Critical Care Pediatric Nephrology and Dialysis: A Practical Handbook

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Dedicated to our patients who are our teachers

Contents

About the Editors

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Part I

Acute Kidney Injury in a Sick Child

Acute Kidney Injury: Definitions and Epidemiology

1

Neziha Celebi and Ayse Akcan Arikan

Case 1

An 11-year-old female with history of acute myeloid leukemia who underwent bone marrow transplant 34 days ago developed fever to 104 °F; her blood pressure was 50/20 and heart rate was 180 beats/min. On physical exam she appeared lethargic, pale, and cold to touch. She was empirically started on broad-spectrum antibiotics and underwent emergency resuscitation with multiple fluid boluses ultimately requiring intubation and pressor support. Her urine output was previously reported as 1 ml/kg/day; however, she made only 30 ml of urine in 6 h after admission to the intensive care unit (ICU). Laboratory studies on ICU admission demonstrated that the electrolytes were normal, the blood urea nitrogen was 50 mg/dl, and creatinine was 0.9 mg/dl (creatinine was 0.6 mg/dl 2 days ago). The urinalysis was unremarkable.

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Case 2
A 14-year-old previously healthy male presented to emergency department for complaints of lower back pain and malaise for which he reported taking ibuprofen in appropriate doses daily last week. Otherwise he did not have fever and reported unchanged amount of urine output. On physical examination the height and weight were normal, the blood pressure was 117/75, and he appeared pale. Laboratory studies demonstrated that the electrolytes were normal, the blood urea nitrogen was 57 mg/dl, and creatinine was 3.2 mg/dl. The urinalysis was unremarkable. Renal ultrasonography demonstrated normal sized kidneys with increased echogenicity and loss of corticomedullary differentiation.

1.1 Acute Kidney Injury: Definition

Acute kidney injury (AKI) is defined as a rapid decline in glomerular filtration rate (GFR) leading to accumulation of waste products. AKI is common, affecting one third of the children admitted to intensive care unit (ICU) and is associated with poor outcomes including increased mortality and morbidity among critically ill children [1]. Severity and progressions of AKI is directly associated with stepwise increase in mortality and other adverse outcomes. Therefore, a standardized definition of AKI is particularly important to diagnose AKI and stratify AKI severity, in order to manage these patients better. In the past, available literature included multiple definitions for renal failure based on different thresholds of serum creatinine or blood urea nitrogen, with or without contribution from urine output, or requirement of renal replacement therapy, which made detection, diagnosis, classification, and study of AKI rather difficult. In an effort to better define AKI, three standardized consensus classifications have been proposed: (1) RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) criteria was developed by the Acute Dialysis Quality Initiative (ADQI) in 2004 for adult patients by using changes in serum creatinine levels from baseline and/or decrease in urine output (Table 1.1) [2]. RIFLE definition was adapted for children by using change in estimated creatinine clearance from baseline, which is referred to as pediatric RIFLE (pRIFLE) definition (Table 1.1) [3]. In an adult study, increase of serum creatinine 0.3 mg/dl was found to be associated with 70% increase in risk of death; those results were replicated later in a pediatric study where increase of serum creatinine of 0.3 mg/dl was associated with increased mortality risk in a population with decompensated heart failure [4, 5]. (2) Further refinement of RIFLE criteria was developed by acute kidney injury network (AKIN) in 2007 which included the additional criterion of 0.3 mg/dl increase in serum creatinine in less than 48 h (Table 1.2) [6]. (3) Finally, in 2012 several aspects of RIFLE, pRIFLE, and AKIN criteria were integrated into a single definition for pediatric and adult patients by the Kidney Disease Improving Global Outcomes (KDIGO) classification (Table 1.3) [7].

