Differential Diagnosis of AKI in Clinical Practice by Functional and Damage Biomarkers: Workgroup Statements from the Tenth Acute Dialysis Quality Initiative Consensus Conference

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Abstract

Acute kidney injury (AKI) is a common but complex clinical syndrome with multiple etiologies. These etiologies target different sites and pathways within the kidney. Novel biomarkers of 'kidney damage' (which can be tubular or glomerular) can be used to diagnose AKI, even in the absence of an increase in serum creatinine or oliguria. These biomarkers of kidney damage can be combined with biomarkers of kidney function to facilitate classification of AKI. A comprehensive review of the literature was performed using the published methodology of the Acute Dialysis Quality Initiative (ADQI) working group and used to establish consensus statements regarding the use of biomarkers in the differential diagnosis of AKI. We recommend that the pathophysiological terms 'functional change' and 'kidney damage' be used in preference to the anatomical classification using the terms pre-renal, renal and post-renal AKI. We further recommend the use of both renal and non-

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renal biomarkers in establishing the specific cause of AKI as soon as possible after diagnosis. The presence of underlying CKD or of sepsis poses additional challenges in differential diagnosis, since these conditions alter both baseline biomarker excretion and biomarker performance. We recommend that biomarkers be validated within the clinical context in which they are to be used. Within that context, combinations of biomarkers may, in the future, allow differentiation of the site, mechanism and phase of injury.

Acute kidney injury (AKI) is a complex clinical syndrome that may arise in response to multiple exposures (e.g. sepsis, nephrotoxins, circulatory shock including acute cardiac failure) and whose underlying pathogenesis is incompletely understood [for recent reviews, see 1–3]. Sepsis is the major cause of AKI, accounting for nearly 50% of cases [4–6]. Approximately one third of hospitalized patients with community-acquired sepsis develop AKI [7, 8]. The various causes of AKI may affect kidney function differently and may injure the kidney in different ways. Biomarkers detect changes in kidney function (mainly glomerular filtration function, also tubular functions) and damage (mainly tubular, but also glomerular injury); both provide complementary information [9].

While clinical practice guidelines exist to aid in determining AKI etiology [10] these do not include kidney damage biomarkers. We propose a systematic approach that incorporates biomarkers not merely in the detection of AKI or risk of AKI, but also in establishing the specific cause or causes of AKI. We recognize that comorbidity, particularly the presence of underlying chronic kidney disease (CKD), poses an additional diagnostic challenge. This is the case, not only in terms of differentiating acute from chronic and from 'acute-on-chronic' disease, but also with respect to determining the etiology of AKI in the setting of underlying CKD. Again, we suggest that biomarkers may help, but special considerations apply.

Finally, we recognize that merely detecting AKI and defining its etiology does not address the nature of the pathophysiological state of the kidney at the time of diagnosis. This will vary in time and intensity with mechanism and duration of AKI, and must be determined in order to target treatment to the specific disease process affecting individual patients. Current biomarkers do not identify these and our proposals, suggestions and recommendations primarily address existing biomarkers. However, we will discuss the potential use of and need for new markers and will outline recommendations for future research.

Methods

Consistent with previous Acute Dialysis Quality Initiative (ADQI) meetings, a modified Delphi approach was followed. We performed a systematic search and review of the available literature pre-conference, as described in detail elsewhere in this volume. We
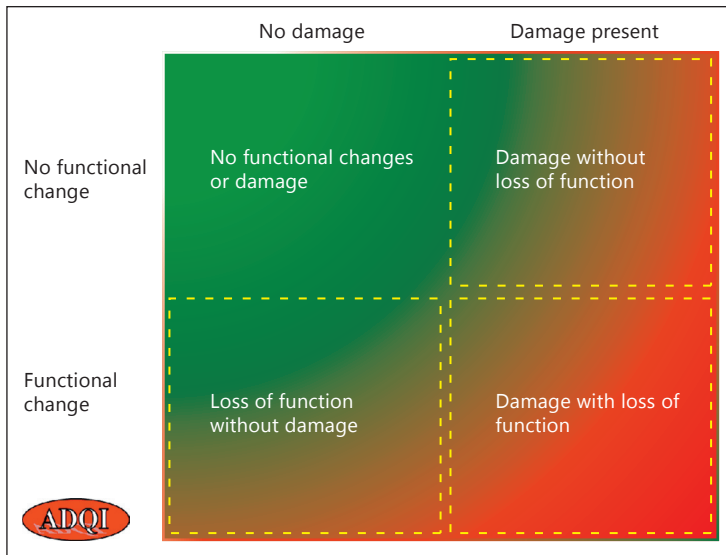
	No damage	Damage present
No functional change	No functional changes or damage	Damage without loss of function
Functional change	Loss of function without damage	Damage with loss of function

