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Early Urethral (Foley) Catheter Removal Positively Affects Length of Stay After Renal Transplantation

Kidney transplantation is cost-effective therapy for end-stage renal disease relative to dialysis (*1*). The most significant contributors to the overall expense are the costs associated with the transplant procedure itself and the length of the initial hospitalization (*2*, *3*). We hypothesized that early removal of the urethral (Foley) catheter would lead to faster recovery and earlier discharge from the hospital. At our center, Foley catheter removal is dictated by individual surgeon preference and occurs on postoperative days 2, 3, or 5.

We performed a retrospective analysis of 141 consecutive renal transplants at the University of Pittsburgh Medical Center from 1 July, 2005 to 1 January, 2006. Kidney transplant recipients were divided into two groups: group A, in whom Foley catheter removal occurred on postoperative day 2; and group B, in whom removal occurred on postoperative days >2. Exclusions included patients who expired within the perioperative period prior to discharge (one in each group). The following endpoints were analyzed: length of stay, acute urinary retention requiring reinsertion of Foley catheter, urine leak, and readmission within 30 days of transplantation. All patients had double J ureteral stents (6 F×12 cm) placed at the time of transplantation. Stents were removed approximately 6 weeks posttransplant. The immunosuppressive regimen included 30 mg alemtuzumab (Campath-1H; Berlex, Seattle, WA) followed by steroid-free posttransplant low-dose tacrolimus monotherapy.

There were 66 patients in group A and 75 patients in group B. The 66 patients who underwent urethral catheter removal at day 2 (group A) were similar to the 75 patients who underwent urethral catheter removal >day 2 (group B) in terms of recipient age, race, and sex, and cold ischemia time (Table 1). Group A comprised proportionately more deceased donor kidney transplantations (100% vs. 49%) and exhibited more delayed graft function (33% vs. 16% $P=0.0164$). The median length of stay was 3.2 days in group A compared to 5.0 days in group B ($P=0.0014$). Urinary retention requiring reinsertion of the urethral catheter occurred once in group A (1.5%) and twice in group B (2.6%). There were no urine leaks. Readmission within 30 days of transplantation was significantly associated with delayed graft function ($P=0.0164$) and longer posttransplant length of stay ($P=0.0014$), but not day of urethral catheter removal ($P=0.1430$).

This analysis of adult kidney transplant recipients demonstrated that Foley catheter removal on posttransplant day 2 is safe and optimizes length of stay, compared to Foley removal on posttransplant days 3–5. Length of stay is a large factor contributing to the cost of kidney transplantation; successful efforts to decrease length of stay, including establishment of an intensive outpatient unit (*1*) and implementation of clinical pathways (*2*) have optimized costs of kidney transplantation (*1–3*). The practice in many institutions is to remove the Foley catheter between 3–6 days after transplantation (*4*, *5*). We have demonstrated that earlier removal is a simple and inexpensive means of reducing length of stay without compromising safety and quality of care.

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TABLE 1. Donor and recipient demographic and transplant characteristics

Characteristic	Group A	Group B	*P* value
n	66	75	
Recipient age, years	56.5±15	53.6±15	0.2531
Recipient sex: male (%)	34 (52)	47 (63)	0.1814
Recipient race: white (%)	53 (80)	53 (75)	0.3536
Recipient renal disease (%)			
Glomerulonephropathy	17 (26)	24 (32)	
Hypertension	16 (24)	18 (24)	
Diabetes	15 (23)	16 (21)	
Other/unknown	18 (27)	17 (23)	
Donor age, years	45.2±16	41.7±15	0.1814
Cold ischemia time, minutes	1,566±524	1,405±429	0.1144
Length of stay, days	3.19	5.00	0.0014
30-day readmission (%)	15 (23)	10 (13)	0.1430
Delayed graft function (%)	22 (33)	12 (16)	0.0164

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Received 5 October, 2006.
Accepted 19 October, 2006.
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ISSN 0041-1337/07/8307-995

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DOI: 10.1097/01.tp.0000259723.92943.8f

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N,N,N-Trimethylglycine (Betaine) Improves Analysis of CDR3 Diversification in Children Reconstituting Their Immune Repertoire After Hematopoietic Stem-Cell Transplantation

Reconstitution and diversification of the B cell repertoire was monitored at different posttransplant time points in children undergoing related or unrelated donor hematopoietic stem-cell transplantation (HSCT), or autologous transplant (*1*), using the CDR3 fingerprinting technique (*2*). The CDR3 fingerprinting profile obtained from normal donors consists of about 16 to 20 bands, each of which corresponds to a particular HCDR3 length ("polyclonal" profile). This profile is reached 1 year or more after allogeneic or autologous HSCT. In the early posttransplant period, HCDR3 fingerprinting shows a limited number of bands with various degrees of mono or oligoclonality, which is related to slow reconstitution as well as to the immunosuppressive therapies that are administrated to control graft versus host disease (*3*). Clearly, analysis of immune reconstitution is important but particularly difficult in the early time points following HSCT. This difficulty is due to the low number of circulating B cells. Moreover, polymerase chain reaction (PCR) amplification (*4*) of the IgH hyper variable regions that can be rich in guanine and cytosine content or that may form secondary structures could result in poor yield of the expected product.

