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ORIGINAL ARTICLE

Gram-negative bacteraemia in haemodialysis

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ABSTRACT

Background. Patients on renal replacement therapy experience higher rates of morbidity and mortality, infection being the second commonest cause of death. In our haemodialysis population, we identify the pathogens, sensitivity patterns, sources of infection and outcomes of Gram-negative bacteraemia.

Methods. Data from the NHS Greater Glasgow & Clyde and NHS Forth Valley haemodialysis population were collected July 2011 to April 2014 through an interrogation of the renal unit electronic patient record, and confirmed by an independent search of the Microbiology database.

Results. Over 544 377 haemodialysis days, 84 patients experienced 95 Gram-negative bacteraemia events, a rate of 0.175 events per 1000 haemodialysis days, which varied with dialysis modality: non-tunnelled central venous catheters 4.77, arteriovenous grafts 0.24, tunnelled central venous catheters 0.21, and arteriovenous fistulae 0.11 per 1000 haemodialysis days. The commonest sources of bacteraemia were central venous catheters (CVCs) (16.8%, $n = 16$), infected ulcers (14.7%, $n = 14$), urinary (10.5%, $n = 10$), biliary (9.5%, $n = 9$) and intra-abdominal (9.5%, $n = 9$).

The principal organisms were *Escherichia coli* (49.5%, $n = 47$), *Enterobacter* spp. (13.1%, $n = 13$), *Klebsiella* spp. (11.1%, $n = 11$), *Proteus mirabilis* (6.1%, $n = 6$) and *Pseudomonas aeruginosa* (5.1%, $n = 5$). Of the Enterobacteriaceae ($n = 84$), 88% were sensitive to gentamicin, 81% to ciprofloxacin, 91% to piperacillin-tazobactam and 100% were sensitive to meropenem.

Three-month case mortality was 25.3% ($n = 24$). Ten patients (11.9%) had more than one Gram-negative bacteraemia; of these, nine patients (90.0%) were the same causative organism, predominantly *E. coli*.

Conclusions. CVCs and diabetic foot ulcers remain significant risk factors for Gram-negative bacteraemia, highlighting the importance of vascular access planning. Despite good levels of antibiotic sensitivity, the early mortality following Gram-negative bacteraemia remains high, supporting aggressive treatment of such pathogens.

Keywords: bacteraemia, Gram-negative, haemodialysis, sensitivity, vascular access

INTRODUCTION

It is well established that the rates of morbidity and mortality are significantly higher for patients on renal replacement therapy (RRT) in comparison to the general population; for example, in the UK the mortality rate for RRT patients aged

35–39 remains 16.6 times that of an age-matched population [1]. Approximately one-fifth of deaths on RRT are due to infection, the second-highest cause of mortality following cardiovascular disease [1]. Targeted reduction of infection-associated morbidity and mortality may be achievable through surveillance, prevention measures and early intervention; indeed, it has been estimated that 20% of all nosocomial blood stream infections (BSIs) are preventable [2].

Historically, nosocomial BSIs were predominantly Gram-negative; though since the 1980s Gram-positive aerobes, in particular Staphylococci, were preponderate in the RRT population, driven by the presence of vascular access devices [3, 4]. More recently the proportion of BSIs caused by Gram-negative pathogens is once again increasing and now accounts for up to 25% of primary healthcare-associated as well as central venous catheter (CVC)-related BSIs [5–7]. While the rate of staphylococcal bacteraemia in the haemodialysis population is well described and closely monitored [3, 8, 9], less is known about the burden of Gram-negative bacteraemia. In this study we characterize Gram-negative bacteraemia in a contemporary period prevalent haemodialysis population, detailing the identity of pathogens, sensitivity patterns, sources of infection and clinical outcome.

