Methicillin resistant *Staphylococcus aureus* infections following cardiac surgery: incidence, impact and identifying adverse outcome traits

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Abstract

**Objective:** To assess the incidence and impact of Methicillin-resistant *Staphylococcus aureus* (MRSA) infections on cardiac surgery outcomes and to identify adverse outcome traits. **Methods:** Retrospective analysis of prospectively collected data from cardiac surgical and microbiology databases between April 2000 and March 2005. The overall and yearly incidence of positive MRSA cultures was examined along with the distribution of clinical infections and the associated mortality. Pre-operative patient characteristics were analysed between non-survivors and survivors of MRSA infections. Multivariate logistic regression was used to assess the relationship between pre-operative patient characteristics and in-hospital mortality in patients with MRSA. A comparison of post-operative outcomes between non-survivors and survivors of MRSA infections was also carried out and included in the logistic regression analysis. **Results:** There were 319 patients with positive MRSA cultures during the study period with an overall incidence of 3.9%. Yearly incidence ranged from 2.4% to 5.2%. There were 120 carriers with pre-operative positive cultures of which 25 developed clinical surgical infections leaving 224 patients as the study group. Overall mortality in patients with MRSA during the study period was 12.9%(41/319). Mortality in the study group was 17.8% (40/224). Mortality comparison between MRSA and non-MRSA sepsis patients revealed that non-survivors had a significantly higher pre-operative risk of 10.4% compared to survivors with a pre-operative risk of 6.2% (\(p=0.003\)). Renal dysfunction and poor ejection fraction were found to be pre-operative factors associated with mortality in MRSA patients following the multivariate logistic regression analysis. Non-survivors had longer stays on intensive care, longer ventilation times, and were more likely to require support with balloon pumps and haemofiltration. MRSA sepsicaemia and length of ventilation were significantly associated with mortality in MRSA patients ahead of pre-operative characteristics. **Conclusions:** The incidence of MRSA is low, but carries a high mortality. MRSA septicemia and mediastinitis have the highest associated mortality; however, this is not significantly different from non-MRSA infections. Patients with MRSA who die have higher pre-operative risk and have a poorer post-operative course than survivors.

**Keywords:** MRSA; Cardiac surgery; Septicaemia; Mediastinitis; Mortality

1. Introduction

Infection with Methicillin resistant *Staphylococcus aureus* (MRSA) evokes serious concern amongst all clinicians. Patients who undergo cardiac surgery by the nature of interventions such as valve implantation, extra corporeal circulation, insertion of mechanical support devices and prolonged indwelling intravenous lines, are exposed to a higher risk of infection. Soon after the introduction of Methicillin in clinical use, the existence of the MRSA strain was reported first by Barber\(^1\) in 1961. Evolution of MRSA is known to have occurred by acquisition of mobile genetic elements called SCCmec cassettes which carry the mecA gene that encodes PBP2a cell wall protein known to offer resistance to Methicillin and other \(\beta\) lactam antibiotics\(^2\). Since then, the existence of different clones has been reported, each with varying degrees of virulence and geographic distribution. By the 1980s, because of a steady increase in MRSA prevalence the impact of these infections...
became apparent. More recently MRSA infection has been perceived to have reached an alarming rate leading to major debate within the media and medical community.

We felt it appropriate and timely to study and report our experience with MRSA. The aim was to identify the incidence of hospital acquired MRSA infections, the incidence of community acquired pre-operative carrier status, its impact on surgical outcomes over a period of 5 years in our institution and compare outcomes between MRSA and non-MRSA infection. We also hoped to identify patient characteristics that might render them susceptible to succumb to this infection by analysis of differences between survivors and non-survivors of MRSA infections.