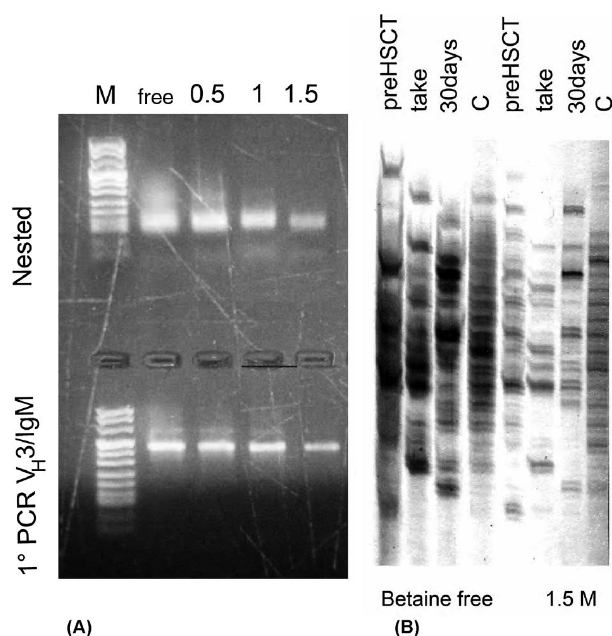

FIGURE 1. (A) 2% First PCR (lower) and nested PCR (upper) amplified with different concentrations of betaine. M, molecular DNA marker VIII; Free, DNA amplified without betaine; 0.5, DNA amplified with 0.5 M betaine; 1, DNA amplified with 1 M betaine; 1.5, DNA amplified with 1.5 M betaine. (B) IgM H CDR3 fingerprinting profile of a 7-year-old child affected by acute lymphoblastic leukemia and subjected to allogeneic HSCT. PreHSCT, 12 days prior to transplantation; take postHSCT, 3 days after polymorphic nuclear cells ≥500 mm^3; 30 days, +1 month posttransplantation; C, normal control. On the left: sample amplified without betaine; on the right: sample amplified with 1.5-M betaine.

Several additives with proven beneficial effects on reaction efficiency can be included in PCR amplification (*5*, *6*), but each target requires different agents to increase yield and specificity (*7*, *8*).

In our experience, DNA amplification of IgH hyper variable regions was improved by N,N,N-trimethylglycine (betaine). Betaine is an isostabilizing amino acid analog that equalizes the contribution of guanine-cytosine (GC) and adenine-thymidine (AT) base pairing to DNA duplex stability (*9*, *10*).

Using betaine as the additive agent in two series of PCR amplifications played a fundamental role in the molecular study of IgM expression in children after HSCT (*1*, *3*).

Peripheral blood mononuclear cell harvest, RNA extraction, cDNA synthesis, and PCR profiles regarding IgH CDR3 analysis have previously been described (*3*). We found that PCR amplification of CDR3 regions was positively influenced by adding betaine. In fact, we observed more efficient DNA amplification when 1.5 M betaine was added to the reaction mixture in first PCR, followed by the addition of 1-M betaine to nested PCR. A stronger band was obtained at these conditions (see Figure). When the sample was amplified without betaine, or at a low concentration of this reagent, nonspecific bands were present, whereas specificity increased when betaine was added to the mixture at specified concentrations. Comparison of the results that were obtained after analyzing PCR products both by 2% agarose gel electrophoresis and by 6.5% denaturing polyacrylamide gel electrophoresis with silver staining (*3*), again revealed

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better signal resolution (see Figure). This improvement allowed us to analyze B cell reconstitution in 60 pediatric patients with various diseases who underwent HSCT at the Department of Pediatric Hematology and Oncology of the G. Gaslini Institute. It was possible to study the very early time points after transplant (+15 or 20 days postHSCT) for all these patients and, as expected, we observed very strong oligoclonality with regards to CDR3 diversification. In the early days postHSCT the amount of targets is often critical since the absolute number of B cells is usually very low (300–500 lymphocytes per microliter), and thus an improvement of amplification is strongly required.

