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Original Article

Daily serum creatinine monitoring promotes earlier detection of acute kidney injury in children and adolescents with cystic fibrosis☆

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Abstract

Background: The epidemiology of aminoglycoside-associated acute kidney injury (AG-AKI) has not been well described in pediatric patients with cystic fibrosis (CF). We aimed to assess the impact of daily serum creatinine (SCr) measurement on detection of AG-AKI at our institution.
Methods: We examined a cohort of hospitalized patients with CF who received an intravenous (IV) aminoglycoside for ≥3 days. We compared the rate, timing, and medical management surrounding detection of AG-AKI during 2 periods: January 2010–May 2011 (Era 1, SCr measured at the discretion of the medical team, $N = 124$) and June 2011–June 2012 (Era 2, SCr measured daily, $N = 103$). Our primary outcome was detection of AG-AKI defined as ≥50% increase in SCr from baseline (lowest value in prior 6 months), or ≥0.3 mg/dL rise within 48 h, occurring after day 2.
Results: The use of once daily tobramycin ($p = 0.02$) and IV fluids ($p < 0.001$) was higher during Era 2, while AG courses were shorter ($p = 0.04$), and fewer concomitant nephrotoxins ($p = 0.04$) were given; higher daily tobramycin doses ($p < 0.001$) were administered. Although the rate of AG-AKI was not significantly different (12% during Era 1 vs. 20% during Era 2, $p = 0.09$), the number of AG-AKI days detected increased (5.5 vs. 2.9 per 100 AG days, $p = 0.003$), and detection occurred earlier (median 6 vs. 9 days, log rank test $p = 0.02$) during the daily SCr period.
Conclusions: Daily SCr measurement promoted earlier and increased detection of AG-AKI in patients with CF at our institution. We suggest systematic evaluation for AKI during aminoglycoside administration in patients with CF.

Keywords: Acute kidney injury; Aminoglycosides; Tobramycin; Drug monitoring; Cystic fibrosis

1. Background

Acute kidney injury (AKI) is defined as an acute decrease in kidney function and clinically characterized by an increase in serum creatinine (SCr) or a decrease in urine output. Nephrotoxic medication exposure represents a common cause of AKI in hospitalized children, accounting for 16% of AKI [1]. Acute kidney injury secondary to aminoglycoside use occurs due to accumulation of the drug within the renal proximal tubule epithelial cells [2], develops during 24–30% of AG courses lasting 5 or more days in non-critically ill children,

Abbreviations: AG, aminoglycoside; AG-AKI, aminoglycoside-associated acute kidney injury; AKI, acute kidney injury; CF, cystic fibrosis; CKD, chronic kidney disease; FEV_1, forced expiratory volume in 1 second; KDIGO, Kidney Disease Improving Global Outcomes; IQR, interquartile range; IV, intravenous; mg/kg/day, milligrams per kilogram per day; SCr, serum creatinine; SD, standard deviation.

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and is associated with longer hospital stays and costs [3]. Individuals who sustain AKI are also at increased risk for increased mortality and development of chronic kidney disease [4–7]. Even small changes in SCr of 0.3–0.5 mg/dl are associated with worse outcomes in children and adults [8–12].

Aminoglycoside use during pulmonary exacerbations in cystic fibrosis (CF) is common due to activity against *Pseudomonas aeruginosa*, the most prevalent CF respiratory pathogen. Most reports of AKI in patients with CF have implicated aminoglycosides as the cause [13–19], and the incidence of AKI in CF is significantly higher than in the general population [13]. However, data on AKI in pediatric patients with CF are limited. Among adults with CF, episodes of AKI are associated with decreased kidney function over time [20]. Some authors have also found that repeated intravenous AG use in patients with CF is associated with long-term kidney damage [21]. Therefore, it is crucial to accurately detect AKI among this high-risk patient population.

