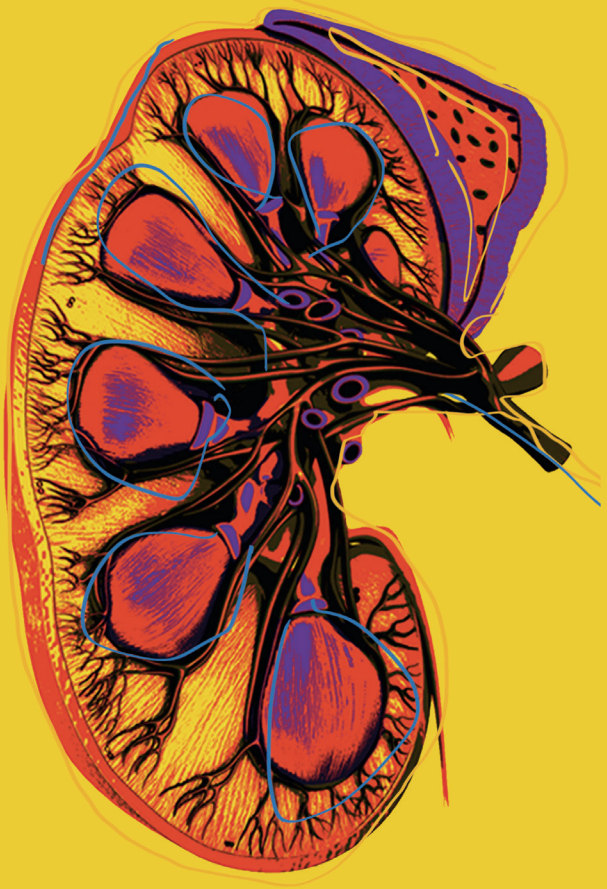
BIOMÉRIEUX

AKI

Acute Kidney Injury



PIONEERING DIAGNOSTICS

PREFACE

I'm often asked, "is there a quick guide to acute kidney injury for the non-expert?" My response is to steer the person asking to various review articles that have been written over the last few years. While these are useful, they tend to either assume a certain level of familiarity with the subject matter or be overly focused on certain aspects (e.g. epidemiology, biomarkers, renal replacement therapy) and may not provide a comprehensive overview of the field.

Textbooks, by contrast, provide comprehensive overviews but lack the practicality and portability of a short reference guide. Of course, the portability problem can be solved by electronic media, but the desired answer to a specific question can still be far from one's fingertips.

With these considerations in mind, I have sought to create a practical, accessible, brief yet comprehensive resource on acute kidney injury for front-line clinicians. I've paid particular attention to address both the basics and the controversial using tables and figures, as well as text. It's my hope that as brief as this resource is, it can provide a useful foundation for trainees as well as a quick reference for the seasoned clinician.

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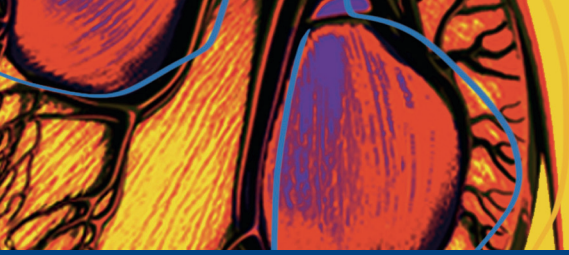
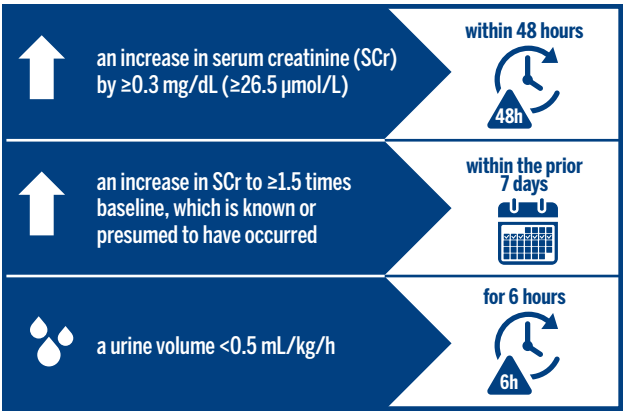


WHAT IS ACUTE KIDNEY INJURY?

