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ORIGINAL ARTICLE

Increasing frequency of acute kidney injury amongst children hospitalized with nephrotic syndrome

Michelle N. Rheault · Chang-Ching Wei · David S. Hains · Wei Wang · Bryce A. Kerlin · William E. Smoyer

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Abstract
Background Nephrotic syndrome (NS) is among the most common kidney diseases seen in children. The major complications of NS include infection, acute kidney injury (AKI), and thromboembolism (TE). The objective of this study was to analyze long-term trends in the epidemiology of major complications of pediatric NS.
Methods We used the Healthcare Cost and Utilization Project Kids' Inpatient Database for the years 2000–2009 to perform an analysis of U.S. hospitalizations of children diagnosed with NS with or without infection, AKI or TE.
Results The frequency of NS hospitalizations complicated by AKI increased by 158 % between 2000 and 2009 ($p < 0.001$). The frequency of NS hospitalizations with infection and TE remained stable overall. Pneumonia was the most common infectious complication while peritonitis decreased by 50 % ($p < 0.001$). Importantly, development of any of these major complications of NS resulted in ~2–3-fold increases in both hospital charges and length of stay.
Conclusions It is concerning that the frequency of AKI in children hospitalized with NS has more than doubled in the past decade. Strategies to prevent or initiate earlier treatments for complications of NS could have a major impact on both morbidity and health care expenses.

M. N. Rheault
University of Minnesota Amplatz Children's Hospital, Minneapolis, MN, USA

C.-C. Wei
Department of Pediatrics, China Medical University Hospital, Taichung, Taiwan

D. S. Hains · W. Wang · B. A. Kerlin · W. E. Smoyer (✉)
Center for Clinical and Translational Research, The Research Institute at Nationwide Children's Hospital, The Ohio State University, Columbus, OH 43205, USA
e-mail: william.smoyer@nationwidechildrens.org

Keywords Infection · Acute kidney injury · Thrombosis · Costs · Length of stay

Abbreviations

NS	Nephrotic syndrome
AKI	Acute kidney injury
TE	Thromboembolism
HCUP	Healthcare Cost and Utilization Project
KID	Kids' Inpatient Database
LOS	Length of stay
ATN	Acute tubular necrosis
RRT	Renal replacement therapy
FSGS	Focal segmental glomerulosclerosis
PCV7	Seven-valent pneumococcal conjugate vaccine
PCV13	Thirteen-valent pneumococcal conjugate vaccine
CNI	Calcineurin Inhibitor

Introduction

Nephrotic syndrome (NS) is among the most common kidney diseases seen in childhood. The incidence of idiopathic NS has historically been reported at 2–3 cases per 100,000 children [1, 2]. NS is characterized by massive proteinuria, hypoalbuminemia, generalized edema, and hyperlipidemia. Children with NS can develop a variety of acute complications that can be potentially serious and life-threatening without prompt diagnosis and treatment. Among these, the major complications of NS include infection, acute kidney injury (AKI), and thromboembolism (TE).

The precise etiologies of these major complications of NS are only partially understood. The massive proteinuria in NS is known to result in losses of immunoglobulins and complement proteins, which are thought to play important roles in the

increased risk for infections, such as spontaneous bacterial peritonitis, sepsis, cellulitis, UTI, and pneumonia [3–6]. In addition, urinary losses of anticoagulant proteins, hyperviscosity, and platelet hyperaggregability are all thought to contribute to the increased risk for TE [7]. Lastly, children with NS are at increased risk for the development of AKI, primarily due to intravascular volume depletion, acute tubular necrosis, interstitial nephritis, nephrotoxic medications, or bilateral renal vein thrombosis [8, 9].

The vast majority of children who develop these complications of NS in the U.S. are admitted to the hospital for treatment. While such complications have been suspected to be developing with increasing frequency and can result in mortality or prolonged morbidity, only minimal information is available regarding the epidemiology, altered mortality, or national health care costs associated with these complications in the modern era. A sound understanding of the epidemiology of NS complications would be an important first step toward the development of successful strategies to prevent and treat these events. We therefore hypothesized that the overall incidence of complications of NS, as well as the costs associated with them, is increasing among children in the U.S. In the current study, we tested this hypothesis by using a large dataset to analyze national trends in the epidemiology of pediatric NS major complications, and to compare the impact of these complications on patient mortality, hospital length of stay, and hospital charges.

