Acute kidney injury in non-critically ill children treated with aminoglycoside antibiotics in a tertiary healthcare centre: a retrospective cohort study

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Abstract

**Background.** Aminoglycosides (AG) cause acute kidney injury (AKI), but the incidence and severity distribution are unclear, particularly in non-critically ill children. We determined the incidence, severity and risk factors of AG-associated AKI and assessed for associations with longer hospitalization and higher costs.

**Methods.** At Texas Children’s Hospital, we conducted a retrospective cohort study of children treated with AG for ≥5 days in 2005, excluding children with admission primary renal diagnoses. AKI was defined by the paediatric Risk, Injury, Failure, Loss, End Stage Kidney Disease (pRIFLE) and Acute Kidney Injury Network (AKIN) definitions. Multiple logistic and linear regression analyses were used to assess independence of associations with outcomes.

**Results.** Five hundred and fifty-seven children [mean±SD age=8.0±5.9 years, 286 (51%) male, 489 (88%) gentamicin] were studied. The AKI rate was 33% and 20% by pRIFLE and AKIN definitions, respectively. Longer treatment, higher baseline estimated glomerular filtration rate, being on a medicine (versus surgical) treatment service and prior AG treatment were independent risk factors for AKI development. AKI by pRIFLE or AKIN was independently associated with longer hospital stay and higher total hospital costs. The pRIFLE definition was more sensitive for AKI detection, but the AKIN definition was more strongly related to outcomes.

**Conclusions.** AKI is common and associated with poorer outcomes in non-critically ill children treated with AG. Future research should attempt to understand how to best define AKI in the non-critical illness paediatric setting.

**Keywords:** acute kidney injury; creatinine; definitions; epidemiology; pRIFLE

Introduction

Acute kidney injury (AKI) in hospitalized adults and critically ill children is associated with poor short- and long-term outcomes [1–6]. Nephrotoxic medication use is a frequent cause of AKI, with aminoglycoside antibiotics (AG) being commonly implicated [7,8]. AG nephrotoxicity results from direct effects on the renal proximal tubular cells leading to acute tubular necrosis and is characterized by lack of oliguria, despite a rise in serum creatinine (SCr) [8–15].

The true incidence and severity distribution of AG-induced AKI is unclear, due to the non-oliguric nature of AG nephrotoxicity which does not prompt SCr assessment and the wide variety of AKI definitions used in previous studies. The recent development of a standard paediatric AKI definition (the paediatric-modified Risk, Injury, Failure, Loss, End-Stage Kidney Disease or pRIFLE criteria) [1,16,17] now enables the systematic study of AKI. A recent update of this definition, the Acute Kidney Injury Network (AKIN) Staging definition, has been proposed but not extensively studied in children [17]. We previously showed in a smaller population that there is little effect on AKI incidence estimation between these two definitions [6], but it is also unclear to what extent using the pRIFLE versus the AKIN definition affects inferences made on AKI–outcome associations in children.

The goals of this study were to determine (i) the incidence of AKI in non-critically ill children who receive AG, (ii) the risk factors for AG-associated AKI, (iii) the effect of AG-associated AKI on hospital length of stay (LOS) and cost and (iv) if defining AKI by pRIFLE versus AKIN definition leads to differences in associations between AKI and outcomes.

Materials and methods

**Setting and patient selection**

We conducted a retrospective database study at Texas Children’s Hospital, Houston, TX, USA. All patients who were hospitalized in non-intensive care units between 1 January and 31 December 2005 and received gentamicin, tobramycin or amikacin for ≥5 days (since AG-induced nephrotoxicity is unlikely before 5 days) [8,18–20] were identified through a
Acute kidney injury in non-critically ill children treated with aminoglycoside antibiotics in a tertiary healthcare centre: a retrospective cohort study

145

Table 1. AKI definition using the estimated glomerular filtration rate criteria of the pRIFLE definition [1] and the serum creatinine criteria of the AKIN Staging[17]

