3 Diagnostic Approach: Differential Diagnosis, Physical Exam, Lab Tests, Imaging, and Novel Biomarkers

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Acute kidney injury (AKI) is a complex and common clinical syndrome that is classically defined as the abrupt loss of kidney function. The internationally accepted definitions and staging systems and epidemiology of AKI are discussed in Chap. 2 [1]. In this chapter we will discuss the differential diagnosis of AKI as well as the physical exam findings and laboratory tests that can be used when evaluating a patient with AKI. Finally, we will discuss the utility of the ever-expanding list of novel biomarkers that are associated with improvements in the diagnosis, risk stratification, and outcome prognostication of hospitalized patients with AKI [2].

3.1 Differential Diagnosis

Traditionally the differential diagnosis of AKI has been classified into prerenal, intrinsic renal/intrarenal, and post-renal causes [3] (Table 3.1). Classically this has allowed clinicians to think about the factors that affect renal function into those which occur before the kidney (prerenal), inside of the kidney, or after the kidney (post-renal—along the remainder of the genitourinary system). This anatomy-based classification system has been utilized for decades, and while more modern schemas have been suggested, the pre-, intra-, and post-renal remains a mainstay of clinical decision-making. Many clinicians believe that these distinctions are important as prerenal and post-renal causes of AKI may progress to becoming intrinsic/intrarenal AKI. Additionally, if diagnosed early, pre- and post-renal AKI may be readily reversible, with regard to changes in glomerular function/serum creatinine, and thus earlier diagnosis may not only mitigate the severity of the AKI but potentially the morbidity and mortality that are associated with it.

Prerenal causes of AKI result from impaired renal perfusion from either true intravascular volume depletion (e.g., GI losses, hemorrhage, or burns) or from decreases in the effective circulating volume (e.g., decompensated congestive heart failure with reduced ejection fraction or end-stage liver disease with cirrhosis). Additionally, several medications, which affect renal vascular autoregulation, have been associated with prerenal AKI. These include nonsteroidal anti-inflammatory drugs (NSAIDs) and calcineurin inhibitors (CNIs), angiotensin-converting enzyme inhibitors (ACE-I), and angiotensin II receptor blockers (ARBs), all of which modify renal vascular autoregulation. NSAIDs can cause afferent arteriole vasoconstriction, leading to fall in renal blood flow and thus a decline in glomerular filtration rate (GFR)/rise in creatinine. Similarly, CNIs including tacrolimus and cyclosporine have been

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Table 3.1 Classical differential diagnosis of AKI

Prerenal causes	Intrinsic renal causes	Post-renal causes
True volume depletion (diarrhea, vomiting, burns, hemorrhage, pancreatitis)	Processes involving renal microvasculature such as vasculitis, TTP, malignant hypertension, and renal atheroemboli	Bladder outlet obstruction including prostate disease in men and pelvic tumors
Renal artery stenosis	Processes affecting primarily glomeruli such as rapidly progressive glomerulonephritis	Ureteral: stones, stricture
Effective circulating volume depletion (decompensated heart failure, cardiac cirrhosis)	Processes affecting the tubulointerstitium such as acute tubular necrosis (ischemic or nephrotoxic), acute interstitial nephritis	Retroperitoneal fibrosis
Abdominal compartment syndrome		

The table displays the common causes of AKI along the prerenal, intrarenal, and post-renal classification. This traditional anatomic approach remains in clinical use despite disease processes crossing over in between categories. For example, persistently prolonged intravascular volume depletion in the setting of concomitant hypotension may lead to intrinsic tubular injury/tubular necrosis, or chronic urinary obstruction may eventually cause tubular loss and fibrosis leading to intrarenal manifestations

shown to cause renal arteriolar vasoconstriction leading to an increased association with AKI as measured by increases in serum creatinine. Additionally drugs which impact the renin-aldosterone system (e.g., ACE-I and ARBs) have been shown to alter renal hemodynamics and thus impact functional biomarkers of AKI (e.g., serum creatinine and cystatin C) but not biomarkers that report structural nephron injury/damage. Thus while ACE-I and ARBs lead to alterations of serum creatinine, the extent to which this is truly AKI remains under-investigated. This failing of currently available biomarker of AKI accounts for the growing push in nephrology to fundamentally change the manner in which we discuss the differential diagnosis of AKI (see new AKI paradigm below). The kidney has the capacity to autoregulate renal blood flow and GFR through changes in afferent and efferent arteriolar tone. However, prerenal conditions, if severe, can overwhelm these compensatory processes and lead to a dramatic fall in GFR. Furthermore in the setting of AKI, these autoregulatory mechanisms can be impaired leading to an exacerbation of initial injury following even mild decreases in blood pressure, eventually potentially converting to an intrarenal injury [4].

In the hospital setting, obstructive uropathy (post-renal) accounts for approximately 10% of cases of AKI [5]. Post-renal causes of AKI can result from obstruction anywhere along the urinary tract but is most commonly from bladder outlet obstruction as seen in prostatic hypertrophy in men [6]. It can also be seen in cases of pelvic masses and tumors compressing bilateral ureters [7]. Common obstructing tumors include those of the prostate, bladder, uterus, and cervix. A rare cause of obstructive uropathy is retroperitoneal fibrosis which may be idiopathic, but it can be associated with previous pelvic irradiation or malignancies such as lymphoma and a variety of solid tumors [8]. Importantly unilateral obstruction in those with two functioning kidneys is often not diagnosed through changes in GFR. Larger changes in GFR, in the setting of obstruction, often represent bilateral obstruction or the presence of a single functioning kidney (e.g., renal transplantation). Further information on post-renal AKI is presented in Chap. 16.

Intrarenal causes of AKI can be subdivided into processes affecting the glomeruli, intrarenal vasculature, or tubules/interstitium. The most common intrinsic cause of AKI is acute tubular necrosis (ATN), which accounts for

roughly 75% of intrinsic AKI in hospitalized patients [5]. In one study done at 13 tertiary care hospitals in Spain, the incidence of ATN among all causes of AKI (including pre- and post-renal) was found to be 45% [9]. ATN is a clinical-pathologic syndrome of intrinsic acute renal injury that is secondary to ischemic (e.g., cardiac surgery or septic shock) or nephrotoxic insults. Common nephrotoxins include drugs such as aminoglycosides, cisplatin, tenofovir, or iodinated radiocontrast media as well as endogenous products such as the hemoglobin and myoglobin pigments that can damage nephrons in the setting of rhabdomyolysis leading to ATN. The histopathologic findings of ATN are frequently patchy. When present on a biopsy, ATN may subtly involve discrete cell injury in the proximal tubule, the collecting duct, and the medullary thick ascending limb without frank necrosis. Thus, the term ATN may often be a misnomer, and the term acute tubular injury may better reflect the physiopathologic dissociation often seen in this entity [10].

