Biomarkers in Pediatric Acute Kidney Injury

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2.1 Clinical Case

NB is a 4-month-old male with hypoplastic left heart syndrome who underwent a cardiac repair procedure requiring cardiopulmonary bypass 3 days ago. He has made no urine postoperatively despite aggressive dosing of furosemide and bumetanide. His serum potassium has been trending 6.1–6.3 mEq/L and serum bicarbonate 15–18 mEq/L. He remains intubated and has not tolerated weaning of respiratory support or vasoactive drips. NB is currently 8% fluid overloaded and appears mildly edematous on exam. The team would like to provide full parenteral nutrition to this postoperative patient but they are concerned that he will not tolerate the volume needed.

Outcome 1 The team decides to initiate renal replacement therapy. Because of previous abdominal procedures, NB is not a candidate for peritoneal dialysis; therefore, a central line is placed and he receives three sessions of daily hemodialysis. Subsequent laboratory tests suggest renal recovery, and no further dialysis is performed.

Outcome 2 The team has been trending NGAL, a non-invasive, inexpensive laboratory test marker of structural acute kidney injury, which demonstrates that the kidney injury is improving, although other labs and urine output remain unchanged. Fluid restriction is maintained and electrolyte abnormalities are managed medically.

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The next day, NB begins producing small amounts of urine and within 48 h all fluid and electrolyte restrictions are discontinued. The increased cost and morbidity of renal replacement therapy are avoided.

Which outcome would you prefer for your patient?

2.2 The Unmet Need for Acute Kidney Injury Biomarkers

Acute kidney injury (AKI) is common in hospitalized children and is a significant cause of morbidity and mortality. Approximately one-third of all pediatric patients worldwide develop AKI during hospital admission [1]. Over 25% of critically ill children develop AKI and over 10% of these cases can be classified as severe, which is defined as Stage 2 or 3 AKI by the Kidney Disease Improving Global Outcomes Work Group staging system [2, 3]. Severe AKI has been shown to confer increased risk of mortality [2, 4], longer hospital stay [3], and heightened risk of developing chronic kidney disease [5, 6].

Traditionally, clinicians have utilized functional indicators to assess a patient's renal status. The most common of these functional markers, serum creatinine and urine output, have several significant limitations, particularly in children. Serum creatinine is a delayed marker of renal impairment, with levels only rising hours to days following kidney insult. Early recognition of structural kidney injury is limited given that a baseline healthy kidney's functional reserve requires a significant injury and functional loss prior to creatinine elevation. It also can be unreliable in several specific clinical contexts, such as variable muscle mass and fluid overload. A large prospective, multinational observational study of pediatric intensive care patients confirmed the inadequacy of serum creatinine for AKI diagnosis, since 67.2% of patients with oliguria-diagnosed AKI would not have been recognized using creatinine-based definitions alone [2]. Unfortunately, urine production is a difficult measure to obtain with high accuracy, particularly in young children without indwelling urinary catheters and patients in non-ICU settings. Furthermore, urine output can be confounded by the hydration status as well as the common use of diuretics in critically ill children.

In contrast to these functional indicators, the use of a structural AKI biomarker improves diagnostic and therapeutic patient care by allowing earlier detection of tissue injury at a time when inciting factors can still be modified and response to interventions trended in real-time [7]. A good biomarker is expected to be valid, reliable, and clinically useful, with biomarker results being both clearly actionable and promptly available to effectively drive clinical care. Non-invasive technique, cost-effectiveness, and the ability to process the biomarker ubiquitously in hospital clinical laboratories or even at the bedside are additional features that render a biomarker more generalizable across a spectrum of patient populations.

Table 2.1 Urinary biomarkers in AKI

Biomarker	Source	Physiologic role	Clinical utility
NGAL	Distal tubule and collecting duct	Regulates iron trafficking, promotes tubule cell survival	• Confirmed early marker of AKI severity, renal replacement need, mortality, and renal recovery • Standard clinical platforms widely available • Results in 15–30 min
KIM-1	Proximal tubule	Promotes epithelial regeneration, regulates apoptosis	• Delayed marker of AKI compared with NGAL • Awaits confirmatory studies • No clinical assays available
IL-18	Proximal tubule	Promotes tubule cell apoptosis and necrosis	• Predicts AKI in post-CPB • No clinical assays available
L-FABP	Proximal tubule	Antioxidant, suppresses tubulo-interstitial damage	• Awaits confirmatory studies • No clinical assays available
TIMP-2, IGFBP7	Proximal tubule	Limits proliferation of damaged tubule cells	• Delayed marker of AKI compared with NGAL • AUC comparable to NGAL for predicting AKI • Requires specialized testing platform

