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# Methicillin-resistant *Staphylococcus aureus* in surgical patients: identification of high-risk populations for the development of targeted screening programmes

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## ABSTRACT

**INTRODUCTION** Methicillin-resistant *Staphylococcus aureus* (MRSA)-related hospital-acquired infection (HAI) in surgical patients is associated with high morbidity, mortality and financial cost. The identification and characterisation of populations of patients who are at high risk of developing MRSA infection or colonisation could inform the design of more effective strategies to prevent HAIs and reduce transmission of MRSA.

**PATIENTS AND METHODS** An analysis of historical discharge data for the whole of 2005 (7145 surgical in-patients) was performed, for all patients admitted to general surgery at the Royal Infirmary of Edinburgh. Analysis specifically focused on MRSA laboratory data and coding data for patient demographics, medical co-morbidities, and progress of in-patient stay.

**RESULTS** A total of 134 (1.88%) individual patients with colonisation or infection by MRSA were identified from indicated laboratory testing. Univariate analysis identified a significant association of concurrent MRSA-positive status with patients aged over 60 years ( $P < 0.01$ ), a duration of inpatient stay  $> 7$  days ( $P < 0.01$ ), presence of a malignant neoplasm ( $P < 0.01$ ), circulatory disease ( $P < 0.01$ ), respiratory disease ( $P < 0.01$ ), central nervous system disease ( $P < 0.01$ ), renal failure ( $P < 0.01$ ), and concurrent admission to ITU/HDU ( $P < 0.01$ ). Multivariate analysis suggested MRSA colonisation or infection was strongest in those with co-morbid malignancy ( $P < 0.0001$ ) or admission to ITU/HDU ( $P < 0.0001$ ).

**CONCLUSIONS** This large observational study has identified cancer patients as a UK surgical patient subpopulation which is at significantly higher risk of colonisation by MRSA. These data could inform the development of focused hospital in-patient screening protocols and provide a means to stratify patient risk.

## KEYWORDS

MRSA – Hospital acquired infection – Screening – Surgery – Cancer – Outcomes

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The UK has one of the highest methicillin-resistant *Staphylococcus aureus* (MRSA) to methicillin-sensitive *S. aureus* (MSSA) blood infection rates in Europe.<sup>1</sup> Recent data indicate that MRSA infection is associated with higher mortality rates and is implicated as the causative organism in 28% cases of *S. aureus* bacteraemia.<sup>2,5</sup>

Addressing the level of MRSA hospital-acquired infection (HAI) rates is a major world-wide problem; whilst recent data have demonstrated a trend towards decreasing numbers of MRSA infections,<sup>4</sup> screening for MRSA could poten-

tially allow earlier detection of those with MRSA. This may allow healthcare workers to target resources efficiently in an attempt to decrease rates of MRSA transmission using isolation or decolonisation strategies.<sup>5</sup>

In order to inform these strategies, further research is urgently required to identify high-risk patient populations in order to direct efficient screening programmes. Screening has now been recommended routinely for all hospital in-patients in some regions;<sup>6</sup> however, whilst these pilot studies will identify the effectiveness of such pro-

grammes, there is considerable debate regarding their expected benefit.<sup>7</sup>

The aim of this study was to undertake a major evaluation of all MRSA colonisations/infections in surgical in-patients within 1 year and evaluate the specific patient characteristics, demographics and variables which would allow for the identification of a patient subpopulation at high risk.

## Patients and Methods

The study analysed data from all in-patients admitted to the Royal Infirmary of Edinburgh (RIE) during 2005. This large university teaching hospital opened in 2005 and serves a population of approximately 880,000 from south-east Scotland. The hospital is a tertiary specialist surgical referral centre for a number of surgical sub-specialities focussing on upper gastrointestinal and hepatobiliary surgery, with lower gastrointestinal surgery being handled in another local hospital.

Bacteriological results from all surgical patients admitted to RIE were obtained from the RIE Department of Microbiology database. Testing at the time of study occurred only as clinically indicated, with no formal MRSA screening programme in place. Most commonly, swab samples were taken from the nose, throat, axilla and groin, with further samples taken from areas which appeared clinically infected. Colonised or infected patients were identified by a positive MRSA culture using conventional microbiological techniques for growth on blood agar plates. MRSA colonisation and infection status were defined as a positive MRSA culture within 24 h of discharge from the surgical admission, to take into account time taken to process positive samples in the laboratory.