Other less common forms of intrinsic tubulointerstitial renal injury include acute urate nephropathy from tumor lysis syndrome, cast nephropathy in the setting of multiple myeloma, and acute phosphate nephropathy. Tumor lysis syndrome in oncology patients with a high tumor burden (e.g., leukemia or lymphoma) can lead to AKI from intratubular obstruction by urate crystals. Acute phosphate nephropathy can occur following the administration of a phosphate containing bowel preparation. Another more common intrinsic tubulointerstitial cause of AKI is acute interstitial nephritis (AIN). AIN is characterized by an inflammatory infiltration of the renal interstitium and is most commonly drug induced although it can be associated with autoimmune diseases and infectious processes. Common agents include antimicrobial agents (β-lactams, sulfonamides, quinolones, antiviral agents), antiulcer agents (proton-pump inhibitors, H2 antagonists), nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, and allopurinol [11].

3.1.1 Rethinking the Differential Diagnosis of AKI

While the pre-, post-, and intrarenal paradigm of AKI has been a mainstay of clinical care, it remains an imperfect classification system with several subtypes of AKI crossing over anatomic categories. For example, persistently prolonged intravascular volume depletion (prerenal) in the setting of concomitant hypotension may lead to intrinsic tubular injury/ATN. Chronic urinary obstruction if left untreated may eventually cause tubular loss and fibrosis (intrarenal manifestations). These faults combined with the imperfections of serum creatinine and urine output as biomarkers of renal function and the emergence of newer kidney injury biomarkers have led to the development of a novel schema of AKI classification [12].

This revamped classification system has been proposed to classify patients based on the presence or absence of changes in functional (e.g., serum creatinine, serum cystatin C, urine output) and structural/injury biomarkers (e.g., neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18) (Fig. 3.1), kidney injury molecule-1 (KIM-1)). Briefly, it is easy to understand that those without a change in functional or injury biomarkers do not have AKI, while those who have changes in both functional and injury biomarkers are akin to those with severe intrinsic AKI (e.g., ATN). Those with a change in functional biomarkers but no change in injury biomarkers can be potentially thought of as those with prerenal AKI, where there has been a drop in GFR in the absence of true tubular injury. Finally, those with changes in their injury biomarkers without a concomitant change in functional biomarkers may be viewed as having "subclinical AKI." This newer entity exists due to the inability of serum creatinine to adequately measure the underlying renal function in those with normal and near normal GFR. This concept of renal reserve [13] has led to several investigations which have demonstrated that in the absence of changes in urine output and serum creatinine,

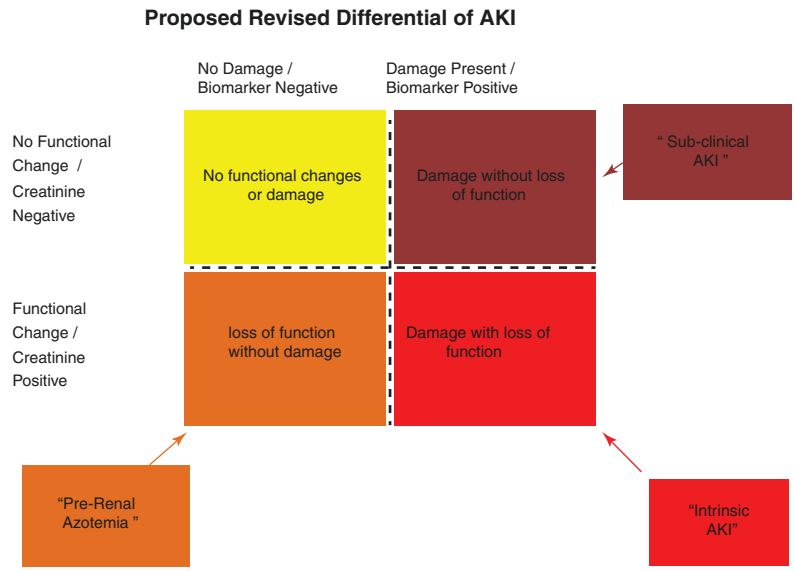

Fig. 3.1 Currently the definition of AKI is made exclusively through changes in urine output and/or serum creatinine, functional biomarkers of the kidney. The ADQI consensus meeting delineated a novel criteria for defining AKI in terms of changes in biomarkers of renal function (serum creatinine, urine output, serum cystatin) and biomarkers of kidney damage/injury (e.g., NGAL, TIMP-2*IGFBP7, IL-18). This paradigm allows for the combination of injury biomarkers with functional biomarkers and has proven useful in the discrimination of patients with AKI (Adapted from: Endre ZH, Kellum JA, Di Somma S, et al. Differential diagnosis of AKI in clinical practice by functional and damage biomarkers: workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. *Contrib Nephrol.* 2013;182:30–44; used with permission)

those with increases in their injury biomarkers are at increased risk of needing renal replacement therapy (RRT) and death [14, 15]. The uses of these newer biomarkers and their clinical implications are discussed further in this chapter.

3.2 Physical Exam

The physical exam findings associated with AKI can involve almost every organ system. In the setting of AKI, the physical findings may be reflective of the AKI itself, i.e., a clinical manifestation of the decrease in GFR and associated retention of uremic toxins and/or total body fluid. However, the physical exam findings may also help the astute clinician identify the underlying etiology causing the AKI.

Hypotension may indicate a state of volume depletion and point toward a diagnosis of intravascular volume depletion/prerenal azotemia (change in biomarkers of glomerular function). However, if hypotension persists for long enough, it may progress to the point of ATN. Importantly, the absence of documented hypotension does not preclude AKI or more specifically ATN given the clinical entity of normotensive acute renal failure [16]. A lower mean arterial pressure (MAP) has been shown to increase the risk of developing severe/progressive AKI. In a multicenter prospective observational study of 423 Finnish subjects with sepsis, a MAP of less than 73 mmHg was associated with increased risk of progressive AKI (defined as a worsening of the Kidney Disease: Improving Global Outcomes (KDIGO) AKI criteria) [17]. Similarly, several other studies have demonstrated the importance of maintaining adequate renal perfusion pressures in the setting of AKI, with higher pressures being associated with decreased risk of adverse patient outcomes [18–22].

