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Methicillin-resistant *staphylococcus aureus* [MRSA] catheter related bloodstream infections in renal dialysis: case report, present and future directions

Abstract

Central venous catheter related blood stream infections in dialysis patients most commonly occur due to Gram positive organisms. Methicillin resistant *Staphylococcus aureus* (MRSA) bloodstream infections can be difficult to treat due to antimicrobial resistance, however newer agents, such as the lipopeptides have increased the therapeutic options. We present a case of a haemodialysis patient dialysing via a central venous catheter, who suffered from four MRSA bacteraemias between 2009 and 2011. These isolates were typed, and found to be non-identical. Whilst the source of the first bacteraemia was a perinephric abscess, no deep focus for subsequent episodes was found. After initial therapy with vancomycin, the patient received progressively longer courses of daptomycin whilst attempts were made at arterio-venous fistula formation. Therapeutic drug monitoring ensured adequate trough levels, in keeping with published literature. For complex dialysis patients with recurrent MRSA bacteremia and limited vascular access, we present the role of long term antimicrobial therapy and its monitoring. We also discuss investigation of infection sources in the domestic environment in such cases.

Keywords: antibiotics, daptomycin, resistance, *staphylococcus aureus*, vancomycin, MRSA, haemodialysis

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Abbreviations: AVGs, arterio-venous grafts; ESRD, end stage renal disease; AVFs, arterio-venous fistulas; CRB, catheter-related bacteraemias; SAB, *staphylococcus aureus* bacteraemia; MRSA, methicillin-resistant *staphylococcus aureus*; MSSA, methicillin-sensitive *staphylococcus aureus*; CKD, chronic kidney disease

Introduction

Central venous catheters in nephrology were originally introduced to provide temporary vascular access for short-term dialysis and were never meant to play a part in the dialysis patients' long term care. Currently, tunneled, cuffed, double-lumen silastic catheters are used for permanent vascular access in many patients, particularly those with limited alternative options for vascular access and those who are unfit for major vascular surgery hence becoming an acceptable form of permanent vascular access.[1–3] Fistulas require a much longer maturation time than grafts driving the duration of catheter-dependence for vascular access substantially in haemodialysis patients. This transition has, also in part, been driven by a change in preference for arterio-venous fistulas (AVFs) rather than arterio-venous grafts (AVGs). In addition, catheters are often used for the initial dialysis session (in 80%of incident haemodialysis patients in some cases) often causing the patient to refuse fistula formation in the future.[2]

Infection accounts for 12-36% of the mortality in patients with end stage renal disease (ESRD) and is second only to cardiovascular disease as a cause of death in this group.[4–9] Long term catheters although a panacea for many ESRD patients, are associated with a number of complications, including catheter-related bacteraemias (CRB). The clinical impact of CRB in haemodialysis patients has, been quantified repeatedly as in the HEMO study, for example, where 7.6 percent of all patients had catheters used for vascular access, yet comprised 32 percent of all study patients hospitalized with access-related infection.[10–12]

The relative risk of tunneled dialysis catheters causing bacteremia in dialysis patients has been estimated to be approximately 10 times higher than the risk of bacteremia in patients with AVFs. In addition, catheter-dependent hemodialysis patients have a two- to threefold higher risk of infection-related hospitalization and infection-related death, as compared to patients undergoing dialysis via a fistula or graft.[13–16]

The frequency of catheter-related bacteremia in several large case series has ranged between 2.5 and 5.5 episodes per 1000 catheter-days, which corresponds to an incidence of 0.9 to 2 episodes of bacteremia per catheter-year. In one prospective study involving 108 tunneled catheter-dependent hemodialysis patients, the cumulative likelihood of catheter-related bacteremia was 35 percent within three months and 48 percent within six months of catheter insertion. Dialysis catheter related bacteraemia is also associated with metastatic complications in 5-10% of patients. This risk varies depending on the infecting pathogen, with *Staphylococcus aureus* causing up to 40% of all metastatic complications.[14,15]

Gram-positive organisms are responsible for most dialysis catheter-related infections. Coagulase-negative staphylococci and *Staphylococcus aureus* together account for 40 to 80 percent of cases.[17] Patients who undergo haemodialysis are in particular, vulnerable to staphylococcal infections with vascular access being the most common source of infection.

