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Surgical Site Infection after Renal Transplantation

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Abstract

Objective—To identify factors associated with the development of surgical site infection among adult patients undergoing renal transplantation.

Design—A retrospective cohort study

Setting—An urban tertiary care center in Baltimore, MD with a well-established renal transplantation program that performs approximately 200–250 renal transplant procedures annually.

Results—441 adult patients underwent renal transplantation from January 1st, 2010 and December 31st, 2011. Fifteen percent (66/441) of cohort patients developed an SSI; 47% (31/66) of these were superficial-incisional and 53% (35/66) were deep-incisional or organ-space. The average BMI among cohort patients was 29.7 and 42% (184/441) were obese (BMI > 30). Patients who developed SSI had a greater mean BMI (31.7 vs 29.4, p =0.004) and were more likely to have a history of peripheral vascular disease, rheumatologic disease, and narcotic abuse. History of cerebral vascular disease was protective. Multivariate analysis showed BMI (Odds Ratio (OR) 1.06; 95% Confidence Interval (CI): 1.02 to 1.11) and past history of narcotic use/abuse (OR 4.86, 95% CI: 1.24 to 19.12) to be significantly associated with development of SSI after controlling for National Healthcare Surveillance Network (NHSN) Score and presence of cerebrovascular, peripheral vascular and rheumatologic disease.

Conclusions—We identified higher BMI as a risk factor for the development of SSI following renal transplantation. Of note, neither aggregate comorbidity scores nor NHSN risk index were

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associated with SSI in this population. Additional risk adjustment measures and research in this area is needed to compare SSIs across transplant centers.

Keywords

Surgical Site Infection; Kidney Transplant; Risk Adjustment

Healthcare-associated infections (HAI) are among the most common complications of hospital care. Nearly 2 million patients develop an HAI each year in the US and approximately 99,000 of them die as a result (1). Surgical site infections (SSI) are the most common HAI among surgical patients and have been associated with increased morbidity, mortality and healthcare costs (2–4). Nearly 20,000 patients receive a kidney transplant each year, and thus are at risk for the development of SSI (National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Institute, 2011 Annual Data Report, http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/). Multiple risk factors for SSI have been identified including both surgical (e.g. duration of procedure) and host factors (e.g. obesity). The literature on risk factors for SSI among patients undergoing renal transplantation, however, is relatively sparse and most studies were not performed in the United States. In this study we aimed to identify factors associated with the development of SSI following renal transplantation in adult patients. We hypothesize that there are identifiable and modifiable risk factors for SSI unique to this population that would allow prospective interventions aimed at decreasing the incidence of SSI.

METHODS

We designed a retrospective cohort study of adult patients (i.e. ≥ 18 years of age) who underwent renal transplantation at the University of Maryland Medical Center (UMMC) between January 1st, 2010 and December 31st, 2011. The transplant program performs approximately 200–250 renal transplant surgeries each year. UMMC guidelines for surgical antimicrobial prophylaxis prior to renal transplantation included weight-based dosing of cefazolin as the first choice antibiotic. This study was approved by the University of Maryland Institutional Review Board.

Eligible patients (i.e. adult patients who underwent renal transplantation during the study period) were identified from the hospital transplant database and confirmed using the central data repository. Patients who underwent dual-transplant (e.g. kidney-liver or kidney-pancreas) were not included in the final analyses. For each patient in the cohort, the patient medical record (including both inpatient and outpatient follow-up) was reviewed by trained and experienced Infection Preventionists for development of SSI within 30 days following the initial procedure. SSIs were classified as either superficial-incisional, deep-incisional or organ-space using criteria established by the National Healthcare Safety Network (NHSN) of the Centers for Disease Control and Prevention (CDC)(5). Potential risk factors were identified via a combination of manual chart review and extraction from central data repositories, which contain administrative, pharmacy, surgical, laboratory and outcome data on all patients. Data contained within the tables of this repository have been validated for this and other research studies and found to have positive and negative predictive values of