Materials and methods

Data source

This study was conducted using the Healthcare Cost and Utilization Project (HCUP) Kids' Inpatient Database (KID), Agency for Healthcare Research and Quality, for the years 2000, 2003, 2006, and 2009 [10]. The KID is the only dataset on hospital use, outcomes, and charges designed to study children's use of hospital services in the United States. The KID is a sample of discharges from all community, non-rehabilitation hospitals in states participating in HCUP. The KID is released every 3 years beginning with 1997 and contains data from 2–3 million pediatric hospital discharges, which occurred during the year of release with validated sample weighting methodology designed to represent the estimated 6–7 million annual discharges nationally. The discharge weighting, based on hospital-level post-stratification on characteristics of urban/rural status, ownership/control, bed size, teaching status, U.S. region, and pediatric hospital status, is provided with the data to allow for calculation of national estimates of utilization and cost. We used the discharge weights provided by the HCUP-KID to weight the sample data in calculating national estimates of utilization and cost [10]. Searching the KID database allows researchers to identify, track, and analyze national trends in health care utilization, access, charges, quality, and outcomes. From 2000 to 2009, the KID has included increasing numbers of state inpatient databases, increasing from 27 states in 2000 to 44 states in 2009, and from 2.5 million discharges in 2000 to 3.4 million in 2009. Beginning with the 2000 edition, the KID has included children 20 years of age and younger. Data on race are missing for a number of states.

Case definitions

Pediatric hospital admissions for NS, as well as the selected major complications, were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes. Nephrotic syndrome was defined as ICD-9-CM codes 581.0-3, 581.8, 581.9, 582.1, and 583.1. Patients with ESRD or post-kidney transplant were excluded from analysis (ICD-9-CM codes 585.5, 585.6, v42.0, and 996.81). Up to 15 diagnoses per discharge are listed in KID from 2000 to 2006, and up to 25 diagnoses per discharge in KID 2009. We searched for NS in any diagnostic position. The major complications of NS were also defined with ICD-9-CM codes. We also included complications of NS listed in any diagnostic position. Infection was defined as *Sepsis/Bacteremia* (995.91-2, 777.81, 790.7, 038.0-4 or 038.8-9), *Cellulitis* (528.3, 681.0-1, 681.9 or 682.0-9), *Pneumonia* (480.0-3, 480.8-9, 481, 482.0-4, 482.8-9, 483.0-1, 483.8, 484.1, 484.3, 484.5-8, 485, 486 or 487.0), *Peritonitis* (567.0, 567.1, 567.2, 567.8, 567.9, or 728.89 for the 2000 and 2003 KID editions and 567.0, 567.1, 567.21-3, 567.29, 567.31, 567.38, 567.39,567.81-2, 567.89 or 567.9 in 2006 and 2009 due to a change in ICD-9-CM peritonitis codes) and *Urinary tract infection* (590.0-9, 595.0-9, 597.0, 597.80-89, 598.0-01, 599.0). Acute kidney injury (AKI) was identified by the 584.5-9 codes or by ICD-9-CM procedure codes for *Renal Replacement Therapy (RRT):* hemodialysis *(*39.95) or peritoneal dialysis (54.98). Thromboembolism (TE) complications were defined by the following codes: 452, 453.0-4, 453.8, 415.11-2, 434.0-1, 434.9, 444.0-2, 444.8-9.

Data analyses

We analyzed hospitalizations of children 18 years of age or younger who were discharged with NS, with and without the major complications listed above. Records that included the HCUP code for "uncomplicated birth" (indicative of a normal, uncomplicated in-hospital birth) were excluded from our analysis. Sample weights provided by KID in each year were used to obtain national estimates of utilization and costs. All parameters including frequencies, percentages, means, and standard errors were weighted statistics for national estimates. We

compared the frequency of hospitalizations with each complication of NS among different years and by demographic characteristic variables including gender, age, race, and hospital region using logistic regression with accounting for survey weights (SURVEYLOGISTIC). Hospital charges and length of stays were compared between NS with any complication and NS without complication within each year by using linear regression methods with accounting for survey weights (SURVEYREGRESSION). Multivariable survey logistic regression was used to test the association of patient and hospital characteristics with AKI. All NS patients for all 4 years were included. Variables included in this model include age, race, sex, region, LOS, TE, and infection. p values <0.05 were considered significant. Statistics based on estimates with relative standard errors (standard error/weighted estimate) >0.30 or with standard errors=0 in the KID statistics were suppressed due to their unreliability. Weighted analyses with ≤10 values in a category were also suppressed due to confidentiality agreements required by HCUP. Dollar values were not adjusted for inflation because comparisons were only made for values within the same year and not between different years. All tests were conducted in SAS 9.3 (SAS Institute, Inc, Cary, NC, USA).

