Vascular access in haemodialysis patients: a modifiable risk factor for bacteraemia and death

P.C. THOMSON, C.M. STIRLING, C.C. GEDDES¹, S.T. MORRIS and R.A. MACTIER

From the Renal Unit, Glasgow Royal Infirmary, and ¹Renal Unit, Western Infirmary, Glasgow, UK

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Summary

Background: Bacteraemia and the development of sepsis syndrome is second only to cardiovascular disease as the leading cause of death in patients on renal replacement therapy.

Aim: To determine the contributions of laboratory and clinical variables to the risk of bacteraemia and death in haemodialysis patients.

Design: Retrospective analysis.

Methods: We analysed all patients receiving haemodialysis in our renal unit at the beginning of January 2004 (n = 263), recording clinical and laboratory variables for each patient at study entry. Bacteraemia and mortality were recorded for the subsequent 18-month period. Multivariate analysis using a Cox proportional hazards model was used to test for independent associations between variables and outcomes.

Results: During the study period, 45 patients (17.1%) developed bacteraemia and 65 (24.7%) died.

Discussion: Use of synthetic vascular access catheters and heightened inflammatory state both have strong independent associations with subsequent bacteraemia and death. Bacteraemia surveillance strategies should be developed, with consideration of vascular access type and baseline inflammatory state as key components.

Introduction

Haemodialysis patients have high rates of morbidity and mortality, and infection is a significant contributor.¹² The immunsuppressive effects of advanced renal failure, co-morbid disease and malnourishment, combined with the repeated intravascular intervention required for haemodialysis, provide an environment conducive to the development of bacteraemia and sepsis syndrome.³ The effect of sepsis can be profound: septicaemia in a haemodialysis patient confers a relative risk for mortality of 2.8, with relative risks of subsequent myocardial infarction, cardiac failure and stroke of 4.1, 5.5, and 4.1, respectively. The development of sepsis syndrome is now classed as second only to cardiovascular disease as the leading cause of death in patients on renal replacement therapy (RRT).²

Vascular access is an established risk factor for sepsis in patients on RRT, and different types of haemodialysis vascular access are associated with differing rates of bacteraemia.⁴⁵ Patients dialysing through a central venous catheter are most at risk, with an associated bacteraemia incidence of 2–6 cases per 1000 catheter days.⁶ Within this group, those dialysing through a non-tunnelled central
venous catheter have comparatively higher rates of bacteraemia than those using tunnelled central venous catheters. The importance of catheter-related bacteraemia is increasingly recognized; recent advances include the use of antibiotic-lock techniques, but these practices are not yet widespread.

Although central venous catheters have a known association with bacteraemia, the independence and relative strength of this association, in comparison with other clinical and laboratory risk factors, is uncertain. Recent studies suggest that diabetes, anaemia and an activated systemic inflammatory response may be associated with bacteraemia, but again the strength and independence of these associations is unclear. This study aimed to determine which factors are independently associated with bacteraemia and death in haemodialysis patients, and how strongly, with particular respect to the different types of vascular access.

Methods

We retrospectively analysed all patients in our renal unit who had been on haemodialysis at the beginning of January 2004. Clinical, demographic and laboratory variables for each patient were retrieved from the unitary electronic patient record. Where multiple measurements of a single variable had been recorded, the first value after 1 January 2004 was used.

Clinical variables collected were age, gender, primary renal diagnosis, the presence or absence of diabetes, length of time on renal replacement therapy, vascular access flow rate on haemodialysis and urea reduction ratio (a standard measure of haemodialysis adequacy). The dialysis access in use at the time of study initiation was recorded as one of four categories: native arteriovenous fistula (AVF) (a surgically created anastamosis between artery and vein to create a robust port of access for haemodialysis); synthetic vascular access graft; tunnelled central venous catheter (TCVC); or non-tunnelled central venous catheter (NTCVC).

Laboratory variables collected at study entry were haemoglobin, serum C-reactive protein (CRP), serum ferritin, serum albumin, serum adjusted calcium and phosphate product, serum alkaline phosphatase, serum parathyroid hormone concentration and total serum cholesterol to HDL cholesterol ratio.

