The characteristics and outcome of bacteremias in renal transplant recipients and non-transplant renal patients

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Abstract

Background: There is lack of outcome data for bacteraemic patients on specialist renal units. We described demographic, clinical, microbiological data and outcomes for bacteraemic adult renal transplant and non-transplant recipients at a London Teaching Hospital. We also assessed the appropriateness of empirical antimicrobial policy.

Methods: From December 2012 - November 2013, demographic, clinical and microbiological data were collected on consecutive patients with bacteraemia on a specialist UK renal unit. Empirical anti-microbial policy, based upon sites of infection, was piperacillin / tazobactam or meropenem for graft pyelonephritis, and vancomycin and gentamicin for suspected central venous catheter (CVC) associated infection.

Results: 113 bacteraemic episodes occurred in 83 patients. One patient had two bacteraemic episodes, one on haemodialysis and another after transplantation so appear in both groups. In the non-transplant group, 30-day mortality was 4/59 (6.8%), more than the renal transplant group, 0/25 (0%). While graft pyelonephritis was the predominant cause of bacteraemic episodes in renal transplant patients, 25/36 (69.4%), there were a variety of other causes in the non-transplant group including uncomplicated line associated bacteraemia, 36/77 (46.8%), complicated line associated bacteraemia, 11/77 (14.3%) and bacteraemia unrelated to vascular access sites 19/77 (24.7%). Overall, commonest isolates were MSSA, 20/77 (26.3%), and E.

coli 28/113 (24.8%). There were no MRSA isolates and, among Enterobacteriaceae, 15/57 (26.3%) were ESBL producers.

Conclusions: Death only occurred in the non-transplant renal group. Empirical antibiotic treatment with either piperacillin/tazobactam and amikacin, or meropenem was appropriate for renal transplant recipients as most bacteraemic episodes were secondary to graft pyelonephritis. Vancomycin and gentamicin was appropriate empirical antibiotic treatment for non-transplant patients with CVC associated infections, but not optimal for other sites of infection.

Introduction

Compared to other speciality inpatients, renal patients are more prone to bacteraemia and have higher infection related mortality[1,2]. This is a consequence of medical devices (which predispose to infection), co-morbidities (which adversely affect outcome) and immunosuppression in renal transplant patients. Haemodialysis patients often have difficult vascular access and dialysis is only feasible via a central venous catheter (CVC), increasing the risk of infection six fold compared to patients with an arteriovenous fistula[3,4]. Early renal transplant patients require urinary catheters and ureteric stents, increasing the risk of graft pyelonephritis, and late renal transplant patients are prone to urosepsis because of previous surgery, structural anomaly and continued immunosuppression[5]. Although patients receiving renal replacement therapy may have an infection related mortality rate up to 25% (Renal Registry Report 2005)[6] there is limited outcome data for bacteraemic patients on specialist renal units and a direct comparison between bacteraemic renal transplant and non-transplant recipients has never been made.

The aim of this study was to describe patient demographic, microbiological and clinical outcomes, in consecutive patients on a specialist renal unit with bacteraemia, and 30-day outcomes for renal transplant and non-transplant recipients. Based on the organisms isolated, susceptibility profiles and sites of infection, we also assessed the appropriateness of empirical antibiotic policy.

Methods

Study setting

The study was undertaken at The Renal Centre at The Royal London Hospital (RLH), a 900 bedded acute major hospital and part of Barts Health NHS Trust. The Renal Centre forms the hub of nephrology services in North East London with satellite dialysis units at Queens Hospital, King George Hospital, Newham General University Hospital and Whipps Cross University Hospital. It serves an elderly and ethnically diverse population in an area of East London, extending into Essex.

The Renal Centre comprises of both inpatient and outpatient areas. Within the inpatient area there are two wards with 62 beds, including a six bedded renal high dependency unit and a six bedded renal surgical unit. Within the outpatient area, there is a Renal Assessment Unit and a 70 station dialysis unit (including a Blood Borne Virus isolation area). The unit has provided services for patients with chronic kidney disease on haemodialysis and peritoneal dialysis as well as those who have undergone kidney transplantation. The unit also supports patients suitable for a 'Home Haemodialysis' service.

Study population

The renal unit provides services for the following groups of patients with renal disease; 975 patients on haemodialysis, 219 on peritoneal dialysis, 1,034 renal transplant recipients, 2,780 general nephrology patients and 392 low clearance

patients (ie. those with an eGFR<20ml/min). From December 2012 to November 2013, we prospectively included consecutive in-patients with bacteraemia.

