Acute Kidney Injury in Children with Kidney Transplantation

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Abstract
Background and objectives AKI is associated with progression of CKD. Little is known about AKI after kidney transplantation in pediatric recipients. We aim to describe the epidemiology, risk factors, consequences, and outcomes of AKI in this population.

Design, setting, participants, & measurements We performed a retrospective longitudinal analysis of pediatric kidney transplant recipients followed at The Hospital for Sick Children (Toronto, Canada) from 2001 to 2012. AKI was defined as an increase in serum creatinine ≥1.5 times baseline, and a rise of serum creatinine ≥1.25 but <1.5 times baseline defined subacute AKI.

Results Of 179 children, 122 were eligible for analysis. At baseline (3 months post-transplant), median age of the children was 13 years old (interquartile range, 9–16 years old), and 53% had CKD stage 2. Congenital anomalies of the kidney and urinary tract accounted for 46% of children. Over the study period (12 years), the incidence of AKI was 37% (n=45 children), and 65% (79 children) experienced subacute AKI. Twenty-seven percent (33 children) did not develop AKI or subacute AKI. The main causes of AKI were infections other than urinary tract infections, rejection, and urinary tract infections. In a multivariable Poisson regression analysis, independent risk factors for AKI included younger age, girls, grafts from deceased donors, and lower baseline eGFR. AKI was significantly associated with lower long-term GFR and graft loss independent of rejection episodes. Moreover, subacute AKI was associated with progression of CKD.

Conclusions AKI and subacute AKI were common after pediatric kidney transplantation, and they were associated with graft loss, lower eGFR, and more rapid progression of CKD.


Introduction
Since the establishment of a universal and standard definition of pediatric AKI (1,2), many studies have described AKI in different pediatric subgroups, including very low–birth weight infants and critically ill children (3–7). Little information, however, exists regarding the occurrence of AKI in pediatric kidney transplant recipients. AKI has been independently associated with worse outcomes in adults and children, including prolonged hospitalization, morbidity, and mortality. As such, it is of particular concern in immunosuppressed children, such as pediatric kidney transplant recipients (4,5,8–12). In addition, there are pediatric and adult studies showing that a smaller rise in serum creatinine (≥1.25 times baseline or an increase of 0–0.5 mg/dl) can affect outcome (duration of mechanical ventilation and mortality) (13–15). The perception exists that perturbations of serum creatinine are fairly benign given potential reversibility. However, a number of studies have shown that those with AKI are at higher risk of developing CKD (16–19) and conversely, that CKD seems to be an important risk factor for AKI (20,21). AKI in kidney transplant recipients is common and was associated with transplant failure and death in a secondary data analysis of adult recipients from the US Renal Data System (22). In addition, the risk of AKI was increased with more advanced stages of CKD (23).

Since the advent of diagnostic criteria for AKI, the epidemiology of AKI in pediatric kidney transplant recipients is not well defined. The aims of this study were to (1) describe the incidence and etiology of AKI and subacute AKI in a pediatric kidney transplant population, (2) determine the main risk factors for AKI in children who underwent kidney transplantation, (3) evaluate and compare outcomes between pediatric kidney transplant recipients with and without a history of AKI and subacute AKI, and (4) describe the extent to which AKI is unrelated to acute rejection, a risk factor for progressive graft dysfunction.

Materials and Methods
Definitions
AKI was defined as an increase in serum creatinine ≥1.5 times the baseline value, and the three stages of
AKI were defined as per the Kidney Disease Improving Global Outcomes (KDIGO) guideline (1,2,24). Urine output criteria were not used due to missing data in many children. Subacute AKI was defined as an increase in serum creatinine ≥1.25 but <1.5 times the baseline level. Baseline serum creatinine was defined as the average of the three most recent serum creatinine measurements before the study period. With serum creatinine instability immediately post-transplant, the initial time point of the study was 3 months post-transplant. If the baseline serum creatinine changed over time, the subsequent baseline serum creatinine was the average of the most recent three serum creatinine values before the AKI or subacute AKI episode. We used the modified Schwartz formula to calculate eGFR (25). The end point occurred when the graft failed, when the participant was transferred to another pediatric or adult center, or on December 31, 2012. The eGFR at discharge was the last available eGFR before the end of the recruitment period. eGFR decline was defined as baseline eGFR minus discharged eGFR. The following definitions were used for causes of AKI and subacute AKI: urinary tract infection: the presence of bacteriuria ([at least 100,000 bacteria per 1 ml] and significant pyuria (>10/mm³]); infection: any viral or bacterial infection other than urinary tract infection; rejection: confirmed by biopsy; genetic cause of ESKD: nonglomerular diseases caused by known genetic mutations; high tacrolimus exposure: a level >1.5 times the target level as per our protocol (target trough levels change during follow-up and also, immunologic risk); and unknown causes with an elevated serum creatinine in an asymptomatic child: on the basis of self-report or report by the child’s caregiver of prescribed daily fluid intake. All children were on our standard immunosuppression protocol at the beginning of the study, which includes tacrolimus, mycophenolate mofetil, and steroids. Some children deemed low risk were not on steroids. Seventeen children were changed from tacrolimus to sirolimus at some point in their follow-up for different reasons, including calcineurin inhibitor toxicity.