Abbreviations: *AKI* acute kidney injury, *NGAL* neutrophil gelatinase-associated lipocalin, *KIM-1* kidney injury molecule-1, *IL-18* interleukin-18, *CPB* cardiopulmonary bypass, *L-FABP* liver-type fatty acid-binding protein, *TIMP-2* tissue inhibitor of metalloproteinases-2, *IGFBP7* insulin-like growth factor-binding protein 7, *AUC* area under the curve

A number of promising structural biomarkers have been investigated in AKI research with varying degrees of clinical applicability ([8], Table 2.1). Of these, neutrophil gelatinase-associated lipocalin (NGAL) is the most well-established, validated in many patient populations, and is already being employed effectively in the clinical setting using widely available standardized clinical platforms [9, 10]; thus, NGAL will be primarily discussed further here.

2.3 Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2, is a 25 kDa glycoprotein released by epithelial tissues and as such can be increased in the systemic circulation in a number of human disease processes apart from AKI (Table 2.2). In the majority of these conditions, urinary NGAL remains low unless there is concomitant renal tubular injury that prevents any filtered NGAL from being efficiently reabsorbed. It is one of the most upregulated genes in the kidney following conditions of ischemic or toxic stress and is released directly into the

Table 2.2 Clinical settings in which NGAL can be elevated independent of AKI

Urinary tract infection
Sepsis
Chronic kidney disease
Malignancy
Pancreatitis

Abbreviations: *NGAL* neutrophil gelatinase-associated lipocalin, *AKI* acute kidney injury

urine by kidney tubule cells, where its role in the iron-chelation process assists in renal protection and tubule cell recovery and proliferation [11]. Following AKI, the released NGAL is also partially reabsorbed into the circulation, thus contributing to the systemic NGAL pool.

NGAL remains stable when stored at 4 °C for up to 24 h in urine and up to 48 h in plasma/serum [12, 13]. While both urine and plasma NGAL levels have been shown to increase within 2–4 h of intrinsic structural AKI, data utilizing urine NGAL is overall more prevalent in the available pediatric clinical and research AKI literature. There are currently three clinical platforms available for testing NGAL levels, one of which is easily adaptable to most standard clinical laboratory platforms and is already in routine clinical use in several institutions worldwide.

Clinically, NGAL has been extensively validated to predict and differentiate intrinsic structural AKI from functional AKI (previously referred to as a prerenal state) and to predict the adverse outcomes of AKI. Several groups have completed systemic analyses of the extensive published literature to date looking at the accuracy of NGAL in predicting AKI diagnosis and prognosis across a variety of clinical settings.

A meta-analysis published by Haase et al. in 2009 looked at 19 prospective, observational, single-center cohort studies investigating the diagnostic and prognostic accuracy of NGAL to predict creatinine-based AKI, dialysis initiation, and in-hospital mortality [14]. These studies represent data from a total of 2538 patients (of which 663 were children) from 8 different countries. It was found that NGAL level accuracy improved with more severe AKI definitions and that an NGAL cut-off of >150 ng/mL using a standardized clinical platform provided optimal sensitivity and specificity to predict AKI with an area under the curve for the receiver-operating characteristic (AUC-ROC) of 0.83 (95% CI 0.741–0.918). Overall, the AKI predictive value of NGAL in children was shown to be substantially high than in adults, with the diagnostic odds ratio (DOR) in children at 25.4 (AUC-ROC 0.93) versus 10.6 (AUC-ROC 0.782) in adults. The predictive values of urine and plasma NGAL were similar (DOR 17.9, AUC-ROC 0.775 and DOR 18.6, AUC-ROC 0.837, respectively). When used to prognosticate adverse outcomes of AKI in all-age pooled data

Table 2.3 AKI risk categories based on urinary NGAL level

AKI risk category	Urinary NGAL level (ng/mL)	Interpretation
Low	<50	Intrinsic structural AKI unlikely
Equivocal	50–149	Gray zone; clinical risk factors and repeat NGAL measurements needed to clarify
Moderate	150–300	Predicts intrinsic structural AKI
High	>300	Predicts severe AKI and adverse outcomes

Abbreviations: *AKI* acute kidney injury, *NGAL* neutrophil gelatinase-associated lipocalin

evaluation, NGAL was shown to be useful, with DOR 12.9, AUC-ROC 0.782 for initiation of renal replacement therapy and DOR 8.8, AUC 0.706 for in-hospital mortality.

