



EDITORIAL

The long and the short of it – the impact of acute kidney injury in critically ill children ☆,☆☆



Em poucas palavras - o impacto da injúria renal aguda em crianças criticamente doentes

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Over the last 15 years, knowledge on acute kidney injury (AKI) epidemiology, risk factors, and outcomes has increased dramatically. In large part, this explosion in AKI research was made feasible by the development of standardized AKI definitions, including the Risk, Injury, Failure, End Stage Kidney Disease (RIFLE), the Acute Kidney Injury Network (AKIN), and most recently, the Kidney Disease: Improving Global Outcomes (KDIGO) definition.¹ In adults, within a few years of developing the first definition (RIFLE), strong evidence demonstrated that AKI, even mild AKI, was strongly associated with short- and long-term mortality. A few years later, many studies in adults showed the association of hospital-AKI with long-term cardiovascular events and incident/worsening chronic kidney disease (CKD), hypertension, end stage renal disease (ESRD), and other clinical outcomes.¹ In adults, this research changed the landscape of AKI management. Indeed, the most recent KDIGO AKI guidelines (KDIGO is an international group which devel-

ops guidelines on all aspects of kidney disease) recommend that adults with AKI be followed up three months after hospital discharge to monitor for AKI resolution and/or new/worsening CKD.¹ Multinational studies and initiatives have been formed to alleviate this growing problem of AKI, a potent risk factor for poor outcomes.²⁻⁴

As a community, we have been a little behind in elucidating the epidemiology of AKI in children. One reason for this is that hospitalized children who suffer from an episode of AKI are most often not followed up after discharge with blood work or urine testing, or in some cases not even with a primary care physician (PCP). Thus, as opposed to adults, data on outcomes and CKD simply do not exist; prospective studies are needed to understand the late outcomes of AKI in children. Despite this challenge, in the last 10–15 years, many studies have shown that pediatric AKI is associated with increased intensive care unit (ICU) and hospital mortality, and with measures of hospital morbidity, including data from a large multinational study (the “AWARE” study).⁵⁻¹² What is clear in these studies is the importance of evaluating risk factors for AKI in different countries and healthcare contexts, as different settings may be associated with particular AKI epidemiologic patterns and causes. The long-term outcomes of pediatric AKI still elude us, but data have begun to emerge. For example, in Canada, in children admitted to the intensive care unit (ICU), AKI was shown to be independently associated with increased healthcare utilization, mortality, and CKD diagnosis at five

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years after discharge.^{10,11} In children undergoing cardiac surgery, the risk for five-to-seven year post-discharge CKD or hypertension was very high, but the association with AKI remains controversial.¹³⁻¹⁵ In non-ICU children treated with nephrotoxic medication, at six months post-discharge CKD prevalence was higher in children with nephrotoxin-associated AKI during hospitalization.¹⁵

Amongst all this research, there remains some uncertainty on how best to define AKI. For example, all three AKI definitions noted above have been evaluated in children, in addition to a pediatric-specific version of the RIFLE criteria (the "pRIFLE" definition). All versions of these definitions have shown associations with hospital outcomes in studies performed in North American children. Whether or not the urine output (staged oliguria) component of these definitions should be used in children is also somewhat controversial, though a recent large pediatric AKI study showed that the criteria of decreased urine output are strongly associated with patient outcomes.¹² Finally, an ever-challenging aspect of AKI definition is how to define the child's baseline kidney function, when most children who present to hospital have never had a blood test before. Thus, there is still much to understand about pediatric AKI epidemiology in different healthcare contexts, as well understanding the long-term impact of AKI on kidney and overall child health.

In this issue of the Journal, Ferreira & Lima¹⁶ retrospectively studied 434 children admitted to their single-center pediatric ICU (non-cardiac surgery; no CKD history), between 2004-2008. This study addressed several of the knowledge gaps outlined above, in the Brazilian tertiary healthcare context. In children without a serum creatinine measured before ICU admission, they used the expected value for age, which was completely reasonable. This approach is especially reasonable if normal-for-age creatinine values are available which are specific to the country and patient population. They excluded patients who did not have enough creatinine values available during PICU admission. While we understand the rationale for doing this (without creatinine, how can we ascertain AKI?), in other studies, an assumption was made for these patients: if they did not have their creatinine measured, they likely were not sick enough to merit creatinine measurement and thus likely did not have AKI. That said, the results of excluding these likely "less sick" patients would have the effect of *decreasing* the association between AKI and patient outcomes; therefore, it is likely that any association between AKI and outcomes found by the authors is actually even *stronger* than they reported. Because they focused on a relatively more critically ill cohort, it is not surprising that 64% of patients developed AKI (about two-thirds being in the severe/stage 2 AKI category). From a local perspective, we find this AKI rate to be quite concerning and hopefully this will stimulate quality improvement initiatives and research to examine whether AKI can be avoided or mitigated (e.g., an examination of nephrotoxic medication use; early management of fluid overload).