Study Population and Design
We performed a retrospective longitudinal analysis of all kidney transplant recipients <18 years of age followed at The Hospital for Sick Children in Toronto, Canada between January 1, 2001 and December 31, 2012. The exclusion criteria are shown in Figure 1. The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the research ethics board at The Hospital for Sick Children. The requirement for participant consent was waived.

Clinical Data and Outcomes
Clinical and biochemical data were obtained from the electronic patient record during inpatient admissions and outpatient clinic visits. Clinical outcomes included decline in eGFR and graft failure. Each episode of AKI and subacute AKI was reviewed using the electronic health

Figure 1. | Inclusion and exclusion criteria and AKI/subacute AKI incidence over a 12-year period (January 1, 2001 to December 31, 2012).
record to confirm the sudden elevation of serum creatinine and corresponding etiology.

Analyses
Medians and interquartile ranges (IQRs) were used for continuous variables and percentages were used for categorical variables for descriptive statistics of the study population. Pearson chi-squared tests or Fisher exact tests were used to compare categorical variables, whereas t tests were used to compare continuous variables. The Wilcoxon–Mann–Whitney tests or Kruskal–Wallis tests were used for continuous versus categorical variables. Poisson regression analysis was used to model frequency of events (AKI frequency) (26). Univariable Poisson regression analysis was used to evaluate the association between AKI frequency and AKI risk factors (age at baseline [i.e., at 3 months post-transplant], sex, etiology of ESKD, donor type [living versus deceased], baseline eGFR, pretransplant panel reactive antibody, and history of dialysis pretransplant). Subsequently, multivariable Poisson regression assessed independent risk factors for development of AKI while controlling for risk factors and accounting for baseline eGFR in all models. Evaluation of interaction terms of AKI and other variables and model fit using deviance goodness of fit tests were performed. eGFR decline was compared between children with and without AKI and among groups with different frequencies of AKI episodes (no AKI, one to two episodes of AKI, and greater than or equal to three episodes AKI) in the overall cohort and in a subcohort of children with no evidence of graft rejection. A similar analysis was performed to assess the association of eGFR decline between children with subacute AKI and children without subacute AKI (after excluding children with AKI) and among children with different frequencies of subacute AKI in the non-AKI cohort and children without AKI and without rejection. Because GFR may decline over time, we conducted sensitivity analyses, in which we performed the same analyses but limited them to a follow-up at 2 years from baseline and other regression analyses controlling for transplant vintage. Statistical significance was taken as a P value of <0.05. Data were analyzed using the STATA statistical software (version 12). This manuscript adhered to “Strengthening the Reporting of Observational Studies in Epidemiology” guidelines.

Results
Study Population
One hundred seventy-nine children underwent kidney transplantation at The Hospital for Sick Children between January 1, 2001 and December 31, 2012. Fifty-seven children were excluded for different reasons (Figure 1). Table 1 shows the clinical characteristics and demographics of the 122 children who formed the final study population. The median age at baseline was 13 years old (IQR, 9–16 years old), and the majority of children (64%) were boys. Congenital anomalies of the kidney and urinary tract were the underlying cause of ESKD in nearly one half (46%) of the children. More than one half of the grafts came from deceased donors (57%). Median time from baseline to the first episode of AKI was 15 months (IQR, 3–33 months). The median dialysis duration before transplantation was 8 months (IQR, 0–19 months), and the median follow-up duration from baseline until the end of the study period was 28 months (IQR, 12–64 months). The majority of children (53%) had a baseline eGFR consistent with CKD stage 2. The median numbers of creatinine measurements per child in the first and second years were 44 (IQR, 37–65) and 19 (IQR, 14–32), respectively, and the median number of days of creatinine measurement before the AKI episodes (baseline creatinine) was 3 (IQR, 1–8).