Definitions

Bacteraemia was considered significant if there was a blood culture isolate obtained from a patient with a compatible clinical syndrome that was unlikely to be a skin or environmental contaminant. This was based upon the patient's history, examination, response to anti-microbial therapy and bacterial isolates from other body sites[7]. Community and hospital-acquired bacteraemia were defined as a positive blood culture obtained either 48 hours before or after admission to hospital. Health care associated bacteraemia, a subset of community-acquired infection, was defined as bacteraemia in patients who had resided in a nursing home or long- term facility 30 days prior to the bacteraemia episode, had been hospitalised for 4 hours or longer in the 90 days before bacteraemia or had attended a hospital or dialysis clinic and received therapy in the 30 days before bacteraemia. Specialities at the time of bacteraemia were categorised as Medicine, Surgery, Critical Care, Obstetrics and Gynaecology, Neonatology and Paediatrics. The medical speciality was subdivided into renal and non-renal medical patients. Renal patients were further categorised into non-transplant renal patients, early renal transplant patients (within 6 weeks of transplantation) and late renal transplant patients (6 weeks post transplantation).

The Centres for Disease Control and Prevention definitions were used to define the sites of infection[8]. For CVC associated infection, this was defined as evidence of

infection (erythema, induration or pus) at the CVC exit site or isolation of the same organism from the line tip or blood. Catheter associated UTIs were defined as infection in patients with indwelling urethral or suprapubic catheters, or patients who intermittently self-catheterised, in the presence of symptoms or signs compatible with a UTI where no other source was identified. Bacteraemia in patients with an unknown source were classified as undefined. Any component of an antibiotic regimen, definitive or empirical, used to treat an infection to which the organism was susceptible in vitro was defined as appropriate treatment. Day one was defined as the day on which a significant blood culture was obtained from the patient.

Empirical antibiotic policy

For renal transplant recipients with presumed graft pyelonephritis, intravenous piperacillin/tazobactam and amikacin, with doses adjusted for renal function, were administered concurrently. For patients with severe sepsis, defined as a Pitt score > 2, or previous infection or colonisation with an extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae, intravenous meropenem was first line empirical treatment.

For patients receiving haemodialysis, and where the site of infection was thought to be CVC associated, empirical intravenous vancomycin and gentamicin, renally dose adjusted, were administered. For other sites of infection, doctors were asked to refer

to the Barts Health NHS antimicrobial guideline for renal transplant recipients, the acute general infection guideline or seek microbiological advice.

Data collection

From 1'st December 2012 to 30'th November 2013, consecutive adult inpatients with bacteraemia on the specialist renal unit based at the RLH were studied. Physicians attending patients who presented with symptoms and signs suggestive of sepsis were encouraged to obtain blood cultures before the administration of empirical antibiotics. One Consultant Microbiologists, aided by several specialist training registrars, reviewed patients' case notes within 72 hours of laboratory confirmation of a positive blood culture result. In all RLH inpatients who developed bacteraemia, demographic data, speciality at the time of the bacteraemia, site of infection, the organism isolated, susceptibility profile, delay in appropriate treatment, Pitt bacteraemia score, Charlson Co-morbidity Index (CCI)[9] and 7 and 30-day outcomes were recorded. The Pitt Bacteraemia Score is a validated scoring system used to quantify severity of infection. It is based on the patient's mental status, the need for mechanical ventilation, temperature and blood pressure. The highest score, 48 hours before or on the day of the first positive blood culture, was recorded.

Patients were empirically treated according to the local hospital guidelines based on site of infection. Once the susceptibility profiles of the bacterial isolate were known, the antibiotic treatment regimens were altered to narrow spectrum agents and time to administration of effective treatment recorded. Patients were followed until

discharge from hospital, recovery or death. Outcomes were recorded as survived or died at 7 or 30 days from blood culture ascertainment. It was assumed that patients who were discharged before the 7th or 30th day survived.

Microbiology data

Blood cultures were analysed using an automated system BacT/ALERT3D (bioMerieux, Mary l'Etoile, France). Isolates were identified using either the VITEK MS system (bioMerieux, Mary l'Etoile, France, database v2.0) or Bruker Biotyper (Bruker Daltonic, Leipzig, Germany, software version 3.0) MALDI-TOF MS systems according to the manufacturer's instructions and the laboratory standard operating procedures. Susceptibility testing was performed on the Microscan walkAway system (Siemans Healthcare Diagnostics, Deerfield, II, US) a minimum inhibitory concentration based susceptibility testing platform.