Table 1.1 RIFLE/pRIFLE criteria for acute kidney injury

	Cr/GFR criteria	Urine output criteria
Risk (R)	Increased Cr × 1.5 or decreased GFR by 25% eCCl decrease by 25%[a]	Urine output <0.5 ml/kg/h × 6 h Urine output <0.5 ml/kg/h × 8 h[a]
Injury (I)	Increased Cr × 2 or decreased GFR by 50% eCCl decrease by 50%[a]	Urine output <0.5 ml/kg/h × 12 h Urine output <0.5 ml/kg/h × 16 h[a]
Failure (F)	Increased Cr × 3 or decreased GFR by 75% or Cr >4 mg/dl (with acute rise of >0.5 mg/dl) eCCl decrease by 75% or Cl <35 ml/min/1.73 m^{2}[a]	Urine output <0.3 ml/kg/h × 24 h or Anuria × 12 h
Loss (L)	Persistent failure—complete loss of renal function for >4 weeks	
ESRD (E)	End-stage renal disease-persistent failure >3 months	

[a]pRIFLE criteria; *eCCL* estimated creatinine clearance, *Cr* creatinine

Table 1.2 AKIN criteria for acute kidney injury

	Cr/GFR criteria	Urine output criteria
Stage 1	Increased Cr × 1.5–1.9 from baseline or increase by ≥0.3 mg/dl	Urine output <0.5 ml/kg/h × 6 h
Stage 2	Increased Cr × 2–2.9 from baseline	Urine output <0.5 ml/kg/h × 12 h
Stage 3	Increased Cr × ≥3 or sCr ≥4 mg/dl with acute rise of ≥0.5 mg/dl	Urine output < 0.3 ml/kg/h × 24 h or Anuria × 12 h

Table 1.3 KDIGO criteria for acute kidney injury

	Cr/GFR criteria	Urine output criteria
Stage 1	Increased Cr × 1.5–1.9 from baseline or increase by ≥0.3 mg/dl	Urine output <0.5 ml/kg/h × 6–12 h
Stage 2	Increased Cr × 2–2.9 from baseline	Urine output <0.5 ml/kg/h × 12 h
Stage 3	Increased Cr × ≥3 or increase in sCr ≥4 mg/dl or initiation of renal replacement therapy or, in patients <18 years, decrease in GFR <35 ml/min/1.73 m^{2}	Urine output <0.3 ml/kg/h × 24 h or Anuria × 12 h

All three definitions have subtle differences and different advantages. Baseline creatinine interpretation differs among definitions; most notably, AKIN uses first creatinine available as the baseline creatinine, whereas pRIFLE requires height to calculate eCCL. Thus, pRIFLE, AKIN, and KDIGO result in different AKI epidemiology. pRIFLE is more sensitive to detect mild AKI. AKIN is less sensitive but more specific to diagnose severe AKI; whereas, pRIFLE and KDIGO detect severe AKI similarly. Since KDIGO is applicable to both pediatric and adult population it has come into wide use. Overall, all three definitions highly correlate with staging of AKI and outcomes [8, 9].

Table 1.4 Modified KDIGO criteria for neonatal acute kidney injury

	Cr/GFR criteria	Urine output criteria
Stage 0	No change in sCr or rise <0.3 mg/dl	Urine output >1 ml/kg/h
Stage 1	sCr rise ≥0.3 mg/dl within 48 h or sCr rise ≥1.5 to 1.9 × reference sCra within 7 days	Urine output >0.5 ml/kg/h and ≤1 ml/kg/h
Stage 2	sCr rise ≥2 to 2.9 × reference sCr	Urine output >0.3 ml/kg/h and ≤0.5 ml/kg/h
Stage 3	sCr rise ≥3 × reference SCr or sCr ≥2.5 mg/dl or receipt of dialysis	Urine output ≤0.3 ml/kg/h

[a]Reference serum creatinine, defined as the lowest previous serum creatinine value available

The criteria for the diagnosis of AKI and staging of severity of AKI are based on changes in serum creatinine and urine output. The caveat here is that serum creatinine is a late marker of decreasing GFR. Additionally, serum creatinine concentrations can be influenced by malnutrition, liver dysfunction, decreased muscle mass, and volume overload, which all can cause underestimation of the degree of renal dysfunction. On the other hand, changes in urine output usually precede the changes in serum creatinine [10]. If only creatinine criteria are used, up to 70% of AKI are missed [1]. However, relying on urine output solely will obviously miss nonoliguric AKI, such as presented in Case 2 in the beginning of the chapter. Since urine output may not be measured routinely in non-intensive care settings, early AKI might easily be missed. The worry for catheter associated urinary tract infection has led to a tendency of not placing indwelling bladder catheters or early removal in the intensive care settings. Clinicians need to be aware of when closer monitoring is needed and order this simple intervention accordingly. All patients who get admitted in shock should receive an indwelling bladder catheter until shock is resolved.