Staphylococcus aureus bacteraemia (SAB) occurrence in haemodialysis patients is strongly associated with vascular access site infections up to 86% of these infections originate from the site of vascular access (56% from catheters and 30% from grafts). Other risk

factors associated with this infection are the presence of diabetes and being on warfarin.[18]

In one study, 21 percent of 11,572 admissions of haemodialysis patients for SAB had one or more complications, the average length of first hospitalization was 13days, and 12 percent of these 11,572 patients were readmitted within 12weeks for treatment of a relapsed infection. In another report, the unadjusted 12week mortality for dialysis catheter-related SAB was 23 percent among patients with SAB due to a dialysis catheter.[19]

In a retrospective cohort study of 22,130 hospitalizations of dialysis patients with septicemia, the overall death rate from *S. aureus* bacteremia after 12weeks of follow-up was 34 percent; the death rate was 20 percent higher than the death rate from bacteremia due to all other organisms.[14]

The total SAB mortality in the dialysis population is 8% and in haemodialysis patients is 20% higher than with other pathogens. Mortality tends to be lower when the infection originates from vascular access and patients are treated for more than 28days. Recurrence of SAB is high- from 14.5 to 44% and may be associated with metastatic complications of meningitis, endocarditis, osteomyelitis and abscess formation.[20]

Patients with long term catheters are also at higher risk of invasive catheter methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Between 12 and 65% of all dialysis patients are colonized with MRSA.[21–25] In a review of 5287 cases of invasive MRSA infection, 15% occurred in dialysis patients. In the UK, 4.2% of all MRSA bacteraemias occur in dialysis patients' of which over three-quarters are dialysing via catheters. The incidence of invasive MRSA infection is 100 times higher in the dialysis population than in the general population (45 versus 0.4 per 1000 patients).[21] Infection with MRSA in dialysis patients is more hazardous than that with methicillin-sensitive *Staphylococcus aureus* (MSSA). Although the data is conflicting; most studies indicate that infection with MRSA has a worse outcome.[23]

A single episode of SAB in a haemodialysis patient can cost up to $20,000 with additional costs if the course is complicated or associated with a catheter. The average cost of a MSSA SAB is less than half of that due to MRSA mainly as result of longer hospitalization time and complications.[20–23]The net result for many dialysis patients is that of a poor outcome if they are unfortunate enough to develop a SAB during the course of their treatment from increased morbidity and mortality.

Case presentation

We report the case of a 61year old Caucasian female who was diagnosed with chronic kidney disease (CKD) stage 4 by her primary practitioner and referred to the urologists in 2004 for investigation of recurrent urinary tract infections. Urological investigations revealed bilateral hydronephrosis from bladder outlet obstruction secondary to a urethral stricture. Further tests showed the presence of both a rectocele and a cystocoele. She underwent urethral dilatation shortly thereafter with stabilization in her renal function but continued to suffer from recurrent urinary infections. She was referred to the renal physicians 12months later with progression to CKD stage 5. An ultrasound of her kidneys at this time revealed gross right hydronephrosis with marked generalized cortical atrophy and a marked hydronephrosis of the left kidney with minor cortical atrophy. In view of the worsening in renal function, she required a period of temporary haemodialysis for 7days and underwent insertion of bilateral nephrostomy resulting in some improvement in her renal function. The nephrostomies were removed 6weeks later and bilateral ureteric stents inserted. Unfortunately her renal function declined again several months' later necessitating further temporary haemodialysis for 15days before opted for peritoneal dialysis and a continuous ambulatory peritoneal dialysis (CAPD) catheter was inserted; she remained on CAPD for 8weeks when she developed a paraumbilical hernia which forced a change to hospital haemodialysis via a cuffed tunneled catheter. Despite a repair to the umbilical hernia she was unable to resume peritoneal dialysis because of adhesions causing tube failure when a further PD catheter was inserted. The patient was deemed unsuitable for a renal transplant because of obesity (body mass index 42).