1 Definition and diagnostic criteria

Acute kidney injury (AKI) is a condition resulting in an abrupt loss of kidney function. Specifically, AKI is defined as any of the following:[1]



For practical purposes this means that when AKI develops under close medical observation (e.g. in the hospital) an increasing SCr or a decreasing urine output should prompt the clinician to consider AKI. Importantly however, neither SCr nor urine output (UO) are specific for AKI and neither criterion itself is sensitive (although sensitivity increases with both criteria together). **Table 1** lists potential confounders that reduce the sensitivity and specificity of SCr and UO for AKI.

Table 1. Confounding conditions for AKI diagnosis using serum creatinine and urine output.

EFFECT/CAUSE	EXAMPLES
Serum Creatinine	
Falsely low (not increased)	
Increased volume of distribution	Fluid overload
Decreased creatinine production	Bed rest, fasting
Subclinical AKI[a]	Renal reserve
Increased not from AKI	
Decreased tubular secretion	Various drugs: cimetidine, trimethoprim, pyrimethamine, salicylates
Increased creatinine release	Muscle breakdown, corticosteroids and vitamin D metabolites
Return of creatinine to baseline	Decreased creatinine (e.g. fluid resuscitation) which is now normalizing
Chronic kidney disease	Patient presenting with unknown medical history
Decreased GFR without injury[b]	Severe dehydration, ACE inhibition
Urine Volume	
Falsely high (not decreased)	
Non-oliguric renal failure	Many forms of nephrotoxic AKI
Diuretics	Especially osmotic diuretics. Not typical of loop diuretics as they require intact tubular function
Oliguria not from AKI	
Lower urinary track obstruction	Clogged or dislodged Foley catheter
Unilateral obstruction	Contralateral disease or one kidney
Oliguria without injury	Severe dehydration

ACE: Angiotensin converting enzyme; GFR: Glomerular filtration rate.
[a]Injury with reductions in GFR less than the threshold for creatinine to rise.
[b]When severe or prolonged usually denotes injury.

2 Clinical judgement

As **Table 1** indicates, there are a number of possible causes for changes in serum creatinine and urine output apart from AKI. Therefore, the clinician must use medical history and physical examination along with his or her clinical judgement to diagnose AKI.

A checklist has been proposed to help with this process (see **Table 2**).[2] Despite the simplicity of the diagnostic criteria, AKI can be a challenging diagnosis. Even if we set aside the sensitivity and specificity concerns with serum creatinine and urine output for accessing kidney function (**Table 1**), the diagnosis can still be difficult. The two main areas of difficulty concern the acuity vs. chronicity of kidney dysfunction and the fact that damage to kidney and kidney function can be dissociated. Thus, the clinician should seek to evaluate kidney function and to understand whether changes in function are attributable to disease and if so, whether it is acute or chronic or both.

One hallmark of AKI is its instability. Kidney function is unstable during AKI, getting better or getting worse but rarely staying the same. Once kidney function stabilizes, the process causing damage has likely ended. If the injury is reversible, function will improve. If not, a new steady state will be reached reflecting the extent of intact nephrons available.

Two caveats should be stated here.

- First, restoration of kidney function may take days to weeks, or even months in some cases.
- Second, reversal of kidney dysfunction is not a guarantee that recovery has occurred. Kidney damage in many forms of AKI is patchy and while some nephrons may be irreversibly injured, others may be spared. Since individual functioning nephrons can increase filtration to compensate for lost nephrons, function may improve without recovery. Unfortunately, these hyper-filtering nephrons may be susceptible to glomerular sclerosis over time and the loss of renal reserve (ability to augment glomerular filtration rate (GFR) further when needed) may predispose to development of AKI with subsequent exposures.[3]

Table 2. A checklist for Acute Kidney Injury.[2]

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	AKI More Likely	AKI Less Likely
Clinical Context		
Susceptible populations		
Volume depletion, Female, Black, CKD, Chronic diseases (heart, lung, liver), Diabetes mellitus, Cancer, Anemia, Over age 65	✓ ✓	
No susceptibilities		
Exposures		
Sepsis, Critical illness, Circulatory shock, Burns, Trauma, Cardiac surgery (especially with CPB), Major noncardiac surgery, Nephrotoxic drugs, Radiocontrast agents, Poisonous plants and animals	✓	
No exposures		
Alternative Diagnosis		
For oliguria		
Dehydration, obstruction, retention		✓
For increased serum creatinine		
Endogenous chromogens (acetone, bilirubin) Medications (e.g., trimethoprim and cimetidine)		
AKI Criteria		
Serum creatinine increase		
≥ 0.3mg /48h		
1.5x reference	✓	
Urine output < 0.5ml/kg/h for ≥ 6h		
Both serum creatinine and UO criteria		
Confirmatory Data		
Active urine sediment		
Serum creatinine		
changing (up or down)		
stable		
Biomarkers		
[TIMP-2]•[IGFBP7]		
≤ 0.3 $(ng/ml)^2/1000$		
>2.0 $(ng/ml)^2/1000$		
NGAL (serum or plasma)		
Low		
High		
Multiple markers		
Negative		
Positive		

