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Nonsteroidal Anti-Inflammatory Drugs Are an Important Cause of Acute Kidney Injury in Children

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Objective

To characterize nonsteroidal anti-inflammatory drug (NSAID)-associated acute kidney injury (AKI) in children.

Study design

We conducted a retrospective chart review of children diagnosed with AKI through the use of *International Classification of Diseases, Ninth Revision* diagnosis code 584.5 or 584.9 from January 1999 to June 2010. Medical records were reviewed to confirm the diagnosis of AKI and to quantify NSAID administration. Pediatric RIFLE criteria were used to codify AKI. Patients were not classified as having NSAID-associated AKI if they had a diagnosis explaining AKI or comorbid clinical conditions predisposing to AKI development.

Results Patients

(N = 1015) were identified through *International Classification of Diseases, Ninth Revision* screening. Twenty-one children had clinical, laboratory, and radiographic studies suggesting NSAID-associated acute tubular necrosis and 6 had findings suggesting NSAID-associated acute interstitial nephritis, representing 2.7% (27 of 1015) of the total cohort with AKI and 6.6% when excluding complex patients with multifactorial AKI. Children with NSAID-associated AKI had a median (range) age of 14.7 years (0.5-17.7 years); 4 patients (15%) were <5 years old. Fifteen of 20 children (75%) for whom dosing data were available received NSAIDs within recommended dosing limits. Patients <5 years old were more likely to require dialysis (100% vs 0%, $P < .001$), intensive care unit admission (75% vs 9%, $P = .013$), and a longer length of stay (median 10 vs 7 days, $P = .037$).

Conclusions

NSAID-associated AKI accounted for 2.7% of AKI in this pediatric population. AKI typically occurred after the administration of correctly dosed NSAIDs. Young children with NSAID-associated AKI may have increased disease severity.

Acute kidney injury (AKI) is common in hospitalized children, and its cause in hospitalized children is frequently multifactorial. When a patient has decreased kidney perfusion secondary to decreased blood volume or to decreased effective circulating blood volume, kidney perfusion is maintained in part by the intrarenal generation of prostacyclin.[1] Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenases I and II, decreasing the production of prostaglandins.[2] There is little evidence that NSAIDs decrease renal blood flow in the setting of normal effective circulating volume.[3] However, when true or effective circulating volume is decreased, NSAIDs decrease renal blood flow through blockade of prostaglandin-mediated vasodilation of the preglomerular (afferent) arteriole.[2] This can result in unopposed preglomerular arteriole constriction via the actions of endogenous catecholamines and other vasoactive compounds.[3]

This can lead to decreased glomerular filtration rate (GFR), decreased natriuresis, and as a consequence of the combined effect of NSAIDs and diminished effective circulating volume, can ultimately result in renal ischemia and acute tubular necrosis (ATN).[1]

NSAIDs are common analgesics and antipyretics. Indomethacin, when administered for patent ductus arteriosus closure, results in adverse renal side effects in as many as 40% of neonates.[4] However, little data are available on NSAID-associated AKI in older children.

Preventing AKI, when possible, should be a goal of clinicians. NSAIDs are perhaps the most common avoidable AKI risk to which children are regularly exposed. This underscores the importance of understanding the natural history of NSAID-associated AKI, including the potential for development of chronic kidney disease.

We sought to characterize NSAID-associated AKI in children through a retrospective chart review of patients at a tertiary care children's hospital. We hypothesized that volume depletion and/or supratherapeutic dosing of NSAIDs would be associated with increased severity of NSAID-associated AKI.

Methods

We screened all patients hospitalized at Riley Hospital for Children at Indiana University Health from January 1999 to June 30, 2010, identifying those who had a recorded *International Classification of Diseases, Ninth Revision* code for AKI (584.5 or 584.9). All patients 18 years and younger diagnosed with AKI were eligible for inclusion. Medical records were reviewed to confirm the diagnosis of AKI and to quantify NSAIDs administered before diagnosis.