Results

Overall

There was an average of 4,701 pediatric NS discharges per KID release (range, 4,363-5,028). Of these, a mean of 1,039 discharges (range, 977–1,099) were associated with at least one major acute complication. The frequency of hospitalizations with acute complications showed an upward trend over the past decade from 20.8±1.1 % in 2000 to 22.3±0.9 % in 2009 (p=0.11; Fig. 1). NS discharges with an acute comorbidity had a greater than 2-fold risk of in-hospital death (ranging from 0.7 to 1.5 %) compared to uncomplicated NS admissions (<0.5 % in all years, exact values suppressed).

Patient demographics

Overall complications occurred with greater frequency in infants (<12 months old) admitted for NS than in any other age group (Table 1). In comparison to children aged 1–5 years, who had the lowest frequency of complications, the odds ratio for complications for children 3–12 months old ranged from 2.01 (95 % CI, 0.9–4.6) in 2009 to 5.03 (95 % CI, 2.5–9.9) in 2006 (Table 1). Race, gender, and geographic region did not consistently influence the likelihood of NS-related complications (Table 1).

Trends in distribution of acute complications of NS

Infection was the most common complication seen among these pediatric NS encounters, occurring in ~17 % of NS discharges. The overall frequency of infection complicating NS hospitalizations remained stable over the study timeframe (p=0.11; Fig. 1). The most commonly occurring infection overall was pneumonia, followed by bacteremia/sepsis, peritonitis, UTI, and least commonly cellulitis. The frequency of NS hospitalizations with peritonitis significantly decreased overall from 5.0 % in 2000 to 2.5 % in 2009 (p<0.001; Fig. 2). Infants under the age of 1 year had a similar hospitalization frequency with infectious complications compared to older ages, ranging from 14.3 % of hospitalizations in 2009 to 17 % of hospitalizations in 2003 and 2006. Pneumonia was also the most common infectious complication in this youngest age group.

AKI was the second most common complication and was the only complication with a statistically significant shift in frequency over the study period, increasing from 3.3 % of discharges in 2000 to 8.5 % in 2009 (p<0.001; Fig. 1). From 2000 to 2009, the need for RRT with AKI was stable, ranging from 0.7 to 1.0 % of NS discharges (p=0.54). AKI increased by 89 % (p= 0.03) in children age 1–5 years and by 160 % (p=0.02) in children age 6–9 years over the study period (Table 2 and Fig. 3). The greatest increase in AKI was in children age 10–18 years with a 212 % increase from 2000 to 2009 (p<0.001). The frequency of hospitalizations complicated by AKI was stable in children under 1 year of age. Multivariable analysis was conducted to evaluate all NS patients for associations between patient and hospital characteristics and discharge coding for AKI. We found that older patients age 6–9 years (odds ratio=2.38, 95 % CI 1.78–3.17) and age 10–18 years (odds ratio 4.09, 95 % CI 3.15–5.30) had a higher probability of AKI compared to age 1–5 years. Females (odds ratio=1.23, 95 % CI 1.009–1.503) and African Americans (odds ratio=1.305, 95 % CI 1.03–1.66) had a higher probability of AKI. Patients with a longer LOS had a higher probability of AKI (odds ratio=1.036 per day longer, 95 % CI 1.02–1.05). Interestingly, infection (odds ratio= 1.439, 95 % CI 1.15–1.80) was also associated with increased AKI discharge coding. Finally, multivariable analysis supported an increase in AKI in 2006 (odds ratio 2.27, 95 % CI 1.49–3.45) and 2009 (odds ratio=2.76, 95 % CI 1.81–4.20) compared to 2000.

TE was the least common complication, with no significant change in frequency of NS hospitalizations over the time period studied (p=0.80; Fig. 1).