MATERIALS AND METHODS

Setting

Observational data were collected on Gram-negative bacteraemia events among inpatients from the renal wards receiving haemodialysis (HD), and outpatients of the seven HD units of NHS Greater Glasgow & Clyde and NHS Forth Valley, over the period July 2011 to April 2014. During the period of data collection, standard CVC locking solution was changed from Heparin 5000 IU to Taurolidine-citrate-heparin (TauroHep500) on the basis of evidence of efficacy in reducing bacteraemia rates [10, 11]. This change occurred on 1 July 2012 for tunnelled central venous catheters (TCVCs) and 1 July 2014 for non-tunnelled central venous catheters (NTCVCs). Aside from this, standard NHS Scotland catheter care and dialysis protocols were consistent throughout the period of observation and across dialysis units; specifically, intention to achieve vascular access via an arteriovenous fistula (AVF) or graft (AVG) for both incident and prevalent patients; maintenance of standard sterile technique during catheter insertion, and on each subsequent occasion when manipulating the catheter hubs thereafter, including hand hygiene and sterile gloves, chlorhexidine/
alcohol cleaning of the insertion site (and exit site during dressing changes), and antiseptic (70% isopropyl alcohol) cleaning of the hub before use. Chlorhexidine-impregnated exit-site patches are not part of this care bundle, but TauroHep500 antimicrobial catheter lock solution is used.

Data collection

Data were obtained through a structured query language interrogation of the Renal Unit electronic patient record database. This electronic record includes all patients attending both inpatient and outpatient renal services, and in real-time imports all West of Scotland microbiology results from any source. Cases were confirmed by an independent search of the Microbiology database, and vascular access and source of infection were cross-checked manually. Consecutive blood culture results >14 days apart were regarded as separate events. Mortality data were collected over the study period and for the subsequent 3 months (until 31 June 2014), maximum follow-up was therefore 36 months.

Microbiology

Blood cultures were incubated and monitored using the BacTAlert (Biomerieux) and those which flagged positive were processed according to the Public Health England Standards for Microbiology Investigations (SMI) [12]. Sensitivity testing was carried out using the VITEK 2 system (Biomerieux); European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used. Extended-spectrum beta-lactamase (ESBL) testing was carried out using combination discs according to the SMI [13]. Cases were defined by positive growth on blood culture of a pathogenic organism; clinical findings were not required when defining a case, as the sensitivity and specificity of clinical assessment in diagnosing Gram-negative BSI is poor. Four cases of mixed Gram-negative infections were encountered. Bacteraemia cases were determined to be CVC-related when the same organism was cultured from line tip after CVC removal (firm diagnosis), or when other primary sources of infection were absent and the patient was treated clinically as such (presumed CVC source).

Standard antibiotic policy for suspected BSI in NHS Greater Glasgow and Clyde and Forth Valley is tailored to the likely source of infection according to clinical findings, and is based on local sensitivity patterns and antimicrobial stewardship policy. In addition, the Renal Unit suggests that any bacteraemia in HD patients felt likely to relate to CVCs be treated empirically with vancomycin and gentamicin until further characterized, unless otherwise decided upon following discussion with the microbiology team.

Analysis

Event rates were expressed as events per 1000 HD-exposed days for each vascular access type. Comparisons between groups were made using Chi square testing. Cause of death is not reported but crude case mortality rates were calculated from the date of death (time censored at 31 June 2014). Informed consent was not required given the observational nature of the study.

RESULTS

Demographics

Over the period of observation, 1242 patients underwent haemodialysis for established renal failure, accruing 544 377 observed haemodialysis days. During this time, 84 patients experienced 95 Gram-negative bacteraemia events, a rate of 0.175 events per 1000 HD days. Baseline demographics are demonstrated in Table 1.

Table 1. Demographics and cross-sectional haemodialysis access prevalence of the NHS Greater Glasgow and Clyde and Forth Valley haemodialysis population, in comparison to the Gram-negative bacteraemia cases (derived from the same population)