2. Materials and methods

2.1. Patient population and data

We conducted a large-scale cohort study using prospectively collected data on 8119 consecutive patients undergoing cardiac surgery between 1st April 2000 and 31st March 2005 at the Cardiothoracic Centre, Liverpool, United Kingdom. Pre-operative, operative and post-operative data was collected prospectively during patient admission as part of routine clinical practice. Methods of data collection and definitions have been previously published and are also available from www.nwheartaudit.nhs.uk [3]. Microbiology data on MRSA were abstracted from a routinely recorded independent electronic clinical microbiology archive, blind to patient characteristics and survival data.

2.2. Statistical methods

Continuous variables are shown as median with 25th and 75th percentiles due to non-normality of data. Categorical data are shown as percentages. Univariate comparisons were made with Wilcoxon rank sum tests and Chi-square tests or Fisher’s exact test as appropriate. The overall and yearly incidence of positive MRSA cultures was examined along with the distribution of clinical infections and the associated mortality. Pre-operative patient characteristics were analysed between non-survivors and survivors of MRSA infections. The logistic EuroSCORE was also calculated to quantify the pre-operative risk of the MRSA patients [4]. Multivariate logistic regression was used to assess the relationship between pre-operative patient characteristics and in-hospital mortality in patients with MRSA [5]. Variables offered to the logistic regression model were: age, sex, ejection fraction, diabetes, respiratory disease, renal dysfunction, peripheral vascular disease, body mass index, pre-op critical state (ventilation, intra-aortic balloon pumps, intravenous nitrates, inotropes, and cardiogenic shock), urgency of operation, prior sternotomy, smoking status, and surgical procedure. A comparison of post-operative outcomes between non-survivors and survivors of MRSA infections was also carried out. These post-operative factors were then added to the logistic regression analysis, along with the site of clinical infection. In all cases, a p-value < 0.05 was considered significant. All statistical analysis was performed using SAS for Windows Version 8.2.

3. Results

There were 319 patients with positive MRSA cultures during the study period (3.9% of the 8119 patients who underwent cardiac surgical procedures at our institution) with an overall mortality of 12.9% (n = 41). This compares to 3.1% in patients with no evidence of MRSA during the hospital admission (p < 0.001). Of the 319 positive cultures, 120 were identified as carriers preoperatively (25 developed clinically relevant surgical infections). The remainder (199) developed MRSA infection following surgery. The study therefore comprises 224 patients: 25 infected carriers and 199 post-operative infections. These patient groups with associated mortality are detailed in Table 1. Annual carrier status and infection rates are depicted in Fig. 1.

Mortality in the study group (n = 224) was 17.8% (n = 40). Distribution of clinical infections was as follows: (1) superficial sternal wound infection in 24 patients (10.7%), (2) mediastinitis in 30 patients (13.4%), (3) chest infections in 74 patients (33%), (4) septicemia in 32 patients (14.3%), (5)...

Table 1 MRSA status and associated mortality

<table>
<thead>
<tr>
<th>MRSA status</th>
<th>Number of patients</th>
<th>Percentage from 8119 cases</th>
<th>Percentage in-hospital mortality (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All positive cultures</td>
<td>319</td>
<td>3.9</td>
<td>12.9 (n = 41)*</td>
</tr>
<tr>
<td>Hospital acquired infections (nosocomial)</td>
<td>199</td>
<td>2.4</td>
<td>18.1 (n = 36)*</td>
</tr>
<tr>
<td>Pre-operative positive cultures (carriers)</td>
<td>120</td>
<td>1.5</td>
<td>4.2 (n = 5)</td>
</tr>
<tr>
<td>Pre-operative carriers with post-op surgical infection</td>
<td>25</td>
<td>0.3</td>
<td>16 (n = 4)*</td>
</tr>
<tr>
<td>Pre-operative carriers without post-operative surgical infection</td>
<td>95</td>
<td>1.2</td>
<td>1.1 (n = 1)</td>
</tr>
</tbody>
</table>

* Significantly different to in-hospital mortality rate for patients with no evidence of MRSA with p < 0.001.