Hospital length of stay, charges per day, and total charges

Mean LOS and total hospital charges were 2–3-fold higher in children with NS complications than in those admitted for NS

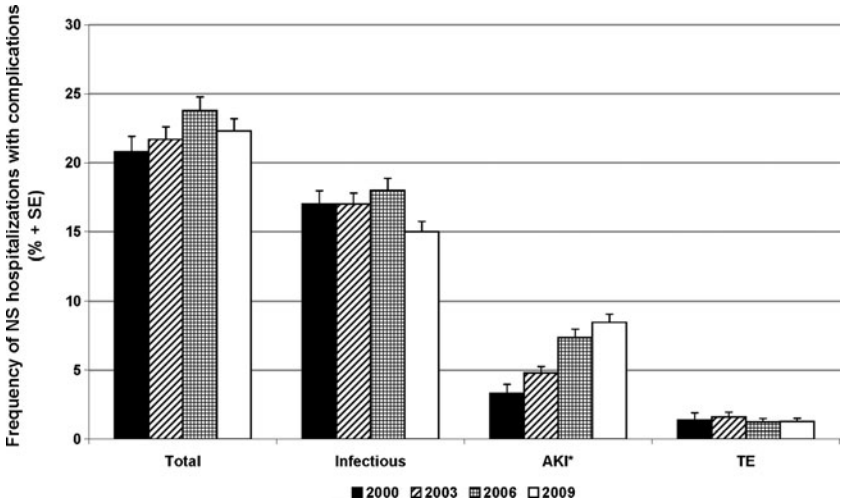

Fig. 1 Infections are the most common acute complication among pediatric nephrotic syndrome (NS) hospitalizations in the US, but acute kidney injury (AKI) is increasingly common. We used logistic regression to analyze trends in frequency of hospitalizations of (NS) with all complications, NS with infection, NS with acute kidney injury (AKI), and NS with thromboembolism (TE). The frequency of hospitalizations for NS with any complication went from 20.8 % in 2000 to 22.3 % in 2009 ($p=0.11$), with AKI increasing from 3.3 % in 2000 to 8.5 % in 2009 ($p<0.001$*). The frequency of NS hospitalizations complicated by infection ($p=0.11$) and TE ($p=0.8$) remained stable

without complications for each year analyzed ($p<0.001$, Table 3). Hospital charges per day were not different for NS patients with complications in comparison to NS patients with no complications for each year analyzed (Table 3).

Discussion

A prior study of the HCUP KID database for the years 2006 and 2009 identified a coded acute complication in up to 60 % of NS discharges with a severe complication (defined as TE, septicemia, peritonitis, pneumonia, or diabetes mellitus) found in 16 % [11]. This study extends the prior analysis to examine trends in the frequency of complications of NS hospitalizations over the past 10 years. In this study, there was a 158 % increase in NS hospitalizations complicated by AKI from 3.3 % in 2000 to 8.5 % in 2009, while the frequency of hospitalization complicated by infection (~17 %) and TE (~1 %) remained stable. The increase in AKI in children hospitalized with NS over the past decade is a concerning finding and deserves further study.

Acute kidney injury is relatively common in adult NS patients, occurring in up to 34 % [12]. The incidence of AKI in children with idiopathic NS is much less common, however, and was reported as 0.8 % (eight of 1,006 children aged 6–17.7 years) in a study including patients from 1990 to 1997 [13]. The reason for the increasing frequency of NS hospitalizations with AKI identified in the present study is unclear. The etiology of AKI in children with NS is variable, and includes pre-renal AKI, acute tubular necrosis (ATN), calcineurin inhibitor (CNI) toxicity, ACE Inhibitor and ARB-induced toxicity, and interstitial nephritis, although data on biopsy findings have rarely been reported. When kidney biopsies are performed in adults during an episode of AKI in NS, they most often demonstrate either acute tubular necrosis (ATN) (55–60 %) or interstitial edema, with rare reports of interstitial nephritis [12, 14]. Patients with NS have several risk factors for ATN. They may be intravascularly volume depleted due to the decreased oncotic pressure that accompanies hypoalbuminemia in NS. Intravascular volume depletion is also often exacerbated by the frequent use of diuretics in this population. Many medications utilized in the treatment of NS, such as the calcineurin inhibitors (CNI) cyclosporine and tacrolimus, can also potentially alter renal perfusion. One randomized controlled trial demonstrated that the acute and reversible nephrotoxicity rate of cyclosporine was up to 50 %, and for tacrolimus was up to 33 % in children with steroid-resistant NS [15]. Since their introduction in the late 1980s as an alternative treatment for NS, CNIs have become a treatment of choice for children with steroid-dependent or steroid-resistant NS [16, 17]. This increasing use of CNIs may partially account for the recent increasing trend in AKI. Other drugs that may alter renal perfusion include angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. While these drugs can be helpful in decreasing proteinuria, they have also been reported as causes of AKI in pediatric NS patients [18, 19]. Medication history is not available in the KID database; therefore we were unable to determine if there was increased use of these medications in our population of patients who developed AKI. Interstitial nephritis is a rare cause of AKI in pediatric patients with NS, and may be due to the use of antibiotics, diuretics, NSAIDS, or complimentary/alternative medicines [20]. Finally, there appears to be an intrinsic decrease in glomerular

