TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Colonisation with methicillin-resistant *Staphylococcus aureus* prior to renal transplantation is associated with long-term renal allograft failure

Carmel Moore, Niall F. Davis, John P. Burke, Richard Power, Ponnusamy Mohan, David Hickey, Gordon Smyth, Molly Eng and Dilly M. Little

Department of Urology and Transplant Surgery, Beaumont Hospital, Dublin, Ireland

Keywords
immunosuppression, kidney transplant, methicillin-resistant *Staphylococcus aureus*, transplantation.

Correspondence
Dr Dilly M. Little, Department of Transplantation and Urology, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland.
Tel.: 00353 1 8093000;
fax: 00353 1 8093962;
e-mail: dillylittle@beaumont.ie

Conflicts of interest
The authors have declared no conflicts of interest.

Received: 12 February 2014
Revision requested: 17 February 2014
Accepted: 19 May 2014
Published online: 7 July 2014

doi:10.1111/tri.12357

Summary

Renal transplant recipients are at an increased risk of developing *Methicillin-resistant Staphylococcus aureus* due to their immunosuppressed status. Herein, we investigate the incidence of MRSA infection in patients undergoing renal transplantation and determine the effect of MRSA colonisation on renal allograft function and overall mortality. Between January 1st 2007 and December 31st 2012, 1499 consecutive kidney transplants performed in our transplant unit and a retrospective 1:2 matched case-control study was performed on this patient cohort. The 1-, 3- and 5-year overall graft survival rates were 100%, 86% and 78%, respectively, in MRSA positive recipients compared with 100%, 100% and 93%, respectively, in the control group ($P < 0.05$). The 1-, 3- and 5-year overall patient survival rates were 100%, 97% and 79%, respectively, in MRSA positive recipients compared with 100%, 100% and 95%, respectively, in the control group ($P = 0.1$). In a multiple logistic regression analysis, colonisation with MRSA pre-operatively was an independent predictor for renal allograft failure at 5 years (hazard ratio: 4.6, 95% confidence interval: 1–30.7, $P = 0.048$). These findings demonstrate that the incidence of long-term renal allograft failure is significantly greater in this patient cohort compared with a matched control population.

Introduction

Solid organ transplant recipients are at an increased risk of developing hospital-acquired infections during the peri-operative period due to their immunosuppressed status. Methicillin-resistant *Staphylococcus aureus* (MRSA) was initially identified in the United Kingdom (UK) in 1961 and can be an extremely difficult bacterial pathogen to eradicate [1]. Although MRSA is associated with a widespread global prevalence, its incidence among renal transplant recipients remains largely unknown. Worryingly, florid MRSA bacteraemia is associated with mortality rates that approach 20% among the general population and it is intuitive that mortality rates may be higher among renal transplant recipients due to their increased immunocompromised status during the peri-operative period [2,3].

It is well established that colonisation with MRSA predisposes patients, in particular immunosuppressed hospitalised inpatients, to the development of active MRSA bacteraemia [4]. Therefore, screening and eradication of the pathogen prior to renal transplantation is performed as part of the renal transplant admission protocol in our transplant centre. Although risk factors for developing active MRSA infections are well described among solid organ transplant recipients, there is a paucity of data on the effect of colonisation with MRSA on allograft function, particularly among kidney transplant recipients. Therefore, the purposes of the present study were twofold. Firstly, we aimed to determine the incidence of MRSA colonisation

among kidney transplant recipients in our centre. Secondly, we aimed to investigate the effect of colonisation with MRSA on overall renal allograft function and on overall mortality.

Methods

Overview of study design

Between January 1st 2007 and December 31st 2012, 1613 consecutive kidney transplants performed in Ireland of which 1499 were performed in our unit [5]. A retrospective 1:2 matched case-control study was performed on this patient cohort. The criteria for the matching process were the gender of the recipient and donor, age of recipient and donor, Charlson comorbidity index (CMI), cause of renal failure pre-operatively, date of transplantation and duration of long-term follow-up. 'Cases' consisted of kidney transplant recipients with MRSA detected during the pre-operative screening process and 'controls' were matched recipients without MRSA detected on initial screening (Table 1). Primary outcome variables were incidence of MRSA pre-operatively and effects of colonisation with MRSA on graft function and overall patient mortality.