Data analysis

Quantitative data are presented as numbers with percentages. Continuous data are presented as mean and standard deviation (SD) or mean and 95% confidence interval (CI).

Clinical Governance

This study was registered as an audit and approved by the clinical governance committee of Barts Health NHS Trust. Ethical approval was not required.

Results:

Bacteraemic episodes

From 1'st December 2012 to 30'th November 2013, there were 594 bacteraemic episodes among 513 patients at the Royal London Hospital. 413 (69.5%) occurred in medical patients, 101 (17.0%) in surgical patients and 80 (13.5%) in other patients. Overall, bacteraemiac episodes associated with 83 adult renal patients accounted for 113/594 (19.0%) hospital episodes and 113 (27.4%) episodes in adult medical patients.

Patient categories and vascular access devices

One patient had two bacteraemic episodes, one whilst on haemodialysis and another 6 weeks after renal transplantation. We report these two episodes separately so the patient appears in both groups. Among renal patients with bacteraemic episodes, 59 (70.2%) were receiving haemodialysis, 23 (27.4%) were late renal transplant recipients and only 2 (2.4%) were early renal transplant patients, so we reported early and late renal transplant groups together. Among the 59 patients on haemodialysis, 43 (72.9%) received treatment via a tunnelled haemodialysis line, 9 (15.3%) via an ateriovenous fistula (AVF), 1 (1.7%) via a polytetrafluoroethylene graft and 3 (5.1%) via a vascath (temporary dialysis access). There were 3 other patients, 2 on peritoneal dialysis and 1 general nephrology patient.

Renal transplant patients

The majority of bacteraemic episodes for patients with renal trasplant were hospital-acquired or health-care associated infections, 31/36 (86.1%) (table 1). The commonest site of infection was graft pyelonephritis, 25/36 (69.4%) (table 1). A small proportion of episodes were severe infections, defined as a Pitt score > 2, 3/36 (8.3%), and the majority of patients received an appropriate antibiotic within 6 hours of blood culture ascertainment, 29/36 (80.6%) (table 1). No renal transplant patient died within 30 days of a bacteraemic episode (table 1).

The commonest organisms causing bacteraemia in renal transplant patients were E. coli, 16/36 (44.4%) or K. pneumoniae, 12/36 (33.3%) (table 1). Among all 29 Enterobacteriaceae, there were 8 (27.6%) extended beta-lactamase producers (ESBLs) but no carbapenemase resistant organisms (CROs). 11 (37.9%) were resistant to co-amoxiclav, 9 (31.0%) were resistant to piperacillin / tazobactam and 6 (20.7%) were resistant to gentamicin. There was no resistance to amikacin.

Non-transplant renal patients

The majority of bacteraemic episodes, 77, occurred in 59 haemodialysis patients (table 1). Most infections were health-care associated 66/77 (85.7%) and 9/77 (11.7%) were severe (Pitt score >2) (table 1). Most sites of infection were related to vascular access sites and were uncomplicated; 36/77 (46.8%) or complicated by metastatic infection including endocarditis, vertebral osteomyelitis and peripheral joint infection 11/77 (14.3%) (table 1). There were 19/77 (24.7%) non-vascular access types

of infection, predominantly UTIs, 9/19 (47.4%), but infection at other sites also occurred (table 1).

38/77 (49.4%) were Gram-positive, 33/77 (42.8%) were Gram-negative and 6/77 (7.8%) were Candida infections (table 1). The commonest organism isolated were MSSA, 20/77 (26.3%), E. coli, 12/77 (15.8%) and K. pneumoniae 7/77 (9.6%) (table 1). Among the 28 Enterobacteriaceae there were 7 (25.0%) ESBL producers and no CROs. Eleven (39.3%) were co-amoxiclav resistant, 7 (25.0%) piperacillin / tazobactam resistant, 5 (17.9%) resistant to gentamicin and 2 (7.1%) resistant to amikacin (table 1). Among the Gram-positive isolates there were no MRSA isolates. Most patients received appropriate empirical treatment within 6 hours of a blood culture, 53/77 (68.8%) (table 1).