<table>
<thead>
<tr>
<th>Paediatric Risk, Injury, Failure, Loss, End-Stage Kidney Disease (pRIFLE)</th>
<th>Acute Kidney Injury Network (AKIN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI severity</td>
<td>Estimated glomerular filtration rate (eGFR) criteria</td>
</tr>
<tr>
<td>‘Risk’ (R)</td>
<td>Decrease by 25%</td>
</tr>
<tr>
<td>‘Injury’ (I)</td>
<td>Decrease by 50%</td>
</tr>
<tr>
<td>‘Failure’ (F)</td>
<td>Decrease by 75% or eGFR &lt;35 mL/min./1.73 m²</td>
</tr>
</tbody>
</table>

9The original pRIFLE and AKIN definitions also contain urine output criteria which were not assessed in this study. The categories ‘Loss’ and ‘End Stage Kidney Disease’ of the pRIFLE definition, representing renal dysfunction of prolonged duration (>4 weeks and 3 months, respectively), were not assessed for this study.

10Estimated GFR was calculated using the updated Schwartz formula [21].

For the AKIN definition in this study, a subject was not required to achieve SCr rise within a 48-h period to attain AKI status.

pharmacy database. One randomly selected treatment episode per subject was retained. Patients with a primary diagnosis of genitourinary or renal disorder at hospital admission were excluded. The Institutional Review Board of the Baylor College of Medicine approved the study protocol and waived the need for informed written patient consent.

Data collection
The pharmacy database contained the following information: primary service directing care at treatment initiation; date of birth; gender; height; weight; AG treatment duration; and dosage with all changes. Average daily dose per kilogram during treatment was calculated and standardized across the three AGs by ranking, to allow comparisons in multivariate models. Once versus multiple daily regimens varied according to patient care team practice.

Data from the medical records department included: race (African American, East Asian, white/Caucasian, Hispanic/Latin and other or unknown), principle admission diagnosis, important underlying chronic diagnoses, hospital LOS and total costs for admission.

SCr and AG concentrations drawn from AG initiation to 72 h after treatment end were collected. Baseline SCr was defined as the lowest within 3 months before treatment initiation [1,16]. Baseline estimated glomerular filtration rate (eGFR) was calculated using the Schwartz formula [21]. When no baseline SCr was available, we assumed a Schwartz eGFR of 120 mL/min/1.73 m² and back-calculated SCr [6].

Acute kidney injury definitions
AKI was first defined using the pRIFLE definition (Table 1) [1]. Only SCr values obtained on or after treatment Day 3 were considered, since SCr rise within the first 2 days of therapy would unlikely be directly related to AG nephrotoxicity and could lead to overestimation of AG-specific AKI. The lowest eGFR on or after Day 3 of AG was calculated using the peak SCr. The maximal percent eGFR drop during treatment was calculated [(Baseline eGFR – Lowest eGFR)/Baseline eGFR × 100] to determine the worst pRIFLE AKI category (pRIFLEmax). For comparison, AKI was defined according to the recent AKIN staging [22], whereby acute changes in SCr (rather than eGFR) are considered (Table 1). The AKIN definition stipulates that SCr rise should occur within 48 h to classify as AKI. We were not able to reliably assess SCr rise ‘within 48 h’, since our data relied on blood tests occurring with routine care with frequently missing daily values for SCr. In a sub-analysis, we evaluated AKIN criteria only in those for whom AKI could be reliably determined based on evaluation of rise over 48 h.

Statistical analysis
Continuous variables were expressed as mean±standard deviation (median). Categorical variables were expressed as proportions (%). Continuous variables with highly skewed distributions were natural logarithm transformed for inclusion in multivariate analyses.

