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ORIGINAL ARTICLE

Acute kidney injury and early fluid load in a retrospective cohort of neonatal sepsis

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Abstract

Background Sepsis and acute kidney injury (AKI) are associated with mortality in the newborn intensive care unit (NICU). There is a paucity of studies that describe AKI and fluid overload in neonatal sepsis and their association with mortality.

Methods Retrospective study of neonates with culture positive sepsis admitted to the NICU between June 2020 and June 2021 was conducted. Primary outcome was in-hospital mortality according to AKI as defined by the neonatal modified Kidney Diseases Improving Outcomes criteria. Secondary outcomes were early fluid overload and vasopressor use.

Results Thirty-three percent of neonates had AKI with sepsis, and 57% of cases were severe AKI. AKI was associated with mortality after adjusting for variables that were different between survivors and non-survivors (aOR 5.7 [95% CI 1.1–36], $p=0.04$). Early fluid overload occurred in 27% of neonates who were at higher risk of having AKI with sepsis (OR 7.4 [95% CI 1.6–26.0], $p=0.01$) and higher risk of mortality (aOR 17.8 [95% CI 2–7545], $p=0.02$).

Conclusions AKI and early fluid overload are associated with mortality in sepsis in our retrospective cohort. Mitigating AKI and early fluid overload in sepsis might be a fruitful strategy in reducing mortality with sepsis.

Keywords Neonatal sepsis · AKI · Fluid overload · Mortality

Introduction

Acute kidney injury (AKI) is a common problem in the neonatal intensive care unit (NICU) and is associated with increased mortality risk, especially in very low birth weight neonates [1–4]. Beyond mortality, preterm infants who experience AKI in their NICU stay are more likely to progress to chronic kidney disease [5].

Neonatal sepsis remains one of the leading causes of mortality [6, 7], and beyond the dichotomy of life and death, preterm neonates who survive are more likely to have long-term neurodevelopment impairments compared to neonates who did not have sepsis in the NICU [8].

Although the occurrence of sepsis is a known contributor to AKI and pathologic fluid accumulation in pediatric and adult patients [9–14], this is not well described in neonates. The interaction between sepsis and AKI and fluid overload is complex. Sepsis causes dilatation of glomerular afferent and efferent arterioles (more so on the efferent end), decreasing the glomerular capillary pressure. Sepsis also leads to a dysregulated immune response causing an infiltration of inflammatory cells in the kidneys with subsequent accumulation of free radicals and necrotic debris [15]. All of that will decrease glomerular filtration rate causing kidney injury and failure. Furthermore, many antibiotics used in neonatal sepsis are nephrotoxic [16, 17], adding further injury to the kidneys during sepsis.

Despite the known interactions between sepsis and AKI and fluid overload, this phenomenon is not well described in neonates. We hypothesize that neonates who acquire AKI and early fluid overload in sepsis are at higher risk of mortality. To study this, we conducted a retrospective analysis of an existing prospective database at our Level III and Level

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IV NICUs to characterize the associations between AKI and fluid overload and mortality in neonatal sepsis.

Materials and methods

The Institutional Review Board committee approved the study at Cincinnati Children's Hospital Medical Center and the University of Cincinnati. This study did not require consent from subjects given that it involves only chart review and was a retrospective analysis of an existing database which poses minimal risk to the subjects.

Study population

This is a retrospective secondary analysis on neonates who were enrolled in a prospective study evaluating biomarkers in neonatal sepsis between June 2020 and June 2021 at the University of Cincinnati Medical Center Level III NICU and Cincinnati Children's Hospital Medical Center Level IV NICU. Only neonates who had a positive blood culture and received antibiotic therapy for at least 5 days were included. Neonates who had a positive culture and died during antibiotic therapy were included, even if they did not survive to the 5-day mark. Exclusion criteria included congenital renal anomalies that required kidney replacement therapy in the 30 days following birth or incomplete data to accurately diagnose AKI: incomplete urine output data (which we defined as any incomplete charting of urine output during the first 7 days of illness) or no serum creatinine level obtained during the first 7-day duration of illness.

Primary and secondary outcomes

The primary outcome of the study is in-hospital mortality. AKI was defined according to the modified neonatal KDIGO definitions [18, 19]. Severe AKI was defined as Stage 2 or 3 AKI. Baseline serum creatinine was defined as the lowest serum creatinine obtained in the 2 weeks leading to sepsis. Fluid accumulation was calculated as follows: cumulative net fluid balance per day (L)/dry weight (kg) for each day of illness in the first 7 days since the diagnosis was made (the day when culture was obtained was considered day 1 of illness) [13]. Dry weight was defined as the most recent weight prior to the sepsis event. A threshold of 0.1 L/kg (i.e., 10%) was defined as fluid overload for the purpose of this study.