In a 2017 meta-analysis, Filho et al. looked at 13 studies (6 which overlapped with the Haase analysis) with a total of 1629 pediatric patients [15]. Through this analysis it was determined that NGAL was able to predict AKI development in children with a sensitivity of 0.76 (95% CI 0.62–0.86) in urine, 0.80 (95% CI 0.64–0.90) in plasma and specificity of 0.93 (95% CI 0.88–0.96) in urine, 0.87 (95% CI 0.74–0.94) in plasma. Overall, the DOR for AKI detection was 26 (95% CI 8–82) and AUC 0.90 (95% CI 0.87–0.94), substantiating previous analyses demonstrating NGAL to have good predictive value and discriminative power in predicting AKI in children. In particular, the negative predictive value of NGAL is especially high, such that a normal NGAL result effectively rules out true structural AKI (irrespective of the serum creatinine or the urine output).

Summative assessment of the NGAL literature to date has demonstrated that AKI risk, severity stratification, and prognosis are dose-dependent. As such, NGAL level thresholds (Table 2.3) have been established for the standardized clinical laboratory platforms, with cut-off levels derived during previous meta-analyses, and their effective application in pediatric clinical care has already been reported in the literature [9, 10]. One example of a clinical algorithm for use of NGAL in the hospital setting is detailed in Fig. 2.1.

It is important to note that, as with every test ordered in patient care, the proper clinical application and interpretation of NGAL levels is only optimized when a patient's clinical status, individual medical history, and AKI risk factors are taken into account. As such, it can be helpful to use a clinical risk stratification method to assist in deciding who should have NGAL testing done and how to act on the results. One example is the renal angina index, a scoring tool developed to identify patients at risk of AKI within the first 24 h of pediatric intensive care admission [16, 17] based on admission characteristics.

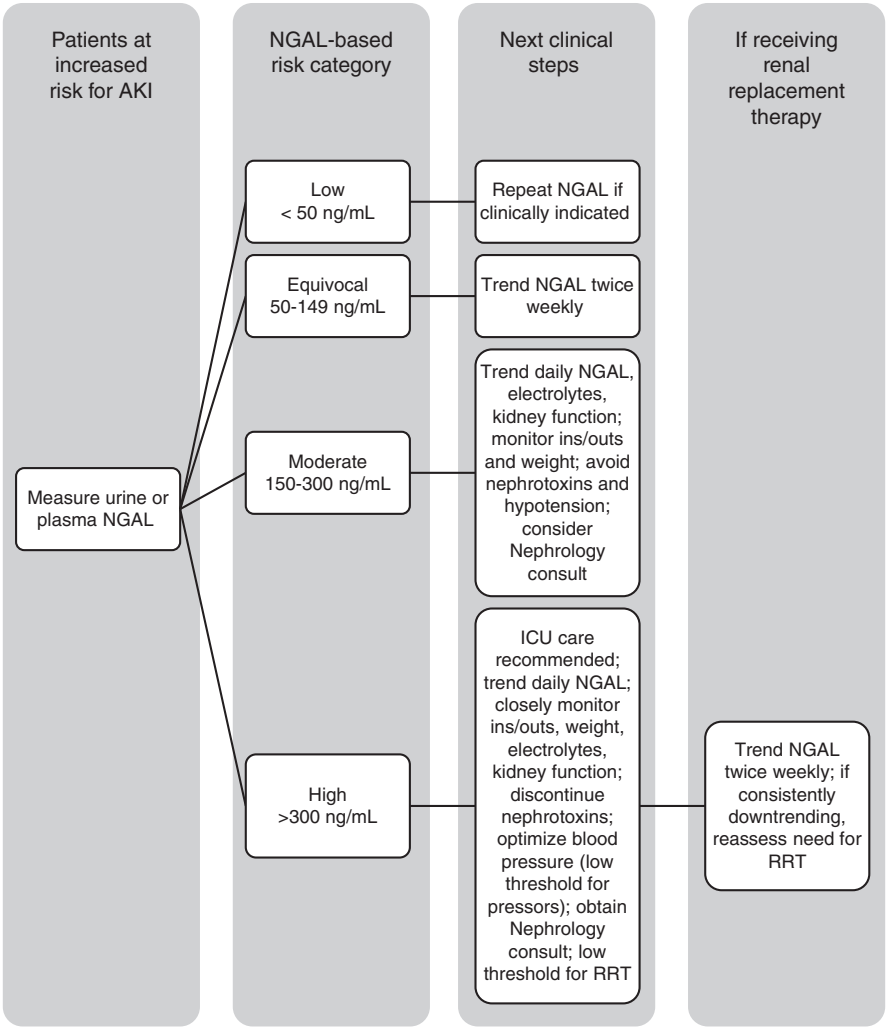

Fig. 2.1 Clinical algorithm for NGAL in AKI

2.4 Conclusion: Key "Take Home" Points

1. Current functional markers of AKI (serum creatinine and urine output) are delayed and inadequate to allow for early detection or to trend intervention effects in real-time.
2. Neutrophil gelatinase-associated lipocalin (NGAL) is a protein biomarker upregulated in and released into urine and plasma from injured kidney tubule cells.