Table 1 Younger age, but not gender, race, or hospital region, was associated with increased frequency of nephrotic syndrome (NS) hospitalizations with complications

	2000				2003				2006				2009			
	%	(SE)	OR	*p* value	%	(SE)	OR	*p* value	%	(SE)	OR	*p* value	%	(SE)	OR	*p* value
Gender																
Male	19.2	1.5	1.00		21.8	1.3	1.00		21.9	1.3	1.00		21.1	1.1	1.00	
Female	23.1	1.5	1.3	0.06	22.2	1.2	1.01	0.94	27.1	1.6	1.34	**0.01**	24.2	1.4	1.21	0.07
Age																
0–3 months	32.0	6.7	2.30	**0.017**	38.2	6.2	2.94	**<0.001**	37.6	6.1	2.22	**0.003**	19.2	5.1	1.12	0.73
3–12 months	43.5	10.6	3.77	**0.003**	45.6	6.1	3.98	**<0.001**	57.7	8.6	5.03	**<0.001**	30.3	8.2	2.01	0.07
1–5 years	17.0	1.6	1.00		17.4	1.3	1.00		21.4	1.6	1.00		17.4	1.3	1.00	
6–9 years	23.3	2.5	1.48	**0.04**	21.1	1.7	1.27	0.09	18.7	2.0	0.85	0.30	22.3	1.7	1.36	**0.01**
10–18 years	20.7	2.0	1.28	0.15	22.9	1.5	1.41	**<0.001**	26.5	1.6	1.33	**0.003**	26.4	1.4	1.70	**<0.001**
Race																
Caucasian	20.4	2.1	1.00		23.1	1.4			20.7	1.7	1.00		19.8	1.4	1.00	
African American	18.5	2.2	0.88	0.49	21.3	1.7	0.90	0.38	26.5	2.1	1.38	**0.01**	24.3	1.8	1.21	0.21
Hispanic	24.6	2.7	1.27	0.25	22.2	1.8	0.94	0.62	25.6	2.1	1.34	**0.04**	21.4	2.2	0.99	0.97
Asian and Pacific Islander	21.6	4.5	1.07	0.81	20.1	4.8	0.83	0.63	25.2	3.8	1.29	0.31	24.9	4.2	1.05	0.86
Other	20.4	3.5	1.00	0.99	27.8	3.9	1.25	0.30	36.2	4.7	2.25	**<0.001**	25.0	3.7	1.43	0.12
Unknown	19.6	2.1	1.06	0.74	19.1	2.1	0.74	0.10	20.8	1.7	1.06	0.71	24.5	2.4	1.37	0.05
Hospital region																
Northeast	18.4	1.9	0.76	0.07	19.1	2.1	0.70	**0.04**	24.3	2.8	0.74	0.08	21.1	1.8	0.85	0.31
Midwest	25.4	5.3	1.13	0.66	19.0	2.0	0.68	**0.04**	23.2	1.9	0.65	**0.004**	23.7	1.9	1.05	0.78
South	19.2	1.6	0.82	0.15	23.4	1.4	0.93	0.60	20.4	1.2	0.55	**<0.001**	21.9	1.4	0.92	0.57
West	23.1	1.6	1.00		22.8	1.9	1.00		29.7	1.9	1.00		22.9	2.0	1.00	

We used logistic regression to analyze the difference in frequency of NS admissions with acute complications by gender, age, race, and hospital region. Percentages reported are NS hospitalizations with complications out of all hospitalizations with NS for each category. Infants (age <1 year) were more likely to have acute complications than the reference age 1–5 years for all years except 2009. Race, gender, and hospital region were not consistently associated with increased frequency of NS hospitalization with complications

filtration rate in patients with NS. Lowenstein et al. hypothesized that this decrease in glomerular filtration rate in NS patients is due to severe interstitial edema causing vascular and/or tubular occlusion [21]. Koomans et al. also observed that nearly 30 % of patients with idiopathic NS had transiently decreased glomerular filtration rates, which improved immediately after achieving remission [22]. Alternatively, the reason for the increasing frequency of NS hospitalizations with AKI might be partly explained by increasing awareness of AKI as a complication of NS by physicians, or by improving coding accuracy. Identification of even mild AKI episodes in children hospitalized with NS may be important for follow-up of these affected children, as AKI is now recognized as a risk factor for future chronic kidney disease and hypertension [23, 24].