Overt neurologic signs and symptoms may occur in advanced kidney injury and may manifest as decreased mental acuity, asterixis, peripheral

neuropathy, and seizures [23]. However, given the nonspecific nature of these signs, it is difficult to attribute a given neurologic sign to one specific source of AKI. The cardiovascular exam may reveal findings suggestive of fluid overload/congestive heart failure such as S3, pedal/sacral edema, and elevated JVD. A pericardial friction rub if present may be indicative of uremic pericarditis, which is traditionally an end-stage manifestation of severely decreased kidney function. The pulmonary exam may reveal coarse crackles that can suggest pulmonary edema due to volume overload but in rare instances may be associated with glomerular disease and result from pulmonary hemorrhage in the setting of an ANCA-associated vasculitis.

The dermatologic exam findings in AKI can be diverse and varied. They include livedo reticularis which may be suggestive of cholesterol emboli particularly in patients who have undergone recent endo-vascular procedures; however, livedo reticularis may also be seen in antiphospholipid antibody syndrome, cryoglobulinemia, and even calciphylaxis. Other dermatologic findings include palpable purpura which has been associated with leukocytoclastic vasculitis. Contrary to popular belief, AIN is infrequently associated with a rash; in a retrospective analysis of over 60 cases of biopsy-confirmed AIN, the incidence of rash at the time of presentation was found to be 21% [24]. Additionally, in this same case series, the incidence of AIN-associated uveitis (tubulointerstitial nephritis and uveitis syndrome (TINU)) was 7%.

The abdominal and genitourinary exams deserve close attention in the evaluation of a patient with AKI. A distended bladder may signify bladder outlet obstruction: a common cause of AKI particularly in elderly males with prostatic disease. The diagnosis of abdominal compartment syndrome (ACS) should be considered in any patient with a tense distended abdomen and concomitant oliguria. The clinical definition of ACS is intra-abdominal hypertension-induced new organ dysfunction without a strict intra-abdominal pressure threshold, since no intra-abdominal pressure can predictably diagnose ACS in all patients [25–27]. For clinical research purposes, ACS has been defined as a sustained intra-abdominal pressure greater than 20 mmHg, and this is different than intra-abdominal hypertension (IAH, defined as greater than 12 mmHg for research purposes). Both ACS and IAH have been associated with increased risk of AKI [28]. Finally, the presence of an abdominal bruit can indicate renal artery stenosis and can be indicative of AKI particularly in the setting of recent initiation of angiotensin-converting enzyme inhibitors or angiotensin receptor blocker use.

3.3 Lab Tests

3.3.1 Blood Tests

The laboratory evaluation of patients with AKI should be driven by their clinical presentation and their risk factors for kidney injury. Initial laboratory tests to be ordered include measurement of blood urea nitrogen (BUN) and serum creatinine, as well as other serum electrolytes, sodium, chloride, potassium, and bicarbonate (carbon dioxide) levels. These tests are important not only for the diagnosis but also for assessment of complications of AKI. In prerenal conditions resulting from enhanced salt and water avidity, the classic teaching is that there is a disproportionate increase in the ratio of BUN to creatinine (>20:1).The increase in BUN may stem from the presence of ADH that acts on distal tubules to increase urea transport from the luminal to the basolateral side. However, recent studies have demonstrated that the BUN to creatinine ratio is quite variable and higher ratios may not be indicative of prerenal etiologies [29]. In the setting of AKI, lab tests may show hyponatremia, due to decreased free water clearance in the setting of positive fluid balance. Hyponatremia is often found in the presence of AKI with several studies linking the two entities; in one prospective observational study of all patients admitted to an urban hospital with hyponatremia, AKI was evident in 32% of patients [30]. In a separate study of hyponatremia, AKI was present in 16% of the hospitalized cohort with AKI rates reaching over 20% in those older than 74 years [31]. Up to one third

of the patients with severe AKI may develop dilution hyponatremia through decreased free water clearance, and this lab abnormality is associated with worse outcomes including an increased risk of death [32, 33].

Hyperkalemia is commonly seen and treated as a complication of AKI. In a multicenter observational study of 923 inpatients with hyperkalemia of >6.5 mEq/L, AKI was present in over 22% of those with normal baseline renal function and in over half (51.8%) of those with pre-existing chronic kidney disease [34]. In one study, hyperkalemia, although known to be a serious complication of AKI, had a smaller effect size/association with inpatient mortality than metabolic acidosis and cumulative fluid balance [35]. This result is likely due to the existence of standardized thresholds to define hyperkalemia and its risk as well as the rapid institution of several reliable therapeutic options for hyperkalemia (diuretics, RRT, and bicarbonate, among others). Such thresholds and treatment options are not as robust for volume overload or metabolic acidosis.

Metabolic acidosis is a common feature of both acute and chronic kidney injuries and results from the accumulation of anions such as urate, hippurate, phosphate, and other anions that are not routinely measured, such as sulfates. In a prospective randomized multicenter trial comparing high and low intensity of continuous RRT, severe acidosis, defined as a pH < 7.2, was present in 34.9% of subjects. Similarly in a post hoc analysis of the Finnish Acute Kidney Injury (FINNAKI) study, 52% of all subjects had a pH < 7.15 prior to the initiation of RRT, with acidosis being cited as the indication for RRT in 35.8% [36, 37]. Metabolic acidosis is thought to interfere with normal functioning of many processes in the body and contributes to adverse outcomes through the promotion of hemodynamic instability via decreased cardiac output and vasodilatation.

3.3.2 Urinary Test

Examination of urine sediment is a crucial component in formulating a differential diagnosis in the setting of AKI [38–40]. There is a growing body of evidence that suggests that urinalysis and the presence of renal tubular epithelial cells and cellular casts correlate with early diagnosis of AKI as well as AKI severity [38, 41–43]. Table 3.2 presents a summary of several of the recently published urinalysis score systems. A recent study demonstrated that a higher urine microscopy severity score, as measured by the increased presence of urinary granular and muddy brown casts, was associated with a greater than sevenfold increased risk of progressive AKI (i.e., a worsening of AKI clinical stage) [42]. However, despite the resurgence of interest in microscopic urinalysis, this clinical tool has not been well integrated into recent large-scale modern biomarker investigations [44–49]. Despite several published scoring systems, there have been no large-scale multicenter validation studies describing the performance of urine microscopy in the setting of hospital-based AKI [40–42].

