Persistent Serum Renin Elevation is Associated with Acute Kidney Injury in Pediatric Septic Shock

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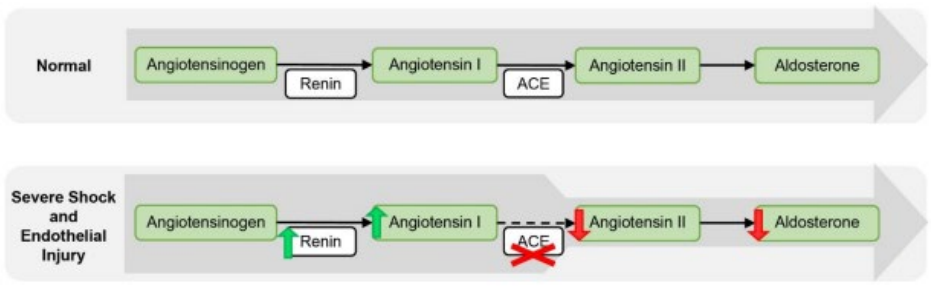
Background

- Sepsis-associated acute kidney injury (SA-AKI) is associated with morbidity and mortality in critically ill children
  - Fitzgerald et al (CCM, 2016): Adjusted OR 3.1 (p <0.001) for mortality in children with severe SA-AKI
  - Stanski et al (ICM, 2020): Adjusted OR 5.6, p<0.001) for mortality in children with severe day 3 SA-AKI
  - Starr et al (PCCM, 2020): Children with severe SA-AKI had poorer health-related quality of life at 3 months
- The pathophysiology of SA-AKI remains poorly understood, which is a limiting factor in identifying effective treatment strategies
- Adult data demonstrate the potential role of the renin-angiotensin-aldosterone system (RAAS), as patients with vasodilatory shock and renin levels above 59 pg/ml have been demonstrated to have higher rates of severe AKI (Bellomo et al, AJRCCM 2020). Furthermore, patients with AKI and elevated renin levels who received angiotensin II therapy had higher rates of renal recovery (Tumlin et al, CCM, 2018). These concepts have not yet been evaluated in children.
- In severe shock, endothelial dysfunction is proposed to lead to decreased angiotensin converting enzyme activity and consequently decreased angiotensin II production, resulting in an upregulation of renin (Figure: Bellomo, AJRCCM, 2020). Thus, restoring angiotensin II via exogenous administration may restore balance in the RAAS system, potentially improving kidney-related outcomes.



Methods

- Secondary analysis of 379 children admitted to the PICU from a multi-center study of the genomics of pediatric septic shock from 2015-2019
- A subset of 69 patients were selected for a pilot study based on the availability of residual Day 1 and Day 3 serum samples, and a representative incidence of Day 3 severe SA-AKI (≥KDIGO Stage 2)
- Serum renin concentrations were measured on Day 1 and Day 3 by Luminex® assay.
- Day 3:Day 1 renin ratios were calculated for each individual patient to assess renin trend at the individual patient level
- Day 1 and Day 3 renin levels, and Day 3:Day 1 renin ratios were evaluated for association with development of Day 3 severe SA-AKI and provision of kidney replacement therapy (KRT). Risk stratified analyses were also performed using the previously validated Renal Angina Index (RAI) and the recently derived PERSEVERE-II AKI Prediction Model (Stanski et al, AJRCCM 2020)

Results

- 26/69 children (38%) developed Day 3 severe SA-AKI, and 12/69 children (17%) required KRT in the first 7 days of PICU stay
- Median Day 1 renin was 4751 pg/ml (IQR 1926-10307) and median Day 3 renin was 2952 pg/ml (IQR 1269-7776) (**Table 1**)
  - No differences in Day 1 renin levels for patients with or without either outcome of interest
  - Day 3 renin levels, and the ratio of Day 3:Day 1 renin levels, were significantly higher in patients with Day 3 severe AKI and those who required KRT

	All	No Day 3 Severe AKI	Day 3 Severe AKI	p
N (% cohort)	69	43 (62)	26 (38)	--
Day 1 Renin (pg/ml)	4751 (1926,10307)	4554 (1842,9297)	6487 (2022,12607)	0.780
Day 3 Renin (pg/ml)	2952 (1269,7776)	2153 (988,5319)	5250 (1487,12824)	0.035
Individual D3:D1 Renin	0.51 (0.30,1.15)	0.41 (0.28,0.75)	0.99 (0.48,1.74)	0.003
	All	**No KRT**	**KRT**	p
N (% cohort)	69	57 (83)	12 (17)	--
Day 1 Renin (pg/ml)	4751 (1926,10307)	3652 (1789,9194)	6874 (4722,20946)	0.12
Day 3 Renin (pg/ml)	2952 (1269,7776)	2221 (1013,5712)	7514 (2545,23837)	0.014
Individual D3:D1 Renin	0.51 (0.30,1.15)	0.51 (0.30,1.2)	1.1 (0.95,2.05)	0.014

Table 1. Association of Renin Levels with Primary Outcomes. Data listed as median (IQR)

- In patients at high risk for Day 3 severe AKI by the RAI and PERSEVERE-II Model, median D3:D1 renin ratios discriminated between true positives (TP) and false positives (FP). In patients classified as low risk by PERSEVERE-II, the D3:D1 ratio also discriminated between true negatives (TN) and false negatives (FN) (**Table 2**)

	High Risk PERSEVERE-II		Low Risk PERSEVERE-II		p
	No AKI (FP)	AKI (TP)	No AKI (TN)	AKI (FN)	
N (% cohort)	20 (29)	23 (33.3)	23 (33.3)	3 (4.4)	--
Individual D3:D1 Renin	0.41 (0.29,0.92)	0.95 (0.41,1.72)	0.42 (0.26,0.59)	1.53 (0.6,9.5)	0.023
	High Risk RAI (RAI≥8)		**Low Risk RAI (RAI <8)**		p
	No AKI (FP)	AKI (TP)	No AKI (TN)	AKI (FN)	
N (% cohort)	32 (46)	26 (38)	11 (16)	0 (0)	--
Individual D3:D1 Renin	0.41 (0.28,0.75)	0.99 (0.48,1.74)	0.89 (0.13, 1.0)	--	0.016

Table 2. Risk Stratified Analyses

Conclusions

- Children with septic shock have renin levels that are **more than 80x higher** than adults on presentation
- **Persistent renin elevation** is associated with severe SA-AKI and provision of KRT, and may discriminate between true positives and false positives in high risk patients identified using existing SA-AKI predictive tools
- Similar to adult studies, these data suggest involvement of the RAAS in SA-AKI pathophysiology that should be further explored. Importantly, renin may be a **predictive enrichment target** to guide angiotensin II therapy and improve outcomes.