greater than 99%(6, 7). The anesthesiology repository contains peri-operative medications and other clinical information; fields obtained were validated for this study and were accurate. Patient variables pre-transplantation considered as potentially associated with the development of SSI were age, sex, race, body mass index (BMI), American Society of Anesthesiologists (ASA) Score, and presence of underlying comorbid diseases. Transplant and surgical variables considered as potentially associated with the development of SSI were repeat transplantation, deceased versus living donor, cold ischemic time, receipt and appropriateness of antimicrobial prophylaxis, induction immunosuppression, procedure duration (the time from incision to wound closure), and estimated blood loss (Table 1). Presence of underlying comorbid diseases were analyzed individually and as part of composite scores as determined by using the Charlson Comorbidity Index, the Chronic Disease Score (CDS) and the CDS-ID. The Charlson Comorbidity Index, an aggregate comorbidity measure, was calculated using discharge codes (International Classification of Diseases, 9th Revision, Clinical Modification, ICD-9-CM) as indicators for comorbid conditions (8, 9). The CDS and the CDS-ID (a modified version of the CDS) utilizes patient medications, ordered within the first 24 hours of hospital admission, as indicators for the presence of comorbid conditions (9, 10)(11) (Table 2). The NHSN risk, which has been previously described elsewhere (12), is used as a measure of risk adjustment and considers the following equally weighted variables: wound class, ASA Score and procedure duration.

All data were analyzed using SAS software version 9.2 (SAS Institute, Cary, NC). The Fisher's exact test and Chi-square test were used to compare categorical variables and the Student's t-test was used for continuous variables. Multivariate logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to identify the risk factors for development of SSI following renal transplantation. Variables that were associated with the outcome ($p < 0.1$) were included in the regression model. Furthermore, NHSN score was forced into the model to explore its utility in risk adjustment.

RESULTS

441 adult patients underwent renal transplantation during the two-year study period. The mean age was 53 years (SD ± 13.1), 58% (257/441) were men, and 47 % (225/441) were African American. The average BMI among cohort patients was 29.7 (SD ± 6.0) and 42% (184/441) were obese (BMI > 30). Additional characteristics of the cohort are provided in Table 1.

Fifteen percent (66/441) of cohort patients developed an SSI; among these, 47% (31/66) were superficial-incisional and 53% (35/66) were deep-incisional or organ-space. Patients who developed an SSI, compared to those who did not, were more likely to undergo a second operation during the index hospitalization and were more likely to be re-admitted within 30 days of discharge from the index admission. One patient, who did not develop an SSI, died of complications related to a subdural hematoma within 30 days of transplantation (Table 1).

98% of patients undergoing renal transplantation (433/441) received prophylactic antibiotics within one hour prior to incision according to current guidelines (13); there was no

difference in receipt of antibiotics between those that developed SSI (97%, 64/66) and those that did not (98%, 369/375) (p = 0.42).. Among all 433 patients that received antibiotics prior to renal transplant, 336 (78%) received cefazolin and 97 (22%) received an alternate regimen. There was no difference among outcome groups with respect to antibiotic choice; 72% (46/64) patients with an SSI received cefazolin, compared to 79% (290/369) patients without SSI (p=0.23). 138 patients with a BMI > 30 received cefazolin as antibiotic prophylaxis, 63% (87/138) of these received 1 gram of cefazolin and thus were under-dosed according to hospital weight-based dosing standards. There was no difference in antibiotic dosing; 60% (15/25) of patients who developed an SSI were under-dosed and 64% (72/113) of controls were under-dosed (p=0.73). Among the 66 patients that developed an SSI, a responsible organism(s) was identified by culture in 63 (95%). In total, 121 organisms were identified from the 66 patients; for 26 (39%) patients the infection was monomicrobial and for 37 (56%) polymicrobial. 86% (104/121) of all organisms identified were considered cefazolin resistant (either based on susceptibilities or known intrinsic resistance). In 86% of patients (57/66) at least one organism was identified that was resistant to cefazolin and in 92% (61/66) at least one organism was resistant to the surgical prophylaxis regimen given. The organisms identified and their relative frequencies are found in Table 3.

The bivariate analysis demonstrated that patients with a higher BMI were more likely to have a SSI; 31.7 versus 29.4, p = 0.004 (Table 1). Although there was no difference in either comorbidity index (Charlson or CDS-ID) between patients who developed an SSI compared to those who did not, individual components each differed between groups. Among transplant recipients who developed an SSI, there was a trend toward increased odds of having peripheral vascular disease (Fisher's Exact p-value = 0.06), and rheumatologic disease (Fisher's Exact p-value = 0.10). In addition, patients with cerebrovascular disease had decreased odds of developing an SSI (Fisher's Exact p-value = 0.06). Finally, history of narcotic use/abuse as indicated by hospital prescription of opioids typically used to treat withdrawal symptoms (e.g. methadone, buprenorphine HCL and naloxone) was associated with development of SSI (Fisher's Exact p-value = 0.03).