In prerenal AKI, urine sediment exam may reveal hyaline casts (see Fig. 3.2a). Hyaline casts

Table 3.2 Summary of three previously published urinalysis severity scores: these scores have been shown to correlate well with severity of AKI and been specific for AKI

Study	Scoring system
Chawla et al. [41]	Grade 1: no casts or RTE Grade 2: at least 1 cast or RTE but <10% of LPF Grade 3: many casts or RTEs (between 10 and 90% of LPF) Grade 4: sheet of muddy brown casts and RTEs in >90% of LPF
Perazella et al. [42]	0 points: no casts or RTE seen 1 point each: 1–5 casts per LPF or 1–5 RTEs per HPF 2 points each: ≥6 casts per LPF or ≥6 RTEs per HPF
Bagshaw et al. [40]	0 points: no casts or RTE seen 1 point each: 1casts or 1 RTEs per HPF 2 points each: 2–4 casts or RTEs per HPF 3 points each: ≥ 5 casts or ≥ 5 RTEs per HPF

Several of these scores have been combined with biomarkers of tubular injury to improve prognostication of AKI and other adverse patient outcomes [40, 42, 43]
RTE renal tubule epithelial cells, *LPF* low-power field, *HPF* high-power field

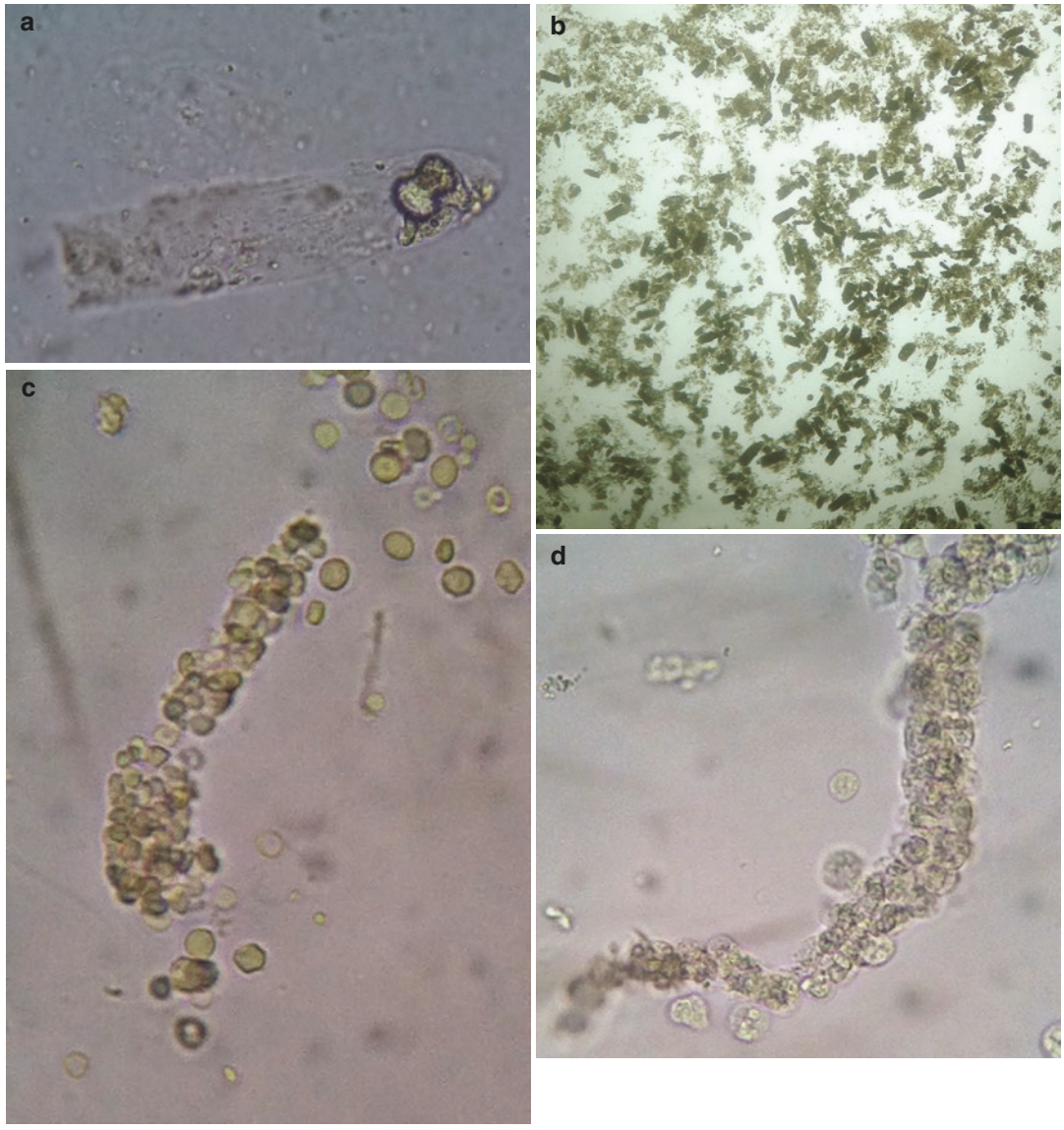

Fig. 3.2 (**a**) Hyaline cast at 400× power. These casts made of Tamm-Horsfall proteins are incredibly sticky and can collect elements in the tubule as seen by the calcium oxalate crystal attached to this hyaline cast. (**b**) Low-power field (40×) of ATN, with a large number of muddy brown casts. (**c**) RBC cast (400×)—where you can see the hyaline outline of the cast and the RBCs forming a multi-layer matrix on top of each other. (**d**) WBC cast (400×) in the setting of AIN. There are several nucleated white cells throughout the cast, and there are renal tubule epithelial cells in the background, which would be expected in the setting of AIN/active AKI. All photos are courtesy of Randy Luciano MD PhD, Yale University

are cylindrical molds of precipitated Tamm-Horsfall protein that are formed in the distal tubule. In ATN, muddy brown, coarse, granular casts are characteristically seen in addition to free renal tubular epithelial cells (Fig. 3.2b). Rapidly progressive glomerulonephritis (RPGN) is part of the differential diagnosis of AKI and is characterized by urine sediment containing RBC casts (Fig. 3.2c). These casts are composed of red cells in the matrix of Tamm-Horsfall protein. The presence of white blood cells (WBCs) in clumps and in casts, in the presence of bacteria, is

suggestive of pyelonephritis, while the absence of bacteria suggests AIN (Fig. 3.2d). Importantly, while previously thought to be a useful tool, urine eosinophils are neither sensitive nor specific for AIN. In a recent retrospective study of renal biopsies with concomitant urine eosinophils ($n = 566$ biopsies, 91 of which had AIN), a cutoff of 1% provided a sensitivity of 30.8% and a specificity of 68.2% [50].