Our study shows that betaine can be helpful in CDR3 analysis, especially shortly after transplant, by enhancing PCR amplification in difficult conditions, such as in the presence of low-amount targets or of templates difficult to amplify.

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Received 11 January, 2007.
Accepted 11 January, 2007.
Copyright © 2007 by Lippincott Williams & Wilkins
ISSN 0041-1337/07/8307-996
DOI: 10.1097/01.tp.0000258728.02932.02

ACKNOWLEDGMENTS

The authors thank Frances Perricone for English proof-reading and supervision, Dr. Giuseppe Morreale for clinical support, and Dr. Paolo Catarsi for scientific support.

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Tacrolimus Dose in Black Renal Transplant Recipients

Black patients require higher doses of tacrolimus to achieve target blood concentrations than do individuals from other ethnic groups (*1*, *2*) leading to concern that they are under-immunosuppressed in the critical early posttransplant period (*3*). Our cohort of black patients, treated with an initial daily tacrolimus dose of 0.2 mg/kg, had twofold lower dose-normalized blood concentrations (median (IQR) 4.08 (3.6–7.7) ng/mL per 0.1 mg/kg) than white patients (8.51 (5.7–12) ng/mL per 0.1 mg/kg) on day 7 posttransplant ($P<0.001$). These data led to the adoption of a twofold higher initial tacrolimus dose for black patients than our standard regimen.

All black renal transplant recipients transplanted in our center between 1995 and 2005 were studied (Table 1). Twenty-two were of African Caribbean origin, 16 from West Africa, and 1 from East Africa. One patient in the 0.4 mg/kg cohort was switched to sirolimus on day 8 posttransplant. We are reporting a change in standard clinical protocol that did not require ethical approval.

Before July 2002 an initial oral loading dose of 0.2 mg/kg was given preoperatively followed by a maintenance dose of 0.1 mg/kg twice daily (0.2 mg/kg daily). Subsequently, the loading dose was 0.4 mg/kg, followed by 0.2 mg/kg twice daily (0.4 mg/kg daily). Subsequent dosing was directed by thrice weekly measurement aiming for 12 hr postdose whole blood concentration of 15–20 ng/mL for days 0–7 and then 10–15 ng/mL. The dose was adjusted by 20% for results outside the target range except for high concentrations when fewer than 3 doses had been given. The Tacrolimus II immunoassay (Abbott diagnostics, Abbott Park, IL performed on an IMx clinical analyser) was used throughout the study. The laboratory was a member of the International Tacrolimus Proficiency Testing Scheme. Methyl prednisolone (500 mg) was given intravenously perioperatively, then 20 mg of oral prednisolone daily.

On day 7, 21/26 patients (80.8%) in the 0.2 mg/kg group had concentrations below the target of 15 ng/mL compared to 3/13 (23.1%) in the 0.4 mg/kg group ($P=0.03$, Figure 1). All patients in the 0.4 mg/kg group achieved the lower target of 10 ng/mL, that would now be regarded as conventional, on day 7 compared with 16/26 (61.5%) in the 0.2 mg/kg group ($P<0.03$). On day 7, 3/26 (11.5%) of the 0.2 mg/kg group had values greater than 20 ng/mL compared with 7/13 (53.8%) in the 0.4 mg/kg group ($P<0.02$). The blood tacrolimus con-

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TABLE 1. Demographics

	Initial daily tacrolimus dose	
	0.2 mg/kg (n=26)	0.4 mg/kg (n=13)
Female/male	7/19	8/5
Age, yr (median/range)	42.5 (17–71)	41 (25–64)
Transplant number		
1st	25	12
2nd	1	1
Diabetic pretransplant	4 (15.4%)	2 (15.4%)
Cadaveric	23 (88.5%)	11 (84.6%)
Living donor	3 (11.5%)	2 (15.4%)
Donor age, yr (median/range)	39 (16–61)	44 (15–63)
Cold Ischemia time, h (median/range)	17 (0–24)	18 (0–37)
A/B/DR mismatch (median/range)	4 (1–6)	3 (0–5)
DR mismatch 0	3 (11.5%)	8 (61.5%)
1	10 (38.5%)	3 (23.1%)
2	13 (50%)	2 (15.4%)
Panel reactive antibody		
(peak) >50%	3 (11.5%)	2 (15.4%)
(at transplant) >0%	5 (19.2%)	4 (30.8%)
Azathioprine	11 (42.3%)	0 (0%)
Mycophenolate mofetil	6 (23%)	6 (46.1%)
CD25 antibody	6 (23%)	13 (100%)