Shading indicates the column that applies to each row. Check marks indicate conditions applicable to the case discussed in the original article.
AKI acute kidney injury, CKD chronic kidney disease, CPB cardiopulmonary bypass. NGAL neutrophil gelatinase-associated lipocalin, TIMP-2 tissue inhibitor of metalloproteinase 2, IGFBP7 insulin-like growth factor binding protein 7.

3 Baseline kidney function

One of the most challenging aspects of diagnosing AKI can be determining the patient's baseline kidney function. Because most people do not have their kidney function checked regularly, it will always be a matter of judgement as to what GFR (and hence creatinine) can be used as their baseline should they develop a condition that can cause AKI. A further consideration is that people have their kidney function evaluated when they are sick, so values obtained during prior hospitalizations may be misleading. Furthermore, all of the considerations pertaining to serum creatinine listed in **Table 1** can also apply to a potential baseline value. As with any measurement, accuracy improves when multiple values are pooled, especially if outliers are omitted. The median of several prior values is therefore the most reasonable estimate of the baseline. However, older values are less likely to reflect current function compared to more recent values.

The following approaches can therefore be used:

- If three or more serum creatinine values are available in the prior six months, take the median of these. If not look for values over the past 12 months, taking the median of these.
- If the two most recent values in the past 12 months are within 20% of each other (e.g. 1.0 and 1.2 mg/dL), use the mean (e.g. **Table 3**). If not use the median of values as described above.
- If only two values are available in the last 12 months, take the mean of these; if only one value is available use it.

Importantly, a sizable number of patients will not have any serum creatinine values available within the last year. Older values (if available) might be useful if the patient's health has been stable. For patients without any historical creatinine values, a baseline value can be estimated from their demographics using an estimated GFR (eGFR) equation and back-calculating a baseline creatinine using a "normal GFR" value. A value of 75 mL/min/1.73m^2 has been reproposed (see **Table 3**).[4]

Table 3 lists reference values for serum creatinine based on age, sex and race. Of note, the adjustments for race have recently been called into question.[5] Although from a population perspective, these adjustments are valid, variation among individuals is great. Particular concern has been raised when the eGFR is determined to be higher among blacks, potentially disadvantaging them for kidney transplant eligibility. From a baseline creatinine perspective, use of adjustments for black race will mean that the estimated baseline will be higher, and AKI could be underdiagnosed. In general, use of the adjustment for black race should be reserved for patients with higher-than-average muscle mass. Alternatively, both adjusted and unadjusted values can be considered, and clinical judgement used to determine which is most appropriate in any given patient.

Table 3. Reference creatinine values based on age, race and sex.[4]

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Estimated baseline creatinine

Age (years)	Black males mg/dL (µmol/L)	Other males mg/dL (µmol/L)	Black females mg/dL (µmol/L)	Other females mg/dL (µmol/L)
20-24	1.5 (133)	1.3 (115)	1.2 (106)	1.0 (88)
25-29	1.5 (133)	1.2 (106)	1.1 (97)	1.0 (88)
30-39	1.4 (124)	1.2 (106)	1.1 (97)	0.9 (80)
40-54	1.3 (115)	1.1 (97)	1.0 (88)	0.9 (80)
55-65	1.3 (115)	1.1 (97)	1.0 (88)	0.8 (71)
>65	1.2 (106)	1.0 (88)	0.9 (80)	0.8 (71)

Estimated glomerular filtration rate=75 (mL/min per 1.73 m^2)=186 x (serum creatinine [S_{Cr}]) – 1.154 x (age) – 0.203 x (0.742 if female) x (1.210 if black)=exp(5.228 – 1.154 x ln [S_{Cr}]) – 0.203 x ln(age) – (0.299 if female) + (0.192 if black).