Urinary electrolyte indices such as the fractional excretions of sodium (FENa) and urea (FEUrea) have long been used by clinicians in order to differentiate etiologies of AKI. The FENa which measures the percentage of filtered sodium excreted by the kidney can be potentially helpful in differentiating decreased intravascular volume and renal perfusion (prerenal) from intrinsic tubular damage (e.g., ATN) [51]. Classically, a FENa below 1% suggests a prerenal etiology, where the kidney is acting appropriately to perceived paucity of renal perfusion by reabsorption of most of filtered sodium load [52, 53]. However, the clinical utility of FENa in critically ill patients with AKI has been challenged [54, 55]. A FENa below 1% can often be found in circumstances of established AKI (ATN) reflecting nonhomogeneous injury to the kidney parenchyma and preservation of tubular function in some regions. Additionally, the FENa may be below 1% in the setting of hepatorenal syndrome (see Chap. 7), radiocontrast administration (Chap. 6), urinary tract obstruction (Chap. 16), and sepsis (Chap. 10) [56–60]. Finally, several recent papers have explored the ability of the FENa to predict the future development of AKI (e.g., in the setting of cardiac surgery) or the presence of progressive AKI and determined that this biomarker is unable to predict any of these AKI outcomes in a significant fashion [61–63]. Similarly the FENa has not been shown to differentiate hepatorenal syndrome from ATN or prerenal AKI or predict AKI progression in those with cirrhosis and AKI [64, 65]. In the original paper by Schrier and colleagues, the FENa was evaluated in the absence of CKD (serum creatinine had to be less than 1.6 at baseline), those with oliguria (<500 ccs of urine per day), and in the absence of diuretics; however, in the decades since this original study, there have been broad acceptance and implementation of the FENa in a variety of AKI clinical setting despite a lack of wide-scale validation [52].

The FEUrea has been cited as a more precise method for discriminating early AKI in those receiving diuretics, which may impact the urinary sodium concentration rendering the FENa difficult to interpret. Importantly, should the urine sodium remain exceedingly low in the setting of active diuresis, this may point to the presence of intravascular volume depletion as the source of AKI. Regardless, a FEUrea of less than 35% has been thought to indicate prerenal AKI, whereas one above 35% is thought to be consistent with intrinsic AKI (ATN) [66]. However, FEUrea has been described in far fewer studies compared with FENa. In a study by Carvounis et al., a FEUrea less than 35% was evident in 90, 89, and 4% for prerenal, prerenal with diuretics, and ATN patients, respectively [67]. Additionally, as with the FENa, attempts to validate the FEUrea as a diagnostic/prognostic tool in the setting of early AKI have failed to demonstrate its clinical utility [61–63].

3.4 Imaging

A variety of imaging techniques have been used in the diagnosis and workup of patients with AKI. In this section we discuss the strengths and limitations of these modalities and then review newer methods for renal imaging.

Ultrasound is often the first-line imaging modality in the evaluation of AKI given its inexpensive nature, wide availability, and safety [68]. It is particularly helpful in diagnosing obstructive causes of AKI. In a study of 286 ultrasound exam reports for 63 consecutive patients who received 64 renal transplants, it was found that the sensitivity of detection of ureteral obstruction with ultrasound was 100% with a specificity of 91.9% [69]. In a large multicenter, pragmatic, comparative effectiveness trial, in 2759 patients with suspected nephrolithiasis, ultrasonography was associated with lower cumulative radiation exposure than initial computed tomography scan

(CT scan), without significant differences in high-risk diagnoses (such as obstructive AKI) with complications [70]. Importantly, the renal caliceal dilation that is a hallmark of ureteral obstruction is not specific to obstructive uropathy as it may be seen in pregnancy as well as diabetes insipidus [71, 72].

Ultrasound also provides information regarding kidney size, shape, anatomic location, and cortical echogenicity. Enlarged kidneys in the setting of AKI may suggest infiltrative diseases such as lymphoma or the presence of pre-existing diseases known to be associated with enlarged kidneys (e.g., HIV or diabetic nephropathy) but can also be seen in RPGN and AIN [73]. Doppler ultrasound can provide valuable information on renal blood flow. In one study of 41 individuals with kidney diseases, comparing Doppler US findings with biopsy results, kidneys with higher tubulointerstitial disease activity had higher resistive index compared to the kidneys with other forms of renal disease, including glomerular disease [74]. Importantly, ultrasound remains limited as a user-dependent tool, as images and their interpretation are only as good as those operating the modality.

Helical CT scan is another commonly used imaging modality for the diagnosis of obstructive AKI, especially in the setting of suspected nephrolithiasis. While CT scan is able to diagnose ureteral obstruction with accuracy on par with ultrasonography, it comes with the higher radiation exposure and is not able to be done at the bedside in unstable patients [70]. CT scans with iodinated contrast are to be avoided in the setting of AKI owing to the further risk of nephrotoxicity from the contrast.

Magnetic resonance imaging (MRI) without gadolinium is of limited utility in the workup of AKI. Imaging with gadolinium is limited in part by the concern of nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD). NSF has been associated with the gadolinium contrast agent particularly in pts with estimated glomerular filtration rates eGFR < 30 mL/min and as such is a concern for both those with AKI and those with end-stage renal disease (ESRD) [75]. However, newer non-gadolinium contrast agents have shown promise and safety in assessing renal blood flow [76]. This advance could improve care in the setting of ischemia-induced AKI while also improving patient safety in the setting of reduced kidney function in human studies.