Fig. 1. Yearly incidence of MRSA infection.
harvest site in 31 patients (13.8%), and (6) multiple sites in 33 patients (14.8%). Mortality rates for these groups are shown in Fig. 2. The highest mortality was in patients with MRSA septicaemia (15/32) followed by mediastinitis (8/30).

A comparison of in-hospital mortality between MRSA septicaemia and non-MRSA septicaemia revealed no statistically significant difference (46.9% [15 out of 32] vs 52.9% [37 out of 70]) \( p = 0.57 \). Post-operative lengths of stay revealed however, that MRSA septicaemia patients stayed in hospital longer than non-MRSA septicaemia patients (median 48 days [21—83] vs 31 days [15—54], \( p < 0.05 \)). Mortality of MRSA mediastinitis 26.7% (8/30) and non-MRSA mediastinitis 17.1% (13/76) was not statistically significant (\( p = 0.26 \)). Post operative length of stay for MRSA mediastinitis patients compared to non-MRSA showed a difference (median 50 days [35—71] vs 41 days [26—60], \( p < 0.05 \)).

An analysis of pre-operative characteristics between non-survivors and survivors of MRSA infections showed that non-survivors were more likely to have renal dysfunction, poor ejection fraction, and peripheral vascular disease (Table 2).

Applying the logistic EuroSCORE to the MRSA patients revealed that non-survivors had a significantly higher pre-operative risk of 10.4% compared to survivors with a pre-operative risk of 6.2% (\( p = 0.003 \)).

Two pre-operative variables were found to be predictive of mortality in MRSA patients following the multivariate logistic regression analysis. These factors were renal dysfunction and poor ejection fraction as shown in Table 3.

An analysis of post-operative outcomes between non-survivors and survivors of MRSA revealed that the non-survivors had a significantly poorer post-operative course. Non-survivors had longer stays on intensive care, longer ventilation times, and were more likely to require support with intra-aortic balloon pumps, inotropes, and haemofiltration (Table 4).

After including these post-operative factors to the logistic regression analyses, along with the site of clinical infection, MRSA septicaemia and length of ventilation were found to be associated with mortality ahead of the pre-operative characteristics (Table 5).

### 4. Discussion

Our study offers insight into outcomes in patients developing positive MRSA cultures following cardiac surgery. We have identified incidence of hospital acquired infection, the incidence of MRSA carrier status and its association with subsequent infective complications in our institution. MRSA septicaemia and mediastinitis have a particularly bleak outlook but is not dissimilar to its non-MRSA infection
equivalent. Pre-operative renal dysfunction and poor ejection fraction were found to be associated with death in patients with MRSA. However, the length of post-operative ventilation and development of MRSA septicaemia were the strongest factors associated with mortality in MRSA patients. Overall, patients succumbing to MRSA were higher risk pre-operatively and also carried greater co-morbidity following surgery (50% renal support; 12.5% IABP).

Several other studies have examined MRSA infections within the setting of cardiac surgery. Carrier and associates reported an incidence of MRSA infections ranging from 0.46% to 0.96% [6]. Mediastinitis occurred in 13 of the 39 patients with 8% mortality in their series. They also found no difference in outcomes between MRSA and non-MRSA mediastinitis. Their study was limited by having only 39 patients in their series. Combes et al. [7], in a series of 371 patients with mediastinitis, again reported similar outcomes in MRSA and MSSA infections. Harbarth et al. [8] have argued that in patients with MRSA and MSSA bacteraemia outcomes are comparable after adjustment for age, length of stay and co morbidity.

Although the reported incidence of MRSA is low, certain risk factors have been identified in the literature. Risk factors for developing MRSA mediastinitis was reported by Dodds Ashley et al. [9] in a series that consisted of 64 patients in MRSA group and 79 patients in MSSA group. They identified diabetes, female sex and age >70 years to be risk variables for MRSA while obesity alone was responsible for Methicillin sensitive mediastinitis. In a non-surgical setting and in relation to MRSA endocarditis, MRSA septicaemia was identified as a risk factor for mortality [10,11].