Pre-operative screening protocol for MRSA

Each anticipated kidney transplant recipient was screened for MRSA on admission to the transplant unit. The screening protocol involved nasal, groin and peritoneal dialysis (PD) catheter site swabs. In the event of a positive culture nasal decontamination was performed with mupirocin® and whole body decontamination with chlorohexidine®. After the decontamination process, repeat swabbing was performed to monitor for clearance of MRSA. Perfusion fluid (University of Wisonsin®) was cultured intra-operatively to outrule the presence of MRSA in donor kidneys.

Peri- and post-operative immunosuppression

During the peri-operative period patients were immunosuppressed with prednisone, tacrolimus and mycophenolic acid mofetil. Tacrolimus levels were maintained between 10 and 15 ng/ml (Microparticle Enzyme immunoassay by Abbot IMX®; Fujisawa Healthcare Incorporated, Co., Kerry, Ireland) for the first 6 weeks after transplantation and between 8 and 12 ng/ml thereafter [6]. All patients received standard antiviral, antifungal and *Pneumocystis* prophylaxis.

Statistical analysis

Statistical analysis was performed on both groups using a 2-tailed Student's *t*-test with unequal variances to compare both groups. Kaplan–Meier estimates were used to compare graft survival and overall mortality between both groups. In addition, stepwise multiple logistic regression analysis was performed to examine predictors of graft failure and mortality using SPSS version 12.0 (SPSS, Inc., Chicago, IL, USA). All variables tested in the univariate analysis with a *P*-value of ≤ 0.10 were included in a multivariate analysis. A *P*-value of <0.05 was considered significant for the multiple logistic regression analysis.

Results

Patient demographics in MRSA positive recipients

Methicillin-resistant *Staphylococcus aureus* screening was positive in 28 (1.9%) recipients of which 15 (54%) were male (Table 1). MRSA was most frequently cultured from nasal swabs ($n = 22/28$) and no intra-operative perfusion fluid samples from donor kidneys cultured MRSA. The mean age at transplantation was 49 (range: 19–72) years in the MRSA group compared with 48 (range: 19–72) years in the control group ($P = 0.9$). There was no significant difference in the mean CMI between both groups; however, the number of cardiovascular comorbidites was significantly greater in patients that were colonised with MRSA (Table 2). Twenty-six (93%) recipients in the MRSA group received a deceased donor renal transplant compared with 51 (91%) in the control group ($P = 0.9$). The mean duration of long-term follow-up in the MRSA group post-transplantation was 77 (range: 24–140) months compared with 76 (range: 22–133) months in the control group ($P = 0.9$).

Table 1. Characteristics of the matched case-control group.

Matched characteristics	Case ($n = 28$)	Control ($n = 56$)	*P*-value
Recipient gender (male: female)	15:13	27:29	$P = 0.9$
Donor gender (male:female)	14:14	36:20	$P = 0.7$
Mean recipient age	49	48	$P = 0.9$
Mean donor age (years)	38.4	41.8	$P = 0.9$
Living – deceased donor transplant	2–26	5–51	$P = 0.9$
Follow-up (months)	77	76	$P = 1$

Table 2. Summary of comorbidities in both study groups.

Comorbidity	MRSA group ($n = 28$)	Control group ($n = 56$)	*P*-value
Cardiovascular	7 (25%)	6 (10.9%)	$P < 0.01$
Hypertension	4 (14.3%)	4 (7.3%)	$P < 0.01$
Previous surgery	6 (21.4%)	9 (16.4%)	$P = 0.8$
Diabetes mellitus	4 (14.3%)	9 (16.4%)	$P = 0.9$
Mean Charlson Comorbidity Index	3.5 ± 0.64	3.4 ± 0.62	$P = 0.3$

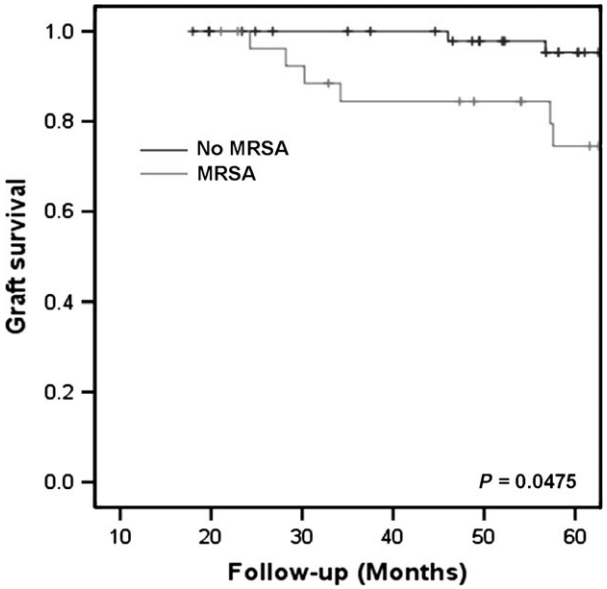

Figure 1 Kaplan–Meier survival curves in renal transplant recipients representing overall renal allograft survival (months) in patients colonised with methicillin-resistant *Staphylococcus aureus* during the peri-operative period compared with a noncolonised control group.