Blood oxygen level-dependent magnetic resonance imaging (BOLD MRI) is a relatively new technique used to noninvasively measure intrarenal oxygenation and may have important implications in future research in the field of AKI [77]. BOLD MRI quantifies the differences in measurements of renal oxygenation based on changes in the magnetic properties of hemoglobin during its conversion from oxyhemoglobin to deoxyhemoglobin. The relationship between BOLD MRI signal intensity and renal oxygen tissue levels has been established by direct measurements of tissue partial pressure of oxygen (pO_2) utilizing oxygen-sensing microelectrodes and fiber-optic probes in experimental models of aortic occlusion. In swine and rat models of aortic occlusion/renal ischemia, medullary and cortical hypoxias were demonstrated during acute ischemia by BOLD MRI followed by an immediate return to baseline oxygenation after reperfusion [77–83]. In an observational study of BOLD MRI in renal transplant allografts performed by Han and colleagues, allografts with ATN had cortical and medullary hypoxia ($n = 7$) as compared with normal functioning allografts studied 10 days postoperatively [83]. However, based on this and other studies in the setting of contrast- and sepsis-associated AKI, the ideal cutoffs for the diagnosis of renal hypoxia and the associated AKI remain unclear [84]. The applicability of BOLD MRI in patients with AKI and more specifically critically ill patients however remains to be seen given that the modality is not point of care and the scans themselves take longer to perform than CT scans. However, in the future it may serve as a method to evaluate renal oxygenation and a trigger to initiate novel therapies aimed and reversing the effects of renal ischemia.

More recently, contrast-enhanced ultrasound (CEUS) has been investigated in animal and human models as a novel method to investigate renal microperfusion [85–88]. This technology

utilizes the systemic infusion of gas-filled microbubbles to assess organ perfusion. Microbubbles have increased echogenicity compared to other tissues, and thus the presence of bubbles can readily identify areas of both ischemia and perfusion. Bonventre and colleagues demonstrated that this technique can be used to monitor changes in renal ischemia over time (24 h) and provide mapping of injured areas in a murine model of renal ischemia reperfusion [85]. CEUS has also been investigated in humans. Bellomo and colleagues performed scans in four patients with hepatorenal syndrome as a proof-of-concept report to estimate the effect of terlipressin on renal microcirculation [86]. This promising preliminary report, which detected increased perfusion in response to terlipressin, serves as a follow-up to their investigations of an ovine model [88]. This same group has reported a 36 scan investigation demonstrating that CEUS was feasible and well-tolerated and can detect decreased renal perfusion within the first 24 h following adult cardiac surgery [87]. We anticipate future investigations around the novel, noninvasive, and portal imaging modality and its ability to identify alterations in renal microcirculation.

While several other imagining modalities such as positron emission tomography (PET) and bioelectrical impedance analysis (BIA) have been explored in the setting of AKI, they remain beyond the scope of this chapter [89].

3.5 Novel Biomarkers

As discussed in Chap. 2, the internationally accepted KDIGO consensus definition of AKI relies on either serum creatinine, urine output, or both to define AKI. Thus the KDIGO criteria, like the consensus definitions before them, rely on long-standing imperfect markers of kidney function [90, 91]. Serum creatinine is not sensitive for the diagnosis of AKI, as there can be a large amount of tubular injury/nephron loss without a significant change in creatinine (e.g., living donor renal transplant and renal reserve). Additionally, creatinine is not 100% specific for renal tubular injury, as previously mentioned prerenal azotemia occurs when there is a change in creatinine in the absence of true tubular damage. Moreover, serum creatinine level can be affected by several clinical factors including muscle mass, age, race, and assay interference (caused by clinical factors such as hemolysis and lipemia as well as certain drugs) [92, 93]. Due to these shortcomings of serum creatinine as well as the ability to manipulate urine output through the use of diuretics, in 2005, the American Society of Nephrology Renal Research Report called for the standardization and discovery of new biomarkers of AKI as its highest research priority. Over the last decade, there has been a proliferation of studies focussing on the detection and validation of new biomarkers of AKI in a variety of different patient populations and clinical settings [2, 94–96].

An ideal AKI biomarker should fulfill several criteria including being highly sensitive and specific to renal injury and inexpensive to carry out and provide information regarding the underlying source of the AKI, AKI severity, and overall prognosis [97]. To date, there have been well over 30 candidate biomarkers for AKI identified and investigated with the characteristics and physiologic action of several of the most widely investigated biomarkers summarized in Table 3.3.

Biochemical biomarkers of AKI can be low molecular weight proteins that are present in the systemic circulation and undergo filtration, enzymes that are released by tubular cells into the urine after cell injury or inflammatory mediators released by renal cells or infiltrating inflammatory cells (markers of degree of damage and indicators of site of injury) [2, 94–96]. More recently functional biomarkers of AKI have been investigated but require large-scale validation [62, 89, 98]. Given that AKI is a heterogeneous complex clinical syndrome, investigations have attempted to focus on specific clinical scenarios (e.g., cardiac surgery/cardiopulmonary bypass, septic shock, end-stage liver disease). Each of these clinical settings has their own unique AKI fingerprint, and it is reasonable to expect that biomarkers that detect post-cardiopulmonary bypass AKI might be different from those for septic shock-associated AKI or AKI from hepatorenal syndrome.

Table 3.3 Characteristics and physiologic action for biomarkers of AKI

Category	Biomarker	Description	Physiologic action
GFR markers	Serum cystatin C	13 kDa protein produced at a constant rate with limited protein binding [94, 124]	Inhibitors of cysteine proteinases cathepsin H, B, and L and calpains [94, 124]. Freely filtered at the glomerulus reflecting underlying GFR, but levels are affected by corticosteroids, hyperthyroidism, hypertriglyceridemia, hyperbilirubinemia, and inflammation [125, 126]
Tubular injury markers	Urine cystatin C	13 kDa protein produced at a constant rate with limited protein binding [94, 124]	Freely filtered in glomerulus and degraded in proximal tubules, so in the absence of injury not present in urine [94]. Urinary level may increase with albuminuria through competitive inhibition of reabsorption [127]
	Interleukin-18 (IL-18)	IL-1 family cytokine precursor cleaved by caspase-1 to 17.2 kDa active form [128]	Induces IFN-ϒ and T-cell activation [128]. Urinary IL-18 found to be a marker of ATN in humans [129]
	Kidney injury molecule 1 (KIM-1)	40–70 kDa glycosylated transmembrane protein receptor expressed in proximal tubules, important in recognizing apoptotic cells [130, 131]	Upregulated after proximal tubule ischemic injury [130]. Expressed by immune cells to activate differentiation of T helper 1, 2, and 17 cells [132] FDA-approved for use in preclinical drug development
	Liver-type fatty acid-binding protein (L-FABP)	15 kDa protein expressed in proximal tubules [133]	Binds free fatty acids and transports them to mitochondria or peroxisomes. Found to be upregulated after ischemic injury [94, 134]. In mouse models found also a marker for COX-inhibitor and cisplatin-induced AKI [135, 136]
	Urinary NAG (*N*-acetyl-β-glucosaminidase)	~140 kDa proximal tubule enzyme, not renally filtered [94]	A sensitive urinary marker of loss of lysosomal integrity in proximal tubule and may reflect improvements in proximal tubular function. Inhibited by urea, industrial solvents, and heavy metals [94]. Not elevated with sepsis [137]
	Neutrophil gelatinase-associated lipocalin (NGAL)	25 kDa lipocalin protein covalently bound to gelatinase from neutrophils. May exist as monomer or dimer. Expressed in the lung, liver, and kidney [138]	Binds to free iron and assists in response to bacterial infection [139]. Upregulated in distal nephron in response to AKI but are also released from the liver and neutrophils in sepsis [140]. Assay differences due to different forms of NGAL [141]. Plasma levels may correlate with GFR/CKD
Cell cycle arrest	Tissue inhibitor metalloproteinase-2 and insulin-like growth factor-binding protein-7 (TIMP-2*IGFBP7)	TIMP-2 is part of the TIMP family of protease inhibitors expressed ubiquitously [142]. IGF-binding protein 7 is expressed in vascular endothelial cells and binds to insulin and insulin-like growth factor [143]	TIMP-2 inhibits matrix metalloproteinases, promoting fibrosis and blocking endothelial proliferation [144, 145]. IGFBP7 inhibits endothelial angiogenesis, among other functions [143, 146]. Both markers are linked to cell cycle arrest and are highly upregulated after kidney injury [44, 106]

