A 12-year review of *Staphylococcus aureus* bloodstream infections in haemodialysis patients: more work to be done

S.F. FitzGerald a, *, J. O’Gorman a, M.M. Morris-Downes a, R.K. Crowley a, S. Donlon b, R. Bajwa b, E.G. Smyth a, c, F. Fitzpatrick a, c, d, P.J. Conlon b, H. Humphreys a, c

a Department of Microbiology, Beaumont Hospital, Dublin, Ireland
b Department of Nephrology, Beaumont Hospital, Dublin, Ireland
c Department of Clinical Microbiology, Royal College of Surgeons in Ireland, Dublin, Ireland
d Health Protection Surveillance Centre, Dublin, Ireland

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SUMMARY

*Staphylococcus aureus* bloodstream infections (BSI) are a significant cause of morbidity and mortality in haemodialysis patients. This study describes a 12-year retrospective review of *S. aureus* BSI in a large haemodialysis centre in a tertiary referral hospital. The overall rate of *S. aureus* BSI was 17.9 per 100 patient-years (range 9.7—36.8). The rate of meticillin-resistant *S. aureus* (MRSA) BSI was 5.6 per 100 patient-years (range 0.9–13.8). Infective complications occurred in 11% of episodes, the most common being infective endocarditis (7.6%). Ten percent of patients died within 30 days of *S. aureus* being isolated from blood. Most cases of *S. aureus* BSI (83%) were related to vascular catheters. The provision of lower-risk vascular access, such as arteriovenous fistulae, and reduced use of intravascular catheters should be priorities in all haemodialysis units. Where alternative vascular access cannot be established, interventions to reduce the risk of catheter-related infections should be implemented to reduce morbidity and mortality in this vulnerable patient group.

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INTRODUCTION

Infection is the second leading cause of death in patients with end-stage kidney disease, accounting for up to one-quarter of all deaths.1 *Staphylococcus aureus* is a common cause of bloodstream infections (BSI) in patients on chronic haemodialysis, and is associated with significant morbidity and mortality. Infectious complications are common, with infective endocarditis being most frequent, and the attributable mortality ranges from 5% to 19%.2 A vascular access device is implicated in 71—89% of cases of *S. aureus* BSI on haemodialysis, with higher incidence associated with intravascular catheters compared with arteriovenous fistulae or vascular grafts.3 4 These infections also have significant economic consequences. A prospective study in the USA estimated that the mean cost of treatment (including outpatient treatment and re-admissions, but excluding other costs such as the patient’s loss of income) of a haemodialysis-dependent patient admitted with *S. aureus* BSI between 1996 and 2001 was approximately $24,000. The mean cost of the initial hospital admission was significantly greater in patients with complicated infection compared with those without complications ($32,500 vs $17,000).3 A retrospective multi-centre German study of nosocomial *S. aureus* BSI in haemodialysis patients between 1999 and 2005 calculated the average cost of treatment to be €20,000. The costs were significantly greater for community-acquired infections and meticillin-resistant *S. aureus* (MRSA) infections than for infections due to meticillin-susceptible *S. aureus* (MSSA).6

Data from the European Antimicrobial Resistance Surveillance Network database in the Republic of Ireland highlight the burden of *S. aureus* BSI in dialysis patients. Between 2004 and 2008, 11% of Irish patients with MSSA BSI and 13% with MRSA BSI were on haemodialysis.7 This paper describes the authors’ experience with *S. aureus* BSI over a 12-year period, including clinical outcomes, in the largest renal centre in Ireland.
Methods

This study was performed at Beaumont Hospital, Dublin, Ireland; an 820-bed adult tertiary referral hospital that includes the national renal, pancreas and small bowel transplant centre. A retrospective analysis was performed using the laboratory database and clinical records. All patients undergoing haemodialysis from January 1998 to December 2009 from whom S. aureus was isolated from blood were included. Demographic data, antimicrobial susceptibility profile, source of BSI and clinical outcome at 30 days were recorded for each episode of infection.