Incidence and Etiology of AKI and Subacute AKI
Of the 122 pediatric recipients, 45 (37%) developed at least one episode of AKI over a median follow-up duration of 28 months (IQR, 12–64 months). Among children with AKI, 35 children had at least one episode of subacute AKI, and ten never had subacute AKI. For the remaining 77 children who never had AKI, 44 children developed at least one subacute AKI episode. The overall incidence of subacute AKI was 65%, where 79 children had at least one episode of subacute AKI over the same follow-up period (Figure 1). In total, 97 episodes of AKI and 213 episodes of subacute AKI occurred during the study period. The average numbers of AKI and subacute AKI episodes per child were 0.8 (range, 0–6) and 1.7 (range, 0–8), respectively. The majority of AKI episodes were associated with intercurrent infections (31%) and episodes of rejection (28%), whereas infection and unknown etiology were associated with the majority of subacute AKI episodes (31% each) (Table 2).

AKI Risk Factors
In the univariable Poisson regression analysis, age, sex, donor type, and pretransplant panel reactive antibody were associated with AKI frequency. In the final model of the multivariable Poisson regression analysis, only age, sex, donor type, and eGFR were statistically significant independent factors associated with AKI frequency (Table 3). There were no significant interactions between the variables, and the model fit was appropriate.

AKI and Subacute AKI as Risk Factors for Decrease in GFR
Using the Wilcoxon rank sum test, a statistically significant difference (P value <0.01) of eGFR decline was found in the AKI versus non-AKI group (Figure 2A) and in different AKI frequency categories (Kruskal–Wallis test; P value =0.002) (Figure 2B).

Forty-four children had a history of at least one episode of subacute AKI with no overt AKI episodes, whereas 33 children had neither AKI nor subacute AKI (Figure 1). When comparing these two groups (after excluding children with a history of AKI [n=45]), the eGFR decline was significantly higher in the subacute AKI group (P value <0.001) (Figure 2C). When comparing subacute AKI frequency categories, the same result was obtained (P value <0.001) (Figure 2D). Comparing children with a history of AKI and subacute AKI (n=35) and children with no AKI but with a history of subacute AKI (n=44), there was a borderline statistical significance (P value =0.05). The eGFR decline in children with subacute AKI who have had AKI (n=35) was not different than that of children with a history of AKI but no subacute AKI (n=10; P value =0.10); however, these subgroups were small.
When comparing AKI stages and GFR, we observed that the eGFR decline was significantly associated with advanced AKI stages (AKI stage 3 versus stages 1 and 2 versus no AKI; *P* value, 0.01).

Nonrejection AKI and Subacute AKI as a Risk Factor for GFR Decrease

When children who experienced rejection were excluded (*n*=35), the eGFR decline was significantly greater in the AKI group compared with the non-AKI group (*P* value <0.01) (Figure 3A), and higher AKI frequency associated with a significantly greater eGFR decline (*P* value =0.03) (Figure 3B). After excluding children with a history of rejection and AKI (*n*=68), similar findings were observed, where subacute AKI was associated with greater eGFR decline than for children without history of subacute AKI (*P* value <0.001) (Figure 3C) and a greater eGFR decline in a higher subacute AKI frequency (*P* value <0.001) (Figure 3D).

### AKI as a Risk Factor for Graft Failure

There were nine episodes of graft failure over the study period. Seven of these had at least one episode of AKI, which was significantly higher than non-AKI (*P* value =0.01). In addition, AKI frequency was significantly associated with graft failure (Fisher exact test; *P* value =0.02).

### AKI and Subacute AKI Adjusted for the Transplant Vintage

To account for transplant vintage, we conducted an analysis in children with available data at 2 years (*n*=108); a...
history of AKI was significantly associated with greater eGFR decline overall and when excluding children with history of rejection (P value =0.02 and =0.04, respectively). When excluding children with a history of AKI (remaining n=87), a history of subacute AKI was significantly associated with greater eGFR decline overall and when excluding children with history of rejection (P value =0.04 and =0.02, respectively). In addition, graft failure was significantly associated with the AKI versus the non-AKI group overall (P value =0.02) in those without rejection (P value =0.04).