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Table 3.4 summarizes the findings of several large-scale multicenter studies that investigated the abilities of several biomarkers to detect clinical endpoints around AKI in a variety of clinical settings. Importantly, novel biomarkers have been investigated for more than just the ability to diagnose/detect AKI earlier than serum creatinine or urine output. Biomarkers have been

Table 3.4 Biomarker performance in detecting AKI from multicenter studies at a variety of clinical time points

	Perioperative AKI				Critically Ill			Emergency room		Liver disease with cirrhosis
	Pre-op AKI risk	Early post-op AKI	AKI progression	Long-term mortality	Early diagnosis of AKI	Type of AKI (transient vs. intrinsic)	Need for RRT	Early diagnosis of AKI	Type of AKI (transient vs. intrinsic)	AKI progression
Urine NGAL	N/A	+	–	+	+	+	+	+	+	+
Blood NGAL	–	+	+	?	–	?	–	?	?	N/A
Blood CysC	+	+	–	?	+	+	+	?	?	+
Urine CysC	N/A	–	–	–	+	+	+	+	+	
Urine IL-18	N/A	+	+	+	+	+	+	+	+	+
Urine KIM-1	N/A	+	–	+	+	–	–	+	+	+
Urine L-FABP	N/A	–	–	+	?	?	–	+	+	+
TIMP-2 IGFBP-7	N/A	+	+	?	+	?	+	?	?	N/A
Urine protein/ albumin	+	+	+	+	?	?	?	?	?	+

+ = data published displays the ability to detect this aspect of AKI
– = data published does not display the ability to detect this aspect of AKI
? = no large multicenter data published on this biomarker/aspect of AKI
N/A (not applicable) (a) Biomarkers of tubular injury have no role in preoperative risk screening
(b) Serum creatinine is intrinsic to the definitions of AKI being tested
Adapted and expanded from: Koyner JL, Parikh CR. Clinical Utility of Biomarkers of AKI in Cardiac Surgery and Critical Illness. *Clin J Am Soc Nephrol.* 2013;8(6):1034–1042; used with permission

shown to detect AKI severity, whether defined as the need for RRT or progressive AKI, help differentiate transient AKI from more intrinsic forms of kidney injury, and also predict short- and long-term mortality.

A seminal investigation by Mishra and colleagues demonstrated the role of plasma and urinary NGAL as a marker of kidney injury in 71 children undergoing cardiopulmonary bypass [99]. In this prospective observational single-center study, the 2-h post-bypass NGAL levels in urine and plasma predicted AKI (defined as a 50% increase from baseline), with an AUC of 0.998 for the urine NGAL and 0.91 for the plasma NGAL. This study, along with several other single-center investigations, served the basis for the formation and funding of the Translational Research Investigating Biomarker Endpoints for AKI (TRIBE-AKI). TRIBE-AKI performed a multicenter prospective observational study of over 1200 adults and over 300 children undergoing cardiac surgery and has measured several AKI biomarkers in the blood and urine. Several of their findings with regard to early AKI, progressive AKI, and long-term mortality are summarized in Table 3.4 [47–49, 100–102]. While other groups have investigated biomarkers in the setting of cardiac surgery, the TRIBE-AKI group remains the largest cohort to date. Ho and colleagues have recently published a meta-analysis of 28 published studies/cohorts around both urine and serum biomarkers of AKI concluding that several biomarkers, including NGAL, KIM-1, IL-18, NAG, and albuminuria, all possess modest discriminatory function when measured within 24 h of cardiac surgery [103]. This conclusion is based on their analyses of the myriad of aforementioned studies which demonstrate that these biomarkers provide a composite AUC of less than 0.75. As of the end of 2015, there is limited single-center data linking tissue inhibitor metalloproteinase-2 and insulin-like growth factor-binding protein-7 (TIMP-2*IGFBP7) with post-CV surgery AKI; we anticipate large-scale validation of this marker in this clinical setting in the near future [104–106].

While TIMP-2*IGFBP7 remains under-validated in the setting of cardiac surgery, these cell cycle arrest biomarkers have been investigated in the setting of mixed medical surgical ICU patients [44, 107–109]. In fact these markers have been cleared for marketing and clinical use by the US Food and Drug Administration for their ability to assist in the risk stratification of those at risk for the future development of severe (stage 2 or 3) AKI. Kashani and colleagues investigated these markers in a multicenter prospective observational study (derivation cohort ($n = 622$) and validation cohort ($n = 744$)) and demonstrated that they exhibited an AUC of 0.80 for the development of stage 2 AKI or higher within the next 12 h [44]. When measured alone, IGFBP7 and TIMP-2 exhibited an AUC of 0.76 and 0.79, respectively, with several other biomarkers (e.g., NGAL, KIM-1, IL-18) demonstrating a similarly modest ability to predict impending severe AKI. TIMP-2*IGFBP7 at the time of ICU arrival was also associated with 9-month long-term outcomes; in an adjusted analysis of 692 subjects, TIMP-2*IGFBP7 values demonstrated a stepwise increase in the long-term risk of death or dialysis in those with AKI [109].