Definition of AKI in critically ill neonates has lagged behind that in older populations. Serum creatinine is difficult to interpret in newborns since it may reflect maternal creatinine during first week of life in term neonates and may persist at maternal levels up to 2–3 weeks in preterm infants. Monitoring the trend of the serum creatinine may be more helpful. Progressive increase in serum creatinine or failure to decrease is consistent with decreased renal function. KDIGO AKI definition was adapted and used for study purposes in the neonatal population (Table 1.4). The overall incidence of AKI in neonates and infants is about 30% and is associated with poor outcomes including higher mortality, similar to other age groups [11].

1.2 Acute Kidney Injury: Epidemiology

Although precise incidence of pediatric AKI is not known, overall incidence of AKI is thought to be increasing and depends on the clinical setting and patient's clinical condition. An administrative dataset screening for physician coding revealed AKI rate of 3.9 per 1000 at-risk pediatric hospitalizations [11]. Twenty seven percent of the critically ill children at pediatric intensive care unit (PICU) developed AKI with 10% of them developing severe AKI (AKI stage 2 and stage 3), and 1% requiring renal replacement therapy. Twelve percent of severe AKI develops within 7 days after ICU admission [1].

Multiorgan dysfunction, need for mechanical ventilation, documented infection, extracorporeal membrane oxygenation, and nephrotoxic medication exposure are identified as risk factors for developing AKI in critically ill children, while nephrotoxic medication exposure has the greatest independent risk [12, 13]. Development of AKI is associated with higher mortality, PICU length of stay, and duration of mechanical ventilation [13, 14]. Severe AKI (stage II or III) has the highest association with mortality. Patients with resolved AKI or those who have improvement in their severity of AKI stage tend to have lower mortality; however, patients with any degree of AKI, even mild, despite complete resolution, still have higher rates of mortality than patients who do not develop AKI at all in the ICU setting [15]. Outside of the PICU, 25% of the non-critically ill children who are exposed to three or more nephrotoxic medications developed AKI [16, 17]. AKI rates of 30% have been reported in infants; whereas, 48% of extremely preterm infants (less than 28 weeks of gestation) develop AKI [18]. The incidence increases to 40–65% in the infants undergoing cardiac surgery depending on the definition used, the rate increasing with lower age at surgery, longer cardiopulmonary bypass, type of repair, and lower gestational age [19, 20] (Table 1.5).

Table 1.5 Risk factors associated with AKI [21]

Critical illness
Sepsis
Shock—hypotension, vasopressor requirement
Mechanical ventilation
Extracorporeal membrane oxygenation
Preexisting renal, hepatic, cardiac, neurologic, or respiratory disease
Oncologic disease
Neonates
Low gestational age
Low birth weight
Perinatal asphyxia
Congenital diaphragmatic hernia
Bronchopulmonary dysplasia
Maternal exposure to angiotensin-converting enzyme (ACE) inhibitors
Solid organ transplants
Bone marrow transplants
Intravascular volume depletion—diabetic ketoacidosis, nephrotic syndrome, diarrhea, vomiting
Venous congestion—congestive heart failure, right heart failure, pulmonary hypertension
Post cardiac surgery—prolonged cardiopulmonary bypass
Nephrotoxic medication exposure[a]
Aminoglycosides
Vancomycin
Piperacillin/tazobactam
Amphotericin B
Chemotherapeutics
Immune modulators
Non-steroidal anti-inflammatory drugs
ACE inhibitors
Intravenous contrast media