Statistical analysis

Categorical variables were described as number of total and/or percentages and compared using the Fisher's exact test. Non-normally distributed continuous variables were described using median and 25th–75th interquartile ranges and two groups were compared using the Mann–Whitney test. Associations were described by calculating the odds ratio and 95% confidence interval using the Baptista–Pike method. Kaplan–Meier survival curves were compared using the Mantel–Cox test. Multiple logistic regression was used to adjust the calculated odds ratio for mortality in neonates with AKI and early fluid overload. Statistical analyses were done using GraphPad Prism (GraphPad Software, San Diego, CA USA) and RStudio (Integrated Development Environment for R, RStudio, PBC, Boston, MA, USA). A p-value of 0.05 was considered significant.

Results

Study cohort

Sixty-one events of sepsis in 56 neonates were evaluated for enrollment. Of those, 7 neonates were excluded for lack of serum creatinine data and/or sufficient urine output data in the first 7 days of illness to diagnose AKI (shown in Fig. 1). There were neonates ($n = 4$) who had multiple sepsis events during their NICU stay, and for this group, we included only the last event they had in the analyses.

AKI in neonatal sepsis

Sixteen of the 49 neonates in the study had AKI during sepsis; severe AKI occurred in 9 neonates (57% of cases) (shown in Fig. 2). Baseline characteristics were comparable between neonates who experienced AKI and those who did not (shown in Table 1). The diagnosis of AKI was made based on serum creatinine criteria and urine output in 7 neonates (44%) and serum creatinine criteria alone in 9 neonates (56%). AKI occurred early in sepsis (median day of illness 2 [IQR 1–3 days]). Among neonates who survived till day 7 of illness, creatinine levels tended to normalize within 2 days of the diagnosis of AKI (median duration 2 days, [IQR 1–3 days]).

AKI in sepsis is associated with mortality and vasopressor use

The overall mortality rate was 11/49 (22%). Neonates with any AKI had a higher rate of mortality compared to those who did not, 7/16 (44%) vs. 4/33 (12%) respectively, OR of 5.6 (95% CI 1.2–19.6), $p = 0.025$. To account for variables that could have an additional impact on mortality, we compared neonates who survived to those who did not (shown in Table 2). Then, we developed a multivariable logistic regression model which included variables that were different between

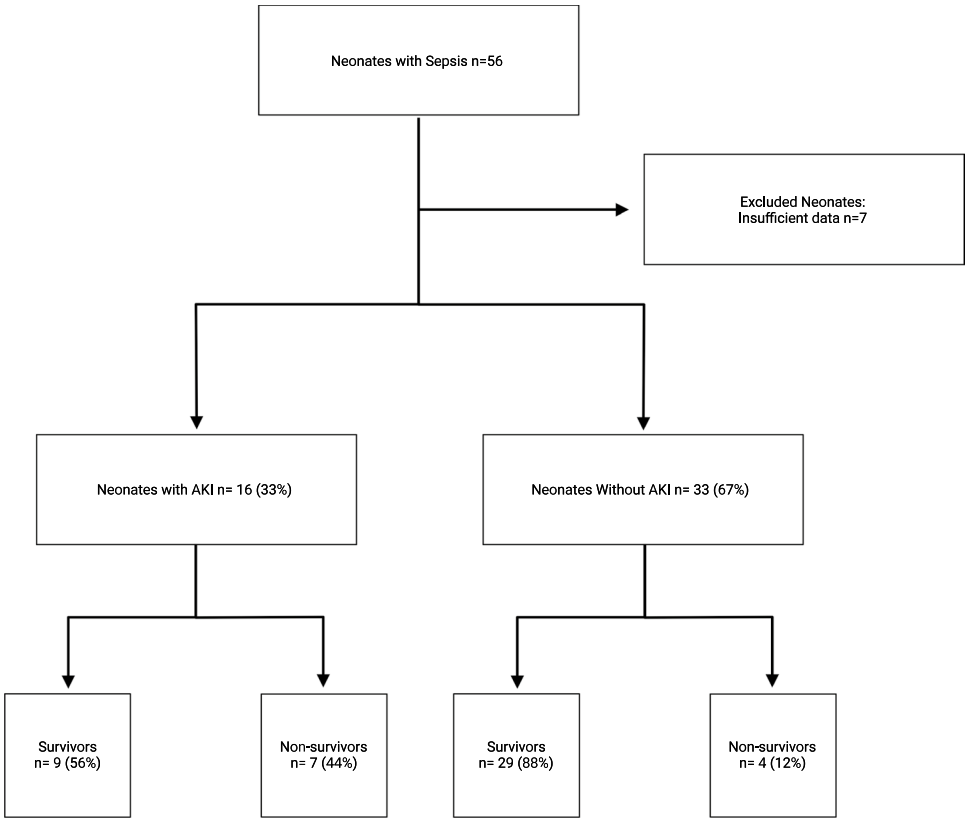

Fig. 1 Study flowchart. Study flowchart showing the distribution of neonates according to AKI and primary outcome