Fig. 1. As shown, the combination of functional and damage biomarkers allows categorization of patients into a specific category after the diagnosis of AKI is made. Currently this is based on diagnosis with standard creatinine and urine output criteria, however in future could include a diagnosis based on damage biomarker criteria. These findings would need to be combined with the clinical and laboratory information to determine the underlying pathophysiology and the contributory factors. Sequential assessments could provide information on which of the factors is prevalent for ongoing injury or resolution and offer opportunities for targeted intervention. Reproduced with permission from ADQI [59].

focused on the role of biomarkers in distinguishing etiology of AKI. Studies were identified via PubMed and Web of Science using the term 'biomarker', and acute kidney injury (AKI)' combined with 'etiology' and 'differential diagnosis'. The large body of literature retrieved generated a series of key questions, which were used to limit the scope of the review. Only representative publications are cited in this review.

Results

Our group started from the premise that AKI had already been diagnosed using a combination of biomarkers of acutely decreased kidney function and/or kidney damage (usually tubular), and defined using those terms (fig. 1). This left the following key questions for consideration with respect to differential diagnosis: (1) Can biomarkers distinguish a 'pre-renal state' from AKI? (2) Can biomarkers differentiate etiology of AKI? (3) Can biomarkers identify the mechanism and time course of AKI? (4) Can biomarkers distinguish AKI from CKD? (5) Can

biomarkers distinguish de novo AKI from AKI superimposed on CKD? (6) What is role of biomarkers from other organs in the context of determining etiology of AKI?

Transient AKI, Not Pre-Renal

A systematic method for the differential diagnosis of AKI should optimize diagnostic assessment and therapeutic intervention. The term 'pre-renal' to classify both a group of causes of AKI leading to renal underperfusion and a unique state of reversible loss of kidney function with evidence of injury is both confusing and controversial despite a long tradition of usage [11, 12]. While grouping the causes of AKI as pre-renal, renal and post-renal causes can be helpful, its imprecision leads to limited diagnostic and therapeutic clarity. For instance, the treatment of intravascular dehydration, often cited as the classic example of pre-renal azotemia, includes rapid rehydration. However, other 'pre-renal' conditions, including nephrotic, hepatorenal and cardiorenal syndromes, can present with similar laboratory findings, yet the management for these conditions requires fluid restriction. Unfortunately, for many clinicians, the statement that a patient is 'pre-renal' has become conflated with being dehydrated.

Similarly, fluid responsiveness is not synonymous with 'pre-renal' AKI. In a recent prospective study of using urinary NGAL to distinguish pre-renal from intrinsic AKI, the investigators were able to classify the pre-renal versus intrinsic renal state based on fluid responsiveness in only 25% of cases [13]. Furthermore, the notion that aggressive fluid resuscitation leads to improved renal perfusion, reversal of the pre-renal state and prevention of intrinsic or established renal injury (or 'acute tubular necrosis' – ATN) has been refuted by animal data demonstrating that improved hemodynamics do not restore the renal microcirculation or renal blood flow after hypotensive shock [14, 15].

Reversibility of renal dysfunction does not define the absence of harm. Even if there is rapid recovery from AKI, there is a cost: several large cohort studies [16–19] and the prospective EARLYARF study [20] have identified that transient (<48 h) AKI was associated with the adverse outcomes of need for dialysis and death, even when AKI resolved within 24 h.