An episode of BSI was defined as the isolation of S. aureus from one or more blood cultures. In the authors’ institution, all patients with S. aureus BSI are reviewed on the ward by the clinical microbiology team to determine clinical significance, source and likely complications, and to provide advice on antibiotic management. Patients were followed until discharge. All isolates of S. aureus in blood cultures during the study period were deemed to be clinically significant and patients were treated with antibiotics. If more than 14 days had passed without a positive blood culture, the subsequent isolation of S. aureus from the blood of the same patient was deemed to be a separate episode. A BSI was judged to be catheter-related if a vascular catheter was in situ within 48 h of the positive blood culture being drawn, and if the isolate was not related to infection at another site.

The overall and annual rates of S. aureus BSI were calculated using 100 patient-years as the denominator. Proportions were compared using Chi-squared test.

Results

Over the 12-year study period, the number of patients receiving haemodialysis at Beaumont Hospital increased from 146 in 1998 to 237 in 2009. S. aureus was isolated from 891 sets of blood cultures from 304 haemodialysis patients. The male to female patient ratio was 1.62. In total, there were 394 separate episodes of S. aureus BSI. Annual numbers of episodes ranged from 19 to 56. The overall rate was 17.9 BSI per 100 patient-years, ranging from 9.7 to 36.8 (see Figure 1). Although the rate increased sharply in 2002, there was a reduction in annual rates over the study period. Vascular access data for the haemodialysis cohort are not available before 2003; from 2003 to 2009, the percentage of patients being dialysed using a catheter decreased from 54.7% to 48.6%.

Overall, 272/394 (69%) episodes were due to MSSA, with the remainder (122/394, 31%) caused by MRSA. The overall rate of MRSA BSI was 5.6 per 100 patient-years, ranging from 0.9 to 13.8 (see Figure 1).

An intravascular catheter was judged to be the source of infection in the majority of episodes (328/394, 83%), and was removed in 232 (71%) cases. Other sites considered to be the source of infection included skin and soft tissue (N = 20), lower respiratory tract (N = 6), abscess (N = 5), vascular graft (N = 5), bone and joint (N = 5), peripheral venous cannula (N = 4), urinary tract (N = 2) and device (N = 1). In 18 episodes (5%), no source could be determined.

Infectious complications occurred during or after antimicrobial therapy in 43 (11%) episodes. Infectious endocarditis was the most common metastatic complication, occurring in 30 patients (see Table I). Twenty percent (6/30) of cases of infective endocarditis were caused by MRSA.

Death occurred within 30 days in 30 patients (9.8% of patients, 7.6% of episodes). Due to the retrospective nature of the study, it was not possible to determine if death was directly attributable to S. aureus BSI. Nineteen (63%) of the patients who died had MRSA isolated from blood. The proportion of deaths was significantly higher for MRSA BSI (19/122, 16%) compared with MSSA BSI (11/272, 4%) (χ^2 = 15.9, df = 1, p < 0.01).

Discussion

Over the 12-year period, S. aureus BSI was a considerable cause of morbidity and mortality in this cohort of haemodialysis patients. Most cases of BSI were associated with vascular catheters, so interventions to reduce reliance on catheters for vascular access, such as the provision of vascular surgical expertise for the insertion of arteriovenous fistulae, along with implementation of best practice guidelines for intravascular catheter care are likely to be beneficial in reducing the number of cases of BSI. Limitations of this study include its retrospective nature, incomplete data for some patients (e.g. whether or not an echocardiogram was carried out, see below), and the absence of typing data to determine the predominant clones. A Europe-wide molecular epidemiological analysis that used spa typing to characterize invasive isolates of S. aureus was not possible to determine if death was directly attributable to S. aureus BSI.