Patients were not classified as having NSAID-associated AKI if they received other known nephrotoxins or if they had comorbid clinical conditions or diseases predisposing to AKI (eg, complex congenital heart disease, malignancy, sickle cell disease). Patients were also excluded from the case definition of NSAID-associated AKI if they had a clear alternate diagnosis explaining their AKI (eg, hemolytic uremic syndrome, transplant rejection, or acute glomerulonephritis). Neonates receiving indomethacin for patent ductus arteriosus closure were not included. Records of patients were reviewed to determine the general distribution of AKI at our institution.

Although volume depletion is an independent risk factor for AKI, patients with a history of volume depletion in the absence of sepsis or multiorgan failure were not excluded from classification as having NSAID-associated AKI, as it is likely that volume depletion increases the risk of NSAID use leading to AKI.

Patient demographics, NSAID administration history, clinical and laboratory markers consistent with AKI, and treatment data were collected and reviewed. Cost data were obtained from hospital and nephrology physician reimbursement records. Billing and reimbursement data from intensivists, surgeons, and other consultants were not available. The NSAID dose was determined from the medical records as reported by the parents and/or the patient. For in-hospital dosing, NSAID doses were obtained from inpatient medication administration records.

Appropriate weight-based dosage range for each patient was determined based on dose recommendations in Lexicomp,[5] a commonly used medical reference tool in our institution. We performed further analysis of dosing based on adjusted ideal body weight,[6] because several of our patients were obese.

AKI was defined as a serum creatinine above age- and sex-related normal values and an estimated GFR (eGFR) <75 mL/min/1.73 m^2.[7, 8 and 9] The Pediatric RIFLE eGFR criteria[10] were used to stage the level of AKI. Decline of renal function was measured by comparing baseline eGFR with eGFR nadir (eGFR calculated using peak serum creatinine level). This was used to allow quantitative comparisons between patients. Although equations estimating GFR are accurate only in the steady state, comparison of eGFR nadir with baseline eGFR has been previously validated as a measure of severity of kidney injury, most notably in development of the RIFLE and pediatric RIFLE criteria. When baseline creatinine measurement was not available, a baseline eGFR of 100 mL/min/1.73 m^2 was assumed for purposes of pediatric RIFLE classification.[10]

Estimates of volume depletion were obtained from the medical records as reported by the parents and/or the patient. Anuria was defined as no urine output for >24 hours, and oliguria was defined by urine output of <1 mL/kg/h for 24 hours in infants, <0.5 mL/kg/h in children <35 kg, or ≤400 mL in 24 hours for patients >35 kg. Urine output data were used to describe AKI, not for AKI classification.

Analyses

In our laboratory, an enzymatic assay for measuring serum creatinine calibrated to reference measurements by isotope dilution mass spectrometry (IDMS) was implemented on December 6, 2008. Before this, the Jaffe assay was used. The new method of creatinine measurement yields more precise and accurate results, but the absolute values are lower than those obtained with the Jaffe assay. To account for this, the updated equation for eGFR determination proposed by Schwartz et al[9] was used for samples processed on or after this date, and the original equations proposed by Schwartz et al[7 and 8] were used for samples processed earlier.

Of note, pediatric RIFLE used the original Schwartz equation in its analysis of AKI. The original Schwartz equations can be problematic to use with data from IDMS-traceable creatinine assays because they can yield significant overestimations of GFR. Because pediatric RIFLE primarily considers percent change in eGFR in codifying AKI severity, its use is still valid with the updated Schwartz eGFR calculations as long as the same version of the estimating equation is used for each patient. In addition, overestimation of GFR by using the original Schwartz equations on new IDMS-traceable data would underestimate the actual degree of renal impairment experienced by our patients.

Statistical analysis was performed with independent-samples *t* test, Fisher exact test, and Mann-Whitney U test. The study was approved by the Indiana University-Purdue University-Indianapolis institutional review board.

