# Acute Graft Pyelonephritis During the First Year After Renal Transplantation

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ABSTRACT

Introduction. Urinary tract infections are the most common infections in renal transplant recipients. Acute graft pyelonephritis (AGPN) is considered a potential risk factor for poorer graft outcomes; however, its clinical impact still remains controversial.

Methods. This study analyzed urine cultures performed within the first 12 months after renal transplantation with reference to clinical data of patients who received a renal transplant at Gdańsk Transplantation Centre between January 2007 and December 2009. Renal function assessed by creatinine concentration and estimated glomerular filtration rate was recorded 24 months after renal transplantation.

Results. This study examined urine cultures and clinical data from 209 renal transplant recipients, including 59.3% men, with a mean age of 46 ± 14 years. We observed 70 AGPN episodes defined as the presence of significant bacteriuria, fever >38°, and/or graft pain and/or acute graft function impairment, including 13 cases of bacteremia, in 46 patients. This accounted for 22% of all diagnosed urinary tract infections. Over 80% of all AGPN episodes were diagnosed beginning from the second month posttransplantation, and the most frequently isolated uropathogen was *Escherichia coli* (65.7%, n = 46). Female sex, vesicoureteral reflux, or strictures at the ureterovesical junction and a history of cytomegalovirus infection emerged as independent predictors of AGPN. The evolution of renal graft function measured by serum creatinine concentration and MDRG eGFR rate did not differ significantly between patients with and without AGPN.

Conclusions. AGPN may be a marker of an underlying impairment of urine flow, eg, due to vesicoureteral reflux or strictures at the ureterovesical junction, whereas it does not affect graft function in renal transplant recipients.

BACTERIAL infections are common complications in renal transplant recipients, with the urinary tract as the most prevalent primary source of infection. The prevalence of urinary tract infections (UTIs) among renal transplant recipients during the first year post-transplantation is up to 60% [1]. Infections are the most common cause of acute kidney allograft injury, and the prevalence of infection-related renal impairment far outnumbers episodes of acute rejection (AR) and calcineurin inhibitor toxicity [2]. Acute graft pyelonephritis (AGPN), including urosepsis episodes, also have potential detrimental effects on long-term graft and renal transplant recipient outcomes.

Pellé et al. showed that AGPN was an independent risk factor for the decline in renal function in a group of 172 renal transplant recipients [3]. Dupont et al. demonstrated that late recurrent UTIs were responsible for renal allograft scarring with multiple focal cortical defects that were not seen in patients with vascular occlusions or chronic allograft nephropathy [4]. However, other reports did not confirm this relationship [5–7]. Even if UTIs do not affect graft

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survival directly, they can exert such an effect indirectly by leading to AR [7,8] or cytomegalovirus (CMV) infection. Kamath et al. reported that AR preceded AGPN in 41% and occurred after an AGPN in nearly 28% of cases [7].

The reports on the influence of UTIs and specifically AGPN on long-term kidney allograft function are inconsistent, and there are also conflicting data on risk factors for UTIs including AGPN in renal transplant recipients. Therefore, the aim of this study was to determine the incidence, microbiology, risk factors, and influence of upper UTIs on renal graft function.

## PATIENTS AND METHODS

We performed a retrospective cohort study reviewing the medical records of patients who received a renal transplant at Gdańsk Transplantation Centre from January 1, 2007, to December 31, 2009. Five patients with renal graft loss and 23 patients who were transferred to another transplantation center after 1 month, and therefore lost to follow-up, were excluded from the study. We compared demographics and clinical data of patients without AGPNs and those suffering from AGPNs. The following variables were considered: etiology of end-stage renal disease, age, sex, comorbidity (estimated with the use of Charlson Comorbidity Index), recurrent UTIs before renal transplantation, dialysis type, pretransplantation dialysis time, repeated transplantation, episodes of AR, acute tubular necrosis, delayed graft function, use of a double-J ureteral stent, type of immunosuppression used (cyclosporine A, tacrolimus, everolimus, mycophenolate mofetil/sodium), induction therapy with monoclonal (basiliximab) and polyclonal antibodies (antithymocyte globulin), CMV infections. To assess renal allograft function, we used serum creatinine concentrations and MDRD estimated glomerular filtration rate at 1, 3, 6, 9, and 12 months posttransplantation.