	HD population $n = 1242$	Gram-negative BSI group $n = 84$ patients, $n = 95$ BSIs
Median age at starting RRT, years (IQR)	60.8 (45.9–72.1)	61.2 (48.9–74.2)
Male	738 (59.4%)	53 (63.1%)
Female	504 (40.6%)	31 (36.9%)
Primary renal disease:		
Primary glomerulonephritis	232 (18.7%)	16 (19.0%)
Interstitial nephropathies	175 (14.1%)	16 (19.0%)
Multisystem diseases	197 (15.9%)	19 (22.6%)
Diabetic nephropathy	211 (17.0%)	21 (25.0%)
Unknown and other	427 (34.4%)	12 (14.3%)
HD access, cross-sectional prevalence on the 1st July:		
% AVF 2011, 2012, 2013 (average)	68.3, 65.4, 61.0 (64.8)	61.3, 57.1, 49.4 (56.1)
% AVG 2011, 2012, 2013 (average)	0.9, 1.8, 1.2 (1.3)	0.0, 5.4, 3.6 (2.9)
% TCVC 2011, 2012, 2013 (average)	28.0, 31.1, 35.0 (31.5)	37.1, 30.4, 43.6 (37.0)
% NTCVC 2011, 2012, 2013 (average)	2.8, 1.6, 2.8 (2.4)	1.6, 7.1, 3.6 (4.0)

The proportions of patients on each different HD access type fluctuated during the observation period with cross-sectional access prevalence recorded at the beginning of year of data collection i.e. 1 July 2011, 2012 and 2013 (full data in Table 1). Based on averages of these cross-sectional data, dominant vascular access of prevalent haemodialysis patients over the observation period was 64.8% arteriovenous fistula (AVF), 1.3% arteriovenous graft (AVG), 2.4% dialysed through a NTCVC, and 31.5% via TCVC. In contrast, access modality at the time of bacteraemia was AVF for 39 of the Gram-negative cases (41.1%), 2 patients (2.1%) dialysed via AVG, 16 (16.8%) via a NTCVC and 38 (40.0%) using a TCVC.

Infection rates

The rate of Gram-negative bacteraemia varied with dialysis modality; the NTCVC rate was 4.77/1000 HD days, AVG 0.24/1000 HD days, TCVC 0.21/1000 HD days, and AVF was 0.11/1000 HD days.

It was hypothesized that the rate of CVC bacteraemia may be influenced by the change from heparin to taurolidine-citrate-heparin catheter lock solution; analysing the TCVC data for the 12 months pre- and post-introduction of taurolidine-citrate-heparin, the rate of Gram-negative BSI fell from 0.28 to 0.19/1000 HD days (31.3% reduction). This equates to an incident rate ratio of 0.59 (95% CI 0.31–1.13, P = 0.12) following the introduction of taurolidine-citrate-heparin.

Causative pathogens

Of 99 organisms cultured, the principal isolates were *Escherichia coli* (47.5%, $n = 47$), *Enterobacter* spp. (13.1%, $n = 13$), *Klebsiella* spp. (11.1%, $n = 11$), *Proteus mirabilis* (6.1%, $n = 6$) and *Pseudomonas aeruginosa* (5.1%, $n = 5$). See Table 2 for a breakdown of organisms. Sensitivities were available for 84 of the 85 isolates of Enterobacteriaceae, with 88% sensitive to gentamicin, and 81% sensitive to ciprofloxacin (see Table 3 for full sensitivity patterns). Six isolates were carriers of ESBL enzymes. All *P. aeruginosa* isolates were sensitive to ciprofloxacin, piperacillin-tazobactam, ceftazidime, gentamicin and meropenem. Ten patients (11.9%) had more than one Gram-negative bacteraemia; of these, nine (90.0%) were the same causative organism, predominantly *E. coli* ($n = 6$, 60%).

Table 2. Gram-negative organisms isolated on culture (99 organisms from 95 BSI events)

Organism	Number of isolates	%
Acinetobacter sp.	1	1.0
Aeromonas sp.	1	1.0
Brevundimonas spp.	1	1.0
Chryseobacterium indologenes	1	1.0
Citrobacter spp.	2	2.0
Enterobacter spp.	13	13.1
Escherichia coli	47	47.5
Klebsiella spp.	11	11.1
Moraxella spp.	2	2.0
Morganella morganii	2	2.0
Neisseria cinerea	1	1.0
Pantoea spp.	1	1.0
Proteus mirabilis	6	6.1
Providencia stuartii	1	1.0
Pseudomonas aeruginosa	5	5.1
Serratia marcescens	2	2.0
Sphingomonas spp.	1	1.0
Stenotrophomonas maltophilia	1	1.0