4 Acute kidney disease

Acute kidney disease (AKD) is a relatively new term. AKD is defined as alterations in kidney structure or function lasting up to 3 months, with implications for health. The criteria for defining various kidney diseases and disorders are shown in **Table 4**. Importantly, in this framework, AKI is a specific subtype of AKD but AKD can also exist without AKI. For example, a patient can develop alterations in kidney structure or function that do not meet the criteria for AKI, but nevertheless have implications for health. In patients cared for in the hospital, AKD with AKI may be most common but outside the hospital, AKD without AKI may be significantly more common.[6]

Table 4. Criteria for defining kidney diseases and disorders.[7]

Reprinted from American Journal of Kidney Diseases, 61(5), Andrew S Levey, Adeera Levin, John A Kellum, Definition and classification of kidney diseases, 686-688, Copyright 2013, with permission from Elsevier.

	Functional Criteria	Structural Criteria
AKI	Increase in SCr by 50% within 7 d, *or* increase in SCr by 0.3 mg/dL within 2 d, *or* oliguria	No criteria
CKD	GFR <60 mL/min for >3 mo	Kidney damage for >3 mo
AKD	AKI, *or* GFR <60 mL/min/1.73 m^2 for <3 mo, *or* decrease in GFR by ≥35% or increase in SCr by >50% for <3 mo	Kidney damage for <3 mo
NKD	GFR ≥60 mL/min/1.73 m^2, stable SCr	No damage

Note: Criteria for AKI and CKD proposed by KDIGO guidelines, based on evidence and expert opinion. Criteria for AKD and NKD proposed to harmonize the criteria for AKI and CKD. GFR may be assessed from measured or estimated GFR. Estimated GFR does not reflect measured GFR in AKI as accurately as in CKD. Kidney damage assessed by pathology, urine or blood markers, imaging, and—for CKD—presence of a kidney transplant. NKD indicates no functional or structural criteria according to the definitions for AKI, AKD, or CKD. Clinical judgment is required for individual patient decision making regarding the extent of evaluation that is necessary to assess kidney function and structure.

Abbreviations: AKD, acute kidney diseases and disorders; AKI, acute kidney injury or impairment; CKD, chronic kidney disease; GFR, glomerular filtration rate; NKD, no known kidney disease or disorders; SCr, serum creatinine.

5 Etiology and pathophysiology

AKI (and AKD without AKI) may be due to a variety of conditions including disease, injury, toxins, drugs or major surgery (especially cardiac). A list of common conditions leading to AKI are shown in **Table 5** along with clinical characteristics and pathophysiology.

Importantly, it is common for patients developing AKI to have multiple etiologies at once. In the past, it was common to classify patients according to presumed pathophysiology using pseudo-anatomic categories as pre-, post- and intra-renal, and in some textbooks this is still the case. The post-renal category refers to urinary tract obstruction and is therefore anatomically correct, but the others are essentially meaningless.

Sepsis, for example has been variably classified as pre-renal, intra-renal or a combination of both. As the understanding of the pathophysiology of AKI has advanced,[8] it has become very clear that this simplistic categorization is misleading.

Sepsis is the most common cause of AKI for patients with critical illness, representing 50% or more in most series.[9-11] For many years it was assumed that sepsis caused AKI through hemodynamic alteration. However, AKI may develop in the absence of renal hypoperfusion and clinical signs of hemodynamical instability,[12-14] and in the presence of normal or increased global renal blood flow.[12,15-21]

A 'unified theory' of sepsis-associated AKI (S-AKI) has been proposed in an attempt to place a variety of mechanisms into a coherent framework of synergic interaction.[22] The inflammatory response is the host's main defense mechanism from invading pathogens. However, a dysregulated inflammatory response may be responsible for organ dysfunction and poor outcome.

During sepsis, various mediators including pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are released in the intravascular compartment. These molecules bind membrane bound pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), present on the surface of immune cells, initiating a downstream cascade of signals that will result in the synthesis and release of proinflammatory molecules. Renal tubular epithelial cells also express TLRs, especially TLR2 and TLR4. When exposed to DAMPs or PAMPs filtered through the glomerulus or through neighboring peritubular capillaries, proximal tubular epithelial cells exhibit an increase in oxidative stress, production of reactive oxygen species (ROS) and mitochondrial injury.[23-26]

Trauma and major surgery (especially cardiac and vascular) are also common causes of AKI in the critically ill. The pathophysiology of AKI associated with cardiac and vascular surgery is complex and poorly understood.[27] Cardiopulmonary bypass (CPB) itself is likely to be responsible for one third to half of AKI in these patients. Hemodynamic disturbances at each level of arterial blood supply, inflammatory, immunological, neuro-humoral and mechanical factors are all significant contributors.

The pathophysiology associated with AKI from these and other causes is summarized briefly in **Table 5**.