![Figure 1.](image-url) Staphylococcus aureus bloodstream infections (BSI) per 100 patient-years in haemodialysis patients, 1998−2009. Open bars, meticillin-resistant S. aureus; Solid bars, meticillin-susceptible S. aureus.
MSSA and MRSA from 2006 to 2007 found much greater genetic diversity in MSSA compared with MRSA. The dominant MRSA type in Ireland was t032, equivalent to epidemic MRSA 15 (EMRSA-15).8 This is in keeping with data from an Irish national typing project in Ireland was t032, equivalent to epidemic MRSA 15 (EMRSA-15).8 This is in keeping with data from an Irish national typing project in Ireland was t032, equivalent to epidemic MRSA 15 (EMRSA-15).8 This is in keeping with data from an Irish national typing project in Ireland was t032, equivalent to epidemic MRSA 15 (EMRSA-15).

A prospective year-long study of all causes of BSI in 10 haemodialysis centres in Canadian hospitals reported a mean rate of 16.6 BSI per 100 patient-years, ranging from 1 to 30.8. S. aureus caused 29% of BSI in that study.10 Most studies analysing S. aureus BSI in haemodialysis patients report numbers of infections rather than rates.3,5,12

The studies reporting rates of S. aureus BSI have used different denominators. One prospective study reported a rate of 1.2 S. aureus BSI per 100 patient-months over an 18-month period (which can be approximated to 14.4 per 100 patient-years).2 Another study reported a baseline rate of 0.1 infections per patient-year over two years (i.e. 10 infections per 100 patient-years).13 The overall rate of S. aureus BSI in the present study (17.9 per 100 patient-years) is higher compared with these two studies, but the annual rate declined gradually over the 12-year study period. Neither of the above studies reported the proportion of patients being dialysed via an intravascular catheter, so it was not possible to determine if the higher rate in the present study may have been partially due to the high number of catheter-dependent patients.

Eleven percent of episodes in this study were associated with infectious complications, which is less than reported in some previous reports. Two retrospective reviews of S. aureus BSI in haemodialysis patients described metastatic infection in 16–17% of patients.14,23 However, higher rates (20–31%) were reported in three prospective studies.3,5,12 The most common infectious complication recorded in the present study was infective endocarditis, which was diagnosed in 8% of episodes of S. aureus BSI. This falls within the range for the five cohort reviews of haemodialysis patients (1–17%).3,5,6,11,12 However, it was not possible to determine whether an echocardiograph was performed for all patients in the present study, nor whether those who did have an echocardiograph had a transthoracic (TTE) or transoesophageal (TOE) procedure.

TOE has been shown to be superior to TTE in the detection of valvular vegetations.14 Failure to perform TOE may have led to underestimation of the number of patients who developed infective endocarditis as a consequence of BSI. Recently published guidelines on the management of intravascular-catheter-related infection conclude that TTE findings are insufficient to exclude endocarditis, and that TOE should be performed in all patients with catheter-related S. aureus BSI, including patients on haemodialysis, as antimicrobial therapy for four to six weeks is required for endocarditis compared with two weeks for uncomplicated S. aureus BSI.15

Death occurred in 30 (9.8%) patients in the present study, and mortality in haemodialysis patients with S. aureus BSI has been reported to be 0–19%.3,5,6,11,12 Almost two-thirds of the deaths in the present study were patients with MRSA BSI, despite just 31% of episodes of infection being caused by MRSA. This finding is consistent with the conclusion of a meta-analysis of the impact of meticillin resistance in S. aureus BSI, which found that MRSA BSI is associated with a significantly higher risk of death than MSSA BSI.16 The most recently reported overall rate of MRSA BSI in haemodialysis patients from 52 English centres (April 2008–March 2009) is 0.88 per 100 haemodialysis patients (range 0–3.49).17 In 2009, the rate at the authors’ institution was 0.84 per 100 haemodialysis patients.