Table 3. Antibiotic sensitivities for 84 of the 85 isolates of Enterobacteriaceae bacteraemia in haemodialysis patients (not all antibiotics tested on all isolates, and intermediate sensitivities not reported)

Antibiotic	Sensitive ($n = 84$)	% of those tested sensitive	Resistant ($n = 84$)	% of those tested resistant
Amikacin	77	93.9	0	0.0
Amoxicillin	14	17.9	64	82.1
Aztreonam	71	86.6	9	11.0
Ciprofloxacin	67	80.7	13	15.7
Co-amoxiclav	47	56.0	33	39.3
Gentamicin	74	88.1	9	10.7
Meropenem	83	100.0	0	0.0
Piperacillin-tazobactam	74	91.4	6	7.4

Table 4. Source of infection by access modality. Regarding death, follow-up is time censored at 31 June 2014

Source of BSI	AVF/G	NTCVC	TCVC	Total
CVC (firm diagnosis)	0 (0%)	2 (12.5%)	14 (35.9%)	16 (16.8%)
Unknown	8 (20.0%)	2 (12.5%)	6 (15.4%)	16 (16.8%)
Foot ulcer/soft tissue	9 (22.5%)	0 (0.0%)	5 (12.8%)	14 (14.7%)
Urinary	6 (15.0%)	3 (18.8%)	1 (2.6%)	10 (10.5%)
Biliary	7 (17.5%)	1 (6.25%)	1 (2.6%)	9 (9.5%)
Intra-abdominal	2 (5.0%)	4 (25%)	3 (7.7%)	9 (9.5%)
AVF/AVG	4 (10.0%)	0 (0.0%)	2 (5.1%)	6 (6.3%)
CVC (presumed)	1 (2.5%)	0 (0.0%)	5 (12.8%)	6 (6.3%)
Respiratory	0 (0%)	4 (25%)	1 (2.6%)	5 (5.3%)
Infected renal cyst	2 (5%)	0 (0.0%)	1 (2.6%)	3 (3.2%)
Calciphylaxis related	1 (2.5%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total number of cases	40 (42.1%)	16 (16.8%)	39 (41.1%)	95 (100%)
Death within 3 months (% of BSI events)	13 (31.7%)	6 (37.5%)	5 (13.2%)	24 (25.3%)
Death during follow-up (% of BSI events)	20 (48.8%)	6 (37.5%)	11 (29.0%)	37 (39.0%)

Table 5. Outcomes of TCVCs following Gram-negative bacteraemia, by source of infection (CVC source versus other source, P < 0.001)

	TCVC removed and replaced	TCVC exchange over guidewire	TCVC not replaced	TCVC removed, switch to alternate HD modality	Died	Total
All TCVCs	12	1	19	3	3	38
%	31.6	2.6	50.0	7.9	7.9	100
CVC source of infection	11	0	8	2	1	22
%	50.0	0.0	36.4	9.1	4.5	100
All other sources of infection	1	1	13	1	2	18
%	5.6	5.6	72.2	5.6	11.1	100

Source of infection and outcomes

Access-related bacteraemia (CVC, AVF/AVG sources) accounted for 29.5% ($n = 28$) of cases, other sources made up 53.7% ($n = 51$), and in 16.8% ($n = 16$) the source was not identified. Table 4 details the sources of infection broken down by access type; the commonest individual sources of bacteraemia were CVCs [16.8% ($n = 16$) with a diagnosis confirmed on line tip culture, in addition to 6.3% ($n = 6$) presumed cases], and soft tissues (overwhelmingly infected foot ulcers) 14.7%, $n = 14$. Table 4 also illustrates differences in both infection source and mortality between access modalities. This distinction will be considered further in the discussion. Overall, mortality among those patients with Gram-negative bacteraemia was high; of 84 patients, early (3 months) mortality was 28.6% ($n = 24$), and 39 patients died (46.4%) over the study period (follow-up was time censored at 31/06/14, maximum 36 months).