Table 5. Common conditions leading to AKI

Etiology	Clinical Characteristics	Pathophysiology
Infection		
Sepsis	Serious infections (e.g. pneumonia) are common causes of AKI and AKI due to systemic infection is sepsis by definition. Oliguria is an almost universal feature.	Sepsis causes AKI through a complex series of events. Damage and pathogen associated molecular patterns directly signal tubular-epithelial cells causing inflammation and injury.
Malaria	Massive hemolysis leading to hemoglobinuria "blackwater fever".	In addition to the direct effects of hemoglobin on tubular cells, systemic inflammation contributes to AKI.
COVID-19	May present with proteinuria.	Still under investigation but similar to sepsis.

Etiology	Clinical Characteristics	Pathophysiology
Medications		
Aminoglycosides	Toxicity is dose dependent and can be reduced with careful therapeutic drug monitoring.	Direct tubular (proximal) toxicity.
Vancomycin	Toxicity is dose dependent and can be reduced with careful therapeutic drug monitoring.	Direct tubular (proximal) toxicity.
Beta-lactams	Significant variation in risk among drug classes. The penems and some cephalosporins have greatest *in vitro* nephrotoxicity while piperacillin-tazobactam is most commonly associated with AKI.	Acylation of target proteins, causing respiratory toxicity by inactivation of mitochondrial anionic substrate carriers; and lipid peroxidation. Allergic interstitial nephritis may be a common cause as well.
Cisplatin	In addition to AKI, disorders of electrolytes and acid base (including Fanconi syndrome) are frequent. Thrombotic microangiopathies have also been reported.	Accumulation in the kidney through active transporters. Toxic metabolites generated which have cytotoxic effects through their interaction with DNA.
Loop diuretics	Allergic interstitial nephritis (AIN) has been reported. Risk may be higher with sulfa allergy, but most patients are not affected.	Apart from rare cases of AIN, direct nephrotoxicity does not occur with loop diuretics. However, they may potentiate toxicity from other causes.
ACE inhibitors, ARBs	Small increases in serum creatinine are generally expected and usually do not indicate AKI. May potentiate AKI from other causes.	These agents reduce GFR but do not directly cause nephrotoxicity. There is controversy as to how much change is acceptable.
Calcineurin inhibitors	Both dose dependent and idiosyncratic nephrotoxicity may cause AKI but chronic toxicity is more common and difficult to manage.	Inhibition of the calcineurin-NFAT signaling by induces COX-2 inhibition which leads to renal vasoconstriction and reduces GFR. This effect is dose-dependent and is usually reversible.

Etiology	Clinical Characteristics	Pathophysiology
Major surgery		
Cardiac	Typically manifests within 72 hours of surgery. Is almost always oliguric.	Multifactorial with contributions from hemolysis, cardiac dysfunction, hemodynamics and inflammation.
Non-cardiac	Early and delayed manifestations appear to have different risk factors.	Tissue injury leading to release of damage-associated molecular patterns. Hemodynamics and inflammation. Abdominal compartment syndrome.
Trauma	Clinical presentation varies by type of injury and complications.	Tissue injury leading to release of damage-associated molecular patterns. Hemodynamics and inflammation. Rhabdomyolysis, especially with crush injury.
Cardiac disease	May occur with both reduced and preserved ejection fraction.	Kidney perfusion may be compromised by both lower forward flow as well as back pressure from right heart failure. Other mechanisms including treatment have been characterized.
Liver disease	Multiple forms of AKI may occur in patients with liver disease. A "pure form" is hepatorenal syndrome type 1.	Intense renal vasoconstriction results from splanchnic vasodilatation. Other causes including bile acid nephropathy and intraabdominal hypertension may also contribute.

Etiology	Clinical Characteristics	Pathophysiology
Endothelial/Vascular		
Thrombotic microangio-pathies	Multiple forms including TTP, HUS and aHUS.	Complement mediated injury, microvascular thrombosis.
Acute Glomerulo-nephritis	Multiple forms including non-crescentic, postinfectious, lupus nephritis and mesangiocapillary.	Mechanisms vary by subtype but involve acute inflammation and infiltration of glomeruli leading to an abrupt decline in GFR.
Cholesterol emboli	Seen with dislodgement of atheroma mainly from surgery or other procedures.	Cholesterol crystals embolize and lodge in the microcirculation causing ischemic injury.
Sickle cell disease	Typically seen as part of an acute crisis.	Hemoglobin-induced tubular cytotoxicity.