Patients with NS are also prone to developing bacterial infections. Previously, spontaneous bacterial peritonitis was thought to be the most common life-threatening infection in NS, however there are inadequate data on the spectrum of infectious disease burden in this population [25]. In our study, an average of 17 % of pediatric NS admissions were complicated by infection. In contrast to our prior understanding, we found that the most common infection overall was pneumonia, followed by bacteremia/sepsis, peritonitis, UTI, and cellulitis. Pneumonia has previously been an under-recognized infectious complication of NS, with only scattered case reports or series from developing countries [5, 25, 26]. A recent report from Taiwan, however, also found a high incidence of pneumonia in children hospitalized with NS [27]. These data suggest that physicians should have a high index of suspicion for pneumonia in NS patients.

Rates of peritonitis in children with NS vary widely in the literature, with a recent report describing an incidence of 2.6 % [28]. The most common causative organisms have historically been *Streptococcus pneumoniae* and *Escherichia coli* [4]. The rate of peritonitis in children hospitalized with NS in our study decreased 50 %, from 5.0 % in 2000 to 2.5 % in 2009 ($p < 0.001$). Routine infant immunization with seven-valent pneumococcal conjugate vaccine (PCV7) began in the US in February 2000 [29]. Overall rates of invasive

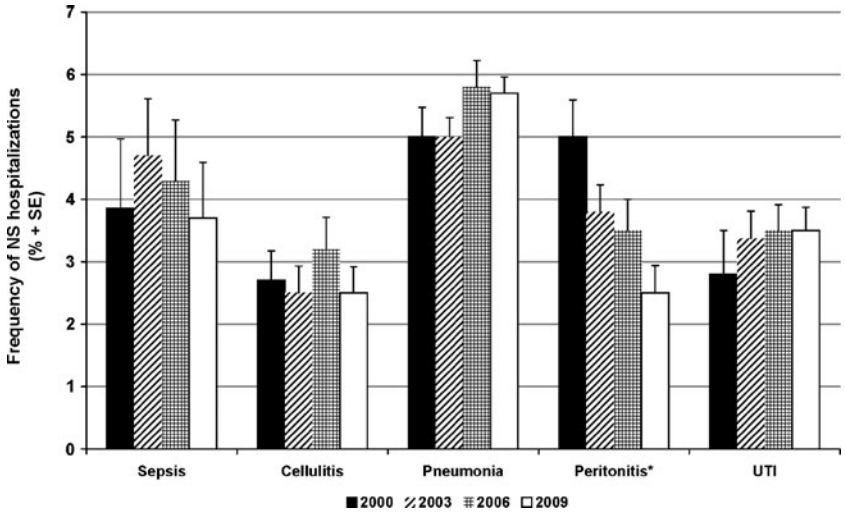

Fig. 2 Trends in the frequency of common infections in pediatric nephrotic syndrome (NS) hospitalizations. We used logistic regression to analyze trends in frequency of NS hospitalizations with specific infections. The most common infectious complication of NS was pneumonia, followed by bacteremia/sepsis, peritonitis, UTI, and cellulitis. The frequency of NS hospitalizations with peritonitis decreased from 5.0 % in 2000 to 2.5 % in 2009 ($p < 0.001$*). The proportion of infections due to pneumonia ($p = 0.47$), bacteremia/sepsis ($p = 0.39$), UTI ($p = 0.47$), and cellulitis ($p = 0.38$) was stable

pneumococcal diseases such as sepsis, pneumonia, and meningitis have declined with widespread use of the PCV7 vaccine [30, 31]. Our observed decrease in peritonitis in NS may thus be secondary to the protective effect of PCV7. The introduction of the PCV13 vaccine in 2010 may lead to a further decrease in peritonitis rates, although further monitoring is required.

Patients with NS are hypercoagulable and prone to development of TE [7]. The incidence of TE in children with NS is reported to range from 1.8 to 5.0 % [32–34]. Some authors suggest that the incidence of TE may be higher than estimated due to sub-clinical micro-embolism, which can only be detected by advanced or invasive studies [35, 36]. Overall, the trends in NS hospitalizations complicated by TE were stable in the past decade.