3. Use of NGAL as a non-invasive AKI biomarker is well-established, validated across many patient care settings, and already effectively being used clinically to assist in modifying fluid balance, ameliorating renal stress exposures, and optimizing the timing and duration of renal replacement therapy.
4. AKI risk, severity stratification, and prognosis are dose-dependent and can be trended in real-time using categories based on NGAL levels: low risk <50 ng/mL, equivocal 50–150 ng/mL, moderate risk 150–300 ng/mL, and high risk >300 ng/mL.
5. Increasing NGAL-based AKI risk indicates a correlating escalation in monitoring, intervention, and nephrology specialty involvement.

References

1. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Algahtani F, Koulouridis I, Jaber BL, Acute Kidney Injury Advisory Group of the American Society of Nephrology. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol. 2013;8(9):1482–93. Erratum in: Clin J Am Soc Nephrol. 2014; 9(6):1148.
2. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL. Epidemiology of acute kidney injury in critically ill children and young adults. N Engl J Med. 2017;376:11–20.
3. Kellum JA, Lameire N, Aspelin P, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury working group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1):1–138.
4. Sutherland SM, Byrnes JJ, Kothari M, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. Clin J Am Soc Nephrol. 2015;10(4):554–61.
5. Cooper DS, Claes D, Goldstein SL, Bennett MR, Ma Q, Devarajan P, Krawczeski CD. Follow-up renal assessment of injury long-term after acute kidney injury (FRAIL-AKI). Clin J Am Soc Nephrol. 2016;11(1):21–9.
6. Madsen NL, Goldstein SL, Froslev T, Christiansen CF, Olsen M. Cardiac surgery in patients with congenital heart disease is associated with acute kidney injury and the risk of chronic kidney disease. Kidney Int. 2017;92(3):751–6.
7. Devarajan P. Neutrophil gelatinase-associated lipocalin: a promising biomarker for human acute kidney injury. Biomark Med. 2010;4:265–80.
8. Ciccia E, Devarajan P. Pediatric acute kidney injury: prevalence, impact and management challenges. Int J Nephrol Renov Dis. 2017;10:77–84.
9. Varnell CD Jr, Goldstein SL, Devarajan P, Basu RK. Impact of near real-time urine neutrophil gelatinase-associated lipocalin assessment on clinical practice. Kidney Int Rep. 2017;2:1243–9.
10. Devarajan P. Kidney attack: is NGAL set to take the stage with troponins? In: Rangaswami J, Lerma EV, Ronco C, editors. Cardio-nephrology: confluence of the heart and kidney in clinical practice. 1st ed. Cham: Springer; 2017.
11. Ostermann M, Phillips BJ, Forni LG. Clinical review: biomarkers of acute kidney injury: where are we now? Crit Care. 2012;16(5):233.
12. Schuh MP, Nehus E, Ma Q, Haffner C, Bennett M, Drawczeski CD, Devarajan P. Long-term stability of urinary biomarkers of acute kidney injury in children. Am J Kidney Dis. 2016;67(1):56–61.
13. Pedersen KR, Ravn HB, Hjortdal VE, Nørregaard R, Povlsen JV. Neutrophil gelatinase-associated lipocalin (NGAL): validation of commercially available ELISA. Scand J Clin Lab Invest. 2010;70(5):374–82.
14. Haase M, Bellomo R, Devarajn P, Schlattmann P, Haase-Fielitz A, NGAL Meta-analysis Investigator Group. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagno-

sis and prognosis in acute kidney injury: a systemic review and meta-analysis. Am J Kidney Dis. 2009;54(6):1012–24.
15. Filho LT, Grande AJ, Colonetti T, Possamai Della ES, da Rosa MI. Accuracy of neutrophil gelatinase-associated lipocalin for acute kidney injury diagnosis in children: systematic review and meta-analysis. Pediatr Nephrol. 2017;32(10):1979–88.
16. Basu RK, Wang Y, Wong HR, Chawla LS, Wheeler DS, Goldstein SL. Incorporation of biomarkers with the renal angina index for prediction of severe AKI in critically ill children. Clin J Am Soc Nephrol. 2014;9(4):654–62.
17. Goldstein SL. The renal angina index to predict acute kidney injury: are adults just large children? Kidney Int Rep. 2018;3(3):516–8.