Regarding vascular access (CVC) outcomes, all patients with a NTCVC had it removed following Gram-negative BSI; considering patients dialysing through a TCVC, the outcome of their vascular access differed between those BSIs due to CVC source compared to other sources of infection, P < 0.001 (see Table 5).

DISCUSSION

This study demonstrates the rate of Gram-negative BSI in a haemodialysis population, both as a whole and stratified by the dialysis access method used. Relatively few studies have quantified the rate of Gram-negative bacteraemia in specific at risk populations, with most focussing instead on the proportion of all BSIs that they comprise. Previous studies in intensive care unit (ICU) populations have quoted a Gram-negative bacteraemia rate of between 0.178/1000 ICU days and 1.13/1000 ICU days with mortality varying between 48% (at 30 days) and 60% (over the duration of hospital admission) [14, 15]. Our own rates are consistent with the lower end of this range and reflect a less acutely unwell population, albeit a population with significant underlying comorbidity. The exception is the NTCVC subgroup, where the rate of Gram-negative BSI was higher than expected (4.77 per 1000 HD days), possibly due to our very inclusive definition of bacteraemia, and the wide confidence intervals associated with the small size of this subgroup. Furthermore, detailed review of the NTCVC cases revealed that this is a group of all-comers—both with established renal failure (ERF) and incident cases commencing HD within the month prior to their BSI, for whom no other vascular access option was available. Although none were acute kidney injury attributed to sepsis, the BSI rate could theoretically be influenced by other factors, such as immunosuppression. Surveillance and registry data on Gram-negative bacteraemia rates are also available for many countries; however, there is marked variation in infection rates between centres which suggests that validity and extrapolation are limited by heterogeneous reporting practices [16, 17].

Considering Table 1, Gram-negative bacteraemia appears to be associated with multisystem disease and diabetic nephropathy as primary renal diagnosis. Whilst factors such as immunosuppression and diabetic foot ulcers may plausibly link aetiology of ERF to risk of Gram-negative BSI, in this dataset we suspect that there is no difference by cause of ERF, and that this is an unfortunate artefact arising from manual cross-checking of data from BSI cases, but not the comparator HD population: the SQL database interrogation labels blank 'primary renal diagnosis' fields as 'unknown cause'; on examination of BSI case records, many of this group labelled as 'unknown' primary renal disease were identified as interstitial nephropathy, multisystem disease or diabetic nephropathy (unsurprisingly, glomerulonephritis is the most reliably entered diagnosis). Unfortunately, the considerable size of the HD population from which our study is drawn makes it unfeasible to similarly cross check all patients' diagnoses.

Traditionally, BSI in haemodialysis populations has largely been viewed as a function of the vascular access method in use. We have previously published data from our HD population which report staphylococcal bacteraemia BSI rates stratified by vascular access modality in use. Comparing these two bodies of work we see that in our HD population staphylococcal BSI rates are consistently higher than those of Gram-negative pathogens; 0.69 versus 0.21 BSI per 1000 HD days respectively with TCVC; 0.26 Staphylococcal BSI per 1000 HD days via AVF/AVG, versus Gram-negative BSI with AVF 0.11/1000 HD days, and AVG 0.24/1000 HD days [8]. On comparing these two studies, the greatest disparity between rates of Staphylococcal and Gram-negative BSI is among patients with TCVC access. The same research demonstrated that taurolidine-citrate-heparin TCVC lock solution led to a 56% reduction in rates of Staphylococcal BSI (1.59 to 0.69/1000 HD days); though the magnitude of effect was not quite matched in TCVC Gram-negative BSIs, a 31% reduction was demonstrated (0.28 to 0.19/1000 HD days). Unfortunately, NTCVCs were not changed to taurolidine-citrate-heparin until near the end of the study period, and given the low numbers within this subgroup, a long follow-up period will be required before any effect may be reliably discerned.