Traditional monitoring for AKI during AG therapy involves non-systematic SCr measurement that is usually based on patient physiology, past history with the medications, or clinician preference. Non-systematic SCr measurement may underestimate kidney damage in patients with CF [22] and does not accurately characterize the prevalence of kidney injury in this population. In June 2011, our institution implemented a hospital-wide policy whereby all non-critically ill patients receiving aminoglycosides for more than 3 days have SCr measured daily [23]. We sought to characterize AKI according to Kidney Disease Improving Global Outcomes (KDIGO) criteria (see Study Definitions, [24]) during AG administration among our CF population during two time periods: January 2010 through May 2011 (Era 1, prior to the implementation of routine SCr measurement) and June 2011 through June 2012 (Era 2, the period of systematic SCr evaluation). Our goal was to determine the impact of daily SCr measurement on AG-associated AKI detection among patients with CF.

2. Methods

2.1. Study design

We conducted a retrospective cohort study of all hospital admissions from January 2010 through June 2012 in patients with cystic fibrosis during which an intravenous (IV) AG was given for at least three consecutive days at Cincinnati Children's Hospital Medical Center. Patients admitted to the pediatric intensive care unit ($N = 4$) or neonatal intensive care unit ($N = 2$) were excluded because AKI is often multifactorial in the setting of critical illness. A prospective database maintained by the Division of Pulmonary Medicine was used to identify all eligible subjects. Prior to June 2011 (Era 1), SCr was measured at the discretion of the medical team. Starting in June 2011 (Era 2), all subjects had SCr measured daily. During both periods, the interpretation of and response to SCr values was left to the medical team; there were no specific interventions implemented related to reducing AKI during either period. We sought to assess the impact of daily SCr measurement on aminoglycoside-associated AKI detection by comparing AG-associated AKI among the two time periods of our study. The study protocol was approved by our institution's Institutional Review Board with a waiver of consent.

Medical records were reviewed to extract data including demographic and clinical information, past medical history, laboratory measurements, and medication and intravenous fluid administration. A complete list of nephrotoxic medications is listed in Table 1 [11,25]. Intravenous contrast administration was also included as a nephrotoxin. Serum creatinine concentrations were collected from the start of AG administration through 72 h after completion of therapy.

2.2. Definitions

Acute kidney injury was defined as a rise in SCr by at least 50% from baseline or a rise in SCr ≥ 0.3 mg/dL within a 48-h period, which was adapted from KDIGO criteria [24]. A SCr value was only considered AKI if it was at least 0.5 mg/dL. The severity of AKI was also assessed according to KDIGO staging. The baseline SCr was defined as the lowest SCr value obtained within 6 months prior to day 3 of AG course; SCr measurements during an AG course which were lower than the baseline were used for subsequent SCr comparisons only. Days on which SCr was not measured were not considered AKI days unless both the preceding and subsequent SCr measurements met AKI criteria.

Hospital admissions from January 2010 to May 2011 were classified as Era 1, while Era 2 was defined as any hospital admission from June 2011 through June 2012. The first calendar day of AG administration was considered day one. Acute kidney injury prior to day 3 of AG administration may be

Table 1
Nephrotoxic medications collected during chart review.

Antimicrobials		
Antifungals	Antivirals	Antibacterials
Amphoteracin B (liposomal)	Acyclovir	Cefotaxime
Amphoteracin B	Cidofovir	Ceftazidime
	Foscarnet	Cefuroxime
	Ganciclovir	Colistin
	Valacylovir	Dapsone
	Valganciclovir	Nafcillin
		Piperacillin/ Tazobactam
		Ticarcillin/Clavulanate
		Vancomycin
Others		
Antihypertensives	Immunosuppressants and chemotherapeutics	Non-steroidal anti-inflammatory drugs
Captopril	Carboplatin	Ibuprofen
Enalapril	Cisplatin	Ketorolac
Furosemide	Cyclosporine	Naproxen
	Ifosfamide	
	Mesalamine	
	Methotrexate	
	Sirolimus	
	Sulfasalazine	
	Tacrolimus	