[a]List in not exhaustive

1.3 Acute Kidney Injury: Pathophysiology

1.3.1 Functional AKI

Functional (prerenal) AKI is caused by decreased renal perfusion due to decrease in either absolute or effective circulating volume. Hypotension, decreased cardiac function, renovascular compromise, and volume depletion can all lead to functional AKI. The hallmark is the improvement of renal function with correction of underlying problem, hence the term functional. Systemic hypoperfusion triggers the activation of sympathetic nervous system, renin-angiotensin axis, and nonosmotic antidiuretic hormone secretion leading to compensatory mechanisms that raise blood pressure. GFR is initially preserved by several intrarenal autoregulatory mechanisms including generation of intrarenal vasodilatory prostaglandins and intrinsic myogenic mechanisms [22]. Prolonged duration and increased severity of the trigger lead to decrease in GFR, manifested as functional AKI. During this phase, subclinical intrinsic renal injury may be demonstrated by novel biomarkers, which typically are proteins expressed in cellular stress and repair. Longer duration of this phase can easily transition into intrinsic injury.

1.3.2 Intrinsic Renal Injury

Prolonged duration of processes leading to functional AKI, exposure to nephrotoxins, or sepsis, among other causes, can lead to intrinsic AKI, especially in the setting of critical illness. Though traditionally referred to as acute tubular necrosis (ATN), histological evidence of ATN is exceedingly rare in the critically ill patients suffering from AKI. Endothelial cell injury can promote the initiation and extension of intrinsic AKI via disrupting the microvascular blood flow. Straight segment (S3 segment) of proximal tubule and medullary thick ascending limb of Henle are particularly sensitive to ischemic changes given inherent high cellular energy needs and relative low oxygen tension in the adjoining renal medulla. Cellular injury leads to cell sloughing from disrupted adhesion molecules and cell necrosis which may further cause tubular obstruction with leakage of proteinaceous material (Tamm–Horsfall protein). Inflammatory processes also contribute to the sequence of events in intrinsic AKI [22].

1.3.3 Postrenal AKI/Obstructive Nephropathy

Anatomic abnormalities of the genitourinary system (for example, posterior urethral valves), functional problems (for example, neurogenic bladder, dysfunctional bladder, or other voiding dysfunction), obstruction at the bladder outlet or bilateral ureters, or blockage of tubules with protein and crystals can lead to urinary retention and AKI. Obstruction affecting bilateral collecting systems is the hallmark of obstructive AKI. Backward pressure from obstruction is transmitted up through the

Table 1.6 Determining type of the renal injury

	FeNa: ([U/P] Na)/([U/P]/Cr) × 100	FeUrea: ([U/P] Urea)/([U/P]/Cr) × 100
Functional AKI	FeNa <1%	FeUrea <35%
	Urine sodium: <20 mEq/l Urine osmolality: >400 mOsm/kg Urine specific gravity: >1020 Urine sediment: bland Urine protein: none to low	
Intrinsic AKI	FeNa >2%	FeUrea >50 to 65%
	Urine sodium: >30 mEq/l Urine osmolality: <350 mOsm/kg Urine specific gravity: <1012 Urine sediment: broad brownish granular cast Urine protein: none to low	

Sodium (Na), Creatinine (Cr), Urine (U), Plasma (P)

urinary system, which counteracts the hydrostatic pressure for filtration at the glomerulus. When it eventually overcomes the hydrostatic pressure in the glomerulus, glomerular filtration stops and AKI occurs [22].

1.4 Differentiation of Functional and Intrinsic AKI

Urinary indices are derived from the assumption that tubular integrity is maintained in the setting of functional AKI. In prerenal/functional AKI state, sodium-retaining mechanism is activated, reducing the urinary sodium; whereas tubular cell damage of ATN causes impaired resorptive capacity of proximal tubule leading to urinary sodium rise. Thus, urine sodium is used as an indicator of volume status and renal tubular integrity. Fractional excretion of sodium (FeNa) evaluates urinary sodium excretion. However, diuretic use limits sodium reabsorption and makes FeNa calculation unreliable in patients who have received diuretics. Fractional excretion of urea (FeUrea), based on the same principal, can be used in these instances (Table 1.6).

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Biomarkers in Pediatric Acute Kidney Injury

2

Eileen Ciccia and Prasad Devarajan

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.