American Journal of Transplantation 2007; 7: 1536–1541
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2007.01790.x

Risk Factors for Urinary Complications After Renal Transplantation

M. J. Englesbe, D. A. Dubay, B. W. Gillespie*, A. S. Moyer, S. J. Pelletier, R. S. Sung, J. C. Magee, J. D. Punch, D. A. Campbell, Jr., and R. M. Merion

Department of Surgery, Division of Transplantation and School of Public Health, Department of Biostatistics University of Michigan, Ann Arbor, MI
**Corresponding Author: Michael J. Englesbe, englesbe@med.umich.edu*
Presented in part at the 2005 American Transplant Congress, Seattle, WA.
Funding source: none

Urinary complications are common following renal transplantation. The aim of this study is to evaluate the risk factors associated with renal transplant urinary complications. We collected data on 1698 consecutive renal transplants patients. The association of donor, transplant and recipient characteristics with urinary complications was assessed by univariable and multivariable Cox proportional hazards models, fitted to analyze time-to-event outcomes of urinary complications and graft failure. Urinary complications were observed in 105 (6.2%) recipients, with a 2.8% ureteral stricture rate, a 1.7% rate of leak and stricture, and a 1.6% rate of urine leaks. Seventy percent of these complications were definitively managed with a percutaneous intervention. Independent risk factors for a urinary complication included: male recipient, African American recipient, and the "U"-stitch technique. Ureteral stricture was an independent risk factor for graft loss, while urinary leak was not. Laparoscopic donor technique (compared to open living donor nephrectomy) was not associated with more urinary complications. Our data suggest that several patient characteristics are associated with an increased risk of a urinary complication. The U-stitch technique should not be used for the ureteral anastomosis.

Received 30 May 2006, revised 19 January 2007 and accepted for publication 2 February 2007

Introduction

It is well established that urinary complications are associated with significant morbidity following the kidney transplant operation (1–13). The literature on urinary complications following kidney transplant is limited to numerous, relatively small single center experiences and these studies are too small to provide risk factor analysis for urinary complications. A comprehensive evaluation of posttransplant urinary complications, focusing on risk factors, management and the effects on graft function, will enable the clinician to better inform and manage patients.

In this series, we review our experience with urinary complications in renal transplantation. We report 105 urinary complications in 1698 consecutive renal transplants. This large number of cases allows us to complete a multivariable analysis to assess the risk factors for urinary complications in various subgroups of patients. In addition, we assess the effects of urinary complications on graft function. Based on our findings, we conclude with clinical recommendations and suggestions for addition study regarding urinary complications.

Materials and Methods

Patient data

Electronic medical records for all recipients of renal transplants performed consecutively between 7/1/1995 and 7/1/2004 (n = 1698) at the University of Michigan Health System were retrospectively evaluated. Patients who received simultaneous kidney-pancreas, kidney-liver, kidney-heart transplants, or did not have a ureteral anastomosis to the bladder were excluded. Data regarding donor, transplant, surgeon (n = 9), and recipient characteristics as well as graft and patient outcomes were obtained from both a prospectively collected database and review of the electronic medical record and from a dataset provided by the Scientific Registry of Transplant Recipients, based on data submitted by our center to the Organ Procurement and Transplantation Network. Urinary complications were identified by review of radiographic, laboratory and operative records. All bladder anastomoses were completed as a Lich-Gregoir (external ureteroneocystostomy) or using the single U-stitch technique (utilized by a single surgeon) Briefly, the Lich-Gregoir is a continuous suture around the spatulated circumference of the ureter and cystotomy mucosal layer, with closure of the bladder muscle layer over the anastomosis to prevent reflux (14). The U-stitch technique entails tacking the hood of the ureter to the inside wall of the bladder with a single "U" stitch. The myotomy is then closed over the ureter creating an antirefluxing tunnel (15–17). Data on operatively placed stents were available from 1/1/2001 to 7/1/2004. Internal double-J ureteral stents were selectively placed per surgeon preference and transurethral catheters were left in place for 48 h. Patients were managed with three agent maintenance immunosuppression in the immediate postoperative period (cyclosporine, corticosteroids and an antimetabolite). Sirolimus was not used for initial immunosuppression. Immunologically high risk recipients (PRA > 30, African American, or previous transplant) received polyclonal antithymocyte globulin.