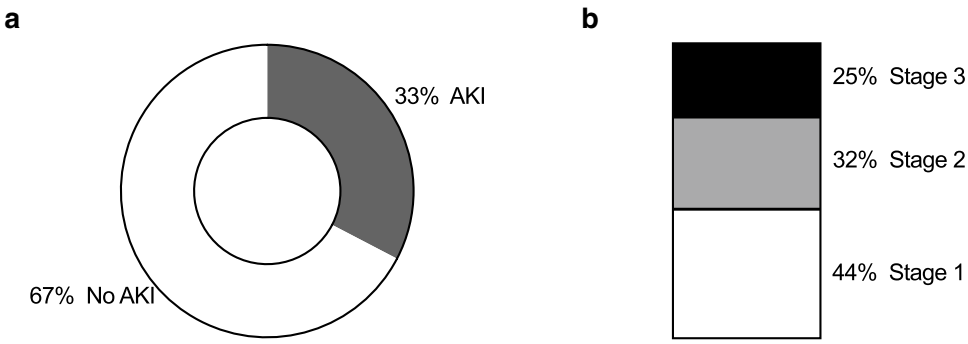

Fig. 2 Distribution of AKI in neonates. **a** Twenty-nine percent of neonates suffered from AKI during sepsis ($n=16$) (gray) while 71% did not ($n=33$) (white). **b** AKI severity by stage: Stage I: 44% ($n=7$) (white), Stage 2: 32% ($n=5$) (gray), and Stage III: 25% ($n=4$) (black)

survivors and non-survivors and had a p-value less than 0.1: gestational age at birth, corrected gestational age at the time of sepsis diagnosis, birth weight, and sepsis caused by coagulase-negative staph. In this model, AKI retained significance with an adjusted odds ratio of 5.7 (95% CI 1.1–36.0), $p=0.04$ (shown in Table 3). Furthermore, survival curves of neonates who experienced AKI and those who did not were statistically different, $p=0.01$ (shown in Fig. 3).

We then focused on neonates who had severe AKI (Stage 2 or 3 AKI). Neonates who had severe AKI with sepsis had a higher mortality rate of 5/9 (56%) compared to 2/7 (29%) of those who had Stage I AKI, but this difference was not statistically significant, $p=0.35$. The odds ratio for mortality was higher in those who experienced severe AKI compared to those who did not have AKI at 9.1 (95% CI 1.5–47.7), $p=0.01$. Even when including neonates who had Stage I AKI with those who did not have AKI, having severe AKI was associated with sevenfold odds of mortality (95% CI 1.4–28.1), $p=0.02$.

When looking at the association between AKI and vasopressor use, neonates who had AKI were more likely to receive vasopressor support compared to those who did not, 10/16 (63%) vs. 9/33 (27%), OR 4.4 (95% CI 1.3–13.7), $p=0.03$. The association between vasopressor use and severe AKI was significant with an odds ratio of 8.2 (95% CI 1.7–41.3), compared to neonates who did not have AKI or had Stage I AKI, $p=0.02$.

Table 1 Baseline characteristics of neonates with and without AKI with sepsis

Characteristic	AKI ($n=16$)	No AKI ($n=33$)	p-value
Gestational age at birth, weeks [IQR]	27 [24–37]	28 [26–37]	0.44[a]
Corrected gestational age at event, weeks [IQR]	32 [27–43]	36 [28–40]	0.88[a]
Birth weight, g [IQR]	1007 [551–2875]	1145 [781–2900]	0.44[a]
Sex			
Female, *n* (%)	11 (69%)	14 (42%)	0.13[b]
Male, *n* (%)	5 (31%)	19 (58%)	
Race			
Black, *n* (%)	6 (38%)	9 (27%)	0.52[b]
Hispanic, *n* (%)	0 (0%)	1 (3%)	
White, *n* (%)	10 (62%)	23 (70%)	
Small for gestational age, *n* (%)	3 (19%)	5 (15%)	> 0.99[b]
Antibiotic duration, days [IQR]	14 [9–14]	10 [10–14]	0.41[a]
Aminoglycoside/vancomycin exposure, *n* (%)	8 (50%)	20 (61%)	0.54[b]