In a multivariable linear regression analysis adjusting for the transplant vintage, a history of AKI and subacute AKI were significantly associated with greater eGFR decline in the total population (AKI: β=13.2; 95% confidence interval [95% CI], 4.1 to 22.4; subacute AKI: β=13.4; 95% CI, 4.0 to 22.7) and in the nonrejection population (AKI: β=14.4; 95% CI, 2.1 to 26.7; subacute AKI, β=11.4; 95% CI, 2.3 to 20.6). In addition, in a multivariable logistic regression analysis, AKI was statistically significantly associated with graft failure when adjusting for the transplant vintage in the total population (AKI: β=2.9; 95% CI, 1.08 to 4.7) and in the nonrejection population (AKI: β=2.3; 95% CI, 0.4 to 4.3).

**Discussion**

In this retrospective longitudinal cohort study over a 12-year period, we showed that AKI after kidney transplant is common and that common causes include infections, rejection, and high tacrolimus exposure. Among those with AKI events, the risks of graft failure and significant drop in eGFR are significantly higher compared with those with no AKI.

Only one quarter of children had a stable creatinine over the study period, whereas the remainder had at least one episode of AKI and/or subacute AKI. AKI incidence in our population is about 37%, which is higher than AKI incidence reported in many pediatric studies (3–5,7,23–26). The difference in the incidence rate, however, may be due to different ages studied and/or different populations, including those in pediatric intensive care units, neonates, those undergoing postcardiac surgery, and recipients of solid organ transplants or bone marrow transplantation (3–5,7,13,27–29). AKI incidence is approximately 11% in Medicare-insured adult kidney transplant recipients, but this is likely an underestimate, because the population studied was restricted to hospitalized events (22). In another adult kidney transplant study, the incidence of AKI was 20.4%. However, the participants differ from our own in that the subjects were adults (>18 years of age) and excluded those with deceased donor transplants and recipients of second or third transplants (30).

It is not surprising that infection and rejection were the main causes of AKI. In the era of the newer potent immunosuppressive agents, infection (other than urinary tract infection) is common after transplant, and it is one of the main risk factors for AKI in nontransplant children.

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**Table 2. Etiology of AKI and subacute AKI episodes**

<table>
<thead>
<tr>
<th>Cause</th>
<th>AKI, n (%)</th>
<th>Subacute AKI, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectiona</td>
<td>30 (31)</td>
<td>65 (31)</td>
</tr>
<tr>
<td>Rejection</td>
<td>27 (28)</td>
<td>21 (10)</td>
</tr>
<tr>
<td>UTI</td>
<td>18 (19)</td>
<td>32 (15)</td>
</tr>
<tr>
<td>High tacrolimus level</td>
<td>11 (11)</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Nephrotoxid drugsb</td>
<td>0 (0)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Unknownc</td>
<td>8 (8)</td>
<td>65 (31)</td>
</tr>
<tr>
<td>Othersd</td>
<td>3 (3)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>97 (100)</td>
<td>213 (100)</td>
</tr>
</tbody>
</table>

UTI, urinary tract infection.

aInfection: viral or bacterial infection other than UTI.

bOther than calcineurin inhibitors.

Unknown: elevated creatinine in an asymptomatic child drinking usual prescribed daily fluid intake with no clear cause of high creatinine and a spontaneous return of serum creatinine to baseline.

Others: BK virus nephropathy (three AKI and one subacute AKI), FSGS and FSGS recurrence (one subacute AKI), mechanical obstruction/bladder-emptying problems (four subacute AKI), and post-transplant lymphoproliferative disorder in graft (one subacute AKI).

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**Table 3. Univariable and multivariable Poisson regression analysis of AKI frequency and possible AKI risk factors**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable Analysis IRR (95% CI)</th>
<th>Multivariable Analysis IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agec</td>
<td>0.94 (0.9 to 0.98)</td>
<td>0.93 (0.89 to 0.97)</td>
</tr>
<tr>
<td>Sexb</td>
<td>0.47 (0.31 to 0.7)</td>
<td>0.4 (0.27 to 0.62)</td>
</tr>
<tr>
<td>Donor typea,b</td>
<td>1.9 (1.2 to 2.9)</td>
<td>1.98 (1.2 to 3.1)</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>0.99 (0.98 to 1)</td>
<td>0.98 (0.97 to 0.99)</td>
</tr>
<tr>
<td>Dialysis duration</td>
<td>1.2 (0.72 to 1.9)</td>
<td></td>
</tr>
<tr>
<td>Pretransplant PRA</td>
<td>1 (1.00 to 1.01)</td>
<td></td>
</tr>
<tr>
<td>Etiology of ESKDb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular</td>
<td>1.5 (0.98 to 2.3)</td>
<td></td>
</tr>
<tr>
<td>Genetics</td>
<td>2.2×10⁻² (0)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0.78 (0.41 to 1.4)</td>
<td></td>
</tr>
</tbody>
</table>