Evaluation of AKI risk factors. The AKI event rate and severity by pRIFLE and AKIN were calculated. In subjects with SCr available at initiation of AG treatment (Day 1), we calculated the proportion with AKI on Day 1 and compared the AKI rate on or after Day 3 of treatment between subjects with and without Day 1 AKI. Risk factors for AKI including gender, age, race variables, service of treatment, principal admission diagnostic category, underlying diagnosis of cystic fibrosis or cancer, baseline eGFR, AG type, presence/absence of separate AG treatment in the previous 1 month, AG dose and treatment duration were evaluated by uni- and multivariate analysis. Backward stepwise logistic regression (entry criteria P = 0.1, exit P = 0.2) was used to identify independent risk factors. Hosmer–Lemeshow goodness of fit test (with area under the receiver operating characteristic curve) was used to assess model fit.

AKI as a risk factor. Using stepwise multiple linear regression (entry criteria P = 0.1, exit P = 0.2), AKI was examined as a risk factor for increased LOS and of total costs associated with the admission, controlling for: gender, age, race, baseline eGFR, treatment on a medical versus surgical service, principal admission diagnosis [categorized as suspected proven abdominal infection or process versus other suspected or proven infection or process (including respiratory) versus haematologic or malignancy primary diagnosis), underlying diagnosis of cancer, drug type, drug dose, treatment duration, frequency of SCr monitoring (number of SCr values/treatment days) and number of days in hospital before initiating AG. We performed these analyses using the pRIFLE and AKIN definitions to compare their associations with outcomes. We also performed these analyses including only subjects who had SCr available at AG treatment start and who did not have AKI at treatment start in order to evaluate the effect of new AKI on or after Day 3 of AG treatment on outcomes. Analyses were performed using Intercooled STATA statistical software Version 10 ®, College Station, TX, USA.

Results

Subject characteristics and acute kidney injury rate
The sample comprised 557 subjects (characteristics in Table 2). Most subjects (n = 528 or 95%) were greater than 3 months old. From Day 3 of AG treatment onwards, 88 of 558 (15.8%) subjects had SCr measured at least once a day, 147 (26.4%) measured at least every 2 days, 227 (40.7%) measured at least every 3 days and 267 (48.1%) measured at least every 4 days.

Baseline SCr was known in 315 (56.6%) of subjects. In these 315 subjects, median (25th, 75th percentile) known baseline SCr was 0.4 (0.3, 0.5) mg/dL, and estimated baseline SCr (by backward calculation from the Schwartz formula) was 0.4 (0.3, 0.5) mg/dL, suggesting that the baseline SCr estimation was fairly accurate.
More children were classified as having AKI by pRIFLE versus AKIN (P<0.001, chi-square test); pRIFLE AKI occurred in 184 of 557 (33.0%, 95% CI 29.1–37.1%) subjects, whereas AKIN AKI occurred in 109 of 557 (19.6%, 95% CI 16.3–22.9%) subjects (Table 3). Table 4 displays the details on agreement level between the two definitions [Kappa statistic=0.63 (P<0.001), with overall stratum classification agreement of 84.4%]. More subjects classified as mild (pRIFLE R) AKI who were not classified as having AKI by AKIN. Conversely, more subjects were classified as having severe AKI by AKIN than by pRIFLE (Table 4).

Of 266 subjects with Day 1 SCr values, 93 (35.0%) had pRIFLE AKI, and 59 (22.2%) had AKIN AKI at treatment start (Figure 1). Sixteen (17.2%, pRIFLE) and 11 (18.6%, AKIN) developed a worse final AKI severity after Day 3 (details in Figure 1). It was impossible to determine if Day 1 AKI resolved before attained final AKI status after Day 3, due to missing consecutive SCr values. Subjects with pRIFLE AKI at treatment start had a higher final pRIFLE AKI rate than those who had no Day 1 AKI (79.6% versus 30.6%, P<0.05); similar results were seen when using the AKIN method (69.5% versus 23.7%).