Risk factors

Risk factors evaluated as possible predictors of urinary complications included era of transplant, sex, age, race, comorbidities, etiology of renal failure, history of previous renal transplant, donor characteristics, ureteroneocystostomy technique, surgeon, rejection and ischemia times. Expanded criteria donor (ECD) were classified according to Port et al. and included all donors greater than or equal to 60 years of age, plus those donors between 50 and 59 years with at least two of the following three factors: serum creatinine greater than 1.5 mg/dL, cerebrovascular accident as cause of death, and history of hypertension (18). Data regarding rejection episodes were limited to the first post-operative year.

Definition of urinary complication

For the purposes of this study, urinary complications were defined as symptomatic urinary leak or ureteral stricture requiring intervention. In the Cox model for graft failure, patients with both a urinary leak and stricture were categorized as having a urinary leak.

Human subjects protection

The study was approved by the University of Michigan Institutional Review Board prior to data collection and analysis.

Statistical analysis

The association of donor, transplant and recipient characteristics with urinary complications was assessed by univariable and multivariable Cox proportional hazards models, fitted to analyze time-to-event outcomes of urinary complications and graft failure. All statistical analyses were performed using SAS version 9.1.

Results

Patient characteristics

The baseline characteristics of the study population (1698 consecutive renal transplants) are detailed in Table 1. The mean posttransplant follow-up was 1446 ± 962 days. Male recipients predominated (58%), and 79% of recipients were white. Diabetes was the most common etiology of renal failure in the study group. Fifty-six percent of the kidneys were from living donors and approximately 40% of the living donor transplants were procured via a laparoscopic approach.

Table 1: Characteristics of transplant recipients

	N	%
Age		
1–17	136	8.0
18–39	518	30.5
40–59	767	45.2
≥60	277	16.3
Sex		
Male	984	58.0
Female	714	42.0
Race		
White	1342	79.0
African American	245	14.4
Hispanic	27	1.6
Other	84	4.9
Etiology of renal failure		
Diabetes mellitus	448	26.4
Glomerulonephritis	300	17.7
Hypertension	227	13.4
Polycystic kidney disease	149	8.8
Obstructive uropathy	67	3.9
Other	507	29.9
Previous transplant		
Yes	214	12.6
No	1484	87.4
Donor type		
Deceased	746	43.9
Living related	704	41.5
Living unrelated	248	14.6
Living donor technique		
Open	574	60.3
Laparoscopic	378	39.7

Urinary complication incidence and management

There were 105 (6.2%) urinary complications observed during follow-up (Table 2). Two complications were from blood clots after biopsy and one was from a stone (excluded from analysis). The overall urinary complication rates for living donor and deceased donor transplants were 5.7% and 7.8%, respectively.

Isolated ureteral stricture without leak occurred in 47 cases (2.8%) and was the most common urinary complication, representing 44.7% of all urinary complications. More than two-thirds (68.1%) of strictures were managed nonoperatively with a percutaneously placed nephroureteral stent with or without balloon ureteroplasty. The remaining 15 patients required operative reconstruction.

Ureteral stricture with associated urine leak occurred in 28 cases (1.7%), representing 26.7% of urinary complications. Of these, 21 (75.0%) were managed with a percutaneous nephrostomy tube or nephroureteral stent, with or without balloon ureteroplasty, while the remainder (n = 7) required an operative reconstruction.