Mortality among Gram-negative bacteraemia cases was notably higher than the baseline mortality rate of patients receiving haemodialysis, estimated at 32% over a comparable follow-up period (maximum 35 months) [18]; it is also greater than registry measures of death rate among all prevalent RRT patients (8.7% per year), and dramatically greater than that of the general population (1.16% per year) [1]. As alluded to earlier, and as demonstrated in Table 4; if patients dialysing via an AVF/AVG get a Gram-negative bacteraemia, it is more likely to reflect a non-access related primary source (e.g. soft tissue ulcer, urinary or biliary) with high early mortality as well as ongoing risk of death persisting through follow-up. In comparison, NTCVCs were associated with high early mortality, but no additional deaths beyond 3 months were encountered. Finally, CVCs are generally only maintained if alternative HD access cannot be achieved, as they increase the risk of bacteraemia and of death as reported here and elsewhere [3, 4, 18], highlighting the importance of vascular access planning. Paradoxically, we demonstrate that associated mortality is lower than other access groups, possibly reflecting CVC-related BSI easily treated with line removal.

For Gram-negative bacteraemia, removal of CVCs is always advised for the following: severe sepsis, complications such as endocarditis, *P. aeruginosa* BSIs, or bacteraemia that persists beyond 72 h of appropriate antibiotics [19]. In our population, all NTCVCs were removed in the context of Gram-negative BSI; 50% of TCVCs ($n = 19$) had attempted line salvage, but with a demonstrable difference in management between bacteraemia attributed to line sepsis compared to other infection sources—in the former group 59.1% ($n = 13$) were removed and 36.4% ($n = 8$) attempted salvage, in the latter group 11.1% were removed ($n = 2$), and 72.2% ($n = 13$) underwent attempted salvage (Table 5). Existing evidence on CVC management suggests that the rate of salvage varies between centres, and has generally been reported as all BSIs due to any organism [20, 21], despite wide acceptance that biofilm formation, pathogen virulence and ease of eradication (hence the need to remove such devices) vary considerably between organisms [19, 22]. Without investigating mortality differences between these groups, and adjusting for the myriad factors that influence survival from BSI, we cannot comment further as to the appropriateness of salvage versus removal of CVCs, though this should be an area for future research.

The preponderant organisms vary with the clinical setting: Gram-negative pathogens cause a greater proportion of community-onset BSIs, as they are more commonly due to infections of urinary, gastrointestinal and respiratory tract; in comparison, hospital-onset are often medical device related [23]. The HD population are an example of healthcare-associated, community-onset infections, creating a hybrid infection pattern [24]. Our data are consistent with this observation, the dominance of *E. coli* reflecting community-onset, but high rates of *Enterobacter* spp. more associated with hospital or ICU settings. Other studies have linked healthcare exposure to increased risk of *P. aeruginosa* (odds ratio 3.14) [24]; *P. aeruginosa* was not a dominant organism in our population, although our empiric choice of vancomycin and gentamicin will provide a degree of anti-pseudomonal cover irrespective.

The pattern of Gram-negative organisms seen in the RRT population is similar to that of the general population in Scotland with *E. coli* and *Klebsiella* spp. being amongst the commonest organisms isolated [25]. The pattern of resistance is also similar to that reported nationally [25] (see Table 6). Slightly higher rates of resistance to amoxicillin, aztreonam and ciprofloxacin are seen, as might be expected from a population with frequent antimicrobial and hospital exposure. It might even be argued that the rates of resistance are lower than expected in comparison with high rates of resistance seen amongst Gram-positive organisms in this population such as vancomycin resistant enterococci and methicillin-resistant *Staphylococcus aureus*.