Outcomes

Outcomes were analysed over an 18-month follow-up, terminating on 1 July 2005. Bacteraemia events were determined by analysis of all positive in-patient and out-patient blood culture results from the renal unit reported by the bacteriology laboratory during the period of study in conjunction with analysis of the patient’s clinical notes and electronic patient record. Bacteraemia was deemed significant if positive blood cultures were associated with a raised systemic inflammatory response (e.g. pyrexia, raised CRP, raised white-cell count). Sub-clinical bacteraemia was not evaluated. This approach is in keeping with the consensus definition of clinically significant bacteraemia, and consistent with that used in routine clinical practice. Where patients had developed a significant bacteraemia, the date of the first positive blood culture result was entered as the event date, and the time to event subsequently calculated. The patient was then removed from further bacteraemia analysis. This study did not examine cases of recurrent bacteraemia and thus was a ‘time to first bacteraemia’ analysis. In all cases of confirmed bacteraemia, the causative organism was recorded and sensitivity profiles were examined. Patients who remained on haemodialysis throughout the observation period and did not develop bacteraemia had a census date of 1 July 2005 recorded.

All patients who died during follow-up had the date of death recorded as an end-point. All patients who were discharged, were transferred to another haemodialysis unit, or who switched renal replacement modality, were assigned a census date corresponding to the date of discharge from the haemodialysis cohort.

Our standard unitary protocol for catheter care was used throughout the observation period. Specifically, this demanded complete sterile barrier precautions during catheter insertion and when manipulating the catheter hub. Following catheter-hub manipulation, the skin surrounding the insertion site was soaked with chlorhexidine solution prior to a sterile dressing being applied.

All haemodialysis patients were on a standard regimen of three haemodialysis sessions per week, each of minimum 4 h per session with subsequent increases in session length up to 5 h in order to achieve a target urea-reduction ratio of 70%. This conformed with UK Renal Association Guidelines.

Analysis

Statistical analysis used SPSS, v. 12.0.1. Normality testing was done for all recorded continuous variables. Student’s t-testing and Mann-Whitney U testing were then used to assess differences between variables in the TCVC and NTCVC groups, using the AVF group as a standard for comparison.
Bacteraemia-free survival and mortality rates for each access type were subject to Kaplan-Meier survival analysis and log rank testing, with \( p < 0.05 \) regarded as statistically significant. The remaining variables were subject to univariate analysis with Students t-testing and Mann-Whitney U testing, as appropriate, to test for associations between characteristics at study entry and the development of bacteraemia and mortality. The relationship between bacteraemia and subsequent mortality was subject to Pearson \( \chi^2 \) testing. After application of the Bonferroni correction, a \( p \) value of \(<0.0025\) was regarded as statistically significant in these univariate analyses.

Multivariate analysis used a Cox proportional hazards model with a stepwise conditional method of analysis to test for: (i) an independent association with the development of bacteraemia; and (ii) an independent association with mortality. To avoid overfitting of the multivariate models, the convention of limiting the number of independent variables entered to approximately 10% of the number of outcome events was followed. In our analysis, independent variables for entry into the models were selected according to their \( p \) values on univariate testing. On multivariate analysis, all reported \( p \) values \(<0.05\) were regarded as significant.

### Results

Our search of the renal unit electronic patient record to identify all patients who underwent haemodialysis between 1 and 3 January 2004, identified 265 patients, of whom 136 (51.3%) were male. Median age was 66.7 years (range 16.3–88.9), and median duration of renal replacement therapy prior to 1 January 2004 was 1076 days (range 7–12 829). All patients had end-stage chronic kidney disease; none was on dialysis for acute renal failure. Diabetes mellitus was diagnosed in 59 (22.3%).

At study entry, 206 (77.7%) were dialysing via native AVF, 31 (11.7%) through a TCVC, 26 (9.8%) through a NTCVC and 2 (0.8%) were dialysing through a synthetic vascular graft. As only two patients were dialysing through a synthetic graft, they were not subjected to further analysis.