The surgical patient population was identified between 1 January 2005 and 31 December 2005, associated with a particular surgical ward/intensive care ward/consultant, taken from the hospital computerised Patient Admission System (PAS) database. Duplicate admissions for each patient were deleted from this list. Additional simultaneous analysis of the Hospital Activities Coding database was performed to obtain details of patient specific relevant International Classification of Disease (ICD)-10 and Office of Population, Censuses and Surveys (OPSC)-4 codes recorded for each surgical admission. Only patients present on all three database interrogations were included in the analysis. Importantly, in order to detect only those who would be a high risk of infection within the hospital environment, patients who had become MRSA infected/colonised outside the duration of their surgical admission were excluded from analysis.

Patient variables such as sex, date of birth, date of admission and discharge, postcode, admitting ward, ITU/HDU

stay during admission, ICD-10 code, and date of positive MRSA culture were recorded from the databases on a Microsoft Office 2004 Excel worksheet and transferred to SAS v.9.1 for later statistical analysis.

For categorical variables such as sex, chi-squared and Fisher's exact tests were used as appropriate. To determine if there was any difference in age by MRSA status, a two-sample *t*-test was performed. The data for length of stay were not normally distributed; therefore, a Mann-Whitney test was used. The value of 0.05 was taken to define statistical significance. In order to take multiple variables into account, a logistic regression on appropriate variables has been performed.

Ethical approval was obtained through The University of Edinburgh; statistical analysis was performed with the help of the Epidemiology and Statistics Core, University of Edinburgh, Wellcome Trust Clinical Research Facility, Western General Hospital Edinburgh.

## Results

A total of 7145 patients were admitted to the speciality of general surgery in 2005. Laboratory databases confirmed that 134 (1.88%) patients were found to be colonised/infected with MRSA. Within this group were 72 (1.01%) cases of colonisation and 62 (0.87%) cases of infection, of which 21 (0.29%) were cases of MRSA bacteraemia.

The mean age of MRSA positive patients was 59.8 years (range, 16–95 years SD 15.6) compared to the mean age of 49.5 years (range, 12–101 years; SD 20.3) for surgical admissions with no evidence of MRSA infection/colonisation ( $P < 0.001$ ).

There were 5159 (44.8%) males compared to 3872 (55.2%) females in the non-infected or colonised group and 69 (51.5%) males and 65 (48.5%) females in the MRSA infected/colonised group. Sex was not associated with MRSA colonisation/infection ( $P = 0.12$  using a chi-squared test).

Social deprivation was evaluated crudely based on the 2001 Carstairs Deprivation Category (depcat score)<sup>8</sup> using the patient's postal code. Using a chi-squared test, there was no evidence of an association between MRSA infection or colonisation and depcat score ( $P = 0.57$ ).

Univariate analysis of co-morbidities demonstrated a significant association between infection/colonisation with MRSA and malignant disease ( $P < 0.001$ ). Of patients with a cancer diagnosis, 10.4% (44) tested positive for MRSA compared to 1.3% (90) of patients without a diagnosis of malignancy. In particular, carcinoma of the oesophagus ( $P < 0.001$  using Fisher's exact test), and pancreatic cancer ( $P = 0.022$  using Fisher's exact test) were significantly associated with MRSA infection and colonisation. Additional co-morbidities including circulatory disease ( $P < 0.01$ ), respiratory disease ( $P < 0.01$ ), CNS disease ( $P < 0.01$ ), renal failure

( $P < 0.001$ ), diabetes mellitus ( $P = 0.028$ ) and infectious or parasitic disease (other than MRSA;  $P = 0.001$ ) were identified as being strongly associated with MRSA infection or colonisation. However, gastrointestinal and genito-urinary disease did not demonstrate a statistically significant link with MRSA infection and colonisation ( $P = 0.074$  and  $P = 0.5471$ , respectively).

In common with other studies, admission to ITU or HDU was significantly associated with MRSA infection and colonisation ( $P < 0.001$ ). While only 7.2% (508) have non-infected or colonised patients admitted to ITU/HDU, 60.4% (81) of those infected or colonised with MRSA were admitted to ITU/HDU during their hospital stay (Table 1).