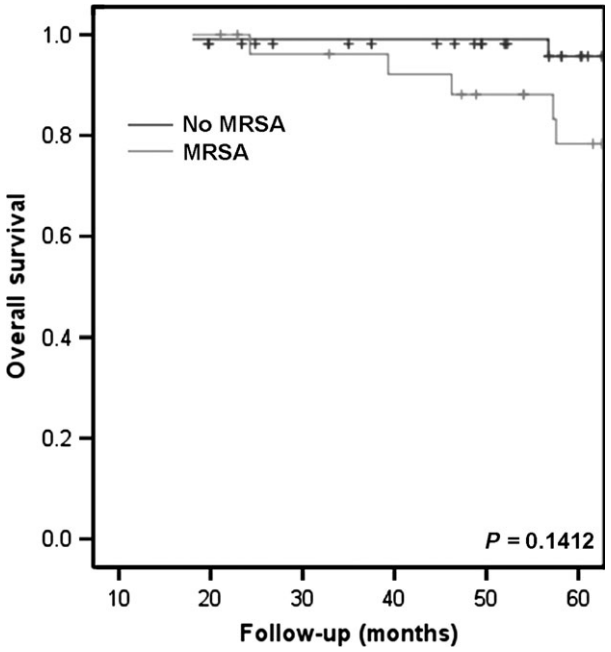

Figure 2 Kaplan–Meier survival curves in renal transplant recipients representing overall post-operative patient survival (months) in patients colonised with methicillin-resistant *Staphylococcus aureus* during the peri-operative period compared with a noncolonised control group.

Table 3. Causes of renal allograft failure and overall mortality in both study groups after 5 years.

Long-term outcomes	Case (n = 28)	Control (n = 56)
Cause of graft failure		
Sepsis (MRSA bacteraemia)	2 (2)	
Chronic rejection	3	4
Total number of graft failures at 5 years (n)	5	4
Cause of mortality		
Malignancy	1	2
Myocardial infarction	1	0
Cerebrovascular accident (CVA)	1	1
Respiratory	1	1
MRSA bacteraemia	1	0
Total number of mortalities at 5 years	5	4

Eradication of MRSA was confirmed with repeat swabbing in all patients ≤14 days after commencing their treatment protocol.

Long-term outcomes in MRSA positive recipients

The 1-, 3- and 5-year overall graft survival rates were 100%, 86% and 78%, respectively, in MRSA positive recipients compared with 100%, 100% and 93%, respectively, in the control group (Fig. 1, $P < 0.05$). Causes of graft failure in both groups are demonstrated in Table 3. The 1-, 3- and 5-year overall patient survival rates were 100%, 97% and 79%, respectively, in MRSA positive recipients compared with 100%, 100% and 95%, respectively, in the control group (Fig. 2, $P = 0.1$). Causes of overall mortality in both groups are also demonstrated in Table 3.

Multiple logistic regression analysis

In a multiple logistic regression analysis, on univariate analysis, recipient >65 years of age (hazard ration [HR]: 24, 95% confidence interval [CI]: 3.6–159, $P = 0.001$) was identified as a significant predictor of long-term renal allograft failure (Table 4). On multivariate analysis, recipient >65 years of age (HR: 36.6, 95% CI: 4.2–316.7, $P = 0.001$) and colonisation with MRSA pre-operatively (HR: 4.6, 95% CI: 1–30.7, $P = 0.048$) were independent predictors of renal allograft failure at 5 years (Table 4). In a multiple logistic regression analysis, on univariate and multivariate analysis recipient >65 years of age (HR: 29, 95% CI: 4.3–200, $P = 0.001$) was identified as a significant predictor of overall patient mortality at 5 years (Table 5).

Discussion

Globally, MRSA is one of the most frequent causes for community and hospital-acquired infections with the majority presenting as moderate to severe infections of the skin and respiratory tract [7]. Short-term complications

Table 4. Univariate and multivariate analysis of factors associated with graft failure.