30-day mortality

There were no deaths at 7-days but 4/59 (6.8%) at 30-days, all non-transplant renal patients; 3 haemodialysis patients and 1 peritoneal dialysis patient (table 1). The organisms isolated were 3 Enterobacteriaceae (K. pneumoniae, E. coli and P. mirabilis) and 1 vancomycin resistant enterococcus (VRE). All were uncomplicated infections; 2 non-catheter associated UTIs, 1 CVC infection and 1 not defined.

Discussion

A comparison between solid organ transplant and non-solid organ transplant bacteraemic patients has previously been made but not exclusively for renal patients[10]. This case-control study, which included renal, liver, kidney/pancreas, small bowel/liver and heart/lung transplant recipients demonstrated a significant survival advantage for transplant patients compared to non-transplant patients. Our study is the first to show outcomes in consecutive adult bacteraemic renal patients who were either renal transplant or non-transplant recipients. At 30-days deaths only occurred in the non-transplant group and it is unclear whether these uncomplicated infections were their primary cause of death.

In renal transplant patients, bacteraemia related mortality ranges from 3-16.7%[2,11]. While most studies report Gram-negative organisms as the commonest causes of bacteraemia and the urinary tract as the commonest site, there is lack of contemporary susceptibility data. One paper found P. aeruginosa to be the commonest blood culture isolate with a cure rate of 55%[12]. Most investigators, like us, found E. coli and K. pneumoniae to be the commonest isolates with cure rates approaching 100%[2,5]. In our study we demonstrated that most bacteraemic infections were caused by graft pyelonephritis and were not associated with death due to antimicrobial failure. For graft pyelonephritis, it therefore appears appropriate to use piperacillin / tazobactam and amikacin as empirical treatment

and meropenem only when treating severe infection, or when patients are known to be colonised or infected with ESBL producing Enterobacteriaceae. Outcomes in the renal transplant cohort were excellent, suggesting that no modification to our empirical antimicrobial policy is required.

Worldwide, there are a limited number of studies of bacteraemia in non-transplant renal patients. In a retrospective, 16-year cohort study of bacteraemic patients undergoing haemodialysis (71 patients and 85 bacteraemic episodes)[13], two-thirds's of episodes were caused by Gram-positive organisms and, overall, mortality was 15%, highest amongst those with shock and infective endocarditis. Other studies focus upon specific categories of infection so mortality rates are not directly comparable to our findings. In a Scottish study of 84 patients on haemodialysis with Gram-negative bacteraemia[14], sources identified were sites unrelated to vascular access such as urinary and biliary tract, a finding similar to ours. A variety of predominantly sensitive organisms were isolated but, despite this, mortality was 24/84 (25.3%). In a Danish cohort study[15], patients with S. aureus bacteraemia on haemodialysis had a 90-day case fatality of 18.2% and in a larger cohort of 3359 haemodialysis-dependent patients[16], mortality at 12 weeks was 20%. Two studies describe sites of metastatic infection following Gram-positive bacteraemia such as infective endocarditis, vertebral osteomyelitis, septic arthritis of peripheral joints and endophthalmitis[12,17]. Some studies describe an association between mortality and co-morbidities and severity of infection[18] and it is not surprising that we found higher

mortality in non-transplant renal patients, an older population with more co-morbidities, compared to renal transplant recipients.

The recent Scottish paper also provides information on susceptibility profiles and assessed the appropriateness of empirical antimicrobial policy for patients on haemodialysis[14]. Compared to this study, we found higher rates of resistance among Gram-negative isolates in non-transplant renal patients (eg. gentamicin 20.7% vs 17.9% and piperacillin / tazobactam 31.0% vs 25.0%) and an unexpectedly high rate of co-amoxiclav resistance, 39.3%. We also found no resistance to meropenem and amikacin. Vancomycin and gentamicin proved effective empirical treatment for complicated and uncomplicated line associated infection, but less effective for other sites of infection due to high levels of gentamicin resistance. Amakicin would have been more appropriate treatment (resistance was 7.1%) but empirical treatment could have been further optimised by careful determination of site of infection, rather than assuming all infections were vascular access associated.

There were limitations to this paper. The number of deaths was small, so we were unable to perform multivariate analysis and adjust for host and other factors when comparing outcomes in renal transplant and non-transplant recipients. We did, however, demonstrate significant differences in age and co-morbidity which may partly explain the differences in survival between the two groups.