Results

One thousand fifteen patients were identified through initial *International Classification of Diseases, Ninth Revision* screening. Twenty-seven (2.7%) of the cohort were identified to have NSAID-associated AKI. Six hundred seven patients had comorbid conditions and multifactorial AKI. When excluding these children with multifactorial causes of AKI, the incidence of NSAID-associated AKI was 6.6%. Two hundred thirty-three patients had an alternate cause of AKI (eg, obstruction, hemolytic-uremic syndrome, glomerulonephritis). One hundred twenty-seven children had AKI due to an isolated hypoxic, ischemic, or non-NSAID nephrotoxic insult; 21 children had unexplained ATN or acute interstitial nephritis (AIN) without an hypoxic or nephrotoxic insult (Figure).

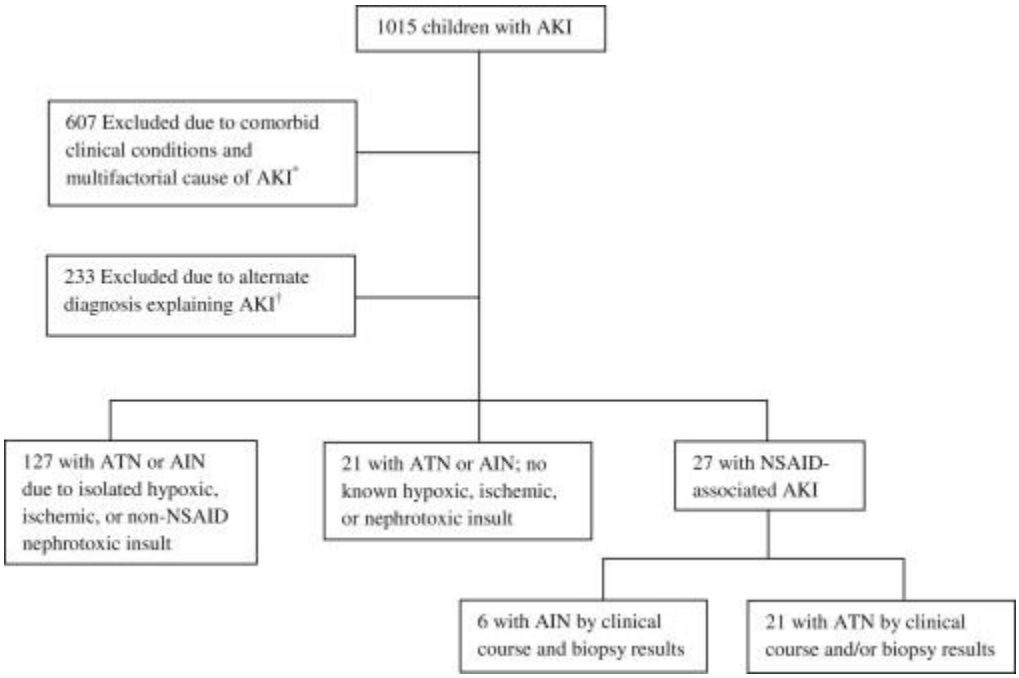

Figure 1 Classification of patients with AKI. ∗Malignancy, complex congenital heart disease, sickle cell disease, etc. †Obstruction, hemolytic uremic syndrome, pyelonephritis, sepsis, transplant rejection, or glomerulonephritis.

Of those patients with NSAID-associated AKI (n = 27), 21 children (78%) presented with clinical, laboratory, radiographic, and/or pathologic studies suggesting NSAID-associated ATN and 6 (22%) with clinical, laboratory, radiographic, and pathologic studies suggesting NSAID-associated AIN.

Demographic and clinical characteristics of the population are presented in Table I. By pediatric RIFLE criteria at time of peak creatinine, 2 patients (7%) were classified as having kidney injury (eGFR decrease of 50%-74%), and the remaining 25 patients (93%) were classified as having renal failure by pediatric RIFLE (eGFR decrease of ≥75% or eGFR <35 mL/min/1.73 m^2).[10] Oliguria or anuria was observed in 6 of 23 patients for whom at least 24 hours of urine output data were available (26%).