The concept of purely functional loss is also challenged by recent studies providing evidence that some, albeit less, damage is actually present in patients with transient AKI. If 'pre-renal' AKI is defined as transient AKI combined with evidence of preservation of renal tubular function (e.g. with a fractional sodium excretion less than 1%), then biomarkers of damage are increased above that observed in 'No-AKI' patients [20]. Even the earliest studies of reversible

azotemia induced in volunteers by water deprivation noted kidney damage as shown by the development of hematuria and proteinuria, which reversed after rehydration [21]. On the other hand, there is good evidence that when AKI biomarkers are positive, even in the absence of apparent change in function, patients have worse hospital survival and even an increased need for dialysis than patients without AKI [22]. Of course, the biomarkers may simply predict changes in function that would manifest later except that competing endpoints such as death or dialysis occur first.

These arguments suggest that the concept of 'pre-renal AKI' is a flawed paradigm [12, 23], both in the presence and absence of sepsis, and that rapidly reversible AKI simply reflects a lesser degree of structural damage [20]. The observations highlight the need to move the approach to AKI differential diagnosis away from a semi-artificial anatomical construct and post hoc clinical determination to a proactive pathophysiological paradigm. An approach where biomarkers can be used to classify AKI by functional change, kidney damage, or both (fig. 1), provides information that is interpretable, and accounts for the dynamic nature of AKI. Both duration of AKI and degree of functional change and damage predict outcome.

We recommend that the terms 'functional change' and 'kidney damage' should be used in preference to the terms 'pre-, intra- and post-renal' in order to narrow the differential diagnosis of AKI. We encourage relevant further diagnostic assessment and therapeutic intervention as outlined below, without presupposing a static clinical state or waiting for a clinical response to treatment.

Etiology of AKI

It is critical that the etiology of AKI is determined as rapidly as possible, regardless of cause, since an important determinant of the response to therapy and long-term prognosis in many types of AKI is early diagnosis. For example, rapidly progressive glomerulonephritis due to anti-glomerular antibody disease can lead to irreversible renal failure within days, whereas immediate intervention with plasma exchange and immunosuppression preserves function [24]. Similarly, uncorrected outflow obstruction causing AKI leads eventually to renal parenchymal loss, while prompt treatment leads to rapid recovery [25]. Delayed diagnosis of AKI has contributed to the repeated failure of pharmaceutical intervention trials in AKI [9, 24]. In part, this delay results from diagnosis by exclusion which has been used in most intervention studies of AKI due to ischemia-reperfusion injury. Diagnosis by exclusion is an inadequate strategy for early diagnosis of any condition and AKI is no exception. While the benefit of early pharmaceutical intervention in AKI secondary to ischemia-reperfusion
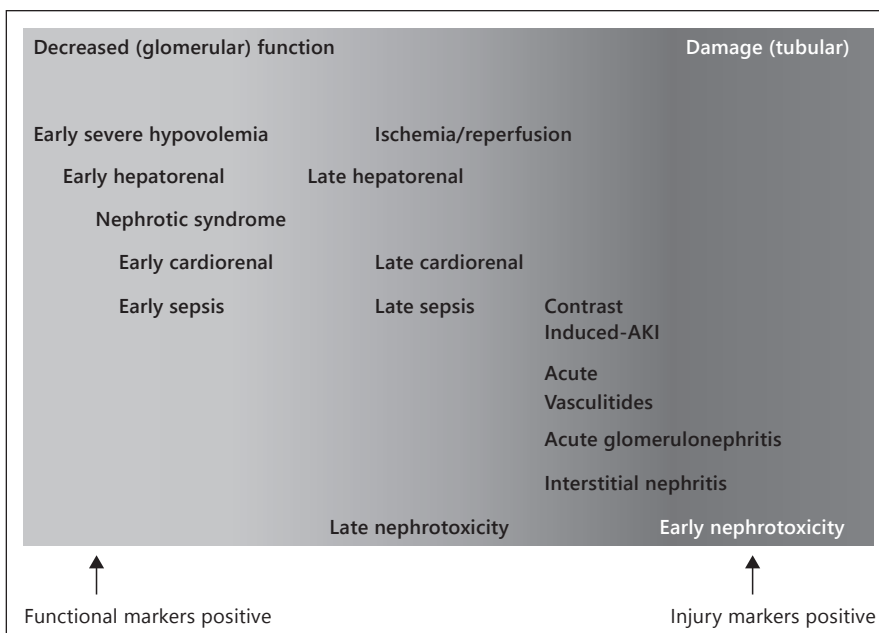
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Decreased (glomerular) function		Damage (tubular)
Early severe hypovolemia	Ischemia/reperfusion	
Early hepatorenal	Late hepatorenal	
Nephrotic syndrome		
Early cardiorenal	Late cardiorenal	
Early sepsis	Late sepsis	Contrast Induced-AKI
		Acute Vasculitides
		Acute glomerulonephritis
		Interstitial nephritis
	Late nephrotoxicity	Early nephrotoxicity
Functional markers positive		Injury markers positive