IRR, incidence rate ratio; 95% CI, 95% confidence interval; PRA, panel reactive antibody.

aAge (baseline age 3 months post-transplant) and donor type (living versus deceased).

bReference subcategory for each of the variables above as follow: sex (girl), donor type (living), and etiology of ESKD (congenital anomaly of the kidney and urinary tract).
The risk of urinary tract infection has been reported at 40%–60% by 3 years post-transplant in pediatric kidney transplant recipients with ESKD secondary to congenital anomalies of the kidney and urinary tract (31). Aki et al. (32) showed that children with lower urinary tract dysfunction have a higher rate of urinary tract infection after kidney transplant. In the 2014 North American Pediatric Renal Trials Collaborative Studies Annual Report, rejection accounted for almost one half of the patients with graft failure (approximately 51%) (33).

Variability in serum creatinine is not uncommon in the clinical setting. In a study of adults, approximately 58% of inpatients experienced variability in serum creatinine of >0.22 mg/dl during hospital admission (34). Other than AKI, many factors, such as laboratory assay variability, dietary variability, hydration status, and certain medications, can lead to fluctuations in serum creatinine (35,36). We detected large percentages of subacute AKI (31%) and to a lesser extent, AKI (8%) episodes with no clear etiology, and all of these events resolved spontaneously. Although it is not clear whether these self-resolving episodes of subacute AKI had long-term adverse outcomes, there is evidence that adult patients with CKD with increased variability in their serum creatinine experience a higher risk of mortality (37,38). Kao et al. (34) found that a creatinine change of >0.1 mg/dl while an inpatient was associated with significantly higher mortality within a year of hospital discharge in adults. Coca et al. (39) reported a twofold increase in the risk of death and a three- to fivefold increase in the risk of death in a meta-analysis of patients with 10%–24% and 25%–49% rises in serum creatinine, respectively.

We found that sex, donor type, and baseline eGFR are independent factors associated with AKI frequency. There is a tendency for younger age to be an independent risk factor for AKI in children after cardiac surgery (6,13,40). Similar findings were reported by Rustagi et al. (41), although other studies have not confirmed an association between younger age and AKI (5). AKI in smaller children has been associated with poorer outcomes (4,42). In our study, the incidence of AKI was higher in girls. The reason for this finding is unclear, particularly given that urologic problems that predispose to AKI are more common in boys (42,43). In children, deceased donor transplants are associated with higher risks of prolonged cold ischemia time, delayed graft function, acute and chronic rejection, and decreased graft survival in comparison with living donor transplants (33). This is consistent with adult kidney
transplant studies showing that deceased donor transplantation is associated with AKI (22,44). Several studies reported a higher incidence of AKI in subjects with CKD and a higher risk of developing AKI with advanced CKD (20–22,45,46).

It is well known that AKI portends a significantly higher risk of developing CKD in nonkidney transplant subjects (47,48). One of the most important findings of our study was the association of AKI with long-term poor graft function and graft loss. This was independent of acute rejection and concurs with adult studies in transplant subjects (22,30). We also sought to assess whether a more modest rise in serum creatinine has negative consequences. Interestingly, we saw the same trend, namely that subacute AKI was associated with decreased GFR on long-term follow-up.

Our study has several limitations. First, this is a single-center study, and therefore, it is difficult to generalize the results to different pediatric populations followed at other institutions. Second, because this is a retrospective study, certain variables could have been potential confounders that were not controlled for in the regression model. Third, using the serum creatinine to estimate GFR has limitations in assessing kidney function. However, a more accurate assessment of GFR using inulin clearance or nuclear GFR is not always practical and carries its own limitations. In addition, we recently validated the modified Schwartz formula in pediatric kidney transplant recipients (49,50). Moreover, most of the children were not hospitalized at the time of onset of AKI; thus, we were unable to obtain a baseline creatinine within 7 days of onset of AKI in many of the AKI episodes as per the KDIGO guideline’s creatinine baseline definition. Collecting data prospectively through the longitudinal design of our study allowed us to capture all AKI episodes in both ambulatory and hospitalized inpatient settings.

In conclusion, AKI or subacute AKI is a common problem experienced by the majority of children after kidney transplantation. More frequent episodes of AKI were associated with worse graft function and graft loss. Special attention must be given to not only AKI but also, subacute rises in serum creatinine to avoid the potential negative long-term consequences.

Disclosures

None.


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