TTP: Thrombotic thrombocytopenic purpura; HUS: Hemolytic uremic syndrome; aHUS: atypical Hemolytic uremic syndrome.

Etiology	Clinical Characteristics	Pathophysiology
Toxins		
Chemicals	Heavy metals, organic chemicals (e.g. pesticides and herbicides).	Various mechanisms depending on the agent.
Plants/ animals	Several plants including some edible or medicinal (e.g. aristolochic acid, henna) can cause both acute and chronic kidney damage. Scorpions and various spiders (Loxosceles).	Various mechanisms depending on the agent.
Crystal-induced	Various drugs (e.g. methotrexate, acyclovir, vit C) and chemicals (e.g. ethylene glycol).	Crystals cause acute necroinflammation, tubule obstruction or crystal granuloma formation and chronic tissue remodeling.
Radiocontrast	Far less common with modern agents. Patients with underlying CKD are at highest risk.	Oxidative injury has been documented but precise mechanisms are not fully known.
Urinary tract obstruction	Lower or bilateral upper urinary tract obstruction (or proximal obstruction in a patient with one kidney) can present as AKI.	Obstruction to flow will cause hydronephrosis if not treated promptly.

THE GLOBAL BURDEN OF AKI

1 Epidemiology

A comprehensive analysis of the global incidence of AKI has not been performed. Various estimates come mainly from hospitalized patients and largely from high-resource countries.

Figure 1 illustrates AKI occurrence among hospitalized patients as reported in several large studies and metanalyses.[28-30] Although ranges are relatively large, most regions report rates between 15-25% of hospitalized patients. However, marked variation in rates of (non-maternity) hospitalization exist even among similar-resourced countries.

For example, in Europe, hospitalization rates per population vary from 8.5% in Portugal and 9.6% in the Netherlands to 25.7% in Germany and 25.3% in Austria. The US has even lower rates at about 7.9%. If we use these data to determine the incidence of AKI in the population (ignoring patients not admitted to hospital), we see that nearly 24 million patients develop AKI annually in the US, EU and Australia. Extrapolating these rates to the rest of the world (where many estimates are even higher) and we find roughly 232 million people will develop AKI on an annual basis. Even if this number is inflated two-fold, there are still more than 100 million new AKI events per year on average around the globe.

Estimates of AKI incidence in North America are further supported by a large community-based study from James et al.[6] These investigators examined AKI and AKD incidence in the province of Alberta, Canada using data from 2008 and found that AKI occurred in 18 per 1,000 population while AKD was even more common, 44 per 1,000 population.

Figure 1. Global incidence and rates in hospital for acute kidney injury.[38]

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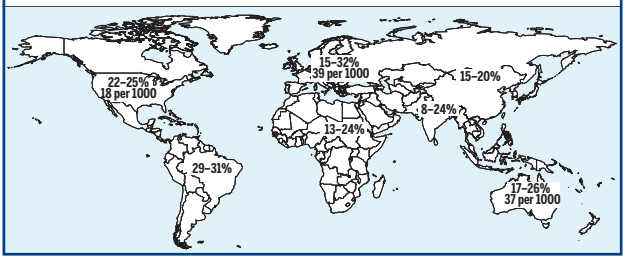

Schematic representation of AKI epidemiology per hospital admission and corresponding incidence by region. Hospitalization rates for the US were obtained from the US Centers for Disease Control (cdc.gov) and for other countries from the Organization for Economic Cooperation and Development (oecd.org). In Europe an average rate of 17% was used. For other regions, information on hospitalization rates are not available. Given that there is a 2-fold variation in population incidence despite similar rates per hospital admission, it seems likely that many AKI occurrences are not captured.

2 Community- vs. hospital-acquired AKI

The majority of AKI cases begin before hospital admission. This is because many of the most common etiologies (e.g. sepsis, acute decompensated heart failure, toxins and drugs) arise in the community. A notable exception is surgery-associated AKI. Of note, many forms of AKI can manifest in the hospital even though the injury began prior to admission.

3 Short and long-term outcomes

AKI is responsible for numerous short and long-term adverse outcomes (see **Table 6**). Importantly, there was once a prevailing view among many clinicians that AKI was not a causal death in critically ill patients but rather a marker of disease severity. The logic was based on the fact that renal replacement therapy is available and that patients rarely die of proximate causes directly attributable to the kidney. The expression "patients die with renal failure not of acute renal failure" was the articulation of this sentiment. However, multiple lines of evidence refute this view.