Rates of *E. coli* bacteraemia are noted to be rising nationally; our data set is over too short a time period to observe this but it will be interesting to see if this is reflected in our population over the next few years. Additionally, although carbapenemase producing strains have been isolated in the renal unit, there have been

Table 6. Antibiotic sensitivities of *Escherichia coli* bacteraemia in haemodialysis patients ($n = 47$ cases), compared to national resistance patterns (not all antibiotics tested on all isolates, and intermediate sensitivities not reported)

Antibiotic	Sensitive	% of those tested sensitive	Resistant	% of those tested resistant	Scottish % resistance
Amoxicillin	9	19.6	37	80.4	64.1
Aztreonam	40	85.1	5	10.6	7.5
Ciprofloxacin	32	69.6	11	23.9	18.8
Gentamicin	42	89.4	4	8.5	9.1
Meropenem	47	100.0	0	0.0	0
Piperacillin/ Tazobactam	41	91.1	3	6.7	6.2

no bacteraemias. However, it is important to stay alert to the possibility of these organisms in this very at risk population.

As outlined above, local empirical antibiotic policy is tailored according to suspected source of infection; in addition our renal unit promotes a policy of vancomycin and gentamicin in suspected CVC-related BSI. Guidelines elsewhere recommend that patients with healthcare exposure (such as haemodialysis) receive a broad-spectrum agent with anti-pseudomonal activity (a fourth generation cephalosporin, carbapenem or piperacillin-tazobactam, with optional aminoglycoside) [19]; however, antimicrobial stewardship policies from the UK National Health Service (including the Scottish Antimicrobial Prescribing group) identify carbapenems and other anti-pseudomonals as 'critically important antimicrobials which should be preserved and protected' [26]. Given the relatively small size of the haemodialysis population, the distinct pattern of organisms causing BSI, the high mortality, and ongoing surveillance of infection rates and sensitivities, we feel that our local policy remains appropriate and is validated by the results outlined above. However, in addition to local patterns of pathogens and sensitivities, empirical antibiotics should be based on history and clinical findings suggestive of source and severity, healthcare exposure, previous culture results, and Gram stain when available.

Limitations of the study relate to the possibility of blood culture contaminants being included as clinically significant BSIs. In clinical practice Gram-negative bacteraemia is considered as significant until proven otherwise, therefore our approach was pragmatic. The accuracy of data pertaining to the source of infection is another potential limitation; for some patients this is very clear, for example in cases of biliary sepsis or when swabs from a foot ulcer culture the same organism and sensitivities as the blood culture; many others however are 'presumed CVC-related' when no alternative source is found, and interpreting such an ill-defined and potentially heterogeneous group will have limited validity. Furthermore, this study carries the intrinsic limitations of observational work; however, similar findings from other centres support the validity and extrapolation of our findings [15, 23]. Finally, achieving adequate statistical power remains challenging in single centre studies; further work should utilize registry data or adopt multi-centre design to combat this issue.

To the best of our knowledge, this is one of the largest haemodialysis cohorts in which Gram-negative BSIs have been characterized. We have demonstrated that early (3 month) mortality following Gram-negative bacteraemia is high, confirming that such pathogens should be treated aggressively; however, we have also confirmed that our empirical antibiotic policy adequately covers Gram-negative BSI, considering the case mix of healthcare-associated, community-onset organisms, and their sensitivities. Furthermore, we have achieved a reduction in the rate of BSIs associated with CVCs through taurolidine based catheter lock solution, though ongoing surveillance of infection rates utilizing the electronic patient database remains essential.

CONFLICT OF INTEREST STATEMENT

The authors declare neither conflicts of interest nor funding. The results presented in this paper have not been published previously in whole or part, except in abstract form.

(See related article by Girndt. Bacteraemia in haemodialysis patients—not always *Staphylococcus aureus*. *Nephrol Dial Transplant* 2015; 30: 1055–1057.)

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ORIGINAL ARTICLE

Predictors of treatment with dialysis modalities in observational studies for comparative effectiveness research*

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*In this article, several baseline and time-varying patient and facility-level variables were investigated in patients treated with different dialysis modalities. These predictors of treatment with dialysis therapies are potential sources of bias and hence should be considered and properly accounted for in studies involving comparative effectiveness of dialysis modalities.

ABSTRACT

Background. The Institute of Medicine has identified the comparative effectiveness of renal replacement therapies as a kidney-related topic among the top 100 national priorities. Given the importance of ensuring internal and external validity, the goal of this study was to identify potential sources of bias in observational studies that compare outcomes with different dialysis modalities.