Fig. 2. Differential diagnosis of AKI. The arrows indicate the most likely type of biomarker to be positive during initial injury. Reproduced with permission from ADQI [59].

injury remains uncertain [26], early dialysis in established AKI may reduce mortality and accelerate recovery [27, 28].

Biomarkers offer the opportunity to diagnose AKI proactively in at risk patients (fig. 2). When the etiology of AKI affects glomerular function early, this will be reflected by early changes in biomarkers of filtration function, such as direct measurements of GFR and later by changes in creatinine or cystatin C. When tubular epithelium is damaged early, AKI will first be detected by changes in biomarkers of tubular injury, such as NGAL, KIM-1, IL-18, L-FABP, GGT and others [29]. In this setting, these biomarkers are non-specific markers of injury and context will identify the likely cause.

As an example, determining the etiology of renal failure in patients with cirrhosis, ascites, and edema remains an important clinical challenge, particularly in patients awaiting liver transplantation where glomerular disease is often present [30]. Differentiation of type 1 hepatorenal syndrome from other forms of AKI is potentially important since initial treatment of each is radically different [31]. A recent prospective cohort study of 115 adults with documented cirrhosis suggests that because the cut-offs were much higher, urinary NGAL could differentiate AKI from early heptorenal syndrome and also from pre-renal AKI and stable CKD in this setting [32].

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In addition to facilitating early recognition, increased urinary or plasma injury biomarkers may identify involvement of specific nephron segments [33]. This may also help define the etiology of AKI. For example, in experimental AKI, nephrotoxins specific for different sites produce characteristic changing biomarker patterns of injury specific for each site [34]. A related approach is to utilize multiple biomarkers specific for different injury pathways to facilitate identify cause of AKI. A recent example is the use of increase in regenerating islet-derived protein III β (reg IIIβ) and gelsolin to differentiate between gentamicin and cisplatin nephrotoxicity [35]. Gentamicin increased the urinary concentrations of both reg IIIβ and gelsolin whereas these markers were not increased by cisplatin, nor were KIM-1 and NGAL increased by both nephrotoxins. reg IIIβ was found to be overexpressed in the kidneys of gentamicin-treated rats and secreted into the urine, whereas gelsolin is derived from plasma and appears in urine after glomerular filtration.

We recommend that the etiology of AKI be determined as soon as the diagnosis is made. Functional and injury biomarkers should be used to help differentiate AKI of uncertain etiology. Further studies will be required to determine the specificity of damage and biomarkers for individual disease states.