The multivariate analysis showed BMI (Odds Ratio (OR) 1.06; 95% Confidence Interval (CI): 1.02 to 1.11) and past history of narcotic use/abuse (OR 4.86, 95% CI: 1.24 to 19.12) to be significantly associated with development of SSI after controlling for NHSN Score and presence of cerebrovascular, peripheral vascular and rheumatologic disease (Table 3). The OR of 1.06 for BMI indicates that there is a 6% increased odds of developing in SSI for every 1-point increase in BMI. BMI remained a risk factor whether it was included in the model as a continuous variable or a categorical variable (e.g. Obesity, BMI > 30) – *data not shown*.

We also examined the outcome of deep SSI. After excluding patients who were identified to have a superficial SSI, 410 patients were in the cohort. Thirty-five (8.5%) of these patients developed a deep SSI. Patients who developed a deep SSI were more likely to undergo a second operation during their index admission and were more likely to be re-admitted at 30 days. Patients who developed an SSI were on average younger and had greater BMI than patients who did not develop an SSI. These patients were also less likely to receive basiliximab as induction immunosuppression. In addition, the presence of rheumatologic,

peripheral vascular and Parkinson's disease was more common among patients who developed a deep SSI. Multivariate analysis showed BMI and the presence of rheumatologic disease to be independent risk factors for the development of deep SSI, after controlling for NHSN Score, age, and the presence of peripheral vascular and Parkinson's disease. In addition, basiliximab as induction immunosuppression remained protective against SSI (Table 4).

DISCUSSION

In this study, we found that BMI was a risk factor for the development of SSI following renal transplantation. Somewhat surprisingly, we did not find other biologically plausible or transplant-specific risk factors such as presence of comorbid conditions, receipt of appropriate (type and dose) antibiotic prophylaxis, organ ischemia time and donor type (cadaveric versus living donor). The receipt of basiliximab as induction immunosuppression, however, was protective for the development of deep SSI. Of note, NHSN risk index, used for decades by the CDC in risk adjustment when comparing SSI rates across different facilities, was not associated with SSI.

Previous studies analyzing risk factors for SSI following renal transplantation have been scarce. To our knowledge, none of the studies considered aggregate measures of comorbidity (e.g. Charlson Comorbidity Index or CDS) or the NHSN risk index as potential associated factors. Furthermore, there was only single study prior to ours performed in the US – reported by Lynch *et al*. (14). They studied 869 patients undergoing renal transplantation from 3003 to 2008 at a single institution and their primary aim was to assess whether obese patients were at higher risk of developing an SSI compared to non-obese patients. Although they did not use NHSN definitions for SSI, and thus direct comparisons cannot be made, they found that age, delayed graft function, and BMI >30 were independently associated with SSI development. Menezes *et al*., have performed the largest study to date, a matched case-control study among 1939 kidney transplant patients in Brazil and found that chronic glomerulonephritis, pre-transplant diabetes, high BMI, acute graft rejection, reoperation, and delayed graft function were all risk factors for SSI (15). However, several potential risk factors identified (i.e. rejection, reoperation and delayed graft function) are measured after the transplant procedure and thus it is not clear if these factors contributed to the development of SSI or if they were the result of an SSI. Finally, Ramos *et al.* considered the risk for development of superficial incision infection in a Spanish cohort (16). Among 1400 patients that underwent renal transplantation, diabetes and the receipt of a sirolimus-based immunosuppressive regimen, demonstrated an increased risk of developing an SSI; neither aggregate comorbidity scores, NHSN risk index, nor obesity were investigated as a potential risk factor for the development of SSI.

Obesity is the most consistently identified risk factor for the development of SSI among renal transplant recipients as well as in other surgical procedures (14, 15, 17, 18). The underlying mechanisms for increased risk of infection is unknown and likely includes obesity-related immune dysregulation, the presence of unmeasured obesity-related confounders and pharmacologic issues such as inadequate dosing of medications. Perhaps, based on this, as well as concern for poor compliance with weight-based dosing and

favorably toxicity profile, new antibiotic guidelines are urging consideration for more routine use of higher doses of commonly used antimicrobial prophylactic agents; for example, routinely using 2 grams of IV cefazolin in place of 1 gm or weight-based dosing (13). However, in this study, we found no association between the receipt, type of dosing of antibiotics and the development of SSI, even after adjusting for BMI.

