Pediatric Nephrology (2023) 38:2907–2910
https://doi.org/10.1007/s00467-023-05985-z

EDITORIAL COMMENTARY

Critically ill children with septic shock: time to rediscover renin?

Isabella Guzzo[1] · **Fabio Paglialonga**[2]

Received: 7 April 2023 / Revised: 10 April 2023 / Accepted: 10 April 2023 / Published online: 22 April 2023

Acute kidney injury (AKI) and sepsis are both associated with morbidity and mortality in critically ill patients. In detail, critically ill children with severe AKI (KDIGO stage 2 or 3) had a higher 28-day mortality than children without severe AKI (11% vs. 2.5%) and sepsis-associated AKI (SA-AKI) was independently associated with increased odds of mortality in a large cohort of children with septic shock [1, 2]. Furthermore, the incidence of SA-AKI has increased over the past two decades, affecting mortality, hospitalization, and costs in this population [3]. Thus, early recognition of children at higher risk of developing SA-AKI could potentially be effective in improving septic patients' management and outcomes.

In a recent paper in *Pediatric Nephrology*, Stanski and colleagues presented the results of a secondary analysis of a large, prospective, observational study, looking at the impact of elevated serum renin + prorenin concentration as a predictor of persistent AKI and mortality in children with septic shock [4]. In a cohort of 233 critically ill children with septic shock, an elevated renin + prorenin concentration at day 1 was predictive of severe persistent AKI in the first week of pediatric intensive care unit (ICU) stay. Similarly, persistence of renin + prorenin elevation at day 3 (as quantified by day 3:day 1 renin + prorenin ratio above an optimal cut-off) was predictive of 28-day mortality [4]. Therefore, the authors suggested that renin may be a valuable prognostic and predictive biomarker in pediatric critically ill patients with septic shock, which, if confirmed by further studies, may potentially guide therapy and improve outcomes in this population.

What we know from studies in adult patients

High renin levels are not a novel finding in critically ill patients. As early as 1981, increased plasma renin activity and inappropriate low aldosterone concentration were reported in critically ill patients with persistent hypotension and high mortality rate [5, 6]. A renewed interest in the renin–angiotensin–aldosterone system (RAAS) in critically ill patients emerged over the last few years. Among others, Gleeson et al. observed a significant association between direct renin measurement and mortality in a prospective observational study of critically ill adults [7]. Consistently, Flannery et al. demonstrated that serum renin measured early after ICU admission was significantly and independently associated with mortality and major adverse kidney events, including kidney replacement therapy or reduced estimated glomerular filtration rate [8]. The prognostic value of renin and the importance of renin trajectory were recently confirmed in patients undergoing cardiac surgery [9]. Looking more in depth at the RAAS, low levels of angiotensin II were associated with higher mortality in adult patients with severe sepsis [10]. A post hoc analysis of the Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) study elegantly showed that both angiotensin I and the angiotensin I/II ratio were higher in patients with catecholamine-resistant vasodilatory shock [11]. In addition, a high angiotensin I/II ratio was associated with greater norepinephrine requirements and it was an independent predictor of mortality [11].

In line with these studies looking at biochemical measurements, a study of patients with sepsis-associated AKI showed that those receiving treatment with RAAS inhibition before ICU admission had an increased risk of developing stage 3 AKI compared to those not treated with these medications [12]. Moreover, a specific angiotensin-converting enzyme (ACE) genotype that predisposes to reduced ACE activity was associated with a higher risk of AKI in critically ill patients [13].

In summary, mounting evidence confirmed that RAAS is often dysfunctional in sepsis and that RAAS dysfunction is associated with a higher risk of AKI and worse prognosis in critically ill adults.