### Table 2. Subject characteristics for all subjects and comparing subjects with AKI versus without AKI by pRIFLE criteria

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects (n=557)</th>
<th>No AKI (n=373)</th>
<th>AKI (n=184)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.0±6.0 (7.3)</td>
<td>7.8±6.4 (6.9)</td>
<td>8.1±5.7 (7.9)</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI percentile (children &gt;= 2 years old, n=437)</td>
<td>63.3±33.8 (77.1)</td>
<td>64.6±33.7 (79.0)</td>
<td>60.5±33.7 (73.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>Weight percentile for length (children &lt;2 years old, n=120)</td>
<td>23.4±19.5 (28.3)</td>
<td>20.1±19.4 (14.5)</td>
<td>28.2±18.9 (23.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Days of aminoglycoside treatment (children &lt;2 years old, n=120)</td>
<td>9.1±5.5 (7)</td>
<td>8.1±4.2 (7)</td>
<td>11.0±7.2 (9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline estimated creatinine clearance (children &lt;2 years old, n=120)</td>
<td>128.1±37.8 (120)</td>
<td>122.1±33.8 (120)</td>
<td>140.2±42.4 (124.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital days before AG treatment (children &lt;2 years old, n=120)</td>
<td>7.3±29.9 (1)</td>
<td>4.8±22.6 (0)</td>
<td>12.4±40.4 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay (children &lt;2 years old, n=120)</td>
<td>18.6±35.3 (10)</td>
<td>14.1±27.6 (8)</td>
<td>27.7±46.1 (13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total costs (USD) (children &lt;2 years old, n=120)</td>
<td>56 793±137 252 (20 196)</td>
<td>38 186±96 264 (16 334)</td>
<td>94 513±190 424 (33 396)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categorical variables</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>286 (51.4)</td>
<td>200 (53.6)</td>
<td>86 (46.7)</td>
</tr>
<tr>
<td>Race</td>
<td>White/Caucasian</td>
<td>189 (33.9)</td>
<td>140 (37.5)</td>
</tr>
<tr>
<td></td>
<td>African-American</td>
<td>88 (15.8)</td>
<td>47 (12.6)</td>
</tr>
<tr>
<td></td>
<td>Hispanic/Latin</td>
<td>233 (41.8)</td>
<td>155 (41.6)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>47 (8.4)</td>
<td>31 (8.3)</td>
</tr>
<tr>
<td>Service of treatment</td>
<td>General paediatric medicine</td>
<td>144 (25.9)</td>
<td>98 (26.3)</td>
</tr>
<tr>
<td></td>
<td>Haematology–oncology</td>
<td>105 (18.9)</td>
<td>42 (11.3)</td>
</tr>
<tr>
<td></td>
<td>Pulmonary</td>
<td>78 (14.0)</td>
<td>50 (13.4)</td>
</tr>
<tr>
<td></td>
<td>Medical subspecialties</td>
<td>50 (9.0)</td>
<td>26 (7.0)</td>
</tr>
<tr>
<td></td>
<td>General surgery</td>
<td>168 (30.2)</td>
<td>148 (39.7)</td>
</tr>
<tr>
<td></td>
<td>Surgical subspecialties</td>
<td>12 (2.2)</td>
<td>9 (2.4)</td>
</tr>
<tr>
<td>Primary admission diagnosis</td>
<td>Appendicitis/peritonitis</td>
<td>139 (25.0)</td>
<td>119 (31.9)</td>
</tr>
<tr>
<td></td>
<td>Other intra-abdominal process</td>
<td>43 (7.7)</td>
<td>32 (8.6)</td>
</tr>
<tr>
<td></td>
<td>Respiratory illness</td>
<td>122 (21.9)</td>
<td>81 (21.7)</td>
</tr>
<tr>
<td></td>
<td>Other type of infection</td>
<td>164 (29.4)</td>
<td>98 (26.3)</td>
</tr>
<tr>
<td></td>
<td>Sickle cell crisis</td>
<td>3 (0.5)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Malignancy/immunodeficiency</td>
<td>45 (8.1)</td>
<td>14 (3.8)</td>
</tr>
<tr>
<td></td>
<td>Other/unclear</td>
<td>41 (7.4)</td>
<td>26 (7.0)</td>
</tr>
<tr>
<td></td>
<td>AG treatment in the previous month</td>
<td>35 (6.3)</td>
<td>15 (4.0)</td>
</tr>
</tbody>
</table>