She had 3 attempts at AVF formation which resulted in immature fistulas unsuitable for dialysis; she therefore remained resigned to dialyse via a tunneled catheter. To date she has had 4 episodes of MRSA bacteraemia within a period of 24months (Figure 1). The first episode was attributable to MRSA urine infection and the later 3 probably resulted from infected tunneled catheters. The patient is allergic to chlorhexidine so decolonisation treatment was initially delayed, whilst an appropriate alternative was found. After the 3rd episode of bacteraemia she was commenced on Octenisan (an alternative antimicrobial body wash) and silver impregnated dressings were used on line exit site. Antibiotic therapy was switched to daptomycin and therapeutic drug monitoring was undertaken to assess efficacy with serum creatine kinase measurements to detect toxicity (Figure 2). Published studies have indicated that whilst the rises in creatine kinase may be idiosyncratic, levels above 24.3mg/L are associated with increasing toxicity.[24] Therapeutic drug monitoring is not currently recommended by the manufacturers.

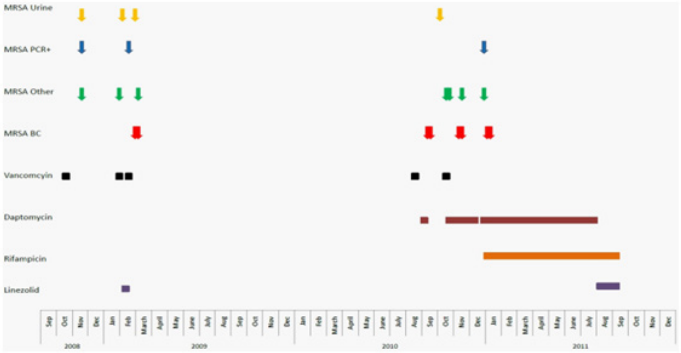

Figure 1 Timeline of bacteraemia and infection.

In our laboratory, all isolates of *S. aureus* recovered from blood cultures undergo quantitative susceptibility tested by Macro E-test in line with national guidelines. Quantitative susceptibility testing was performed by inoculating Iso-Sensitest agar (Oxoid) with a 0.5 McFarland suspension and applying an antibiotic-impregnated Etest strip (AB Biodisk). Those isolates with a vancomycin minimum inhibitory concentration (MIC) of >1.5mg/L were sent for population analyses (Table 1).

During initial investigation of the multiple MRSA bacteraemias, two abdominal computerised tomography scans, and two transthoracic echocardiograms were reported as negative. A transesophageal echocardiogram was not tolerated by our patient. The focus of infection was thought to be the tunnelled line. The source of the MRSA was not clear, raising the possibility the patients' cat, as a possible source of

MRSA. After discussion with local and national veterinary experts it was felt that the cat could not be screened or decolonised even if she was the source of infection. Discussion took place regarding the possibility of removing the cat from the domestic environment but this was not favoured by the patient.

After successfully completing two courses of daptomycin for four weeks and eight weeks respectively, one course of daptomycin and rifampicin for seven months and finally a six week course of linezolid and rifampicin the patient has suffered no further MRSA bacteraemias since early 2011. We have taken the approach that each episode of Gram positive sepsis (whether line related or not) is treated empirically with daptomycin unless there is a defined pneumonic component. We have not been able to demonstrate any daptomycin resistance in any *S. aureus* isolates from this patient.

Table 1 Summary characteristics of isolates recovered from blood culture

Date	Isolate	Vancomycin MIC (mg/L)	Teicoplanin MIC (mg/L)	Daptomycin (mg/L)	Strain	*spa* type	Population analysis profile
13/02/09	MRSA	1.5	0.5	0.125	EMRSA-15	t032	*h*VISA detected
4/10/2010	MRSA	1	0.25	0.5	EMRSA-15	None	*h*VISA not detected
1/11/2010	MRSA	1	0.38	0.125	Not tested	Not tested	*h*VISA not detected
23/1/11	MRSA	1	0.12	0.19	Not tested	Not tested	*h*VISA not detected

MRSA, methicillin resistant *staphylococcus aureus*; MIC, minimum inhibitory concentration