[a]*p*-value calculated using the Mann–Whitney test

[b]*p*-value calculated using the Fisher's exact test

Table 2 Comparison between survivors and non-survivors from sepsis

Characteristic	Survivors ($n=38$)	Non-survivors ($n=11$)	p-value
Gestational age at birth, weeks [IQR]	32 [26–38]	25 [24–27]	0.02[a]
Corrected gestational age at event, weeks [IQR]	37 [28–42]	28 [26–32]	0.04[a]
Birth weight, g [IQR]	1455 [748–570]	807 [570–1207]	0.06[a]
Sex			
Female, *n* (%)	6 (55%)	20 (53%)	> 0.99[b]
Male, *n* (%)	5 (45%)	18 (47%)	
Race			
Black, *n* (%)	12 (32%)	3 (27%)	> 0.99[b]
Hispanic, *n* (%)	1 (3%)	0 (0%)	
White, *n* (%)	25 (65%)	8 (73%)	
Small for gestational age, *n* (%)	7 (18%)	1 (9%)	0.66[b]
Causative agent			
Gram-negative bacteria, *n* (%)	10 (26%)	5 (45%)	0.27[d]
Gram-positive bacteria[*], *n* (%)	16 (42%)	4 (36%)	> 0.99[d]
CONS[c], *n* (%)	10 (26%)	0 (0%)	0.09[d]
Candida, *n* (%)	2 (6%)	2 (19%)	0.21[d]
Presence of congenital anomalies	13 (34%)	2 (18%)	0.46[b]

[*]Includes all Gram-positive bacteria except for coagulase-negative staph

[a]*p*-value calculated using the Mann–Whitney test

[b]*p*-value calculated using the Fisher's exact test

[c]Coagulase-negative staph

[d]Calculated using the Fisher's exact test comparing each category to the rest combined

Table 3 Odds ratio for mortality with AKI and early fluid overload

Variable	Odds ratio for mortality	Adjusted odds ratio[a]	Adjusted p-value
AKI	5.6 (95% CI 1.2–19.6)	5.7 (95% CI 1.1–36.0)	0.04
Early fluid overload	21.3 (95% CI 3.1–118.6)	17.8 (95% CI 2.0–7545.0)	0.02

[a]Variables included in the model: gestational age at birth, corrected gestational age at first day of sepsis, birth weight, and sepsis caused by coagulase negative staph

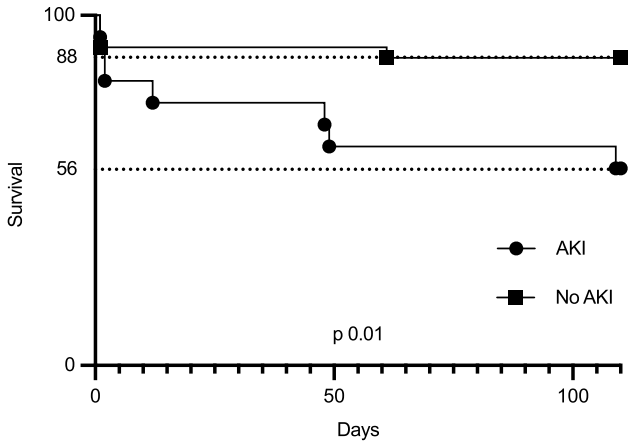

Fig. 3 Survival curves of neonates according to AKI. Neonates who experienced AKI (circle) were at higher risk of mortality that persisted even after the initial sepsis event compared to neonates who did not have AKI (square). The curves were statistically different ($p = 0.01$) using the Mantel–Cox test

Fluid overload in sepsis

There were 4 neonates who experienced mortality within the first 24 h of illness; therefore, we could not calculate early fluid overload for these neonates. Early fluid overload (defined as cumulative net fluid in the first day of sepsis/dry weight of greater than 0.1 L/kg) occurred in 12/45 neonates (27%). In neonates with early fluid overload, the rate of AKI was higher compared to those without it, 8/12 (67%) vs. (33%), OR 7.4 (95% CI 1.6–26.0), $p = 0.01$. When assessing the association between mortality and fluid overload on the first day of illness, neonates who had early fluid overload were more likely to not survive compared to those who did not have it, OR 21.3 (95% CI 3.1–118.6), $p = 0.002$, and this association remained significant when adjusting for variables different between survivors and non-survivors in our multiple logistic regression model (shown in Table 3).