Of the MRSA-positive patients, 92 (68.7%) had a duration of in-patient stay greater than a week, compared to 1060 (15.1%) of the non-colonised or infected patients. Using a chi-squared test for linear trend, there was evidence of a linear trend between MRSA and length of stay when it is treated as a categorical variable (same day, 1–2, 3–7, 8–30, > 30 days;  $P < 0.001$ ). The median length of stay for those with MRSA infection/colonisation was 14 days, compared to 2 days in patients without MRSA ( $P < 0.0001$  using a Mann–Whitney test).

Using those variables which reached statistical significance or which had a  $P$ -value of less than 0.1 on the single variable analysis, a logistic regression model was produced. Although CNS disease, diabetes and pancreatic cancer reached statistical significance at the 5% level in the univariate analysis, they were not included in the multi-

**Table 1 Univariate analysis of risk factors**

Variable	Chi-squared	$P$ -value
Sex	2.40	0.1213
Circulatory disease	39.87	< 0.0001
Respiratory disease	18.38	< 0.0001
Digestive disease	3.19	0.0740
Renal failure	29.78	< 0.0001*
Genito-urinary disease	0.88	0.3471
Previous infection	13.85	0.0013*
CNS disease	16.13	0.0024*
Pancreatic cancer	8.26	0.022*
Oesophageal cancer	255.28	<0.001*
Malignant neoplasm	177.63	<0.001
Diabetes mellitus	5.82	0.0279*
ITU/HDU	492.03	< 0.0001
Deprivation score	4.81	0.5683

\*Using Fisher's exact test due to small expected counts.

**Table 2 Multivariate regression analysis of risk factors**

Variable	Odds ratio	95% CI (lower; upper)	$P$ -value
Circulatory disease	1.8294	(1.1763, 2.8451)	0.0074
Digestive disease	1.5770	(1.0560, 2.3549)	0.0260
Oesophageal cancer	4.3614	(1.9902, 9.5581)	0.0002
Malignant neoplasm	3.9232	(2.3800, 6.4669)	<0.0001
ITU/HDU admission	13.0241	(8.9098, 19.0383)	<0.0001

variable analysis due to small patient numbers. Evidence from the regression model suggested that circulatory disease, digestive disease, oesophageal cancer, malignant neoplasm or being in ITU/HDU independently increase the risk of developing MRSA colonisation or infection (Table 2).

## Discussion

The introduction of a UK-wide, risk-stratified policy for the management of MRSA in 1998 has done little to halt the spread of MRSA.<sup>9</sup> However the UK, France and Slovenia may be reversing the trend and have recently reduced the rates of MRSA to MSSA bacteraemia.<sup>10</sup> A recent review of the clinical and cost-effectiveness of MRSA screening has emphasised the importance of the identification of patients at high risk of infection with MRSA, but found that the cost of universal screening is prohibitively high.<sup>11</sup> A better understanding of risk factors might allow a more focused approach to screening.

Here, we have identified several risk factors associated with MRSA infection and colonisation which have already contributed to changes in infection control policies at the RIE. In particular, we identified that carcinoma of the oesophagus is a specific risk factor for MRSA infection and colonisation. This is significant, as patients with head and neck cancer who develop MRSA infection have been shown to have increased surgical morbidity and mortality.<sup>12</sup> Further research has implicated neoplasia as an independent risk factor for mortality from nosocomial *S. aureus* bacteraemia.<sup>15</sup> Health economy issues are also relevant given the high costs associated with hospital stay for oncology patients.<sup>14</sup> This has changed the policy at the RIE by focusing more attention to the regular screening of patients with oesophageal cancer.