Urine leaks occurred in 27 cases (1.6%) and represented 25.7% of the ureteral complications. Three patients with obvious urine leaks in the immediate postoperative period were taken directly to the operating room. The remainder of the patients had initial placement of a percutaneous nephroureteral stent. If an internal stent had been placed at the time of the operation, it was removed at the time of the nephroureteral stent placement. Eighteen (66.6%) of the urine leaks were ultimately managed either with a

Table 2: Incidence of urinary complications and percent amenable to nonoperative management (n = 1698)

Complication	N	Percent of transplants	Percent managed without reoperation
Stricture	47	2.77	68.1
Leak and stricture	28	1.65	75.0
Leak	27	1.59	66.6

Table 3: Univariable Cox regression analysis of risk factors for the development of a urinary complication following renal transplantation

	HR	95% Lower	95% Upper	p-Value
"U" stitch technique	1.99	1.66	2.32	0.04
Male recipient	1.87	1.65	2.08	0.004
African American recipient	1.88	1.66	2.11	0.005
ECD donor*	2.09	1.74	2.45	0.04
Lap nephrectomy (compare to DD)**	0.58	0.21	1.00	0.052
Open nephrectomy (compare to DD)**	0.83	0.62	1.05	0.829
Nondiabetic recipient	1.50	1.25	1.75	0.10
Female donor	1.47	0.95	1.94	0.08
Previous transplant	1.30	0.59	2.28	0.38
Recipient age (per 10 years)	1.10	0.90	1.20	0.86
Donor age (per 10 years)	0.90	0.80	1.00	0.13
Recipient BMI (per 5 kg/m^2)	0.95	0.85	1.1	0.68

* ECD donor = expanded criteria kidney donor.
** Compared to deceased donor renal transplant.

percutaneous nephrostomy tube with nephroureteral stent while the remainder of the urine leaks required an operative reconstruction.

All of the urine leaks, with or without strictures, presented within 100 days of the renal transplant (median time from renal transplant to presentation with a urine leak was 11.5 days (interquartile range [IQR] 8, 24.5)). Interestingly, 16 (34.0 %) of the ureteral strictures without leaks presented greater than 100 days following the transplant (median time from renal transplant to presentation with a stricture was 19 days (IQR 8,69)).

Overall, 73 (69.5%) of the urinary complications were managed percutaneously without operative reconstruction.

Risk factors for urinary complications

Factors significantly associated with urinary complication in univariable analysis included U-stitch technique, male recipient, African American recipient, ECD kidney, and laparoscopic donor nephrectomy (compared to deceased donor renal transplants). (Table 3) Urinary complications were not associated with previous transplant, warm ischemia time, cold ischemia time, surgeon identifier, total ischemia time, donor or recipient body mass index (BMI), episode of acute rejection or donor or recipient age.

A multivariable Cox proportional hazards regression model (adjusted for U-stitch, recipient sex, recipient race, recipient diabetes and technique of organ procurement (laparoscopic living donor nephrectomy, open living donor nephrectomy or deceased donor) was fitted to define independent risk factors for a urinary complication (Table 4). We found that U-stitch technique, male recipients, and African American recipients were all associated with a higher risk of a urinary complication.

Placement of an intraoperative ureteral stent was commonly done (30.4% of all transplants done between 1/1/2001 and 7/1/2004 (n = 681). Of patients who did not have a stent placed, 5.7% had urinary complications, compared to 4.3% in patients who had a stent placed at the time of transplant. This difference was not statistically significant. Patients with an internal stent and complications presented with urinary leaks. The complication rate directly related to the stent was difficult to assess, but obstruction thought related to the stent occurred in only one patient and the stent was removed earlier than initially planned (6–8 weeks) in 1.8% of patients due to persistent urinary tract infections.

A multivariable Cox proportional hazards regression model (adjusted for year of transplant, ureteral stricture, ureteral leak, recipient diabetes, recipient race, recipient sex and technique of organ procurement) was completed to identify independent risk factors for graft loss. This model noted that ureteral stricture (but not ureteral leak), recipient diabetes, African American recipient, and deceased donor nephrectomy (compared to laparoscopic living donor nephrectomy and open living donor nephrectomy) were all independently associated with graft loss (Table 5).