	Univariate			Multivariate*		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Recipient male	1.0	0.3–3.7	1.000			
Donor male	1.1	0.3–4.2	0.909			
Donor on vasopressin	0.8	0.2–3.0	0.699			
Recipient diabetic	2.1	0.4–11.4	0.408			
Recipient PCKD	0.8	0.2–4.0	0.764			
MRSA	3.5	0.9–13.8	0.068	5.6	1.0–30.7	0.048
Recipient > 65 years	24.0	3.6–159.0	0.001	36.6	4.2–316.7	0.001

HR, hazard ratio; CI, confidence interval; PCKD, polycystic kidney disease; MRSA, methicillin-resistant *Staphylococcus aureus*.
*Adjusted for all other variables in the table, $N = 84$.

Table 5. Univariate and multivariate analysis of factors associated with mortality.

	Univariate			Multivariate*		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Recipient male	0.5	0.1–2.0	0.299			
Donor male	0.9	0.2–3.5	0.858			
MRSA	2.8	0.7–11.5	0.147			
Donor on vasopressin	0.6	0.2–2.5	0.510			
Recipient PCKD	0.9	0.2–4.8	0.906			
Recipient diabetic	4.9	1.0–23.8	0.051	3.6	0.5–24.3	0.187
Recipient > 65 years	29.2	4.3–200.0	0.001	25.3	3.5–182.7	0.001

HR, hazard ratio; CI, confidence interval; PCKD, polycystic kidney disease; MRSA, methicillin-resistant *Staphylococcus aureus*.
*Adjusted for all other variables in the table, $N = 84$.

associated with MRSA in the transplant population are well described and include pneumonia, urinary tract infections (UTIs), intra-abdominal collections, disseminated bacteraemia and wound dehiscence [8]. The main finding of the present study is that colonisation with MRSA during the peri-operative period is an independent predictor for renal allograft failure within 5 years of transplantation. Although there was no significant difference in overall mortality between both groups, a higher mortality rate was also noted in the colonised group.

In general, approximately 20% of the general population are persistent nasal carriers of *Staphylococcus aureus* and 1.5% are asymptomatic carriers for MRSA [9–11]. In immunosuppressed hospitalised patients the incidence of MRSA is markedly higher as demonstrated in one similar study on liver transplant recipients where the incidence of active MRSA infection approached 4% during the peri-operative period [12]. Interestingly, there is a paucity of data available on the incidence of colonisation and active infection with MRSA in renal transplant recipients. Our results suggest that the incidence is relatively low at 1.9% despite high levels of immunosuppression. Data from another similar study by Oliveira-Cunha *et al.* [8] also demonstrated a low incidence (1.25%) in their cohort. It is likely that the increased rate of MRSA colonisation among liver transplant recipients may be due to the increased acuity of liver transplant recipients, extensiveness of the transplant operation, increased duration of inpatient stay and greater rates of ICU admissions.

The Charlson comorbidity index (CMI) is a validated scoring system for predicting mortality [13]. The mean pre-operative CMI in the present study ranged from 3.5 ± 0.64 in the colonised group to 3.4 ± 0.62 in the control group. A CMI of 3–4 is associated with a 52% 1-year patient mortality [14]. Intuitively, transplant recipients are at an increased risk of nosocomial contact with MRSA due to long-term haemodialysis and hospital admissions for exacerbation of comorbidities. Furthermore, central venous catheters are required for haemodialysis and are potential sources for colonisation. Although the mean CMI was not statistically significant between both groups, the number of cardiovascular comorbidites was significantly greater in the colonised group (Table 2). Cardiovascular comorbidities are also associated with recurrent inpatient hospital admissions, and this may have been a contributing factor to colonisation with MRSA in transplant recipients [15].

Despite the eradication of MRSA during the peri-operative period in all patients with positive cultures, it is notable that two patients in the present cohort developed MRSA bacteraemia during their long-term follow-up period. The renal allograft ultimately failed in both patients after 22 and 38 months, respectively. One patient developed MRSA

bacteraemia from a central venous catheter, and the second patient developed an intra-abdominal abscess that had culture proven MRSA. These findings may emphasise the importance of long-term screening for MRSA in an immunosuppressed transplant population with a prior history of MRSA colonisation [8]. Perhaps allograft failure may have been prevented if both recipients had undergone annual screening and treatment with a repeat eradication protocol in the event of recurrent colonisation.