First, experimentally-induced AKI directly causes neutrophil dysfunction and therefore reduces bacterial clearance and shortens survival.[31]
Second, the clinical correlate of these animal experiments can be found in randomized trials where a drug was found to be nephrotoxic and resulted in reduced survival apparently through its effect on AKI. Such was the case in the 6-S trial where patients with sepsis randomized to receive hydroxyethyl starch had reduced survival.[32] The apparent explanation for the reduced survival was increased AKI, a direct result of the drug.

Table 6. Selected short- and long-term consequences of Acute Kidney Injury.

Short-Term (90 days)	Long-Term*
Death	Reduced survival
Immune dysfunction (increased infection risk)	Chronic kidney disease
Fluid overload	Cardiovascular events (MI, Stroke)
Impaired excretion of multiple drugs	Impaired excretion of multiple drugs
Acid-base and electrolyte abnormalities	Acid-base and electrolyte abnormalities
Platelet dysfunction / increased bleeding risk	Renal cancer
Encephalopathy	
Increased ICU and hospital duration	

*Generally seen when there is residual renal dysfunction following AKI (i.e. non-recovery).

However, some increased risk for death and cardiovascular disease persists even in patients who appear to recover following AKI. Also, complications listed on the left (short-term) can also occur in the long-term if chronic kidney disease is not well managed.

Adverse drug events are particularly problematic for AKI because kidney function is unstable. Drugs can easily be overdosed because of decreased clearance but they may also be underdosed when kidney function improves. The former leads to toxicity while the latter may result in treatment failures. Readmissions following AKI are common and drug dosing is a common precipitating cause.

Long-term outcomes are tightly correlated with recovery of kidney function. For example, in patients surviving critical illness, survival to 1 year is >90% for patients who recovery kidney function within 7 days and remain recovered (no relapses or second events) until hospital discharge. Conversely, patients who never resolve AKI have a 1-year survival of only 40%.[33]

Figure 2. Survival following Acute Kidney Injury as a function of recovery status.[33]

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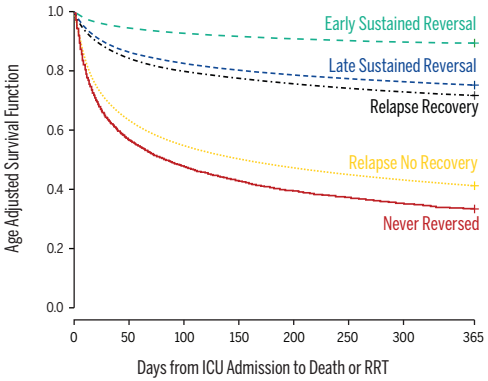

No. at risk

Early Sustained Reversal	4,507	4,404	4,317	4,235	4,176	4,122	4,070	4,026
Late Sustained Reversal	1,642	1,529	1,424	1,357	1,310	1,272	1,242	1,203
Relapse Recovery	3,823	3,535	3,245	3,061	2,910	2,818	2,719	2,625
Relapse No Recovery	2,496	1,386	1,190	1,114	1,075	1,052	1,027	1,008
Never Reversed	4,496	2,127	1,922	1,826	1,757	1,709	1,678	1,648

Age-adjusted survival by recovery pattern. Survival differences are highly significant overall ($p<0.001$). All pairwise comparisons are also significant. Early sustained reversal indicates return of kidney function to baseline (creatinine <150% times baseline) within 7 days and no relapse prior to discharge. Late sustained reversal is defined as return of kidney function to baseline after 7 days and no relapse prior to discharge. Relapse recovery indicates return of kidney function to baseline within 7 days but with relapse and then recovery prior to discharge. Relapse no recovery is the same as relapse recovery except that recovery does not occur prior to discharge and never reversed is no return to baseline kidney function during the hospitalization.
ICU: intensive care unit; RRT: renal replacement therapy.

However, survival is a crude measure of long-term consequences of AKI. Development or progression of chronic kidney disease including end-stage disease is also common. For example, in patients developing stage 3 AKI by creatinine criteria in the setting of cardiac surgery, more than 10% were still dialysis-dependent by 90 days.[34] Furthermore, even patients with isolated oliguria (no change in serum creatinine) had an increased risk of new chronic kidney disease 8.1% (228/2827) compared with 5.2% (65/1248) in patients without AKI (p=0.0001). Rates of long-term outcomes following AKI are depicted in **Figure 3**.