Figure 1 notes the adjusted rates of urinary complications among African American and non-African American males and females.

Discussion

We have shown that recipient factors of male sex, African American race and the U-stitch anastomotic technique, are each significant and independent risk factors for urinary complications after renal transplantation. These findings may be useful to better inform patients about the risks of complications and to assist surgeons in making decisions about management of the urinary reconstruction.

Some interesting insights into the pathophysiology of urinary complications can be gained from our results. Urine leak is presumably related to technical issues (either with

Table 4: Risk factors for development of a urinary complication from a Cox proportional hazards regression model

	HR	95% Lower	95% Upper	p-Value
'U' stitch technique	1.95	1.59	2.27	0.045
Male recipient	1.94	1.72	2.15	0.002
African American recipient	1.73	1.50	1.96	0.019
Non diabetic recipient	1.53	0.96	2.10	0.089
Lap nephrectomy (compare to DD)*	0.63	0.18	1.09	0.111
Open nephrectomy (compare to DD)*	0.91	0.80	1.02	0.659

* Compared to deceased donor renal transplants

the donor operation or the transplant itself) and, as expected, presented early. Conversely, one-third of isolated strictures presented late (more than 100 days posttransplant). These strictures frequently involved a long segment of the donor ureter and were often located proximal to the bladder anastomosis. In addition, ureteral stricture is a significant risk factor for graft loss, while urinary leak is not. Even though late strictures may be related to ischemia or rejection (11, 19), patients with late strictures in our study did not have seem to have more early rejection (data not shown). The correlation between graft loss and ureteral stricture may be related to rejection and further study is needed to define this relationship. Nonetheless, these data suggest that urinary leaks and strictures can represent different pathophysiologic processes and should be separated in future analyses.

Among the most interesting findings in the risk factor models are that male and African American recipients had significantly more urinary complications than female and non-African American recipients, respectively (Figure 1). Thus, African American males were almost four times more likely to have a urinary complication compared to non-African American females. It is possible that the anastomosis is technically more difficult in males related to a deeper, narrower pelvis. Along similar lines, one might posit that BMI would be an independent risk factor for urinary complications (higher BMI being associated with a technically more difficult operation), but this has not been the case in either our study or the reported experience from other groups (20, 21). There are likely many complex urodynamic factors (such as bladder size and function, urinary outflow obstruction, length of time anuric prior to transplant) and other clinical factors which predispose male and/or African American recipients to urinary complications, and further study is warranted. There is a modest amount of data reporting more urinary complications in pediatric boys compared to girls (8). It is notable that we did not assess induction therapy as a potential risk factor for a urinary complication, and this may affect African American being a truly independent risk factor for urinary complications. African American recipients received polyclonal antithymocyte induction at the time of transplant, compared to only a small subset of non-African Americans. Further study is needed to determine if antibody induction therapy influences urinary complication rates.

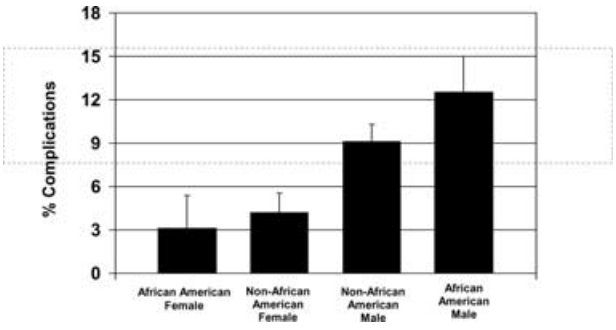

Figure 1: Adjusted ureteral complication rates among 1698 consecutive renal transplants.

The U-stitch anastomotic technique, which was associated with significant risk, has not been utilized at our center for a number of years, and we recommend against its use.