In this study, we found that infants (<1 year old) with NS were prone to have more acute complications compared to older children. Infants with NS are defined as either "Congenital NS" (disease onset <3 months) or "Infantile NS" (disease onset 3–12 months). Treatment of congenital or infantile NS is challenging for nephrologists because these patients are highly resistant to standard NS medication regimens and often have rapid progression to ESRD [37–39]. The increased prevalence of life-threatening infections, TE, and AKI in this population may be the consequence of prolonged, poorly controlled NS.

Males have been reported to have a higher incidence of idiopathic NS and a higher incidence of steroid-resistant NS and FSGS [40, 41]. Similarly, in this study there were more males than females represented (females 42.0 % of all NS, 95 % CI, 40.5–43.4 %). However, gender was not a consistent risk

Table 2 Trends in the frequency of acute kidney injury (AKI) in pediatric nephrotic syndrome (NS) admissions by age

	2000				2003				2006				2009			
	%	(SE)	OR	*p* value	%	(SE)	OR	*p* value	%	(SE)	OR	*p* value	%	(SE)	OR	*p* value
Age																
0–3 months	9.0	(5.6)	5.52	**0.03**	8.3	(3.3)	6.64	**<0.001**	7.2	(3.25)	2.61	0.06	12.4	(4.4)	4.04	**0.002**
3–12 months	8.5	(8.2)	5.20	0.14	1.3	(1.4)	0.99	0.99	10.5	(5.6)	3.98	**0.03**	3.3	(3.3)	0.96	0.97
1–5 years	1.8	(0.5)	1.00		1.3	(0.4)	1.00		2.9	(0.7)	1.00		3.4	(5.8)	1.00	
6–9 years	3.0	(1.0)	1.75	0.22	4.9	(0.9)	3.76	**<0.001**	4.5	(1.0)	1.58	0.09	7.8	(1.1)	2.31	**<0.001**
10–18 years	4.2	(0.7)	2.45	**0.007**	7.2	(0.8)	5.68	**<0.001**	12.1	(1.1)	4.63	**<0.001**	13.1	(1.0)	4.32	**<0.001**

We analyzed the difference in frequency of NS hospitalizations complicated with AKI by age. Children age <3 months and 10–18 years of age were consistently more likely to have AKI than children age 1–5 years

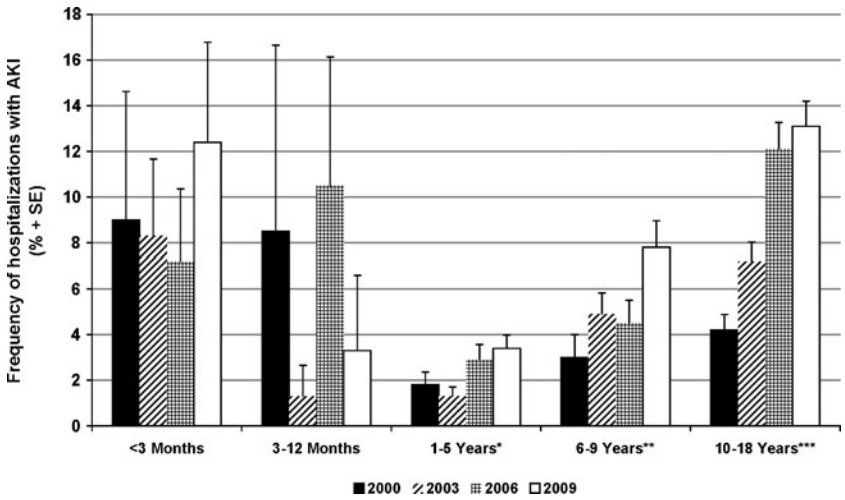

Fig. 3 Acute kidney injury (AKI) is increasingly prevalent among toddlers, children, and adolescents hospitalized for nephrotic syndrome (NS) in the US. We analyzed the frequency of NS hospitalizations with AKI by age and also analyzed their trends using logistic regression. From 2000 to 2009, the frequency of NS hospitalizations complicated by AKI in 1–5 year olds increased significantly from 1.8 to 3.4 % ($p=0.03$*), from 3.0 to 7.8 % ($p=0.02$**) in 6–9 year olds, and 4.2 to 13.1 % ($p=<0.001$***) in 10–18 year olds. The frequency of AKI in children <3 months ($p=0.81$) and 3–12 months ($p=0.28$) hospitalized with NS, did not change over the study period

factor for developing complications. A few studies have reported that African Americans and Hispanics are more likely to have steroid-resistant NS and FSGS [42, 43], while Asians appear to have a higher incidence of MCNS and steroid-sensitive NS [40, 44]. However, neither race nor ethnicity was a predictor of acute complications of pediatric NS in this study.

