Long-term Infectious Complications Among Critically Ill Children with AKI

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Introduction

- Despite improvements in recognition and prevention, AKI occurs in up to 56% of critically ill children admitted to pediatric ICUs globally.
- Given the lack of specific therapies, understanding how AKI leads to morbidity in critically ill children is critical to improve AKI outcomes.
- Several observational studies have shown an association between AKI and risk for de novo infection in critically ill children, however little is understood about the duration of time at which AKI place children at risk for subsequent infection.
- The objective of this study was to explore long-term infectious complications among critically ill children with AKI.

Methods and Materials

Patient Population

- Data was obtained from the Pediatric High-Density ICU (Peds HiDenIC) Database which contains data on >12,000 admissions to the cardiac and pediatric ICUs at UPMC Children's Hospital of Pittsburgh from 2010-2014.
- Exclusion Criteria: Patients with insufficient data to categorize AKI status during their ICU admission, age greater than 18 years, history of CKD or renal transplant, history of primary immunodeficiency, sepsis prior to the initial ICU admission.

Statistical Analysis

- The exposure was non-septic AKI occurring during the index ICU admission; defined by the pediatric KDIGO criteria utilizing serum creatinine and urine output measures.
- The outcome was infection occurring within two years of hospital discharge from the index hospitalization; defined by ICD-9 codes.
- Infection was classified into 6 categories: 1) respiratory tract infection, 2) urinary tract infection, 3) skin, soft tissue, joint and bone infection, 4) GI and hepatobiliary infection, 5) Bacteremia, sepsis, and septicemia, 6) Other bacterial/viral infection, non-localized infection.
- The relationship between non-septic AKI and the development of infection was assessed using Cox Proportional Hazards models.

Table 1. Cohort Characteristics

Measure	No AKI n=4232 (80.6%)	AKI n=1016 (19.4%)	Total n=5248
Age, mean (SD), years	6.5 ± 5.6	7.9 ± 6.1	6.8 ± 5.7
Males No. (%)	2453 (58%)	570 (56%)	3023 (58%)
Race No. (%)			
Caucasian	3276 (77%)	817 (80%)	4093 (78%)
African American	732 (17%)	149 (15%)	881 (17%)
Other	224 (5%)	50 (5%)	274 (5%)
History of heart failure No. (%)	66 (2%)	38 (4%)	104 (2%)
History of liver failure No. (%)	26 (0.6%)	15 (2%)	41 (0.8%)
History of non-renal solid organ transplant No. (%)	246 (6%)	47 (5%)	293 (6%)
History of bone marrow transplant No. (%)	2 (0%)	2 (0.2%)	4 (0.1%)
History of malignancy No. (%)	144 (3%)	44 (4%)	188 (4%)
Surgery prior to ICU admission No. (%) [a]	1516 (36%)	485 (48%)	2001 (38%)
Cardiac bypass surgery [a]	358 (9%)	151 (15%)	509 (10%)
ePIM2 Likelihood of mortality (%), mean (SD) [ab]	1.1 ± 2.6	1.9 ± 4.4	1.3 ± 3.0
Exposure to immunosuppressant agents from ICU admission through hospital discharge No. (%) [a]	1671 (40%)	356 (35%)	2027 (39%)
Endotracheal intubation No. (%) [a]	568 (13%)	249 (25%)	817 (16%)
Indwelling central line No. (%) [a]	857 (20%)	363 (36%)	1220 (23%)
Severe Neutropenia No. (%) [a]	49 (1%)	32 (3%)	81 (2%)
Hospital acquired sepsis No. (%) [a]	188 (4%)	97 (10%)	285 (5%)
Exposure to renal replacement therapy No. (%) [a]	1 (0%)	9 (0.9%)	10 (0.2%)
AKI/AKD at hospital discharge No. (%) [a]	10 (0.2%)	139 (14%)	149 (3%)
ICU length of stay, mean (SD) [a]	3 ± 4	5 ± 17	3 ± 9
Hospital length of stay, mean (SD) [a]	6 ± 10	10 ± 23	7 ± 14

Abbreviations: AKI, acute kidney injury; AKD, acute kidney disease; ICU, intensive care unit; ePIM2, electronic pediatric index of mortality 2; SD, standard deviation.
[a]During index hospitalization [b]Measured within the first 24 hours of ICU admission

Results

Two-year follow-up data was available on 5248 children (92.2% of the initial ICU cohort).

- 31 deaths occurred during the index hospitalizations
  - 19 (0.4%) from the non-AKI group and 12 (1%) from the AKI group

Table 2. Incidence of Infection in the 2 Years Following Hospital Discharge

Outcome	No AKI n=4232 (80.6%)	AKI n=1016 (19.4%)	*P-value*
Cumulative incidence of infection	15.2 infections per 100 children	18.4 infections per 100 children	0.035
Total number of children with infection, No. (%)	562 (13.3%)	156 (15.4%)	0.048
1	344 (8.1%)	90 (8.9%)	
2+	218 (5.2%)	66 (6.5%)	
Respiratory tract	463 (10.9%)	123 (12.1%)	0.29
Requiring hospital readmission [c,d]	46 (1.2%)	23 (2.6%)	0.004
Urinary tract	47 (1.1%)	14 (1.4%)	0.48
Skin, soft tissue, joint and bone	40 (0.9%)	11 (1.1%)	0.69
GI, hepatobiliary [c,d]	67 (1.6%)	25 (2.5%)	0.05
Bacteremia, sepsis, septicemia	23 (0.5%)	13 (1.3%)	0.01
Other infections, non-localized	5 (0.1%)	1 (0.1%)	0.88

[b] Statistically greater at 30 days, [c] Statistically > at 90 days, [d] Statistically > at 365 days

AKI during the index hospitalization was a significant predictor of developing infection in the two years following hospital discharge.

- Any infection: aHR 1.24, 95% CI 1.03-1.48 (p=0.021)
- Multiple infections: aHR 1.33, 95% CI 1.07-1.65 (p=0.009)
  - Maximum stage 1 AKI: aHR 1.28 (0.99-1.64)
  - Maximum stage 2 AKI: aHR 1.55 (1.09-2.22)
  - Maximum stage 3 AKI: aHR 0.89 (0.36-1.93)

Other significant predictors of infection in the multivariable models included surgery and occurrence of sepsis during the index hospitalization, history of solid-organ transplant and patient age.

Discussion

- AKI is an independent predictor of subsequent infection in critically ill children.
- Critically ill children who develop AKI appear to be at increased risk for developing GI or hepatobiliary infections, as well as bacteremia and sepsis following hospital discharge.
- While overall rates of respiratory infections were similar in the AKI and non-AKI groups, respiratory infections requiring hospital readmission were two-times higher among children with prior AKI compared to those without at 30, 90 and 365 days after the index hospitalization.
- These data support AKI as a clinically relevant immunocompromised state.

Conclusions

- AKI may lead to sustained immunomodulatory effects placing critically ill children at heightened risk for infection following hospital discharge.
- Further studies are needed to understand the mechanisms by which AKI modulates immune function in critically ill patients.