Recent studies have shown that prolonged stay on the intensive care unit increases the risk of MRSA infection [12–14]. Patients who have prolonged ventilation will of course require longer periods in intensive care, putting them at risk of MRSA. However, the association of increased ventilation and increased risk of mortality within our data does not necessarily translate into cause and effect. This is more likely a marker of severity of illness in the patients, with sicker patients who eventually die requiring longer periods ventilated.

From Fig. 1, it is apparent that our yearly incidence of hospital acquired MRSA infections has been increasing. The same trend has been observed in community acquired carriers incidence. Although MRSA is associated with high mortality, it must be recognized that this is not dissimilar to MSSA and that the vast majority of patients who develop clinical MRSA infections survive.

Our study has shown non-survivors to be much sicker with additional co-morbidity. It is arguable on this basis alone that they were at a higher risk of mortality even without the occurrence of MRSA infection. The extent to which this infection contributed to their demise is impossible to ascertain in this study. Many clinicians have expressed the opinion that MRSA infection is one of many conditions afflicting these patients which has the capacity to lead to multi organ failure and death. In these circumstances it may be justifiable to postulate that patients with MRSA die with the infection and not necessarily of the infection. Although, it should be noted that Zangrillo et al. [15] recently concluded that mortality following cardiac surgery is strongly associated the development of MRSA, however, cause and effect remained unproven.

In conclusion, the incidence of MRSA is low, but carries a high mortality. MRSA septicaemia and mediastinitis have the highest associated mortality; however, this is not significantly different from non-MRSA infections. Length of ventilation and MRSA septicaemia were significantly associated with mortality in MRSA patients. Patients with MRSA who die have higher pre-operative risk and have a poorer post-operative course than survivors.

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References


Table 5
Patient characteristics associated with the risk of MRSA mortality

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Direction of association</th>
<th>Odds ratio with 95% confidence intervals</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of ventilation</td>
<td>Positive</td>
<td>1.04 (1.02—1.06)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRSA septicaemia</td>
<td>Positive</td>
<td>8.2 (3.3—20.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

MRSA, methicillin resistant *Staphylococcus aureus*.

* For every additional 24 h.

Appendix A. Conference discussion

Dr R. Dion (Leiden, The Netherlands): What is the clinical relevance of your paper? What did you change in your daily practice to match these results?

Dr Reddy: This paper gives evidence that MRSA infection, as previously thought, is not a death sentence. No doubt, it is a nuisance and we have to be very diligent about how we deal with it. This paper identifies the high-risk groups as those patients who are being mechanically ventilated for long periods of time, and those with septicaemia. These are the ones that are likely to die.

We are in the process of looking at the impact our infection control measures such as isolation, barrier nursing are having and whether we’re winning on that front. We hope that it will be another story for another time to come back and see what impact we have had with those measures.

Dr S. Brose (Dresden, Germany): How were the MRSA detected? Do you do a routine screening preoperatively, or was it only by accident, if the patient had some signs of infection and you looked for a specimen?

And did it change your daily practice? Do you think that a screening is needed?

Dr Reddy: In our institution we are paranoid about MRSA infections. Nobody gets admitted into the hospital without being screened for their MRSA status. Same is true for the emergency cases. We always presume a patient to be with MRSA even if you had to admit them as an emergency till they prove themselves to be negative. Until that point we barrier nurse them and isolate them. And yes, to that extent MRSA screening is very prevalent and every patient undergoes MRSA screening.

In case of postoperatively acquired infection, obviously there has to be a clinical relevance for us to suspect that there is an infective phenomena going on. If a wound infection becomes very obvious, then they all get investigated. If patients become productive in their cough, then they all get their sputum sent for cultures routinely.

And apart from that, we also have very rigid protocols for infection screens which are sent at fairly regular intervals. These protocols are drawn up by our microbiology colleagues and they adhere to that very rigidly. We have a very active infection control team that take a lot of interest in what exactly we do with these patients. We feel all these measures are essential.