Setting, Mechanism and Time Course of AKI

Novel biomarkers of AKI have been validated in a limited variety of clinical settings, including cardiac surgery, sepsis and contrast-induced AKI. Several biomarkers have been shown to diagnose or predict the future development of AKI at early clinical timepoints (e.g. 2 h after initiation of cardiopulmonary bypass). However, not all biomarkers have performed well in every setting. Individual biomarkers have their own unique physiological and anatomical properties/fingerprints that determine their ability to differentiate the etiology of AKI. For instance, IL-18 is upregulated as part of the inflammatory response to cellular injury (activating macrophages, promoting T-cell differentiation and stimulating interferon-γ release by NK/T cells) [36]. Thus, IL-18 may not be well suited for diagnosing sepsis-associated AKI [37], in contrast to its performance in the setting of cardiac surgery-associated AKI where ischemia-reperfusion is presumed to be the dominant source of renal injury [37].

A summary of the current findings for the five most widely published biomarkers in several of the most widely investigated clinical settings is shown below (table 1). Note the inherent publication bias since negative biomarker findings often go unpublished. To date, there is no clinical evidence to support an individual biomarker or a panel of biomarkers in differentiating between dis-

Table 1. Novel AKI biomarker performance in different clinical settings

	NGAL	IL-18	KIM-1	CysC	L-FABP
Hypovolemic AKI	+/−	+/−	+/−	+/−	+/−
Sepsis	+	+/−	?	+	+
Post-cardiopulmonary bypass	+	+	+	+	+
Contrast-induced	+	+	+	+	+
Nephrotoxic	+	+	+	?	+
Delayed renal graft function	+	+	+	+	?

The table summarizes the literature as related to the most widely published biomarkers in extensively studied clinical settings. Cardiac surgery-associated AKI (especially after cardiopulmonary bypass) is the most widely published setting, and NGAL the most widely published biomarker. The table makes no attempt to compare the data for individual settings or biomarkers. Since the time course of each biomarker varies, the optimum sampling time will vary for each clinical context. NGAL and cystatin C data refer to both urinary and plasma values, the other biomarkers represent urinary values.

NGAL = Neutrophil gelatinase-associated lipocalin; IL-18 = interleukin-18; KIM-1 = kidney injury molecule 1; CysC = cystatin C; L-FABP = liver fatty acid-binding protein. + = Able to detect AKI in this clinical setting; − = not able to detect AKI in this clinical setting; ? = inconclusive data on ability to detect AKI in this setting.

Table 2. Five urinary biomarkers in AKI complicated by sepsis

	Non-sepsis No-AKI (n = 178)	Non-sepsis AKI (n = 95)	Sepsis No-AKI (n = 30)	Sepsis AKI (n = 36)
L-FABP, ng/ml	6.8 (1.5–17.3)	35.9 (6.8–156.0)[b]	21.5 (4.6–46.1)	64.5 (18.8–543.3)[a]
NGAL, ng/ml	11.5 (4.7–33.2)	32.8 (13.3–136.9)	137.8 (39.2–323.5)	271.0 (118.1–1,593.6)[a]
IL-18, pg/ml	45.3 (20.0–110.6)	122.9 (34.5–390.2)	206.2 (133.5–802.1)	405.0 (209.6–1,043.9)
NAG, U/l	7.5 (3.8–14.7)	11.9 (5.4–22.6)[b]	22.8 (9.3–40.2)	22.4 (11.9–45.8)
Albumin, mg/dl	2.9 (1.1–7.1)	6.2 (3.0–26.5)[b]	7.8 (3.5–21.1)	15.4 (7.4–43.7)

Values are presented as median (interquartile range). [a] $p < 0.05$ vs. non-sepsis/non-AKI, non-sepsis/AKI, and sepsis/non-AKI. [b] $p < 0.05$ vs. non-sepsis/non-AKI. Data from Doi et al. [48].

tinct clinical etiologies of AKI (e.g. cardiac surgery-associated versus radiocontrast). Larger studies with higher sensitivity biomarker assays are needed to validate current findings and to define the role of these biomarkers in the differential diagnosis of AKI. Note also that the threshold concentrations for AKI diagnosis with these biomarkers are likely to be context-specific, particularly in the context of sepsis where baseline biomarker concentrations are higher in the No-AKI group (see table 2 and the next section).