Like many centers, we now use laparoscopic (hand-assisted) donor nephrectomy to procure approximately 95% of living donor kidneys. Contrary to other published reports (22–24), laparoscopic donor nephrectomy was not associated with more urinary complications, even when controlled for the year of transplant. Actually, compared to open living donor nephrectomy, there was a trend towards fewer complications. This finding could be related to meticulous attention to preservation of periureteral tissue. In our group's experience, it is easier to preserve periureteral tissue when the operative field is under laparoscopic magnification.

For many years, we have utilized a mainly nonoperative approach to the management of leaks and strictures, employing percutaneous nephrostomy tube drainage and conversion to a universal stent with balloon ureteroplasty as needed. Our results support this practice, as the majority of patients can be successfully managed without the need for a secondary operation. Further study is needed to characterize those patients who fail percutaneous management of their urinary complication. Identification of risk factors for failure of the percutaneous approach would reduce the incidence of prolonged and ultimately unsuccessful nonoperative management. The observation that urinary leaks were not associated with graft loss is reassuring both to caregivers and to patients who experience a leak and

Table 5: Risk factors for graft loss from a Cox proportional hazards regression model adjusted for year of transplant

	HR	95% Lower	95% Upper	p-Value
Ureteral stricture	1.69	1.45	1.93	0.033
Recipient diabetes	1.49	1.38	1.60	0.001
African American recipient	1.37	1.06	1.68	0.017
Lap nephrectomy (compare to DD)*	0.58	0.39	0.77	0.005
Open nephrectomy (compare to DD)*	0.61	0.50	0.72	0.001
Transplant year (per year forward)	0.95	0.89	1.01	0.055
Male recipient	1.08	0.98	1.19	0.473
Ureteral leak	1.16	0.90	1.41	0.630

* Compared to deceased donor renal transplants.

require a nephrostomy tube in the months following a kidney transplant.

There are multiple case series and five randomized trials indicating that ureteral stents reduce urinary complication rates with minimal risk of stent-related complications (2, 4–6, 9, 10). Considering the selection bias related to decision to place an intraoperative stent, it is not possible to compare rates of ureteral complications between the stented and nonstented patients in our cohort. In addition, the study was not designed to inform decision making regarding stenting practices.

It is important to point out the limitations of this study. Its design as a retrospective, single center cohort analysis hampers our ability to ascribe direct causality to any of the significant risk factors we have identified. In addition, despite the identification of multiple independent risk factors for urinary complications, the mediation of their effects may be complex, unexplored interactions among the factors may exist, and additional confounders may remain unmeasured and therefore uncharacterized.

In summary, our series has noted several significant risk factors for ureteral complications. We conclude that the U-stitch technique should not be used for the ureteral anastomosis. This comprehensive evaluation of posttransplant urinary complications, focusing on risk factors, management, and the effects on subsequent graft failure, should enable clinicians to better inform and manage patients. Further study is needed to attribute causality of these risk factors to higher rates of urinary complications.