Table 3 Hospital charges and length of stay in individual pediatric admissions, pediatric nephrotic syndrome (NS) without acute complications, and pediatric NS with acute complications

Variable	KID	NS without complications	NS with complications	*p* value
Length of stay, mean (SE), days				
2000	4.15 (0.06)	4.06 (0.23)	8.74 (0.66)	<0.001
2003	4.17 (0.06)	4.15 (0.20)	9.24 (0.66)	<0.001
2006	4.36 (0.07)	3.88 (0.16)	10.32 (1.08)	<0.001
2009	4.39 (0.07)	3.87 (0.14)	9.33 (0.72)	<0.001
Charges per day, mean (SE), $				
2000	2,974 (70)	2,774 (109)	3,019 (130)	0.03
2003	3,960 (72)	3,839 (157)	3,984 (165)	0.36
2006	5,193 (96)	4,472 (164)	4,975 (194)	0.003
2009	6,677 (135)	5,965 (233)	6,233 (232)	0.28
Total charges, mean (SE), $				
2000	11,933 (368)	11,385 (746)	30,514 (2876)	<0.001
2003	15,947 (423)	15,254 (844)	41,075 (4162)	<0.001
2006	21,018 (557)	16,783 (942)	49,861 (4373)	<0.001
2009	27,260 (724)	21,777 (1,094)	61,886 (5384)	<0.001

Length of stay, charges per day, and total hospital charges were analyzed comparing NS without complication to NS with complications in the same year. Mean length of stay (LOS) and mean total charges increased 2–3 fold in pediatric NS admissions with acute complications compared to those without complications in 2000, 2003, 2006, and 2009 ($p=<0.001$ for each year analyzed). The mean charge per day did not show statistically significant differences between pediatric NS with vs. without complications. *NS* nephrotic syndrome, *SE* standard error

In comparison with the total KID discharge population, mean LOS and mean total hospital charges were not different from those reported for uncomplicated NS discharges during the study period. However, for complicated NS discharges, the mean LOS and mean total charges were 2–3-fold higher (Table 3). Not surprisingly, patients admitted with complicated NS had longer, more expensive hospitalizations. The estimated overall mortality was exceedingly low in patients hospitalized with uncomplicated NS (<0.5 %) but was approximately twofold higher in patients with any complication. We were unable to analyze mortality risk by complication due to HCUP reporting restrictions against publishing any tabular data for groups containing less than or equal to ten records. Gipson et al. recently reported several predictors of higher hospitalization charges in children with NS including age >15 years, African American race, hypertension, and higher socioeconomic status [11]. Similar to our findings, they also reported increased hospitalization costs associated with AKI, TE, and infections [11]. Further studies evaluating risk factors and preventive strategies for these complications are required to improve the quality of care and decrease the economic burden of NS.

Limitations

The authors acknowledge several limitations to this study. The identification of children with NS and all complications is

based on ICD-9-CM discharge coding. Individual patient information is not available to confirm the accuracy of coding diagnoses. One study demonstrated discharge coding accuracy rates of 82–91 % in the United Kingdom, however the accuracy of discharge coding in the KID database has not been established, and likely varies from hospital to hospital and from year to year [45]. Increased physician awareness or coding for AKI could potentially account for the at least a portion of the increase in AKI diagnoses in this study. Further research on a patient level is required to determine the true frequency of AKI in NS hospitalizations. Misclassification or reporting bias are other potential limitations. Additionally, the KID database does not allow for longitudinal evaluation of a single patient, therefore it is impossible to determine whether a single patient with NS was hospitalized once or several times with the same complication. Finally, this data is reflective of the United States population only and may not be generalizable to children with NS in other countries.

Conclusions

This analysis of a large pediatric discharge cohort reveals concerning trends in the complications associated with hospitalizations for childhood NS in the United States. Most concerning is that the frequency of NS hospitalizations complicated by AKI has more than doubled with a particularly striking increase in older children age 10–18 years. Further studies are needed to identify specific risk factors for AKI in this population. The distribution of infectious complications in NS appears to be changing in the modern era with a higher frequency of hospitalizations with pneumonia and a lower frequency with peritonitis than were previously reported. Given the approximately twofold increase in patient mortality, LOS, and hospital charges associated with NS complications, strategies to prevent such complications could have a major impact on both quality of life and health care expenses for this population.

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