According to the NHSN/CDC, 3.8 to 6.6% of US patients undergoing renal transplantation from 2006 to 2008 developed an SSI (19). For over two decades, the method of risk adjustment, in order to make comparisons of rates between facilities, involved the use of the NSHN risk index that includes three equally weighted variables: wound class, procedure duration and the ASA score. A major limitation of this method is that for most surgical site procedures only one of the three variables (e.g. procedure duration) can be used because the other two variables are the same for all patients. In fact, in our population all patients had the same wound class and 98% of the patients fell into the same NHSN classification for ASA score. In addition, the use of procedure duration in risk adjustment is debated because of controversy as to what the procedure duration variable represents; a longer duration may represent a more complicated procedure due to patient factors or it may represent a less-skilled surgeon. This risk index has undergone considerable criticism and numerous observations have been made regarding situations where the risk index performed poorly (20–23). NHSN is currently exploring the use of additional risk factor adjustment; their most recent adjustment also includes the variables age, sex, emergency, trauma, general anesthesia, ASA score, wound classification, procedure duration, medical school affiliation, number of hospital beds, endoscope, and outpatient (24, 25). Even this may have significant limitations; using renal transplantation as an example, only age, sex, procedure duration, medical school affiliation and number of hospital beds are useful, as the other variables are either not relevant or likely to be the same for all patients. Further, no studies to date have identified sex or procedure duration as potential risks factors for the development of SSI in this population and since no multicenter studies have been performed in the US, it is not clear whether medical school affiliation or number of hospital beds are indeed risk factors. Larger, multicenter studies are needed to identify potentially modifiable risk factors and to improve risk adjustment strategies.

There are several limitations of our study. First, although our study is large compared to other studies in the literature, the sample size is still relatively small and was performed at a single site. Second, our study was retrospective. Finally, there are inherent limitations to the comorbidity scores used, specifically the reliance on ICD-9 coding with the Charlson.

In conclusion, our study identified body mass index as a predictor of surgical site infection among renal transplant patients. Larger, multi-institution projects are needed to analyze risk factors for SSI among renal transplant recipients. This future research will hopefully lead to the identification of modifiable risk factors for the development of SSI and to improvements in risk adjustment when making comparisons across different healthcare facilities.

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Table 1

Characteristics of the Cohort

	Entire Cohort (N=441)	SSI (N=66)	No SSI (N=375)	p-value
Age, in years	53 (±13.1)	52.2 (±11.1)	53.2 (±13.5)	0.55
Sex, men	257 (58%)	39 (59%)	218 (58%)	0.88
Race, African American	225 (52%)	37 (57%)	188 (51%)	0.36
Body Mass Index (BMI), mean (SD)	29.7 (±6.0)	31.7 (±5.7)	29.4 (±5.9)	0.004
BMI < 25	117 (27%)	13 (20%)	104 (28%)	--
BMI ≥ 25 and < 30	130 (30%)	14 (21%)	116 (30%)	0.93
BMI ≥ 30	184 (42%)	37 (56%)	147 (39%)	0.01
Chronic disease score, mean (SD)	10.8 (±3.5)	11.4 (±3.6)	10.7 (±3.5)	0.19
Charlson score, mean (SD)	3.3 (±1.6)	3.4 (±1.8)	3.3 (±1.5)	0.64
Donor type, cadaveric	315 (71%)	46 (69%)	269 (72%)	0.74
Repeat transplant	56 (13%)	6 (9%)	50 (13%)	0.34
Ischemia time, in minutes	1127.5 (869)	1184.3 (927.3)	1116.3 (858.1)	0.57
NHSN risk index				
= 1	35 (7.9%)	5 (8%)	30 (8%)	
= 2	316 (73%)	43 (73%)	268 (72%)	
= 3	90 (20%)	13 (20%)	77 (21%)	
Surgical Prophylaxis*	433 (98%)	64 (97%)	369 (98%)	0.42
Induction Immunesuppression				
Thymoglobulin	70 (16%)	12 (18%)	58 (15%)	0.58
Alemtuzemab^	224 (51%)	37 (56%)	187 (50%)	0.35
Basiliximab^	144 (33%)	17 (26%)	127 (34%)	0.20
Procedure duration, in minutes	197.4 (±71.3)	192.9 (±62.7)	198.2 (±72.8)	0.58
Estimated blood loss, in ml	408 (±395)	413 (±377)	408 (±398)	0.93
Hospital length of stay, Median (interquartile range)	6.2 (5.1 to 8.5)	6.7 (5.3 to 9.9)	6.0 (5.0 to 8.4)	
Second operation during index hospitalization	61 (14%)	15 (23%)	46 (12%0	0.02
Readmission at 30 days	50% (220)	94% (62)	42% (158)	<0.01
Death at 30 days	1 (0.2%)	0	1 (0.3%)	--

SSI – Surgical Site Infection

*Surgical prophylaxis – documentation of receipt of appropriate antibiotics (as defined by University of Maryland Medical Center protocol) within 1 hour of surgical incision

^2 patients received both alemtuzemab and basiliximab as induction immunesuppression

Table 2

Chronic Disease Score (CDS) and CDS-ID Components for Patients with or without Surgical Site Infection (SSI)