✉ Fabio Paglialonga
fabio.paglialonga@policlinico.mi.it

[1] Pediatric Nephrology, Dialysis and Transplant Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

[2] Pediatric Nephrology, Dialysis and Transplant Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Pathophysiology

The mechanisms underlying these findings remain debated. Hypotension, hypoxemia, reduced tissue perfusion, decreased sodium delivery to the distal tubule, and sympathetic activation are all detected by the juxtaglomerular apparatus, which induces renin secretion. Renin is a proteolytic enzyme involved in the conversion of angiotensinogen to angiotensin I, which in turn is converted to vasoactive angiotensin II by ACE. Finally, angiotensin II is responsible for vasoconstriction and the release of aldosterone from the adrenal cortex [14]. In case of sepsis, a dissociation may occur from the physiological response between renin and aldosterone resulting in hyperreninemic hypoaldosteronism, observed in more than 20–30% of critically ill patients [14, 15]. It is possible that the endothelial dysfunction and inflammatory response that occur in sepsis may cause reduced ACE activity and subsequent dysregulation in the RAAS and organ dysfunction. Another mechanism advocated as a possible cause of RAAS dysregulation in critically ill patients is increased angiotensin II degradation by endopeptidase.

However, not only RAAS dysregulation but also RAAS activation was described. Doerschug et al. reported renin and angiotensin II equally elevated and correlated with microvascular dysfunction in a cohort of 30 patients with severe sepsis [16]. In this setting, increased capillary leak, commonly observed in sepsis, could be secondary to RAAS over-activation and angiotensin II–induced mechanisms. In particular, angiotensin II has proinflammatory and procoagulant activity and can enhance the expression of endothelium-derived adhesion molecules [15]. Thus, it is possible that at various stages of sepsis, the expression levels of RAAS may differ and that repeated measures of renin (and angiotensin II) may be useful to identify the appropriate time and patient, who may benefit from a specific therapy. In the study by Stanski et al., samples from day 1 and day 3 were analyzed and a trend in serum renin + prorenin concentration was evaluated rather than a single measure [4]. A similar approach should be implemented in future studies to better characterize critically ill septic patients at different time points and to correctly interpret data of a heterogeneous pediatric ICU population. Notably, the median day 1 renin concentrations were higher than those measured in critically ill adults, which could be related to the peculiar characteristic of the enrolled cohort. A high variability in renin concentration in the pediatric population and an age-related decline in levels across all pediatric age groups have been observed [17]. Additionally, renin and prorenin levels correlate with several diseases and high renin levels have been reported in congenital cardiac malformations, whereas elevated prorenin concentration has been associated with microalbuminuria in diabetic children [17].

What is actually far from being elucidated is whether high renin is just an innocent marker or an active player in this scenario. Some experimental studies showed that the (pro) renin receptor is expressed on leukocytes and that binding of renin and prorenin to the (pro)renin receptor can stimulate inflammation and profibrotic pathways [18], thus advocating a possible active role of renin in worsening the prognosis of critically ill patients.

The pediatric experience

Although the paper by Stanski et al. does not contribute to a better understanding of the pathophysiologic mechanisms underlying RAAS dysregulation in sepsis, it has the undoubted merit of being the first large pediatric study emphasizing the importance of renin measurement in septic shock. The literature on RAAS in critically ill children is scanty. In 2004, Lichtarowicz-Krynska et al. reported, in 60 children admitted to the pediatric ICU, lower plasma aldosterone concentration in children with meningococcal sepsis and elevated risk of mortality compared to patients with other diagnoses [19]. In 15 patients of the meningococcal group, renin was also measured and values were either normal or high with inappropriately low aldosterone/renin ratio supporting RAAS dysregulation [19].

Measurement technique

Among the main limitations of the study, the technique used to measure renin deserves some comments. In the past, plasma renin activity was indirectly measured by assessing the generation of angiotensin I, which was strongly dependent on the angiotensinogen level as substrate, with several associated limitations and huge inter-laboratory variability. In recent times, renin levels are directly measured by different immunoradiometric methods. The assay used by Stanski et al. measured not only renin but also its precursor prorenin, whose plasma concentration in healthy subjects is significantly higher than that of its active form. Although renin production in stressful states exceeds prorenin release by 50–100-fold and prorenin is more stimulated by longer stimuli than by acute events, new low cross-reactivity assays for prorenin will be required in future trials, such as in some recent studies in adult patients [8]. Some concerns have been raised in the past about possible factors influencing renin levels in critically ill patients, but recent studies have clearly demonstrated that renin levels are not impacted by diurnal variation, medications, or continuous kidney replacement therapy (CKRT) [7].