Table I.	
Demographic and clinical characteristics of patients with NSAID-associated AKI (n = 27)	
Age, y*	14.7 (0.5-17.7)
Weight, kg†	63.9 (8.3-154.2, SD 37.3)
Age- and sex-specific body mass index percentile	83 (6.8-99.9)
Male patient, No.	12 (44%)
White, No.	24 (89%)
NSAID used, No.	
Ibuprofen	18 (67%)
Naproxen	3 (11%)
Ketorolac	2 (7%)
Ibuprofen and naproxen	2 (7%)
Ibuprofen and ketorolac	2 (7%)
History of volume depletion, No.	18 (67%)
History of decreased urine output, No.	15 (56%)
Duration of NSAID use, d*	4 (1-729)
History of exceeding recommended dose§	25% (5 of 20)
Median eGFR at presentation, mL/min/1.73 m^2*	21 (7-65)
Length of stay, d*	8 (1-24)
Patients requiring ICU stay, No.	5 (18%)
Patients requiring dialysis, No.	4 (15%)
Time to recovery of GFR >75 mL/min/1.73 m2, d*	15 (1-180)

ICU, intensive care unit

∗Data reported as median (range).
†Data reported as mean (range, SD).
‡Length versus weight percentile if age <2 years.
§Dose information unavailable for remaining 7 patients.

Eighteen patients (67%) had a history of volume depletion. eGFR nadir was compared between patients reporting volume depletion and patients for whom volume depletion was not reported. Median eGFR nadir was 12.3 mL/min/1.73 m^2 (range 6.2-36.9 mL/min/1.73 m^2) in patients reporting volume depletion and 23.2 mL/min/1.73 m^2 (range 8.4-48.9 mL/min/1.73 m^2) in patients not reporting any signs or symptoms of volume depletion (P = .076).

The most commonly documented presenting complaints were vomiting (20 patients, 74%), abdominal pain (18 patients, 67%), and decreased urine output (15 patients, 56%); further details are presented in Table II. Twenty-one patients (78%) had been using NSAIDs for <7 days, 2 patients (7%) had been using it between 7 days and 4 months, and 2 patients (7%) had been using it for an unspecified chronic duration. Dosage history for NSAID administration was available in only 20 patients. Fifteen (75%) of the patients received NSAIDs in accordance with recommended dosing. Two patients (10%) received over twice the recommended single dose, and 3 patients (15%) received a dose that was <25% above the recommended upper limit. eGFR nadir was calculated and compared between groups receiving appropriate and supratherapeutic

dosing. Median eGFR nadir was 23.2 mL/min/1.73 m^2 (range 7.8-36.9 mL/min/1.73 m^2) in patients receiving appropriate dosing and 13.1 mL/min/1.73 m^2 (range 7.1-48.9 mL/min/1.73 m^2) in patients receiving supratherapeutic dosing (P = .497).

Because 12 of the 27 patients (44%) were at or greater than the 95th percentile for body mass index or weight:length, we examined dose per adjusted ideal body weight to assess whether obese patients had received doses appropriate for their actual weight but inappropriate for their adjusted ideal body weight.[6] Based on this analysis, 2 additional patients were classified in the "mild overdose" range (<25% above recommended upper dosing limit). However, even in this analysis, 13 of the 20 (65%) for whom dosage history was available received NSAIDs within recommended dosing limits.

AIN as diagnosed on the basis of biopsy and clinical course was seen in 6 patients. Treatment for AIN was pulse methylprednisolone followed by oral steroids in 4 of 6 patients. In 1 patient, a lower dose of methylprednisolone was chosen and was not followed by oral steroids. In 1 patient, no steroids were given.

Unexpectedly, we found that patients <5 years of age were more likely to require renal replacement therapy (100% vs 0%, P < .001), intensive care unit admission (75% vs 9%, P = .013), and a longer median length of stay (10 vs 7 days, P = .037) than were older patients. Renal replacement therapy consisted of peritoneal dialysis with a median duration of 5.5 days (range 2-23 days). Patients <5 years of age did not differ significantly from the group of children ≥5 years of age in terms of ethnicity, NSAID dosing, sex, or body mass index percentile (Table III).