Intravascular catheters were implicated as the source of infection in 83% of patients in the present study. The use of intravascular catheters in haemodialysis patients confers a higher risk of infection and non-infectious complications compared with synthetic arteriovenous grafts and native arteriovenous fistulae, and is also associated with greater all-cause and infection-related mortality than the other types of vascular access.18 The most important strategy in preventing infections in haemodialysis patients is to use the lowest-risk vascular access and, in particular, to minimize the use of intravascular catheters. Clinical practice guidelines for vascular access from the National Kidney Foundation in the USA recommend that catheters should be avoided for haemodialysis, and should only be used when other options are not available.19 Despite this, recent years have seen an increase in catheter use for vascular access, with at least 23% of haemodialysis patients in Belgium, Sweden, the UK, Canada and the USA being haemodialysed using a catheter.20 Factors contributing to the greater use of catheters for vascular access include late presentation with end-stage kidney disease, lack of access to vascular surgeons experienced in fistula formation, the presence of comorbid conditions such as cardiac disease, failure of fistulae and the increasing age of dialysis-dependent patients.20 Even where every effort is made to increase the number of haemodialysis patients with native vascular access, it is inevitable that a proportion of patients will be dependent on vascular catheters for haemodialysis access. Hence, prevention of catheter-related infection is vital in reducing infection-related morbidity and mortality in haemodialysis patients. Adherence to hand hygiene and aseptic technique when inserting and manipulating intravascular catheters has been shown to reduce the risk of catheter-related BSI, particularly when these interventions are used together as part of a care bundle.21

The use of catheters impregnated with antimicrobials or antiseptics in adults is advised in units where the rate of catheter-related BSI is higher than the institutional goal, despite complications with basic infection prevention practices in high-risk patient groups.23 However, the data on the use of impregnated catheters in chronic haemodialysis patients are currently insufficient to make recommendations regarding their routine use in this patient population. One randomized trial in haemodialysis patients showed a reduction in catheter-related infection with minocycline–rifampicin-impregnated catheters compared with conventional catheters.23 However, no benefit was seen in another randomized study comparing silver-coated catheters with non-impregnated catheters.24

The topical application of antimicrobial ointments to reduce infections in dialysis patients has been studied. A systematic review of 10 trials found that the topical application of mupirocin ointment to the catheter exit site appears to be effective in reducing the risk of catheter-related bacteraemia. However, the absence of data on mupirocin resistance was noted.25 Canadian haemodialysis best practice guidelines recommend the use of topical antimicrobials, whereas the American and European guidelines do not advocate this practice specifically.19,26,27

Much attention has been paid to the potential benefits of using an antimicrobial catheter lock solution (both antibiotic and non-antibiotic) between haemodialysis sessions instead of heparin. Four recent meta-analyses, involving between seven and 19
studies, concluded that antimicrobial lock solutions are associated with a reduction in catheter-related infection compared with heparin, with no significant antimicrobial resistance or adverse effects reported. However, the authors of all four reviews had reservations about the required length of follow-up to detect resistance to the agents used, and felt that further studies were warranted.28–31 In addition, due to a lack of direct comparisons between different antimicrobial lock solutions, the most effective agent has not been identified to date. The use of antimicrobial lock solutions to prevent infection is not mentioned in either the American or Canadian best practice guidelines, which were last updated in 2006.19,26 The European guidelines, published in 2007, state that the pre-emptive use of citrate locking solutions has been warranted.28 Heparin, with no significant antimicrobial resistance or adverse effects, decreases the incidence of Staphylococcus aureus bacteremia: a meta-analysis. Clin Infect Dis 2003;36:53–59.

Over a 12-year period, intravascular-catheter-related S. aureus BSI were associated with significant morbidity and mortality in the studied cohort of haemodialysis patients. The use of intravascular access should be avoided in preference to arteriovenous grafts. Interventions such as topical antimicrobials and antimicrobial catheter locks may help to reduce catheter-related infections, but further studies in this group of patients are required.

**Conflict of interest statement**

HH has had recent research collaborations with Steris Corporation, 3M, Inov8 Science, Pfizer and Cepheid. He has also received lecture and other fees from 3M, Novartis and Astellas. SF has received speaker fees from Pfizer, Astra-Zeneca and Leo. ES has received lecture fees and other honoraria from Pfizer and MSD.

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**References**