Practical implications

The last two decades have dramatically changed the field of AKI, both in adults and in children. New definitions have been proposed, large epidemiological studies and long-term follow-up trials have been performed, and the epidemiological scenario of AKI has completely changed, as the main causes of AKI are now entirely different than 20 years ago [1]. The short- and long-term consequences of AKI have been investigated, and AKI is now recognized as an independent risk factor for mortality in the critically ill child [1]. Although the pathophysiology of AKI, particularly in the setting of sepsis and septic shock, has been better explored, no therapies specifically acting on the mechanisms leading to AKI and significantly affecting outcome have been found. What is now clear is that AKI is a complex event and that a one-size-fits-all approach does not help in improving prognosis. This has opened the door to the need for a precision medicine approach, based on personalization of care and on the concept of enrichment, that is, the separation of a heterogeneous group of patients into more homogenous subgroups of subjects, which are characterized by similar prognosis and treatment. The investigation of RAAS in critically ill children could perfectly fit in this scenario, as a tool for both prognostic and predictive enrichment. Prognostic enrichment consists of identifying a group of patients with a similar probability of reaching a same outcome, for example, mortality. Several biomarkers have been investigated so far under this point of view, with conflicting results and limited practical implications. The literature on RAAS seems to suggest that renin can allow for selecting a subgroup of children with a significantly higher risk of AKI and mortality [20]. However, the most important limitation of the available biomarkers is their limited value in predictive enrichment, that is, the selection of a subgroup of patients characterized by common pathophysiologic disease mechanisms and potentially similar response to a specific treatment. This could be the case for renin, particularly after the publication of some studies documenting the potential benefits of angiotensin II infusion in patients with shock [21, 26]. This strategy was first proposed almost 30 years ago in a few case reports in patients with septic shock unresponsive to noradrenaline [21, 22], including a report on two children with severe septic shock, who survived after angiotensin II infusion [23]. The results of the ATHOS-3 trial are of utmost importance in this field. It was a randomized controlled trial that assigned 344 adult patients with vasodilatory shock receiving more than 0.2 μg of norepinephrine per kg of body weight per minute (or an equivalent dose of another vasopressor) to receive infusion of either angiotensin II or placebo. The primary end point (increased mean arterial pressure at 3 h) was reached by more patients in the treatment group than in the placebo group. Mortality at 28 days was not significantly lower in patients receiving angiotensin II infusion [24]. A post hoc analysis of this study showed that in those patients with AKI needing CKRT, 28-day survival and mean arterial pressure response were higher, and the rate of KRT liberation greater, in patients receiving angiotensin II infusion than placebo [25]. And notably, another secondary analysis of the same trial found that in patients with renin concentrations above the study population median, infusion of angiotensin II significantly reduced 28-day mortality compared with placebo (50.9% vs. 69.9%; $p = 0.012$). In summary, renin seems to identify a subset of patients who are more likely to respond to angiotensin II infusion [26].

Conclusions

To conclude, what we know from adult studies is that RAAS can be dysregulated in shock and that high renin levels can identify a subgroup of patients with a higher risk of AKI and mortality, and higher probability to respond to angiotensin II infusion. The paper by Stanski et al. is welcome, as it could be an important starting point in pediatrics, by showing that serum renin + prorenin concentration at pediatric ICU admission is high in children with septic shock, and associated with severe persistent AKI and mortality. We are far from a personalized treatment of pediatric septic shock, but the search for prognostic and predictive biomarkers based on AKI pathophysiology seems the right direction to proceed.