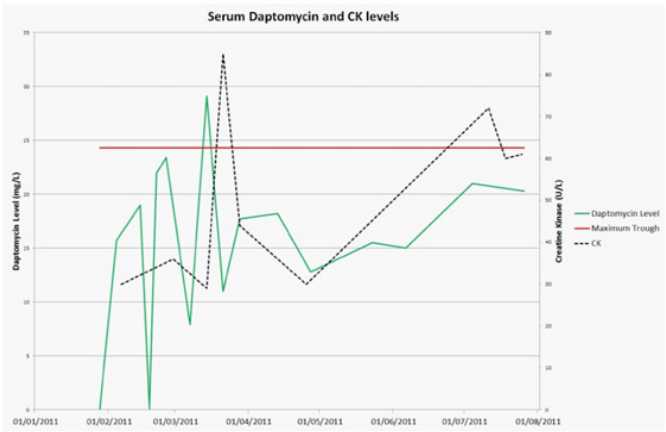

Figure 2 Serum daptomycin and CK levels.

Discussion

The forever changing microbial world continues to present new challenges within the hospital setting and organisms such as MRSA present the nursing and medical profession with a daunting task of protecting patients.[26] The nature of patients in the hospital setting automatically puts them at risk, where invasive devices are inserted which break the body's natural defence system; the skin.[27]

In conjunction with the Health Act 2006,[28] the Saving Lives: reducing infection, delivering clean safe care document[29] states that the transmission risk of MRSA is a major problem in the hospital setting; potential carriers need to be identified and treated to reduce the risk of bacteraemias, as well as managing environmental decontamination.[30] Once treatment is commenced the risk of developing a bacteraemia or transmission to another patients is reduced substantially.

In Safer practice in renal medicine[31] a key objective was to ensure trusts have a clear policy of infection surveillance and MRSA screening and decolonisation in place. In line with this, a guideline was introduced for the screening of Chronic Haemodialysis patients at the Heart of England Foundation Trust (HEFT) which adhered to the national initiatives of reducing MRSA and *S. aureus* infections and thus decreasing mortality and morbidity.

Patients colonised with *S. aureus* have an increased risk of infection and other complications such as bacteraemias and routine decolonisation is an efficient strategy to reduce bacteraemias. Decolonisation of patients may fail or patients can be re-colonised with new strains hence repeated screening is required to detect recurrence of carriage.[32]

In our hospital all chronic haemodialysis patients, irrespective of access type, get screened for both MRSA and *S. aureus* from nose and access site; whether fistula, graft or dialysis line. All positive results' patients get commenced on decolonisation treatment which includes daily antiseptic body wash, Chlorhexidine Gluconate 4% Solution for 5days and Mupirocin 2% nasal ointment thrice daily for 5days, after which patients are re-screened and course repeated if required, up to a maximum of two courses per quarter. If the patient is thought to be sensitive to the chlorhexidine gluconate 4% solution then Octenisan antimicrobial wash lotion is used.

All dialysis patients are also screened for *S. aureus* prior to any dialysis catheter insertion and decolonisation treatment is commenced until the results are available.

The Saving lives document[29] integrates the latest evidence-based guidelines and provides a way for health care workers to measure compliance of key procedures to improve upon infection rates and ensure every patient receives the right care every time. The Renal dialysis catheter care bundle, high Impact Intervention (HII) no.3; is based on EPIC2 guidelines, expert advice and other national infection prevention and control guidance. 'The risk of infection is reduced when all elements within the clinical process are performed every time and for every patient'.[33] The Trust's guideline for the care of dialysis lines was based on this document and the dialysis unit's use the HII N0. 3 care bundle monthly to ensure all elements of care are performed. By auditing practice we can standardise care, identify and remedy poor practice and ultimately improve patient care which is evidence based.[34] For skin preparation Alcoholic 2% Chlorhexidine Gluconate is the preferred solution[35] as it provides rapid antimicrobial

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action and excellent residual activity. If the patient is not sensitive to alcoholic 2% chlorhexidine it is used for the cleaning of the dialysis line exit site, fistula and graft prior to needle insertion. The dialysis line has a chlorhexidine impregnated dressing applied which is then secured with Tegaderm; a sterile semi-permeable transparent dressing and left on for 1week.