Table 1 compares the characteristics of the full cohort, while Table 2 compares the clinical characteristics for each main access type and Table 3 the laboratory variables for each main access type. Table 2 and 3 compare the characteristics for each catheter group with those of the AVF group.

As expected, patients dialysing through a TCVC \((n = 31)\) had a significantly lower haemodialysis blood flow rate than those dialysing through an AVF. Otherwise, those using a TCVC demonstrated trends towards lower serum albumin, lower serum cholesterol to HDL ratios and longer median duration on RRT, compared to those dialysing through an AVF. Overall, 26 were dependent on their TCVC as their only remaining option for vascular access, while five were using a TCVC prior to definitive vascular access being created.

Patients dialysing through a NTCVC \((n = 26)\) had significantly lower haemoglobin and lower haemodialysis blood flow rates than those dialysing through either a TCVC or AVF. Of the 26, 14 (53.7%) had been on dialysis for \(>3\) months and had temporary vascular access problems requiring NTCVC insertion, and 12 (46.2%) had started RRT for end-stage kidney disease within 3 months of study entry, which accounts for the significantly shorter duration on RRT in the NTCVC vs. the TCVC and AVF groups \((p = 0.001)\). Patients dialysing through a NTCVC had trends towards lower albumin and urea-reduction ratios, as well as higher CRP compared to the AVF group.

During the observation period, 15 patients underwent renal transplantation, five transferred to other renal units, two switched to continuous ambulatory peritoneal dialysis (CAPD) and one patient recovered renal function and was subsequently discharged.

### Bacteraemia

One or more episodes of bacteraemia occurred in 45/263 (17.1%) patients over the 18-month
period: 39 (86.7%) secondary to staphylococci (including 15 coagulase-negative staphylococci and 5 MRSA); 3 (6.7%) due to Gram-negative bacteria and 3 (6.7%) secondary to other bacterial sub-species (Figure 1). Analysing bacterial resistance profiles, 9/13 (69%) cases involving coagulase-negative staphylococci where antibiotic sensitivities were available, showed resistance to flucloxacillin.

Of the 45 patients who developed bacteraemia, 17 (37.8%) died during the 18-month observation period.

We used univariate analysis on the laboratory and clinical variables recorded at the start of the study period to test for an association with development of bacteraemia. Actuarial 18-month bacteraemia-free survival was significantly higher in patients dialysing via AVF at study entry than in those using TCVC or NTCVC (88.8% vs. 54.8% and 69.2%, respectively; \( p < 0.001 \)) (Figure 2) although no significant difference in bacteraemia event rates was found when directly comparing TCVCs with NTCVCs (\( p = 0.29 \)). Patients who developed bacteraemia had trends towards higher CRP levels and lower serum albumin levels at study entry than their bacteraemia-free counterparts but these did not reach the Bonferroni-corrected significance level (Table 4).

Under multivariate analysis, hazard ratios (HR) for the development of bacteraemia with TCVCs and NTCVCs were 5.43 (95%CI 2.67–11.0) (\( p < 0.001 \)) and 3.14 (95%CI 1.32–7.48) (\( p = 0.01 \)), respectively, compared to those with an AVF (Table 4). There was also an independent association between elevated CRP at study entry and the risk of developing bacteraemia over an 18-month period (HR 1.49, 95%CI 1.12–1.98, \( p = 0.006 \)).
Mortality

The 65/263 (24.7%) patients who died during follow-up period had significantly elevated serum CRP, lower serum albumin and greater age at study entry, compared with those who survived. Actuarial 18-month patient survival was better in those using AVF at study entry than in those using TCVC or NTCVC (79.1% vs. 64.5% and 57.7%, respectively; \( p < 0.019 \) (Figure 3). Trends of association with mortality by univariate analysis were seen with elevated serum alkaline phosphatase levels and lower levels of haemoglobin and the product of serum calcium and phosphate at study entry. A diagnosis of diabetes mellitus was associated with mortality (21/58 (36.2%) diabetics vs. 44/205 (21.5%) non-diabetics, \( p = 0.02 \)), as was a diagnosis of dialysis-related bacteraemia (17/45 (37.8%) bacteraemics vs. 48/218 (22.0%) non-bacteraemics, \( p = 0.026 \)).