References

1. Khauli RB, Ayvazian PJ. Modified extravesical ureteroneocystostomy and routine ureteral stenting in renal transplantation: Experience in 300 consecutive cases. Transplant Proc 2001; 33: 2665–2666.
2. Dominguez J, Clase CM, Mahalati K et al. Is routine ureteric stenting needed in kidney transplantation? A randomized trial. Transplantation 2000; 70: 597–601.
3. Cimic J, Meuleman EJ, Oosterhof GO, Hoitsma AJ. Urological complications in renal transplantation. A comparison between living-related and cadaveric grafts. Eur Urol 1997; 31: 433–435.
4. Bassiri A, Amiransari B, Yazdani M, Sesavar Y, Gol S. Renal transplantation using ureteral stents. Transplant Proc 1995; 27: 2593–2594.
5. Benoit G, Blanchet P, Eschwege P, Alexandre L, Bensadoun H, Charpentier B. Insertion of a double pigtail ureteral stent for the prevention of urological complications in renal transplantation: A prospective randomized study. J Urol 1996; 156: 881–884.
6. Kumar A, Kumar R, Bhandari M. Significance of routine JJ stenting in living related renal transplantation: A prospective randomised study. Transplant Proc 1998; 30: 2995–2997.
7. Jaskowski A, Jones RM, Murie JA, Morris PJ. Urological complications in 600 consecutive renal transplants. Br J Surg 1987; 74: 922–925.
8. French CG, Acott PD, Crocker JF, Bitter-Suermann H, Lawen JG. Extravesical ureteroneocystostomy with and without internalized ureteric stents in pediatric renal transplantation. Pediatr Transplant 2001; 5: 21–26.
9. Mangus RS, Haag BW. Stented versus nonstented extravesical ureteroneocystostomy in renal transplantation: A metaanalysis. Am J Transplant 2004; 4: 1889–1896.
10. Pleass HC, Clark KR, Rigg KM et al. Urologic complications after renal transplantation: A prospective randomized trial comparing different techniques of ureteric anastomosis and the use of prophylactic ureteric stents. Transplant Proc 1995; 27: 1091–1092.
11. Rigg KM, Proud G, Taylor RM. Urological complications following renal transplantation. A study of 1016 consecutive transplants from a single centre. Transpl Int 1994; 7: 120–126.
12. Shoskes DA, Hanbury D, Cranston D, Morris PJ. Urological complications in 1,000 consecutive renal transplant recipients. J Urol 1995; 153: 18–21.
13. Ohl DA, Konnak JW, Campbell DA, Dafoe DC, Merion RM, Turcotte JG. Extravesical ureteroneocystostomy in renal transplantation. J Urol 1988; 139: 499–502.
14. Secin FP, Rovegno AR, Marrugat RE, Virasoro R, Lautersztein GA, Fernandez H. Comparing Taguchi and Lich-Gregoir ureterovesical reimplantation techniques for kidney transplants. J Urol 2002; 168: 926–930.
15. Zomorrodi A, Bahluli A. Evaluation of urologic complications in 30 cases of kidney transplantation with technique of proper exposure edge of bladder mucosa and U-stitch ureteroneocystostomy. Transplant Proc 2003; 35: 2662–2663.
16. Modlin CS, Flechner SM, Boparai N, Goldfarb DA, Novick AC. U-stitch ureteroneocystostomy: A new renal transplantation ureteral reimplantation technique associated with reduced urologic complications. Tech Urol 2000; 6: 1–4.

17. Sumrani NB, Lipkowitz GS, Hong JH, Hanson P, Butt KM. Complications of "one stitch" extravesical ureteric implantation in renal transplants in the cyclosporine and precyclosporine eras. Transplant Proc 1989; 21(1 Pt 2): 1957–1959.
18. Port FK, Bragg-Gresham JL, Metzger RA et al. Donor characteristics associated with reduced graft survival: An approach to expanding the pool of kidney donors. Transplantation 2002; 74: 1281–1286.
19. Faenza A, Nardo B, Catena F et al. Ureteral stenosis after kidney transplantation. A study on 869 consecutive transplants. Transpl Int 1999; 12: 334–340.
20. Singh D, Lawen J, Alkhudair W. Does pretransplant obesity affect the outcome in kidney transplant recipients? Transplant Proc 2005; 37: 717–720.
21. Marks WH, Florence LS, Chapman PH, Precht AF, Perkinson DT. Morbid obesity is not a contraindication to kidney transplantation. Am J Surg 2004; 187: 635–638.
22. Philosophe B, Kuo PC, Schweitzer EJ et al. Laparoscopic versus open donor nephrectomy: Comparing ureteral complications in the recipients and improving the laparoscopic technique. Transplantation 1999; 68: 497–502.
23. Nogueira JM, Cangro CB, Fink JC et al. A comparison of recipient renal outcomes with laparoscopic versus open live donor nephrectomy. Transplantation 1999; 67: 722–728.
24. Kuo PC, Cho ES, Flowers JL, Jacobs S, Bartlett ST, Johnson LB. Laparoscopic living donor nephrectomy and multiple renal arteries. Am J Surg 1998; 176: 559–563.