Table III.			
Comparing course and characteristics by age			
	Age <5 (n = 4)	Age≥5 (n = 23)	*P* value
Male patient, No.	2 (50%)	10 (43%)	1
White, No.	4 (100%)	20 (87%)	1
History of exceeding recommended dose<comma> No.*	0 of 1 (0%)	5 of 19 (26%)	1
Body mass index percentile†	55 (26.1-99.5)	87 (6.8-99.1)	0.417
AIN, No.	1 (25%)	5 (22%)	1
Length of stay, d‡	10 (8-24)	7 (1-12)	0.037
Required dialysis, No.	4 (100%)	0 ()	<.001
Required intensive care unit stay<comma> No.	3 (75%)	2 (9%)	0.013

∗ Dose information unavailable for remaining 7 patients.
† Length versus weight percentile if age <2 years.
‡ Data reported as median (range).

Average hospital reimbursement for our 27 patients was $12 502 and average nephrologist reimbursement was $1398. For the patients <5 years of age, average hospital reimbursement was $27 157 and average nephrologist reimbursement was $2796. Patients ≥5 years of age had average hospital reimbursement of $9953 with average nephrologist reimbursement of $1119.

Sixteen of 23 patients with follow-up lab tests available demonstrated a return of eGFR to >90 mL/min/1.73 m^2 at most recent testing. Six had eGFR >60 but <90 mL/min/1.73 m^2, and 1 patient had an eGFR of 56 mL/min/1.73 m^2. None had an ongoing need for renal replacement therapy. Median time from presentation to most recent follow-up laboratory testing available was 272 days (range 20-2728 days).

Diagnostic Studies

Eleven of the 27 patients had a renal biopsy. Findings consisted of AIN with eosinophils consistent with acute drug reaction in 5 patients. One patient had a mixed picture of ATN and AIN, and 2 had ATN with focal active interstitial inflammation, consistent with drug reaction. One patient had acute tubulointerstitial disease, predominantly consisting of tubular necrosis. One patient had blebbing and loss of brush borders consistent with ATN, and another had diffuse ATN with a pattern of proximal tubular injury more consistent with toxic than with ischemic injury.

Twenty-six patients had an abdominal ultrasound. Findings consisted of large echogenic kidneys consistent with medical renal disease in 8 patients, echogenicity without enlargement of kidneys in 5 patients, and increased kidney size alone in 3 patients. One patient had grade III hydronephrosis, and 1 patient had mild right hydronephrosis with increased echogenicity and an absent left kidney. Eight patients had normal ultrasound findings.

^{99m}Tc-mercaptoacetyltriglycine (MAG3) scan was performed in 13 of the 27 patients. Findings consisted of normal perfusion with persistence of radiotracer in the kidneys for >50 minutes consistent with ATN in 7 patients. Three patients had minimal persistence of radiotracer >50 minutes consistent with mild ATN. One patient had poor clearance of radiotracer with left kidney demonstrating 73% of renal mass. One patient had absent left kidney tissue and an enlarged right kidney with adequate perfusion and persistence of radiotracer in the kidney >4 hours. One patient had multiple peripheral defects in the right kidney representing scarring versus infarcts and adequate perfusion with some retention of radiotracer >50 minutes; a subsequent kidney magnetic resonance angiography/imaging did not demonstrate perfusion defects, and on biopsy this patient was found to have interstitial nephritis.

Discussion

As in other recent studies, we found that AKI is most commonly associated with comorbid conditions and that the most common cause of AKI is multifactorial.[11 and 12] NSAID-associated AKI has been previously reported in 54 infants and children through case reports or small case series. Ibuprofen,[13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24] naproxen,[17, 20, 21, 25, 26 and 27] ketorolac,[16, 21 and 28] diclofenac,[17, 27 and 29] dipyrone,[17 and 30] ketoprofen,[13] flurbiprofen,[23] sulindac,[27] rofecoxib,[31] and niflumic acid[32] have all been reported in cases of NSAID-associated AKI, either alone or in combination with other NSAIDs.