Under multivariate analysis, death was independently associated with the use of TCVCs (HR 2.75; \( p = 0.012 \)) and NTCVCs (HR 3.39; \( p = 0.001 \)) compared with AVFs, low serum albumin (HR 0.92, 95%CI 0.87–0.97, \( p = 0.003 \)), elevated alkaline phosphatase (HR 1.002, 95%CI 1.000–1.003, \( p = 0.011 \)) and increasing age (HR 1.04, 95%CI 1.02–1.07, \( p < 0.001 \)) (Table 5).

Discussion

Bacteraemia is a common occurrence in patients on haemodialysis and contributes to patient morbidity and mortality. The cost of treating dialysis patients with bacteraemia is high, with average costs of up to $32 000 for each patient hospitalized with bacteraemia in the US.\(^{14,15}\) While the RRT population continues to grow, the clinical burden of bacteraemia is expected to rise correspondingly, with major implications for both clinical workload and logistical costs in renal service provision.

![Figure 1. Distribution of pathogenic organisms in cases of clinically significant bacteraemia.](image1)

![Figure 2. Kaplan-Meier plot of time to bacteraemia, by haemodialysis vascular access type. AVF, arteriovenous fistula; Tunnelled CVC, tunnelled central venous catheter; Non-tunnelled CVC, non-tunnelled central venous catheter.](image2)

Table 4

<table>
<thead>
<tr>
<th>Variable (at study entry)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacteraemia</td>
<td>No bacteraemia</td>
</tr>
<tr>
<td>Tunnelled catheter (( n = 31 ))</td>
<td>14 (45.2%)</td>
<td>17 (54.8%)</td>
</tr>
<tr>
<td>Non-tunnelled catheter (( n = 26 ))</td>
<td>8 (30.8%)</td>
<td>18 (69.2%)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>25.3 (2.9)*</td>
<td>16.0 (2.9)*</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>36.0 (4.9)</td>
<td>37.9 (4.7)</td>
</tr>
<tr>
<td>HD flow (ml/min)</td>
<td>283 (56)</td>
<td>303 (60)</td>
</tr>
</tbody>
</table>

Univariate data are number (%), means (SD) or *geometric means (SD). CRP, C-reactive protein; HD, haemodialysis. \(^a\)Pearson \( \chi^2 \) test, \(^b\)Student’s t-test.
These implications are increasingly recognized, and recent reports have suggested surveillance strategies to monitor bacteraemia, define at-risk groups and then target them to prevent and treat bacteraemia\textsuperscript{16,17}

Our patients appear fairly representative of a typical UK haemodialysis population, with rates of bacteraemia (17.1\%) and mortality (24.7\%) over an 18-month period similar to those published for other groups. We were able to demonstrate an independent association between a number of common variables and subsequent outcome, and to identify the typical pathogenic organisms accounting for clinically significant bacteraemia in our cohort.

Of particular note, the use of synthetic vascular access catheters had an especially strong association with risk of bacteraemia and death, an effect that was independent of age, sex, diabetes, anaemia, and the other clinical and laboratory variables that were studied. Although tunnelled catheters were used in patients who had been on dialysis longer, this was the result of patients whose peripheral vasculature had been exhausted of attempts to create an arteriovenous fistula or graft. None of the TCVC group had been exposed to bacteraemia in (at least) the 3 months prior to commencement of the study. Indeed, the demographics and co-morbidities of the tunnelled catheter group and arteriovenous fistula group were very similar and thus the independent risk associated with TCVC use would appear to be consistent. The non-tunnelled catheter group contained a higher proportion of patients who had started RRT for end-stage kidney disease within three months of study entry, and in this setting the co-morbidities that often arise during this period may contribute to the difference in clinical outcomes seen in this particular group.