Currently available biomarkers are used as non-specific markers of kidney damage. Thus, although each of the most widely studied biomarkers (especially those in table 1) has at least one defined role in the pathway leading to or from

injury, these biomarkers are presently used for diagnosis or prediction of AKI or outcome and not to identify the specific pathways involved. Biomarker performance is known to vary, inter alia, with baseline renal function, duration of injury, and etiology [38]. Each biomarker has a specific time course in a specific setting of injury [38–40]. From a consideration of biomarkers in nephrotoxic AKI, it is likely that these biomarker profiles will be setting-dependent [34, 41, 42]. We recommend using *only* biomarkers with validated test characteristics for detection of AKI in the clinical context where they are being used (e.g. sepsis, contrast) and indeed the best validation strategy will include unselected patients with multiple etiologies since these are the varying types of patients that will be encountered in clinical practice.

Research recommendation: we recommend that biomarkers be validated in multiple different etiologies.

Differential Diagnosis in the Presence of CKD

The etiology of AKI is needed to identify the optimal therapeutic strategies for patient care. Several clinical studies have reported biomarker levels for different AKI etiologies. Most were dedicated to differentiating supposedly functional pre-renal AKI from established AKI. Urinary NGAL in the emergency department was significantly higher in patients with established AKI compared with pre-renal azotemia, regardless of cause [13, 43]. These two urinary NGAL studies showed that a urinary NGAL level >104 ng/ml supported established AKI, whereas a urinary NGAL level <47 ng/ml was suggestive of other conditions. Nevertheless, about 25% of AKI patients in the latter cohort were clinically unclassifiable and had urinary NGAL levels in an intermediate range.

Because AKI occurring in the ICU is frequently complicated by sepsis [4] and since sepsis and AKI synergistically increase mortality rate [44], identifying sepsis as the cause of AKI is of great potential significance in clinical management. Plasma NGAL has been reported to be higher in septic than in non-septic AKI patients in several [44, 45], but not all [46] studies. Both sepsis and AKI increased urinary cystatin C and their effects appear to be additive [47]. Similarly, evaluation of five urinary biomarkers (NGAL, IL-18, L-FABP, NAG, and albumin) in a mixed ICU revealed that the highest values were all in septic AKI patients, with L-FABP able to discriminate AKI in both septic and non-septic patients (table 1) [48]. These results suggest that higher thresholds of single and multiple biomarkers may differentiate septic from non-septic AKI.

Observational studies have described CKD in approximately 30% of the AKI patients in the ICU [4, 49]. Both baseline concentration and injury response vary

amongst biomarkers in the presence of reduced renal function. Baseline urinary and plasma NGAL levels are known to be increased in CKD patients under stable conditions [50–52]. Urinary L-FABP is higher in CKD than in healthy control subjects [52]. Injury response and biomarker performance are modified in the presence of CKD (baseline eGFR <60 ml/min) [38, 53, 54]. A probable additional cause of increased baseline urinary biomarker concentrations in CKD is the presence of proteinuria, a common feature in CKD. Urinary albumin and protein competitively increase the concentration of filtered low molecular weight protein biomarkers such as NGAL and cystatin C, proteins normally reabsorbed by megalin-cubulin transport in the proximal tubule [55]. Thus in CKD patients, higher cut-off values are probably necessary to detect AKI superimposed on CKD as distinct from de novo AKI. Medication may also modify baseline biomarker concentration in the case of plasma NGAL (but not cystatin C); a reduction in plasma NGAL was observed following chronic atorvastatin treatment [54]. Thus both negative and positive associations with baseline renal function are possible. Negative associations are more common though biomarker concentration may increase after an initial delay in in patients with CKD [38].

Taken together, these features indicate that the magnitude and range of biomarker increase in AKI is modified by reduced GFR in CKD. It is therefore essential that the pattern of biomarker increase is evaluated over time when the CKD status is unknown. The slope of the increase, peak value, time to peak, as well as slope of decrease and time to decrease may help differentiate between AKI superimposed on CKD and de novo AKI. Thus, the biomarker threshold and pattern over time as well as the baseline level must be considered when determining the etiology of AKI in patients with underlying CKD.