Three case series of 6-7 children with NSAID-associated AKI have been reported. Ulinski et al[13] report NSAID-associated AKI in 7 patients; 6 were previously healthy and 1 had a history of a kidney transplant. Ibuprofen was used by 6 of the patients and ketoprofen by 1. The patients all

took NSAIDs in accordance with recommended dosing. Kause et al report 7 patients aged 13-18 years presenting after ingestion of over-the-counter antipyretics, 6 of whom ingested NSAIDs (naproxen, diclofenac, dipyrone, and/or ibuprofen) and 1 who ingested an overdose of acetaminophen.[17] Six patients reported vomiting or less than usual fluid intake. Three patients underwent kidney biopsy, with 1 showing mild interstitial inflammation. Lantz et al reported 7 cases of AKI associated with niflumic acid intake.[32] The medication was given in recommended doses in all 7 cases. Five patients reported decreased oral intake during their acute illness. Five were suspected based on clinical course to have AIN, and 3 of these were confirmed by kidney biopsy. One patient did not recover renal function and required ongoing dialysis. One patient recovered some renal function after 28 days but 6 months later required hemodialysis.[32]

Several other reports of NSAID-associated AKI have been reported and are summarized in Table IV. A total of 54 patients are represented in case reports and series from 1993 to 2009. Twenty-eight (53%) were reported to have decreased oral intake before admission, 38 (70%) used the NSAID for ≤1 week, and 30 of 50 for which data were reported (60%) took normal recommended NSAID doses.

Our study is the largest series to date demonstrating that NSAIDs are a common cause of AKI in children. During an 11.5-year period, NSAID use accounted for 2.7% of episodes of AKI at our institution. However, it should be noted that in our population, many patients who were deemed to have developed multifactorial AKI (and thus were not included in the case definition of NSAID-associated AKI) did have NSAID exposure as one of their multiple risk factors for AKI. Furthermore, many patients in our excluded population developed AKI as a complication of inpatient therapy for an unrelated primary illness or condition. Therefore, we may have underestimated the role of NSAIDs as an etiology of AKI in children. Interestingly, NSAID-associated AKI typically occurred in children who had ingested NSAIDs at the recommended dose.

There may be a trend toward more severe AKI based on eGFR nadir in patients who reported volume depletion, although that did not reach statistical significance. Volume depletion has been previously reported to be a factor in development of NSAID-associated AKI.[1, 3, 13, 17, 29 and 32] There was no statistically significant difference in eGFR nadir in patients taking more than the recommended dose of NSAIDs compared with those with normal dosing.

Surprisingly, we found that younger children with NSAID-associated AKI may have more severe disease than older children. The reason for this finding is unknown but could be due to an increased susceptibility to the toxic renal effects of NSAIDs.

The cost of care by physicians is markedly underrepresented in our calculation, as billing data from intensive care specialists, renal pathologists, pediatric surgeons, and other consultants were not available to be included. During 11.5 years of study, a minimum total of $375 293 was spent at our institution on the care of patients with NSAID-associated AKI. This represents a significant cost, especially when considering that NSAID-associated AKI is avoidable. Further contributing to the health care cost burden in these patients is the cost of chronic kidney disease management. Only 16 of the 23 patients (70%) for whom follow-up lab results were available

returned to an eGFR of >90 mL/min/1.73 m^2, suggesting an increased risk of progressive chronic kidney disease, with its associated costs and complications.