If the patient is sensitive to chlorhexidine then patch testing is to be done and a 'deviation from practice form' placed in the patient's notes and povidine-iodine 10% antiseptic solution is used as a cleaning solution. For our patients who are sensitive to the alcoholic 2% chlorhexidine but tolerate chlorhexidine gluconate 4% wash their limb in chlorhexidine Gluconate 4% then a chlorhexidine 0.05% aqueous solution to clean the skin prior to the insertion of needles.

The gradual reduction of susceptibility of staphylococci to vancomycin[36] has led to an increasing reliance on new agents. We have recently adopted a clinical breakpoint of 1mg/L for vancomycin, which has allowed fine tuning of patient's antimicrobial therapy based on subtle quantitative changes in the organism's in vitro susceptibility. When this is coupled with the possibility of an occult non-removable site and confirmation of a heterogeneous vancomycin intermediate *Staphylococcus aureus* (hVISA) by population analysis, decision about the choice of agent and role of combination therapies can be made. This led to a therapeutic decision to use long term daptomycin in combination with rifampicin[37] in this patient.

The pharmacokinetics of daptomycin is not well understood in obesity and in those on renal replacement therapy. We have demonstrated a lack of accumulation, whilst maintaining a trough level of >15mg/L with the regime of high dosing (up to 8mg/kg thrice weekly). Based upon Monte-Carlo simulations,[38] a 50% dose increase may be required to reach therapeutic area under the curve (AUC48-72) whilst minimising trough concentrations[24] of >24.3mg. Many patients who undergo outpatient haemodialysis attend three sessions per week, with the largest gap over the weekend. It is in this time period that drug levels are at greatest risk of becoming sub therapeutic. In this patient, although we ensured that the daptomycin was administered in the last 40 minutes of dialysis, a steady state required several weeks of therapy.

Exit site infections are diagnosed clinically with signs of inflammation distal to the cuff, which include localized erythema, fluctuance, tenderness, and purulent discharge from the exit site. Tunnel infections present with signs deep to the cuff suggestive of inflammation (including track erythema, fluctuance, tenderness, and purulent discharge from the exit site on squeezing of cuff). Both exit site and tunnel infections are usually diagnosed before culture results are reported from blood or from subcutaneous exudates Lumen infections can be suspected clinically, but can only be confirmed by positive blood cultures. Lumen infections may co-exist with exit site or tunnel infections.

Management of the infection will therefore depend on the site of the infection. Exit site infection without cuff involvement and a clinically stable patient can be treated with empirical oral antibiotics without removal of the line. If the tunnel or cuff is infected, intravenous antibiotics coupled with line removal within 24 hours is desirable. If feasible, placement of new permanent HD access at a new site should be delayed until the patient has been treated with antibiotics for at least 48 hours. For luminal infections, the line must always be removed and intravenous antibiotics administered for a minimum period of 14days.[39]

Whilst the most common staphylococcal commensal amongst dogs and cats is Staphylococcus pseudointermedius, *S. aureus* can be infrequently found.[40] Various studies have described suspected interspecies transmission of MRSA between human patients, their family members, and pets living in the same household.[41] In a recent study,[42] MRSA isolated from pets living in households with MRSA-infected children did not clearly define the index source in the household. In such scenarios there is no strong evidence that domestic animal should be screened for MRSA, nor is there evidence that they should be decolonised. Mitigation of risk may simply involve following sensible infection control practices in the home, and, minimising contact with such animals during periods of immunosuppression or removing the animal if possible from the patients environment.

This case clearly demonstrates the need for a multidisciplinary approach in the management of patients with recurrent MRSA bacteraemias in dialysis patients. A multitude of factors, including patient lifestyle and domestic circumstances should be considered when deciding the choice of therapy The choice of agent and duration of therapy will depend on several factors including the type of isolate, environmental sources, identification of a focus and tolerability. We recommend that all isolates from recurrent cases of MRSA septicaemia from dialysis patients are sent for typing, as well as population analysis for isolates with a vancomycin MIC >1mg/L. For patients on long term daptomycin, therapeutic drug monitoring is necessary to assess accumulation, but more importantly to ensure adequate serum levels. This can be done safely, effectively and cheaply with serum creatinine kinase levels.

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Conflict of interest

The author declares no conflict of interest.

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