### Table 3. Comparison of AKI classification by the pRIFLE versus the AKIN definitions

<table>
<thead>
<tr>
<th>AKI severity</th>
<th>pRIFLE criteria n (%)</th>
<th>AKIN staging n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AKI</td>
<td>373 (67.0)</td>
<td>448 (80.4)</td>
</tr>
<tr>
<td>pRIFLE R/AKIN Stage 1</td>
<td>138 (24.8)</td>
<td>69 (12.4)</td>
</tr>
<tr>
<td>pRIFLE I/AKIN Stage 2</td>
<td>44 (7.9)</td>
<td>26 (4.7)</td>
</tr>
<tr>
<td>pRIFLE F/AKIN Stage 3</td>
<td>2 (0.4)</td>
<td>14 (2.5)</td>
</tr>
</tbody>
</table>

### Table 4. Depiction of level of agreement between pRIFLE and AKIN AKI definitions

<table>
<thead>
<tr>
<th>pRIFLE</th>
<th>No AKI</th>
<th>pRIFLE R</th>
<th>pRIFLE I</th>
<th>pRIFLE F</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKIN No AKI</td>
<td>373</td>
<td>69*</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>AKIN 1</td>
<td>0</td>
<td>69</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AKIN 2</td>
<td>0</td>
<td>0</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>AKIN 3</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

*Values in italics represent subjects for whom there was disagreement between the AKIN and pRIFLE definitions.
Acute kidney injury risk factors

Table 2 displays the comparison of subject characteristics between those with and without pRIFLE AKI. Subjects with pRIFLE AKI (versus no AKI) tended to be African American, have longer treatment duration, have higher baseline eGFR, have been treated with AG in the previous month, have been in hospital for longer before initiating AG and be admitted under the Haematology–Oncology service. Subjects on medical services had higher AKI rates than those on surgical services (42.5% versus 12.9%, P<0.001). The AKI rate was highest in subjects with a primary admission diagnosis of haematologic or malignant disease (64.6%), followed by those with suspected or proven infection of non-abdominal origin (37.3%) and subjects with suspected or proven abdominal infection (17.0%).

In a stepwise multiple logistic regression, the following variables were independently associated (P<0.05 in the final model) with AKI by pRIFLE: African American race, underlying diagnosis of cancer, higher baseline eGFR, longer treatment duration, being treated by a medical (versus surgical) care team and presence of AG treatment in the previous month. When AKI was defined according to AKIN, similar risk factors were found, except for African American ethnicity and cancer diagnosis. For both models, the Homer–Lemeshow test suggested good model fit and area under the curves for predicting AKI of 0.77 and 0.82, respectively.

Association of AKI with length of stay and total hospital costs

In stepwise multiple linear regression analyses, the presence of pRIFLE and of AKIN AKI were independently associated with longer LOS, with a stronger association from AKI defined by AKIN (Table 5). Other independent predictors were younger age (P=0.05), being on a medical service (P=0.001), longer treatment (P<0.001) and, as expected, being in hospital for a longer period before initiating AG (P<0.001).

AKI by pRIFLE and AKIN staging were independently associated with higher total hospital costs, with a stronger relationship for AKIN (Table 5). Being on a medical service, longer treatment duration (P<0.001), underlying cancer diagnosis and more hospital days before AG initiation were also independently associated with higher costs. When subjects were classified as having pRIFLE I or F AKI (versus No AKI or pRIFLE R) or as AKIN Stage 2/3 (versus no AKI, Stage 1), the AKI–outcome associations were stronger (shown in Table 5).