The reasons for the link between MRSA acquisition and malignant disease are likely to be multifactorial and have been examined in other research. Several recent reviews have identified the relationship between cachexia, low serum albumin and the systemic inflammatory response as

significant prognostic and predictive factors in cancer patients.<sup>15,16</sup> It can be hypothesised that tumours associated with high rates of anorexia and rapid weight loss (such as oesophageal and pancreatic cancer) confer a poorer prognosis and increased susceptibility to MRSA infection. Further supportive evidence has shown that patients had a reduced ability to produce anti-pneumococcal polysaccharide IgG following oesophageal surgery, leaving them more prone to MRSA infections.<sup>17</sup> Prospective study suggested that the application of mupirocin calcium hydrate ointment to the nasal cavity,<sup>18</sup> and the use of pre-operative antimicrobial therapy may reduce the incidence of MRSA infection in high-risk patients.<sup>19</sup>

Previous research has shown that patients over 60 years of age who are infected with *S. aureus* have significantly higher rates of mortality compared to younger patients,<sup>20</sup> and surgical site infections (SSIs) are associated with poorer functional status in elderly patients.<sup>21</sup> Patients with respiratory, circulatory and central nervous system (CNS) disease were also identified as at significant risk of being colonised or infected with MRSA. Previous reports have linked chronic illness to increased risk of both community-acquired<sup>22</sup> and hospital-acquired MRSA infection.<sup>23</sup> In particular, respiratory diseases,<sup>24</sup> circulatory diseases<sup>25</sup> and CNS diseases<sup>26</sup> have previously been linked with *S. aureus* infections.

While initial univariate analysis failed to demonstrate a significant association between MRSA colonisation/infection and digestive disease, further multivariate analysis established that, when all other factors were taken into account, there was a significant association to the 5% level. The discrepancy is likely due to the high load of gastrointestinal patients (> 50%) admitted during our period of study to the RIE, complicating the initial analysis. This association is supported in further research demonstrating a significant association between recent gastrointestinal disease and MRSA colonisation.<sup>27</sup>

In-patient stay is significantly associated with increased risk of infection and colonisation with MRSA. Research from the US has also demonstrated that MRSA infection was linked with increased length of hospitalisation when compared to uninfected patients.<sup>28</sup> It is unclear, however, if length of hospital stay is the cause of MRSA transmission, or whether it is part of the sequelae of infection. Further investigation of this issue is likely to be complicated, as identifying the cause and timing of infection is notoriously difficult. However, from a pragmatic perspective, the screening of patients with prolonged hospital stay may help reduce rates of transmission in either clinical situation. The timing of this screening requires further clarification; however, hospital stay greater than 7 days may be a benchmark for future prospective study.

While ITU/HDU stay is evidently associated with increased rates of MRSA, what requires further clarification is the timing of colonisation and infection with regards to

ITU/HDU admission. One study found 6.8% of patients screened on admission to ITU were colonised with MRSA, with a further 11.4% becoming colonised during their ITU admission. The risk of infection increased proportionally with duration of admission.<sup>29</sup> The inability to discern the point of patient colonisation or infection with MRSA, however, presents a limitation to the interpretation of these results; it is for this reason that current prospective research is underway to investigate the stage at which MRSA acquisition occurs in surgical patients admitted to ITU/HDU.

### Study limitations

The most significant limitation of this retrospective data analysis is the inability to examine other known MRSA-associated variables such as prior hospital admission, antibiotic prescriptions and residence (*i.e.* long-term nursing care); further study would aim to include this information for analysis. Furthermore, the total number of cases of MRSA has been under-represented due to the lack of a screening programme in place during 2005 at the RIE and the transfer of infected or colonised patients from the RIE surgical wards to those wards not included in our initial database search. Additionally, our lack of patient data post-discharge, particularly for those patients undergoing minor surgery, means cases of MRSA presenting after discharge were not available for evaluation. All of these factors are likely to have contributed to an underestimation of the true incidence of MRSA infection and colonisation at the RIE during 2005. In addition, the changing epidemiology of MRSA and the identification of community-acquired cases is an important issue. However, as this study was concerned only with reducing transmission within the hospital setting, we aimed to exclude confounding community associated factors. Further prospective study would aim to examine this.

### Conclusions

These data identify specific subpopulations of surgical patients that are at higher risk of MRSA infection/colonisation. This is particularly relevant in patients with malignancy. We propose that factors including malignancy, circulatory disease, digestive disease, ITU admission or in-patient length of stay be included in future risk stratification for targeted screening to detect those who have MRSA infection/colonisation. Increased education and surveillance of cancer patients within the hospital environment may help to decrease MRSA-associated morbidity and mortality.

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