The risk factors for AKI identified by the authors were similar to other studies, mainly related to illness severity (e.g., ventilator, inotropic support) and nephrotoxins (specifically amphotericin). The fact that other nephrotoxic

medications did not emerge as risk factors should not mislead readers to think they do not play a role; it is possible that there were not enough patients receiving other nephrotoxins or that amphotericin use might be associated with other nephrotoxins used concurrently in sick patients (e.g., aminoglycosides). Diuretics use and reduced diuresis (oliguria) were also independently associated with AKI in the multivariable analysis. However, we caution interpretation of that result; it is possible that these two variables were highly correlated and therefore, within the same model, may not be telling us different things. We caution that readers do not interpret this as meaning that diuretics cause AKI. It is possible that patients with oliguria were appropriately prescribed diuretics. This is an example of what may be worthwhile examining at a local level, to understand the practice of diuretic use. While these results on risk factors were not novel from the perspective of overall AKI research, they were important. Locally, these risk factors may serve as a starting point for clinicians, policy makers, and quality officers to examine ICU and pre-ICU practices related to AKI risk. Also, because risk factors were similar to what is known in non-Brazilian studies, future AKI risk prediction models developed in non-Brazilian ICUs could conceivably be tested and/or applied, and/or vice-versa. Another finding described in other studies, but key to understanding AKI prevention, was that most children had AKI at ICU admission. This highlights the need to screen for AKI risk *before* ICU admission. If patients could be identified shortly after hospital admission or in the emergency room for high AKI risk, the implications on clinical outcomes could be substantial.

The authors found that AKI was associated with hospital mortality and longer length of stay, as in other studies, described above. In multivariable analyses, illness severity markers (e.g., vasoactive drugs, ventilation) were also associated with mortality. However, they reported that worse (higher) fluid overload and lower weight were also independently associated with mortality. Fluid overload has been shown in many studies to be associated with poor outcomes in children, described in a systematic review.¹⁷⁻¹⁹ Because fluid overload is related to urine output, which is related to AKI, teasing out the contribution to poor outcome between fluid overload and AKI is challenging. However, based on these results, future research evaluating the impact of avoiding or reducing fluid overload in ICU patients is worth considering. In terms of the decreasing weight association with mortality, this is a little more challenging to interpret and may be strongly related to the patient's age; moreover, weight is inherent to fluid overload calculation, thus there are concerns of collinearity between those two variables. We propose that in future prediction models weight should not be used, but rather only fluid overload and age. There is one finding that the authors did not place much importance on, but that we feel was an important and novel outcome in children. The ICU readmission rate in AKI patients was almost *four times* that of non-AKI patients. From the perspective of hospital resources and patient morbidity, this has important implications; we believe that more research should be done to examine the role of AKI on this clinical outcome, and whether post-ICU management of AKI patients may be optimized to avoid readmission. We are curious to know what the reasons were for ICU readmission.

One of the most important aspects of this study, from the perspective of overall pediatric AKI research, was the evaluation of post-discharge mortality. More research on associations of AKI with post-discharge outcomes is sorely needed. We were quite impressed with the fact that data were available on 70% of survivors. Of those who died, (61.3%) had AKI in the PICU; of those with AKI, the long-term mortality was about 18%. When considering the general population mortality in children, this is a very high and very concerning mortality rate. In the multivariable analysis, they found that illness severity markers and reduced diuresis were independent predictors of post-hospital discharge mortality, but AKI was not. This differs from two recent large pediatrics studies (one from Canada and one from the United States).^{10,12} However, we caution against concluding that AKI was not associated with mortality, because we believe that low diuresis may be strongly related to the presence of AKI. In fact, in the two aforementioned studies, the KDIGO urine output (oliguria) criteria were used to define AKI. Therefore, we might conclude that reduced diuresis was evidence of acute kidney dysfunction and was independently associated with post-discharge mortality. As acknowledged by the authors, what was lacking from this study was data on post-discharge kidney outcomes, comparing AKI vs. non-AKI survivors. We also acknowledge that obtaining such data prospectively is not only cost-prohibitive, but logistically extremely challenging.

A major question that remains is what to do with this information. From this study and from other recent studies, we know that the risk for post-discharge mortality is higher in children who develop acute kidney dysfunction and/or oliguria. They are probably also at risk for chronic kidney outcomes, but more research is needed to elucidate the magnitude of this association. Clearly, there is a need to pay special attention to children with AKI during hospitalization after discharge; but in what way? Who should follow them? Their family physician, pediatrician, or a nephrologist? In many healthcare contexts, many children do not have PCPs and access to specialist care is limited. We believe that a first step is to begin understanding in detail what is actually happening to these patients once they leave the hospital: what physician, if any, is following them; geographically, where they are located; what other health issues they have; what local resources are actually available; whether or not they continue to be at risk for AKI (e.g., receiving nephrotoxic medication at their next hospital admission); and other process-of-care and risk-related data. By understanding these factors in detail, we can begin to understand the cases in which intervention and/or prevention is actually feasible. Ideally, all children who develop AKI and who are at increased risk for late mortality or other outcomes would be identified prior to hospital discharge and provided with a patient-specific targeted care plan. How this vision will become a reality remains to be seen and will likely greatly differ depending on the healthcare context.

Conflicts of interest

Dr. Zappitelli is Chair of the Data Safety Monitoring Board (unpaid/voluntary) for a multi-center clinical trial of the

Selective Cytopheretic Device (company: CytoPheryx Inc). He is also Co-Chair of the Safety Review Committee for a drug study in children with cystinosis (company: ELOXX), for which he receives reimbursement. Neither of these conflicts impact the editorial in any way whatsoever. Dr. Noone declares no conflict of interest.

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