Our study has limitations and our results should be viewed with caution. It is a single-centre, retrospective analysis of a prospectively maintained database. However, comprehensive long-term follow-up of all transplant recipients colonised with MRSA was undertaken, and no patients were lost to follow-up. It is also arguable that patients colonised with MRSA may have had a greater number of pre-operative comorbidities, higher CMI and prior history of active MRSA infection compared with the control group. To eliminate these potential confounders, all cases were matched according to age, date of transplant and CMI during the matching process. However, it is notable that there was a significantly greater number of pretransplant cardiovascular comorbidites in patients colonised with MRSA group, and this may have contributed to poorer transplant outcomes.

Conclusion

This is the first study to demonstrate the long-term effects of peri-operative colonisation with MRSA on allograft function in renal transplant recipients. Our findings demonstrate that patients colonised with MRSA have a significantly higher risk of allograft failure compared with a matched control population. We hope that information gathered from this study emphasises the importance of peri-operative and long-term screening for MRSA in renal transplant recipients.

Authorship

CM and NFD: study design, data analysis and drafting of manuscript. JPB: statistical analysis and drafting of manuscript. RP, PM and DH: supervision. GS: data analysis. ME and DML: supervision and drafting of manuscript.

Funding

None.

References

1. Benner EJ, Morthland V. Methicillin-resistant *Staphylococcus aureus.* Antimicrobial susceptibility. *N Engl J Med* 1967; **277**: 678.
2. Engemann JJ, Carmeli Y, Cosgrove SE, *et al.* Adverse clinical and economic outcomes attributable to methicillin resistance among patients with *Staphylococcus aureus* surgical site infection. *Clin Infect Dis* 2003; **36**: 592.
3. Bert F, Galdbart JO, Zarrouk V, *et al.* Association between nasal carriage of *Staphylococcus aureus* and infection in liver transplant recipients. *Clin Infect Dis* 2000; **31**: 1295.
4. Torre-Cisneros J, Herrero C, Canas E, Reguera JM, De La Mata M, Gomez-Bravo MA. High mortality related with *Staphylococcus aureus* bacteremia after liver transplantation. *Eur J Clin Microbiol Infect Dis* 2002; **21**: 385.
5. Davis NF, McLoughlin LC, Little DM. Long-term outcomes after deceased donor renal transplantation in patients with genitourinary tuberculosis. *Transpl Int* 2014; **27**: e18.
6. Davis NF, McLoughlin LC, Dowling C, *et al.* Incidence and long-term outcomes of squamous cell bladder cancer after deceased donor renal transplantation. *Clin Transplant* 2013; **27**: E665.
7. DeLeo FR, Otto M, Kreiswirth BN, Chambers HF. Community-associated meticillin-resistant *Staphylococcus aureus*. *Lancet* 2010; **375**: 1557.
8. Oliveira-Cunha M, Bowman V, di Benedetto G, *et al.* Outcomes of methicillin-resistant *Staphylococcus aureus* infection after kidney and/or pancreas transplantation. *Transplant Proc* 2013; **45**: 2207.
9. Tacconelli E, De Angelis G, de Waure C, Cataldo MA, La Torre G, Cauda R. Rapid screening tests for meticillin-resistant *Staphylococcus aureus* at hospital admission: systematic review and meta-analysis. *Lancet Infect Dis* 2009; **9**: 546.
10. Jeyaratnam D, Whitty CJ, Phillips K, *et al.* Impact of rapid screening tests on acquisition of meticillin resistant *Staphylococcus aureus*: cluster randomised crossover trial. *BMJ* 2008; **336**: 927.
11. Florescu DF, Qiu F, West SB, *et al. Staphylococcus aureus* infections in kidney transplantation: a matched case controlled study. *Scand J Infect Dis* 2012; **44**: 427.
12. Schneider CR, Buell JF, Gearhart M, *et al.* Methicillin-resistant *Staphylococcus aureus* infection in liver transplantation: a matched controlled study. *Transplant Proc* 2005; **37**: 1243.
13. O'Connor KM, Davis N, Lennon GM, Quinlan DM, Mulvin DW. Can we avoid surgery in elderly patients with renal masses by using the Charlson comorbidity index? *BJU Int* 2009; **103**: 1492.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373.
15. Rochon PA, Katz JN, Morrow LA, *et al.* Comorbid illness is associated with survival and length of hospital stay in patients with chronic disability. A prospective comparison of three comorbidity indices. *Med Care* 1996; **34**: 1093.