In summary, the majority of bacteraemic episodes in renal transplant patients occurred in late transplant recipients and the commonest site of infection was graft pyelonephritis. There were no associated deaths and the antibiotic policy, based on likely isolates and susceptibility profiles, was appropriate. For non-transplant patients, predominantly on haemodialysis, there were a variety of sites of infection which included CVC associated infections (uncomplicated or complicated) and other sites unrelated to vascular access. Although mortality at 30-days was < 7%, these patients need to be properly assessed and investigated as vancomycin and gentamicin is not always appropriate treatment for non-vascular access site infections. Younger age and fewer co-morbidities may partly explain better outcomes in renal transplant recipients. Overall, compared to other renal units with published bacteraemia data, our unit had exceptionally good outcomes.

Table 1: Demographic, Microbiological and Clinical Outcome data of 83 renal patients with 113 bacteraemia episodes

	Transplant	Non-Transplant
Patients	25	59
Bacteraemic episodes	36	77
Age*, n (%)		
16-30	2 (8.0)	4 (6.8)
31-50	9 (36.0)	16 (27.1)
51-70	13 (52.0)	28 (47.5)
>70	1 (4.0)	11 (18.6)
Gender*, n (%)		
Male	11 (44.0)	35 (59.3)
Female	14 (56.0)	24 (40.7)
Pitt score, n (%)		
0	17 (47.2)	44 (57.1)
>0 and ≤2	16 (44.4)	24 (31.2)
>2	3 (8.3)	9 (11.7)
CCI, n (%)		
0	2 (5.6)	2 (2.6)
>0 and ≤2	23 (63.9)	24 (31.2)
>2	11 (30.6)	51 (66.2)
Where infection was acquired, n (%)		
CAI	5 (13.9)	1 (1.3)
HAI	12 (33.3)	10 (13.0)
HCAI	19 (52.8)	66 (85.7)
Organism, n (%)		
MSSA	1 (2.8)	20 (26.0)
E coli	16 (44.4)	12 (15.4)
K pneumonia	12 (33.3)	7 (9.1)
E faecalis	1 (2.8)	7 (9.1)
Candida	2 (5.6)	6 (7.8)
CoNS	0	4 (5.2)
E cloacae	0	4 (5.2)
P aeruginosa	0	4 (5.2)
P mirabilis	1 (2.8)	3 (3.9)
S marcescens	0	2 (2.6)
VRE	1 (2.8)	2 (2.6)
E faecium	2 (5.6)	1 (1.3)
S. milleri	0	1 (1.3)
S pneumoniae	0	1 (1.3)
Viridans Streptococcus	0	1 (1.3)
B fragilis	0	1 (1.3)
Missing	0	1 (1.3)

	Transplant	Non-Transplant
Patients	25	59
Bacteraemic episodes	36	77
Sites of infection, n (%)		
Fistula	0	1 (1.3)
Uncomplicated line associated	1 (2.8)	36 (46.8)
Complicated (line associated)	0	11 (14.3)
Infective endocarditis (native)	0	5 (6.5)
PPM endocarditis	0	2 (2.6)
Vertebral column	0	2 (2.6)
Peripheral joint (native)	0	2 (2.6)
Other	31 (86.1%)	19 (24.6)
UTI (non-catheter associated)	25 (69.4)	7 (9.1)
UTI (catheter associated)	4 (11.1)	2 (2.6)
Liver abscess	0	2 (2.6)
Renal abscess	0	1 (1.3)
Tooth abscess	0	1 (1.3)
LRT (non-ventilator associated)	0	1 (1.3)
Skin and soft tissue infection	2 (5.6)	2 (2.6)
GI tract	0	1 (1.3)
Biliary tract	0	1 (1.3)
Osteomyelitis (contiguous)	0	1 (1.3)
Not defined	4 (11.1)	10 (13.0)
Time from blood culture ascertainment to administration of appropriate antibiotics (hours), n (%)		
<6	29 (80.6)	53 (68.8)
<24	4 (11.1)	11 (14.3)
<48	1 (2.8)	8 (10.4)
<72	1 (2.8)	3 (3.9)
>72	1 (2.8)	2 (2.6)
Mortality*, (%)		
7 days	0	0
30 days	0	4 (6.8)

CCI: Charlson Co-morbidity Index; CAI: community acquired infection; HAI: Hospital acquired infection; HCAI: Heath care association infection; PPM: permanent pacemaker; UTI: urinary tract infection; LRT: lower respiratory tract; GI: gastrointestinal

One patient had a bacteraemic episode while receiving haemodialysis and another > 6 weeks after renal transplantation so appear in both groups

*patient specific variables so reported as a percentage of patients

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