When subjects with known Day 1 SCr and no Day 1 AKI were evaluated separately, the presence of AKI on or after Day 3 of treatment remained independently associated with longer LOS and higher total costs, when defined by the AKIN criteria; when defined by the pRIFLE criteria, only pRIFLE I or F AKI remained statistically significantly associated with outcomes (Table 5).

Secondary analyses

Of 109 subjects who fulfilled AKIN criteria for AKI, 59 had SCr measurement frequency and timing available to determine if SCr rise occurred in ≤48 h. Of these, 39 (66%) developed AKI within 48 h [36 (61%) Stage 1; 11 (19%) Stage 2; 12 (20%) Stage 3]. In the remaining 20 subjects, AKI-fulfilling SCr rise occurred over >48 h. Comparing the 39 subjects with ‘within 48-h’ AKI versus those without, there were no significant differences in characteristics displayed in Table 2 (not shown). There were no differences in LOS or total cost outcomes between...
those who did versus those who did not fulfil the 48-h SCr rise criterion, respectively [median (IQR) LOS: 28 (48) versus 28.5 (26.5) days; total costs: $90 092 ($177 097) versus $121 486 ($117 764)].

Our finding that higher baseline eGFR was associated with AKI was unexpected. In a secondary analysis, we evaluated if this occurred due to baseline eGFR over-estimation in subjects with unknown baseline SCr. We re-defined AKI by using the Day 1 SCr (reducing the sample size to 266 subjects) and repeated the stepwise logistic regression analysis for risk factors of AKI: higher baseline eGFR remained independently associated with AKI (OR = 1.02, 95% CI 1.01–1.03). We explored the possibility that malnourished children may have higher risk for AKI and also falsely low baseline SCr. For example, subjects with underlying cancer diagnosis had lower body mass index (BMI) percentile than the rest of the cohort (not shown). We repeated the stepwise logistic regression analysis of AKI risk factors, including BMI percentile and an interaction term of BMI percentile × baseline eGFR. Higher baseline eGFR remained significantly associated with AKI. There was no difference whether pRIFLE or AKIN methods were used to define AKI.

Discussion

Aminoglycosides are filtered at the glomerulus and transported into the proximal tubular cell lysosome by endocytosis, leading to tubular cell necrosis via several mechanisms [9,11]. Our study population represents all children treated with AGs for at least 5 days, over 1 year in a tertiary health care paediatric centre.

Studies from the last 10–20 years describe AG-associated nephrotoxicity rates ranging from 3% to 35% [18–20,23–32] due to variable AKI definitions and study populations. Since the derivation of the pRIFLE and AKIN definitions, paediatric AKI studies have been mostly limited to critically ill populations [1,4,33–37]. One-third of children developed AKI when pRIFLE was used to define AKI; only 19% of children were classified by AKIN staging as developing AKI. This finding is consistent with a previous study wherein we found that the pRIFLE criteria appeared to be more sensitive for detecting AKI [6]. These percentages represent the minimal AKI rate, since we assumed that all children without SCr measurements obtained after Day 3 of treatment did not develop AKI. This information will be useful for calculating conservative sample size estimation in future AKI studies.

While the pRIFLE definition was more sensitive, with more subjects classified as having mild AKI, the association of AKI with outcome was stronger with the AKIN definition, perhaps associated with increased specificity. There is controversy in the adult literature on which definition is more strongly associated with outcome [38–41]. In future studies or trials, if higher sensitivity is desired for AKI diagnosis, the pRIFLE might be favoured, and the AKIN should be used if high specificity is desired. The associations between AKI and LOS and total costs were independent of several factors, including duration of AG therapy. These AKI–outcome associations have been previously established in adult hospitalized patients and in critically ill children [1,3,6]. This is the first study displaying that AKI in non-critically ill children is associated with outcome, whether or not subjects with AKI at treatment initiation are included or excluded. Future prospective studies are required to elucidate a causal link, if present.