Fluid overload on any day of illness was common in neonates with sepsis, occurring in 44/45 (98%) of neonates. Although the rate was not different between neonates who had AKI and those who did not, neonates with AKI had fluid overload earlier in sepsis compared to those without it, day 1 [IQR 1–2] vs. day 2 [IQR 2–4], respectively, $p = 0.01$.

Discussion

Our study supports the limited existing literature that AKI is a common occurrence in neonatal sepsis. In our cohort, AKI was severe in more than half of the cases and was strongly associated with mortality, and this strong association retained significance when accounting for variables that were different between survivors and non-survivors. Also, we saw an association of AKI and use of vasopressor support during sepsis, which associates cardiac dysfunction with kidney dysfunction. This might not be surprising given that cardiac dysfunction leads to poor end-organ perfusion, leading to AKI. However, this association could hint that neonates with AKI in sepsis have more severe illness. Additionally, given the strong association between mortality and AKI in sepsis, AKI can be used as a marker of illness severity to enhance situational awareness, guide counseling of families, and provide a metric and a target for quality improvement efforts.

Congruent to what has been described in pediatric and adult cohorts [20], we have shown that early fluid overload was strongly associated with mortality in sepsis. Early fluid overload occurred in more than 25% of the neonates in our cohort, and this occurred despite the fact that unrestricted fluid resuscitation in sepsis for hypotension is routinely avoided in neonates given the increased theoretical risk for intraventricular hemorrhage, especially in the first few days of life [21]. This could be attributable to the need of parenteral nutrition and IV hydration during sepsis and the relatively large volume of fluids to body weight that is essential to provide medications. Therefore, providers should pay meticulous attention to fluid prescription, volume from extraneous sources such as flushes, and consider concentrating any medications as much as possible early in the diagnosis.

Off-label use of Aquadex™ has been used successfully in AKI in neonates with fluid overload [22, 23], and with the recent approval of a dedicated neonatal continuous kidney replacement therapy in neonates, Carpediem™, by the United States Food and Drug Administration [24], this could be a potential approach of supportive care in neonates with sepsis to potentially mitigate some of the mortality risk. Specifically in neonatal sepsis, Peruzzi et al. demonstrated that Carpediem™ can be used to support a neonate with AKI from *Escherichia coli* sepsis, where despite the presence of disseminated intravascular coagulation and severe metabolic acidosis, the neonate not only survived, but also had normal kidney function and development at 9-month follow-up [25]. However, recognition of neonates who will benefit from this therapy will be key to its success, and this is challenging for many reasons. First, there is no consensus definition of neonatal sepsis to date [26] and relying on blood culture results, which typically take hours to days to be completed [27], makes the early use of the device challenging. Second, most cases of neonatal sepsis occur in extreme preterm babies [7], and the use of Carpediem™ is limited to infants weighing at least 2.5 kg. Lastly, the use of Carpediem™ requires subspecialty support and training, which is not attainable in all NICUs.

There are limitations to our study. First, this study is largely limited by the small sample size. Further validation

in larger cohorts is needed. Second, we did not inform the decision to obtain serum creatinine measurements, although both units where this study was conducted obtain renal profiles when evaluating for sepsis and continue to do so at least weekly while the infant is receiving IV fluids or nephrotoxic medications. Therefore, there are possible cases of AKI that were missed and that could impact the associations described. Finally, the retrospective nature of the study does not allow to determine causal relationship between AKI and fluid overload. Despite these limitations, further exploration of this topic is greatly needed to understand if mitigation of AKI and/or fluid overload in neonatal sepsis could positively impact outcomes, especially as treatment options for AKI and fluid overload become more readily available and better understood in this vulnerable population.

Conclusion

AKI and fluid overload are associated with mortality in sepsis in our retrospective cohort. Mitigating AKI and fluid overload in sepsis might be a fruitful strategy in reducing mortality with sepsis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00467-022-05840-7.

Author contribution Faris Al Gharaibeh, Shruthi Mohan, Cara Slagle, and Stuart Goldstein conceptualized and designed the study. Faris Al Gharaibeh, Shruthi Mohan, and Michael Santoro collected the data. Faris Al Gharaibeh and Shruthi Mohan conducted the analysis presented. Faris Al Gharaibeh drafted the initial manuscript, and it was reviewed and revised by Faris Al Gharaibeh, Cara Slagle, and Stuart Goldstein. All authors approved of the manuscript prior to submission.

Data availability All datasets used in this study are available upon reasonable request from the corresponding author.

Declarations

Ethical approval and consent This study was reviewed by the Institutional Review Board at Cincinnati Children's Hospital Medical Center and the University of Cincinnati and was granted waiver of consent (approval number 2021–0640).

Competing interests The authors declare no competing interests.

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