We acknowledge the limitations incurred by the retrospective study design and subsequent extrapolation of a ‘snapshot’ of vascular access related to long-term outcome. In particular, our method of analysis was not sensitive to potential changes in vascular access type over the period of observation. One would, however, expect that this potential confounding would weaken any association between vascular access and clinical outcome, since risks presumably lower when patients convert from central venous catheter to arteriovenous fistulae. It would be interesting to quantify the changes in risk associated with change in vascular access type for an individual patient, and this is now the subject of on-going prospective study. We were also unable to record and assess any more detailed data on comorbidity, other than the data we included regarding age, duration on RRT and diabetes. While this will account for some of the main

![Figure 3. Kaplan-Meier survival plot of mortality, by haemodialysis vascular access type. AVF, arteriovenous fistula; Tunnelled CVC, tunnelled central venous catheter; Non-tunnelled CVC, non-tunnelled central venous catheter.](image)

**Table 5** Associations with mortality under univariate and multivariate analysis

<table>
<thead>
<tr>
<th>Variable (at study entry)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>Alive</td>
<td>$p$</td>
</tr>
<tr>
<td>Non-tunnelled catheter (n = 26)</td>
<td>11 (42%)</td>
<td>15 (58%)</td>
</tr>
<tr>
<td>Tunnelled catheter (n = 31)</td>
<td>11 (35%)</td>
<td>20 (65%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.6 (13.2)</td>
<td>62.0 (14.7)</td>
</tr>
<tr>
<td>ALP (U/l)</td>
<td>221 (107–976)*</td>
<td>192 (58–943)*</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>35.8 (4.8)</td>
<td>38.1 (4.6)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>27.2 (2.8)**</td>
<td>14.6 (2.8)**</td>
</tr>
</tbody>
</table>

ALP, alkaline phosphatase. Univariate data are number (%), means (SD), *medians (IQR), or **geometric means (SD). $^a$Pearson $\chi^2$ test, $^b$Student’s t-test, $^c$Mann-Whitney U test.
comorbidities in this population, a prospective study incorporating comorbidity-scored data would be of great benefit in bringing clarity to this perpetual confounder of studies of vascular access.

The use of central venous catheters has a clear association with facilitating the passage of cutaneous pathogens into the bloodstream. The major role of vascular access in bacteraemia in our patients is further implicated by our finding that 86.7% of bacteraemia was secondary to staphylococci. This finding is consistent with bacteraemia rates published in the literature, where the vast majority of clinically significant infection in dialysis patients are secondary to staphylococcal subspecies. In our patients, methicillin-resistant staphylococcus aureus (MRSA) accounted for 11.1% of all bacteraemia.

Not only is the identity of the causative organisms important, but the spectrum of antibiotic resistance is also of importance in determining first-line antibiotic treatment. Two-thirds of all coagulase-negative staphylococci isolated on blood cultures were flucloxacillin-resistant. This, in conjunction with an 11.1% prevalence of MRSA, suggests that current antibiotic protocols that use flucloxacillin as first-line therapy may require re-consideration with regard to local patterns of anti-microbial resistance.

There is a growing body of evidence that bacteraemia is linked to a pre-existing heightened inflammatory state, and our findings of an independent association between CRP at study entry and the inflammatory state, and our findings of an independent association between infection, inflammation and outcome remains to be clarified, although there does appear to be a close association between each of these states and mortality, possibly through a process of vascular endothelial dysfunction, subsequent atherogenesis and a resultant tendency towards cardiovascular events. The increased cardiovascular risk in the haemodialysis population is well known, but not all of it can be explained by traditional risk factors, and sepsis may be a predisposing factor in many cardiovascular deaths.

In summary, our data represent a typical chronic renal failure haemodialysis cohort at differing points in the vascular access cycle. We found an especially clear, strong and independent association between vascular access catheter use, the development of bacteraemia, and death. Obviously, limiting catheter use would considerably reduce the burden of disease, but there will always be a need for the use of central venous catheters in the provision of haemodialysis for patients with late presentation of end-stage renal failure and sudden failure of vascular access. There thus remains a pressing need to develop effective strategies that limit the propensity of central venous catheters to transmit and disseminate pathogenic bacteria. We should add bacteraemia prevention to cardiovascular disease prevention as standard components of the assessment and management of patients on haemodialysis.

References