Data availability Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL; AWARE Investigators (2017) Epidemiology of acute kidney injury in critically ill children and young adults. N Engl J Med 376:11–20
2. Stanski NL, Cvijanovich NZ, Fitzgerald JC, Bigham MT, Wong HR; Genomics of Pediatric Septic Shock Investigators (2020) Severe acute kidney injury is independently associated with mortality in children with septic shock. Intensive Care Med 46:1050–1051. https://doi.org/10.1007/s00134-020-05940-8
3. Khatana J, Thavamani A, Umapathi KK, Sankararaman S, Roy A (2023) Increasing incidence of acute kidney injury in pediatric severe sepsis and relate adverse hospital outcomes. Pediatr Nephrol. https://doi.org/10.1007/00467-022-05866-x
4. Stanski NL, Shakked NP, Zhang B, Cvijanovich NZ, Fitzgerald JC, Jain PN, Schwarz AJ, Nowak J, Weiss SL, Allen GL, Thomas NJ, Haileselassie B, Goldstein SL (2023) Serum renin

and prorenin concentrations predict severe persistent acute kidney injury and mortality in pediatric septic shock. Pediatr Nephrol. https://doi.org/10.1007/s00467-023-05930-0
5. Zipser RD, Davenport MW, Martin KL, Tuck ML, Warner NE, Swinney RR, Davis CL, Horton R (1981) Hyperreninemic hypoaldosteronism in critically ill: a new entity. J Clin Endocrinol Metab 53:867–873. https://doi.org/10.1210/Jcem-53-4-867
6. Davenport MW, Zipser RD (1983) Association of hypotension with hyperreninemic hypoaldosteronism in the critically ill patient. Arch Intern Med 143:735–737. https://doi.org/10.1001/archinte.1983.00350040125016
7. Gleeson PJ, Crippa IA, Mongkolpun W, Cavicchi FZ, Van Meerhaeghe T, Brimioulle S, Taccone FS, Vincent J-L, Creteur J (2019) Renin as a marker of tissue-perfusion and prognosis in critically ill patients. Crit Care Med 47:152–158. https://doi.org/10.1097/CCM.0000000000003544
8. Flannery AH, Ortiz-Soriano V, Li X, Gianella FG, Toto RD, Moe OW, Devarajan P, Goldstein SL, Neyra JA (2021) Serum renin and major adverse kidney events in critically ill patients: a multicenter prospective study. Crit Care 25:294. https://doi.org/10.1186/s13054-021-03725-z
9. Kullmar M, Saadat-Gilanik WR, Massoth C, Lagan A, Cortes MN, Gerss J, Chawla LS, Filser D, Meersch M, Zarbock A (2021) Kinetic changes of plasma renin concentrations predict acute kidney injury in cardiac surgery patients. Am J Respir Crit Care Med 203:1119–1126
10. Zhang W, Chen X, Huang L, Lu N, Zhou L, Wu G, Chen Y (2014) Severe sepsis: low expression of the renin-angiotensin system is associated with poor prognosis. Exp Ther Med 7:1342–1348. https://doi.org/10.3892/etm.2014.1566
11. Bellomo R, Wunderink RG, Szerlip H, English SW, Busse LW, Deane AM, Khanna AK, McCurdy MT, Ostermann M, Young PJ, Handisides DR, Chawla LS, Tidmarsh GF, Albertson TE (2020) Angiotensin I and angiotensin II concentrations and their ratio in catecholamine-resistant vasodilatory shock. Crit Care 24:43. https://doi.org/10.1186/s13054-020-2733-x
12. Flannery AH, Kiser AS, Behal ML, Li X, Neyra JA (2022) RAS inhibition and sepsis-associated acute kidney injury. J Crit Care 69:153986. https://doi.org/10.1016/j.jcrc.2022.153986
13. du Cheyron D, Fradin S, Ramakers M, Terzi N, Guillotin D, Bouchet B, Daubin C, Charbonneau P (2008) Angiotensin converting enzyme insertion/deletion genetic polymorphism: its impact on renal function in critically ill patients. Crit Care Med 36:3178–3183. https://doi.org/10.1097/CCM.0b013e318186a299