We recommend that research studies should be performed to determine the thresholds, biomarker profiles and disease profiles that differentiate among etiologies. We also recommend studies to clarify the frequency of measurement of biomarkers and that baseline levels of biomarkers be established for patients with various stages of CKD. Biomarkers need to be validated in cohorts with CKD.

Non-Renal Biomarkers and Etiology of AKI

In the differential diagnosis of AKI, context-specific biomarkers will assist in determining AKI etiology. Similarly in the context of a specific clinical presentation, structural and functional biomarkers of renal injury will define the presence of complicating AKI (fig. 3). The diagnostic and prognostic roles of natri-
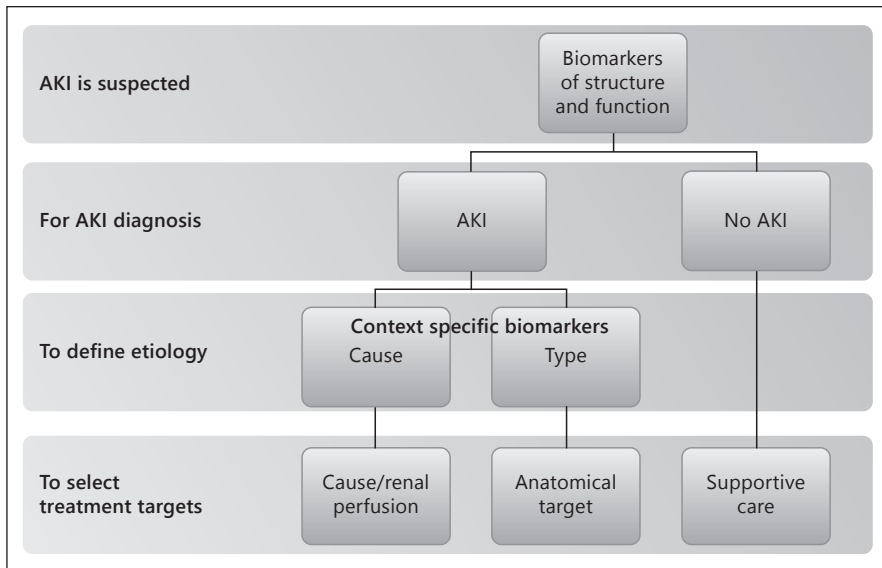
Fig. 3. Biomarker utility in differential diagnosis of established AKI and in the identification of injury pathways. Reproduced with permission from ADQI [59].

uretic peptides (BNP, NT-proBNP, MD-proANP) and procalcitonin (PCT) as biomarkers are well established in patients with heart failure and sepsis [56–58]. Renal injury is common in these patients and will result in poorer outcomes. Combining biomarkers of cardiac failure or sepsis with those of structural and functional kidney damage should facilitate both early detection of AKI and facilitate differential diagnosis.

Both acute or chronic cardiac failure compromise renal perfusion with consequent sodium and water retention, arterial vasoconstriction, venous congestion and impaired kidney function defining cardiorenal syndromes type I and II. There is an inverse relationship between renal function and NT-proBNP values in cardiac failure patients, where BNP has a prognostic role and predicts the development of AKI [53]. The combination of BNP with NGAL has a diagnostic and prognostic utility in patients with cardiorenal syndrome [54].

Conclusion

We propose a systematic approach to the diagnosis of AKI that incorporates a combination of functional and damage biomarkers for the diagnosis of AKI and in establishing the specific cause or causes of AKI. The presence of underlying CKD poses an additional diagnostic challenge, not only in terms of differentiat-

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ing acute from chronic and from 'acute on chronic' disease, but also with respect to determining the etiology of AKI in the setting of underlying CKD. We recommend that functional and damage biomarkers be validated within the context or domain in which they are to be used. Within that context, combinations of biomarkers may, in the future, allow differentiation of the site, mechanism and timing of injury.

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