Investigations around these most common biomarkers remain ongoing with studies looking to validate their use in other clinical settings as well as determine factors that impact their prognostic abilities. There remains uncertainty around the impact of baseline chronic kidney function and other clinical factors such as diabetes or sepsis on the individual biomarker performance [110–115]. Similarly it remains unclear if biomarkers measured at the time of AKI are associated with the long-term development of CKD, but this is also an area of current investigation [116].

Finally, investigators have begun to examine the utility of these new biomarkers of AKI in the context of the aforementioned revised differential diagnosis of AKI proposed by the Acute Dialysis Quality Initiative (Fig. 3.1). Several studies have demonstrated that elevation in damage biomarkers (e.g., KIM-1 or NGAL) in the absence of changes in functional markers (e.g., serum creatinine and urine output) (this correlates with the "subclinical AKI" group in Fig. 3.1) places patients at increased risk of adverse events such as the need for RRT or inpatient mortality [14,

15, 100]. Some of these same studies have demonstrated that the risk of "subclinical" AKI is similar to the risk for those who have increases in functional marker without the increase in damage markers (prerenal azotemia).

Haase and colleagues conducted a pooled, prospective study (n = 2322) that designated subjects as NGAL-positive or NGAL-negative and creatinine-positive or creatinine-negative. In this compilation of ten previously published biomarker cohorts, AKI (creatinine-positive) was defined by the RIFLE-Risk criteria (50% increase in serum creatinine). Subjects who were NGAL-negative-creatinine-positive had similar lengths of ICU and hospital stay compared to those who were NGAL-positive-creatinine-negative. Additionally, individuals who were NGAL-positive-creatinine-negative received RRT more than 16 times more often than those who were NGAL- and creatinine-negative [14]. NGAL-positive-creatinine-negative patients were also in the ICU and hospital longer and more likely to experience inpatient mortality compared to NGAL-negative creatinine-negative.

NGAL's clinical utility and this concept of "subclinical AKI" are further strengthened in a similar analysis by Nickolas et al. who investigated NGAL and KIM-1, among other biomarkers in an international, prospective, observational study of 1635 unselected emergency room patients. Using a cutoff of 104 ng/mL for urine NGAL and 1.4 mg/dL for serum creatinine, Nickolas demonstrated that 5.3% of those who had NGAL defined subclinical AKI (NGAL >104 ng/mL and a creatinine <1.4 mg/dL) received RRT or experienced inpatient mortality. This was not different from the 5.1% of those who were NGAL-negative-creatinine-positive who experienced the same composite endpoint but was significantly higher than those who had no elevation in either their serum creatinine or NGAL [15]. The authors demonstrated a similar trend for KIM-1 (cutoff 2.82 ng/mL) and creatinine with those patients with KIM-1 defined subclinical AKI (KIM-1 > 2.82 ng/mL, creatinine < 1.4 mg/dL) being at increased risk for the same composite endpoint. In this study, as in the Haase pooled analysis, those subjects who were biomarker-positive-creatinine-positive were at highest risk for all of the adverse patient outcomes, again demonstrating the strength of combining biomarkers with serum creatinine to improve AKI risk stratification [14, 15].

Finally, Basu and colleagues have investigated the utility of combining urine NGAL (cutoff of 200 ng/mg creatinine) and serum cystatin C (another functional marker, cutoff of 0.8 mg/L). In a cohort of 345 pediatric cardiac surgery subjects, they demonstrated that the composite of NGAL-positive/cystatin-positive outperformed the change in serum creatinine for both the development of severe AKI (defined as KDIGO stage 2 or higher) and persistent AKI (defined as lasting more than 48 h) [117]. Thus the combination of a glomerular function and tubular injury biomarker improved diagnostic precision over serum creatinine alone.

This idea of combining novel biomarkers with each other as well as with serum creatinine is attractive. Several studies have attempted to combine two or more biomarkers to improve their predictive capabilities for early and severe AKI [44, 49, 118–120]. While some studies have simply used the product of two biomarkers and then assessed the AUC, others have used techniques such as logistic regression to assess the AUC for two or more biomarkers. No consensus for the statistical methods for combining biomarkers exists, and this topic remains an area of continued investigation. More recent studies have acknowledged the premise that individual biomarkers will have their own specific kinetics and that combining biomarkers from different time points may improve their predictive capabilities [49]. As we learn more about the pathophysiologic and clinical factors that impact these new tests, our ability to combine them in a clinically meaningful manner will increase, and this in turn will lead to improved clinical care.

With data demonstrating a clear association between biomarker-positive-creatinine-negative patients and adverse outcomes, clinicians

will increasingly face the challenge of caring for these patients. There is limited data on the how best to care for such patients; however, recent studies demonstrate a clear benefit of guideline-driven care in the setting of early AKI and biomarker-defined AKI [121–123]. Kolhe et al. investigated outcomes in a cohort of patients whose treating physicians received an interruptive electronic alert when those patients developed clinical AKI (AKIN and KDIGO definitions). This AKI alert was linked with a care bundle that followed simple guideline-based recommendations (assess history and examine patient, check a urinalysis, attempt to classify AKI, and treat the AKI) [122]. Completion of the AKI care bundle (which occurred in only 12.2%, $n = 306$) was associated with significantly improved patient outcomes including decreased progression to more severe AKI and lower inpatient mortality [122]. Similarly, Zarbock and colleagues conducted a single-center randomized controlled trial investigating the implementation of the KDIGO treatment guidelines in patients deemed to be high risk for AKI (as measured by a TIMP-2*IGFBP7 > 0.3) following adult cardiac surgery [123]. Biomarker-positive patients who were randomized to receive a KDIGO cardiac surgery care bundle (avoidance of nephrotoxins, discontinuation of renin-angiotensin agents for 48 h, volume management through a prespecified algorithm with a cardiac output monitoring catheter, avoidance of hyperglycemia, and strict monitoring of inputs and outputs) developed KDIGO AKI less frequently than those with elevated biomarkers receiving usual care (71.7% vs. 55.1%; $p = 0.004$). More specifically, those receiving the care bundle had fewer episodes of stage 2 and 3 AKI (29.7% vs. 44.9%) with an odds ratio (95%CI) of 0.52 (0.32–0.85) and $p = 0.009$ [123]. Thus while there are many exciting and novel therapeutics being investigated for the treatment (and prevention) of AKI, recent data demonstrate a clear benefit to simple guideline-driven interventions in the setting of early creatinine-based AKI as well as biomarker-defined AKI.

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