CDS-ID Category	Components	SSI (n=66) *n* (%)	No SSI (n=375) *n* (%)	*P*	Weighting Scheme	
					CDS	CDS-ID
Heart disease	a) Anti-coagulants	29 (44%)	170 (45%)	0.83	3	--
	b) Cardiac agents (includes ACE inhibitors)	9 (14%)	47 (13%)	0.80	4	--
	c) Loop diuretics	36 (55%)	121(32%)	0.26	5	--
Respiratory illness	a) Isoproterenol	0	0	--	One class = 2	1.38, any class
	b) Beta-adrenergic*	9 (14%)	34 (9%)	0.25		
	c) Xanthine products	0	0	--	Two or more classes = 3	
	d) Bronchodialators and mucolytics	1(2%)	5 (1%)	--		
	e) Epinephrine	0	4 (1%)	--		
Asthma, rheumatism	Glucocorticoids	58 (88%)	336 (90%)	0.68	3	--
Rheumatoid arthritis	Gold salts	1(2%)	1(0.3%)	--	3	--
Cancer	Antineoplastics	33 (50%)	188 (50%)	0.98	3	1.07
Parkinson's	L-Dopa	0	1 (0.3%)	--	3	--
Hypertension	a) Antihypertensives and calcium channel blockers (excludes ACE inhibitors)	62 (94%)	349 (93%)	0.80	2	--
	b) Beta-blockers and diuretics	13 (20%)	68 (18%)	0.76	1	--
Diabetes	Insulin and oral hypoglycemic	50 (76%)	276 (74%)	0.71	2	1.57
Epilepsy	Anticonvulsants	14 (21%)	62 (17%)	0.35	2	--
Asthma, rhinitis	Cromolyn	1 (2%)	0	--	2	--
Ulcers	Cimetidine	27 (41%)	120 (32%)	0.16	1	1.83
Glaucoma	Opthalmic miotics	2 (3%)	0	--	1	--
Gout	Uric acid agents	8 (12%)	2 (0.5%)	0.65	1	--
High cholesterol	Cholesterol lower agents	11 (17%)	43 (12%)	0.23	1	--
Tuberculosis	Antitubercular agents	0	0	--	1	--
HIV	Antiretroviral agents	1 (2%)	6 (2%)	--	--	--
Renal	Calcitrol, calcium acetate, hematopoetic agents	8 (12%)	55 (15%)	0.60	--	3.13
Narcotic use	Opiod agonitsts, narcotic antagonists	4 (6%)	5 (1%)	0.01	--	--
Acne	a) Anticane tretinoin	0	0	--	1, either class	--
	b) Topical macrolides	0	0	--		--

CDS-ID Category	Components	SSI (n=66) *n* (%)	No SSI (n=375) *n* (%)	*P*	Weighting Scheme	
					CDS	CDS-ID
Migraines	Ergot derivatives	0	0	--	1	--

Table 3

Organisms Responsible for Surgical Site Infection

	Organism	**Relative Frequency, number (%) (Total N= 121 organisms)**
Gram-positive		
	Coagulase-negative Staphyloccci	39 (32%)
	Gram-positive rods	15 (12%)
	Enterococcus spp	14 (12%)
	Staphylococcus aureus	7 (6%)
	Streptococcus spp	3 (2%)
Gram-negative		
	Escherichia coli	8 (7%)
	Klebsiella spp	5 (4%)
	Pseudomonas aeruginosa	5 (4%)
	Enterobacter cloacae	4 (3%)
	Proteus spp	4 (3%)
	Other[*]	4
Anaerobes		
	Peptostreptococci	4 (3%)
	Other [^]	3
Fungi		
	Candida albicans	4 (3%)
	Candida tropicalis	1 (0.8%)
	Saccarolyticus	1 (0.8%)

[*]Other Gram-negative organisms included one each of the following: *Serratia* spp, *Achromobacter xylosoxidans*, *Acientobacer* spp, and non-aerugina *Pseudomonas* app.

[^]Other anaerobic organisms included one each of: *Proprionobacterium* spp, *Veillonella* spp, and *Prevotella bivia*

Table 4

Multivariate Analysis

	Outcome = Surgical Site Infection	Outcome = Deep Surgical Site Infection
Variable	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
Body mass index	1.06 (1.02 to 1.11)	1.07 (1.01 to 1.12)
Narcotic use/abuse	4.86 (1.24 to 19.12)	6.91 (1.17 to 41.04)
Peripheral vascular disease	--	4.12 (1.33 to 12.78)
Induction with basiliximab	--	0.27 (0.10 to 0.74)