14. Nethathe GD, Cohen J, Lipman J, Anderson R, Feldman C (2020) Mineralocorticoid dysfunction during critical illness: a review of the evidence. Anesthesiology 133:439–457
15. Chung KS, Song JH, Jung WJ, Kim YS, Kim EK, Chang J, Park MS (2017) Implication of plasma renin activity and plasma aldosterone concentration in critically ill patients with septic shock. Korean J Crit Care Med 32:142–153. https://doi.org/10.4266/kjccm.2017.00094
16. Doerschung KC, Delsing AS, Scmidt A, Ashare A (2010) Renin-angiotensin system activation correlates with microvascular dysfunction in a prospective cohort study of clinical sepsis. Crit Care 14:R24. https://doi.org/10.1186/cc8887
17. Burdman I, Burckhardt BB (2021) Prorenin and active renin levels in paediatrics: a bioanalytical review. Clin Chem Lab Med 59:275–285. https://doi.org/10.1515/cclm-2020-0857
18. Narumi K, Hirose T, Sato E, Mori T, Kisu K, Ishikawa M, Totsune K, Ishii T, Ichihara A, Nguyen G, Sato H, Ito S (2015) A functional (pro)renin receptor is expressed in human lymphocytes and monocytes. Am J Physiol Renal Physiol 308:F487–F499. https://doi.org/10.1152/ajprenal.00206.2014
19. Lichtarowicz-Krynska EJ, Cole TJ, Chamacho-Hubner C, Britto J, Levin M, Klein N, Aynsley-Green A (2004) Circulating aldosterone levels are unexpectedly low in children with acute meningococcal disease. J Clin Endocrinol Metab 89:1410–1414. https://doi.org/10.1219/jc.2003-030305
20. Khanna AK (2019) Tissue perfusion and prognosis in the critically ill-is renin the new lactate? Crit Care Med 47:288–290. https://doi.org/10.1097/CCM.0000000000003582
21. Thomas VL, Nielsen MS (1991) Administration of angiotensin II in refractory septic shock. Crit Care Med 19:1084–1086. https://doi.org/10.1097/00003246-199108000-00020
22. Wray GM, Coakley JH (1995) Severe septic shock unresponsive to noradrenaline. Lancet 346:1604. https://doi.org/10.1016/s0140-6736(95)91933-3
23. Yunge M, Petros A (2000) Angiotensin for septic shock unresponsive to noradrenaline. Arch Dis Child 82:388–389. https://doi.org/10.1136/adc.82.5.388
24. Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, Busse LW, Altaweel L, Albertson TE, Mackey C, McCurdy MT, Boldt DW, Chock S, Young PJ, Krell K, Wunderink RG, Ostermann M, Murugan R, Gong MN, Panwar R, Hästbacka J, Favory R, Venkatesh B, Thompson BT, Bellomo R, Jensen J, Kroll S, Chawla LS, Tidmarsh GF, Deane AM; ATHOS-3 Investigators (2017) Angiotensin II for the treatment of vasodilatory shock. N Engl J Med 377:419–430. https://doi.org/10.1056/NEJMoa1704154
25. Tumlin JA, Murugan R, Deane AM, Ostermann M, Busse LW, Ham KR, Kashani K, Szerlip HM, Prowle JR, Bihorac A, Finkel KW, Zarbock A, Forni LG, Lynch SJ, Jensen J, Kroll S, Chawla LS, Tidmarsh GF, Bellomo R; Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3) Investigators (2018) Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. Crit Care Med 46:949–957. https://doi.org/10.1097/CCM.0000000000003092
26. Bellomo R, Forni LG, Busse LW, McCurdy MT, Ham KR, Boldt DW, Hästbacka J, Khanna AK, Albertson TE, Tumlin J, Storey K, Handisides D, Tidmarsh GF, Chawla LS, Ostermann M (2020) Renin and survival in patients given angiotensin ii for catecholamine-resistant vasodilatory shock. A clinical trial. Am J Respir Crit Care Med 202:1253–1261. https://doi.org/10.1164/rccm.201911-2172OC