Table IV.								
Reports of NSAID-associated AKI in the literature								
Author (reference)	**No. of patients**	**Decreased oral intake**	**NSAID used**	**Duration of use**	**Recommended dosage used**	**Age, y**	**Peak creatinine, mg/dL**	**Recovery time (creatinine normalized)**
Ulinksi et al13	7	5 of 7	Ibuprofen: 6	1-5 d	7 of 7	13 (4-15)	3.2 (1.9-7.3)	7 d (median)
Ketoprofen: 1								
Lantz et al32	7	4 of 7	Niflumic acid: 7	1-5 d (3-14 d before admission)	7 of 7	0.9-12	1.7-9	4-28 d: 5 patients
								Ongoing impairment: 2 patients
Krause et al17	7 (6	6 of 7	Dipyrone: 2	1-4 d	6 of 7	13-17.5	1.7-8.3	7-16 d
			Ibuprofen: 1 Naproxen/diclofenac: 1					
			Dipyrone/diclofenac: 1					
			Ibuprofen/naproxen: 1					
			Ibuprofen/dipyrone: 1					
	1	No	Zafanello et al14	2 d	Yes: 5 mg/kg/dose	5	6.34	32 d
Moghal et al15	1	Yes	Ibuprofen	7 d (6 doses)	Yes: 5 mg/kg/dose	1.5	5.9	Ongoing impairment
Kallangdowar et al16	2	1 of 2	Ketorolac	2-3 d	2 of 2	0.75; 12	2.2; 6.3	4; 12 d
Wong et al18	1	Yes	Ibuprofen	2 d	Yes: 5 mg/kg/dose	0.75	2.4	21 d
Del Vecchio and Sundel19	1	No	Ibuprofen	2 d	No data	1.2	3.4	9 d
Schaller and Kaplan20	4	0 of 4	Ibuprofen/naproxen: 1	1-4 d	3 of 4	3.5-19	1.7-6	7-90 d
			Naproxen: 1					
			Ibuprofen: 2					
Nakahura et al21	3	1 of 3	Ibuprofen: 1	3-270 d	No data	13-17	2.2-2.6	<1 y: 1 patient
			Toradol: 1					Ongoing impairment: 2 patients
			Naproxen: 1					
Wattad et al22	1	Yes	Ibuprofen	1 d (2 wk before admission)	Yes	14	4.7	21 d
McIntire et al23	2	1 of 2	Flurbiprofen: 1	4-8 d	0 of 2	14-Dec	2.3-5.2	10 d: 1 patient
			Ibuprofen: 1					No data: 1 patient
Kim et al24	1	No	Ibuprofen	1x— only	No	2	2.1	3 d
Kovacevic et al25	1	Yes	Naproxen	4 d (1 wk before admission)	No	17	4	90 d
Becker-Cohen and Frishberg26	2	No	Naproxen: 1	2-30 d	2 of 2	10	6.3	10 d
			Diclofenac: 1					
Kulling et al27	3	0 of 3	Sulidinac: 2	1x— only	No	14-19	2.1-2.3	14 d: 1 patient
			Naproxen: 1					No data: 2 patients
Buck and Norwood28	1	Yes	Ketorolac	3 d	Yes	17	8.4	14 d
Matthews-John et al29	4	4 of 4	Diclofenac: 3	2-180 d	4 of 4	14-Jul	1.7-7.1	3-5 d: 3 patients
			Ibuprofen/diclofenac/indomethacin: 1					Ongoing impairment: 1 patient
Abu-Kishk et al30	3	No data	Dipyrone: 3	1x— only	No	14-17	2.5-4.9	10-12 d
Fletcher et al31	3	1 of 3	Rofecoxib: 3	1-3 d	2 of 3	1.5-14	1.9-3.3	6-28 d

These concerns lead into the question of whether renal functions should be obtained as per routine before the administration of NSAIDs. In the outpatient setting, this would not be feasible, but with increasing recognition of NSAIDs as a cause of AKI and the pathophysiologic understanding of NSAID-associated AKI, ascertainment of renal function may be indicated before NSAID administration to inpatients.

Because this is a retrospective study, we are limited in our ability to draw conclusions regarding timing of onset of AKI with respect to timing of NSAID exposure. Also, the majority of children in our study were previously healthy, so very few had serum creatinine values determined before they presented with AKI. Finally, because many of the patients presented with an acute illness causing dehydration, it is possible that some patients would have experienced AKI even had they not been exposed to NSAIDs. However, given the proposed mechanism of NSAID-associated AKI, it is likely that NSAID use played an important role.

Appendix

Table II.	
Presenting complaints	
Complaint	No.
Vomiting	20 (74%)
Abdominal pain	18 (67%)
Decreased urine output	15 (56%)
Fever	10 (37%)
Headache	10 (37%)
Diarrhea	7 (26%)
Weight loss	6 (22%)
Flank pain	4 (15%)
Hematuria	3 (11%)
Edema	3 (11%)

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