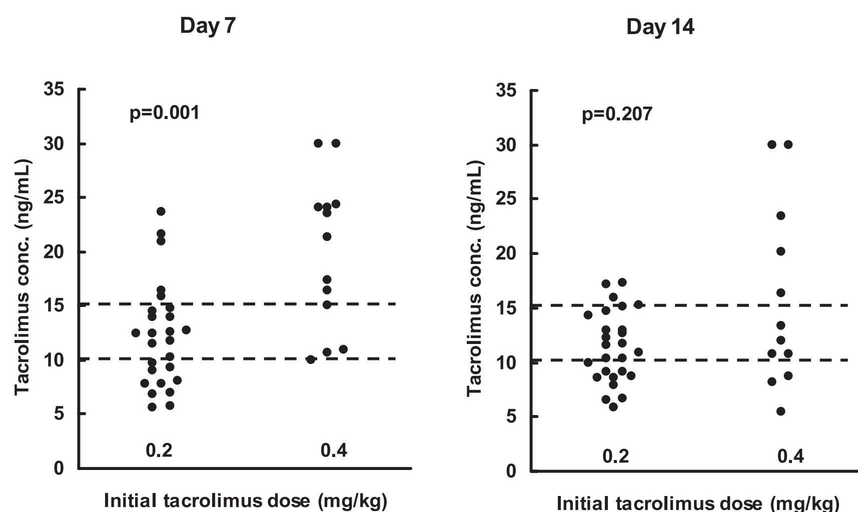

FIGURE 1. Blood tacrolimus concentrations. The 12-hr postdose tacrolimus concentration on days 7 (±1 day) and day 14 (±1 day) after transplantation are shown for individual patients. The dashed lines represent the minimum target blood tacrolimus concentrations at which we were aiming: 15 ng/mL during week 1 and 10 ng/ml during week 2. The area between these lines represents what would now be regarded as an appropriate therapeutic range. Values for the 0.4 mg/kg group were significantly higher than for the 0.2 mg/kg group on day 7 (Mann–Whitney $P=0.001$), but not on day 14.

centration exceeded 15 ng/mL on day 7 in 5/26 patients (19.2%) in the 0.2 mg/kg group and 10/13 (76.9%) with the higher dose ($P<0.007$).

An increase in the initial daily tacrolimus dose from 0.2 mg/kg to 0.4 mg/kg allowed most patients to achieve minimum target blood concentrations during the first week posttransplant, but at the expense of potentially toxic blood concentrations. The degree to which the patients in the 0.4 mg/kg group exceeded the target range was surprising. Tacrolimus exposure increases linearly with increasing doses up to 10 mg (*4*) but there are no published data for higher doses. A possible explanation would be a saturable barrier to drug absorption with greater oral bioavailability at higher tacrolimus doses. An initial daily dose of 0.4 mg/kg is probably excessive and provides the basis for testing an initial starting dose of tacrolimus at 0.3 mg/kg.

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Nidyanandh Vadivel has received a travel grant from Roche. David W. Holt is an advisor to a number of pharmaceutical companies, including Astellas Pharma, on drug pharmacokinetics and monitoring. Rene W.S. Chang has received research and travel grants from Astellas, Roche, Wyeth and Novartis. Iain A.M. MacPhee has received research grants from Amgen, Novartis, Wyeth and travel grants from Astellas, Roche, Novartis.
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Accepted 15 January, 2007.
Copyright © 2007 by Lippincott Williams & Wilkins
ISSN 0041-1337/07/8307-997
DOI: 10.1097/01.tp.0000259248.60448.8a

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Response: Organ Donation and the Law

The recent analysis by C. Rudge (*1*) should remain as a significant milestone in the literature on this topic. As a transplant surgeon, I had opportunities to serve as an expert or as a consultant to lawyers and parliamentary committees in charge of transplantation legislation (mostly in Switzerland where I used to practice). The fact is that a specialist's advice is only one of many that may or may not be taken into account for the final draft of a law. In addition, because it usually takes years until a law is empowered, it may no longer fit contemporary medical and bioethical needs when enacted. Worse, some legislators are tempted to impose such a rigid legal framework that it may make improvements of practice difficult, if not impossible. This possibility is all the more worrisome because, once a law has been passed by a parliament and a government, it is again a lengthy procedure to alter it. In addition to the pertinent conclusions of C. Rudge, it follows therefore that whenever we specialists have an opportunity to give advice to legislators, we ought to put at least as much emphasis on what may harm organ donation as to what may favor it.

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Received 15 January, 2007.
Accepted 15 January, 2007.
Copyright © 2007 by Lippincott Williams & Wilkins
ISSN 0041-1337/07/8307-999
DOI: 10.1097/01.tp.0000259250.57851.20

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