### Immunosuppressive Treatment

All patients initially were maintained on a triple or quadruple regimen, including induction with monoclonal (basiliximab) and polyclonal antibodies (antithymocyte globulin) in some patients. Patients were given tacrolimus + mycophenolate mofetil/sodium + glucocorticosteroids or cyclosporine A + mycophenolate mofetil/sodium + glucocorticosteroids or cyclosporine A + everolimus + glucocorticosteroids. The treatment of AR consisted of intravenous glucocorticosteroid bolus for 5 consecutive days, followed by a course of antithymocyte globulin in the case of glucocorticoid resistance.

### Prophylaxis for Infections

All patients received ceftriaxone perioperatively, usually for 7 days. This antibiotic was recommended by the hospital's epidemiologist because it takes account of current antibiotic resistance of Gram-negative strains. In the case of positive donor's cultures, the antibiotic was chosen according to susceptibility profiles. A urethral catheter was inserted in each patient perioperatively, and removed between day 4 and 7 posttransplantation, whereas the double-J ureteral stent was removed 4 to 6 weeks after renal transplantation. Recurrent UTIs were considered an indication for a premature double-J ureteral stent removal. All patients received 480 mg of trimethoprim/sulfamethoxazole daily for 6 months. Patients also were educated to drink a lot of fluids and to urinate frequently. Patients also were on vitamin C, and either methylene blue or cranberry preparations.

### Definitions of UTIs

All UTIs were classified into 1 of the 4 following categories: (1) asymptomatic bacteriuria (AB), (2) lower UTI, (3) upper UTI (AGPN), (4) urosepsis. Asymptomatic bacteriuria was defined as isolation of bacterial strain in quantitative counts $\geq 10^5$ colony-forming units (CFU) in clean-catch voided urine specimens in the absence of any symptoms of lower or upper UTI (including leukocyturia; and in women, in 2 consecutive specimens, the second obtained after at least 24 hours) or $<10^5$ CFU in patients treated with antibiotics or $\geq 10^2$ CFU in a single catheterized urine specimen. Lower UTI were diagnosed in the presence of bacteriuria and clinical manifestations of dysuria, frequency, or urinary urgency and fever $<38^\circ$C in the absence of AGPN criteria. Upper UTI was defined by the presence of significant bacteriuria, fever $>38^\circ$C, and/or graft pain and/or acute graft function impairment. The diagnosis of urosepsis was made when simultaneous positive blood and urine cultures were obtained with the isolation of the same bacterial strain.

UTIs were classified as a new infection, relapse, or reinfection. Relapse was defined as the isolation of the same microorganism that caused the preceding infection in a urine culture obtained $\geq 2$ weeks after finishing the previous treatment. Reinfection was defined by a new episode of UTI with the isolation of an agent other than the one that caused the previous infection. Cases of AB were considered cured after obtaining 2 negative consecutive urine cultures. In symptomatic UTIs, an additional criterion was a complete resolution of clinical and laboratory symptoms.

### Antibiotic Treatment

Every diagnosed episode of a UTI was treated with antibiotics, including cases of AB. In AB, antibiotics chosen according to the susceptibility profile were administered for a period of 7 to 14 days. In symptomatic infections, empirical treatment was initiated usually with amoxicillin clavulanate or ciprofloxacin and then changed according to susceptibility profiles, unless clinical response to initial treatment was satisfactory. In lower UTIs treatment lasted 7 to 14 days, whereas in upper UTIs it lasted at least 14 days.

### Statistical Analysis

All analyses were performed using Statistica 10.0 (StatSoft) software. The 2-tailed Student unpaired $t$ test was used to compare continuous variables, and the Fischer exact test was used to compare proportions. To assess the significance of changes of renal graft function measures, a 2-way ANOVA for the repeated measures was used. Logistic regression analyses were performed to find independent risk factors for AGPN. Statistically significant variables in the univariate analysis were introduced in a multivariate model based on forward stepwise logistic regression. Associations are given as odds ratios (ORs) with a 95% confidence interval (CI); $P \leq .05$ was considered to be statistically significant.

## RESULTS

We analyzed demographic and clinical data, together with urine cultures, of 209 consecutive renal transplant recipients, 85 women and 124 men with a mean age of 46.38 ± 14.05 years and mean dialysis duration of 26.56 ± 30.61 months. The etiologies of end-stage renal failure were as follows: primary glomerulonephritis (70, 33.5%), autosomal dominant polycystic kidney disease (32, 15.3%), diabetic nephropathy (23, 11.0%), hypertensive nephropathy (17,