysis or transplant units and big intensive care units can expect relatively higher bacteraemia rates. Table 3 ranks some European countries according to the percent of all SAB due to MRSA. Many centres worldwide have even higher rates than the highest in Europe with such robust data coming from USA, Japan, Taiwan and Hong Kong.

Some countries such as the UK have had compulsory notification of all cases of MRSA bacteraemia for several years now although initial data may have underestimated the problem, as only clinically significant cases were reported by some hospitals. Currently in the UK, not only are all MRSA cases reported but also all cases of MSSA bacteraemia. The UK has one of the highest rates in Europe despite several recent years of record expenditure on infection control and it is interesting to speculate why this is the case.

Table 2

Predictors of mortality in SAB
Inappropriate treatment
MRSA
Age
Pneumonia
Community onset
Persistent bacteraemia/fever
Shock
Persistent foci
Treatment duration
Acute systemic illness

Table 3
MRSA rates in SAB from selected European countries

Countries with changing rates (%)		Countries with stable rates (%)	
Netherlands*	0.93	Iceland	0
Denmark*	1.70	Norway	1
Finland*	2.91	Sweden	1
Slovenia†	10	Estonia	2
Czech Rep.*	13	Spain	27
Slovakia*	19	Italy	37
Hungary*	19	UK	44
Germany*	21	Portugal	47
France†	27	Romania	61

* A significant increase since 1999 or 2001.
† A significant decrease since 1999 or 2001.

4. The treatment of MRSA bacteraemia – why is the gold standard substandard?

While the increased mortality of MRSA bacteraemia over MSSA bacteraemia, as previously described, may in some cases be due to particular strain virulence or delay in initiation of appropriate antibiotic, there is a growing consensus that the problem lies with the glycopeptides themselves [7]. Only two glycopeptides are in widespread clinical use and they share common characteristics. They are large molecules that diffuse slowly and poorly into crucial tissues such as lung, they are only slowly bactericidal and resistance, albeit difficult to detect, is increasing. While vancomycin may not