An unexpected finding was the persistence of higher baseline eGFR as a predictor of AKI, despite our sensitivity analysis attempts to correct for possible baseline estimation errors or confounding by malnutrition. This issue can likely only be addressed by future studies with reliable anthropometric data. Of note, our known and estimated baseline SCr values were fairly similar within individuals, and regardless of our baseline SCr methods, our AKI–outcome findings remained relatively unchanged. Accurate baseline renal
Acute kidney injury in non-critically ill children treated with aminoglycoside antibiotics in a tertiary healthcare centre: a retrospective cohort study

function estimation in hospitalized children warrants further study.

There were limitations to this study. The use of databases limited us to SCr values obtained during routine care, with inability to accurately describe rate of SCr rise [17]. However, as a first step to understanding non-critical illness AKI, a database study is appropriate, as performed by other initial landmark AKI studies in adults [3,5]. Though we assumed that patients with no SCr values did not develop AKI, this would lead to underestimating AKI occurrence and likely to a reduced AKI–outcome relation (null hypothesis). We had no urine output data due to the sole use of databases. In general, non-critical care units do not accurately record urine output, and AG nephrotoxicity is typically not associated with oliguria. Several large studies in adults [40–42] and our original study on the pRIFLE criteria [1] strongly suggest that the urine output criteria have little effect on final AKI designation and on associations of AKI and outcomes. Future prospective studies should explore this in children and help elucidate how urine output information may improve disease description and prognosis. In children, comparing pRIFLE and AKIN definitions is different from the same comparison performed in adults, since eGFR (in pRIFLE) is simply the inverse of SCr multiplied by a constant (K × height), whereas in adults, eGFR includes other variables [43]. Our findings that pRIFLE is more sensitive for AKI may seem obvious, given the relation between eGFR and SCr. However, the AKIN also states that a 0.3-mg/dL SCr rise qualifies as AKI, regardless of the presence of a 50% SCr rise. We demonstrated that this additional AKIN criterion did not lead to AKI overestimation in this population. However, this cannot be extrapolated to adults, and in younger populations with lower baseline SCr, this finding may also differ. We did not evaluate other nephrotoxins as confounders or effect modifiers of the effect of AKI on outcomes. We also did not include a group of children who did not receive AGs, preventing us from directly attributing AKI to the use of AGs, an issue which will hopefully be addressed by further prospective studies. Although we controlled for several medical factors potentially associated with illness severity (e.g. SCr monitoring frequency; being on a medical versus a surgical service; treatment duration), we could not completely control for illness severity. About 40% of our patients had unknown baseline SCr, which may have impacted on our determination of the presence/absence of AKI. While we do not show this data, we repeated all AKI–outcome analyses (using similar regression methods) by utilizing estimated baseline SCr (via the Schwartz formula) on all subjects; AKI remained an independent predictor of LOS and of total hospital costs (not shown). Most of our cohort was not neonatal. While the pRIFLE AKI rate in neonates (<3 months) was almost identical (39%) to the rest of the cohort (33%), our findings may not be generalizable to this age group.

The AKIN definition stipulates that AKI-defining acute SCr rise must occur within a 48-h period. As noted by others [44], this requirement renders significant limitations to using the AKIN definition with database studies, since very frequent SCr monitoring is necessary, particularly around the day of initial AKI attainment. As a pilot sub-

analysis in AKI patients who had the required SCr measurement frequency, we found that AKI risk factors and outcomes were extremely similar between subjects with and without AKI, by this 48-h constraint. While these are limited preliminary data, we believe that future research should clarify the importance of including the 48-h rise stipulation.

AKI is common in non-critically ill hospitalized children treated with AGs and is associated with longer LOS and higher total hospital costs. Future prospective studies on AG-associated AKI are warranted, and larger-scale studies on early AKI diagnosis using biomarkers and eventually preventative treatments should be initiated.

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