Figure 3. Absolute risks of clinical events for patients in high-income countries in the year after hospitalization with AKI.[35]

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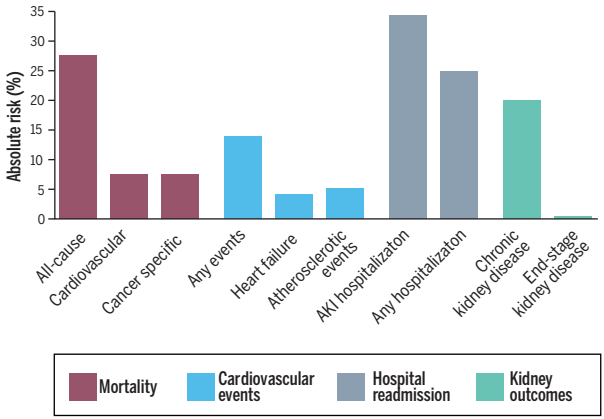


Absolute risks of the most common clinical outcomes following discharge from hospitalization with acute kidney injury (AKI). Absolute risks within 1 year of discharge are illustrated for kidney outcomes, cardiovascular outcomes, all-cause and cause-specific mortality, and hospital re-admission with AKI. The absolute risk of rehospitalization of any cause refers to the risk of rehospitalization within 90 days of hospital discharge.

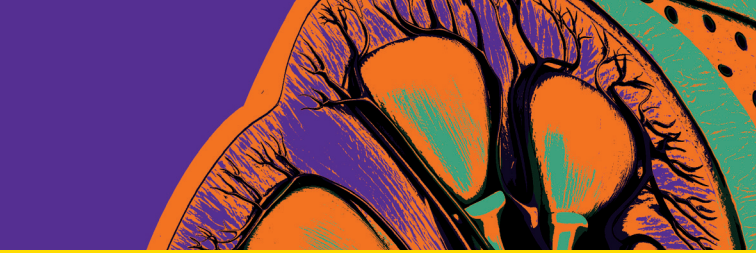
4 Economic burden

Since accurate information on global AKI incidence is lacking, it is difficult to accuractely determine the full economic impact of AKI. Some determinants of cost can be estimated from available information.

➔ Since AKI doubles hospital duration (the main driver of cost) we can estimate that overall hospital expenditures increase as a function of AKI.

- In the US, annual hospitalization costs are approximately 1.2 trillion USD. If 25% of patients develop AKI and this doubles their costs, the expenditures attributable to AKI would be 240 billion USD! Even if AKI only affects 10% of patients and increases costs by only 50%, the expenditures attributable to AKI would still be 57 billion USD.
- In Germany, hospitalization costs are estimated at 105 billion euros. If 25% of patient develop AKI and this doubles their costs, the expenditures attributable to AKI would be 21 billion euros.

Of course, these estimates of economic impact do not take into account the fact that patients developing AKI may just be more expensive to care for. Conversely the costs do not include outpatient care. Overall, these estimates serve to illustrate the enormity of the problem.



CLASSICAL AND NOVEL BIOMARKERS OF AKI

1 Acute kidney injury or impairment

In the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guideline, the term AKI was defined as *"acute kidney injury or impairment"*. This was an effort to acknowledge the reality that, at the time, the available clinical indicators used for the diagnosis of AKI were measures of kidney function not damage. The implications of this fact are that:

- If kidney damage occurs that does not impact kidney function, it will not be ascertained using markers of kidney function.
- Not all changes in kidney function are due to kidney damage.

Several points follow from these implications.

First, absent kidney histology, there was no acceptable way to identify kidney damage for the majority of patients. A very small minority of patients have evidence of damage using markers of glomerular injury (e.g. albuminuria, hematuria) but most forms of AKI spare the glomeruli. Traditional indicators of tubular damage such as muddy brown casts lack sensitivity and also require some skill to identify correctly, leading to interobserver variation.[36]

Second, because healthy human beings have excess kidney functional capacity (referred to as renal functional reserve), a significant amount of damage can occur before GFR is affected. This is the physiological principle that explains why kidney donation is feasible - with the loss of 50% of functioning nephrons most donors can maintain a normal GFR. Thus, damage to the kidney frequently goes undetected using serum creatinine.

Third, alterations in kidney function may occur that are unrelated to kidney damage. For example, the loss of free water from the plasma will result in hemo-concentration and ultrafiltrate made from concentrated plasma will also be concentrated. When this ultrafiltrate hits the distal tubule, tubular-glomerular feedback will turn down GFR. This adaptive impairment of solute excretion will result in azotemia (increased serum creatinine as well as urea) such that criteria for AKI may be met. However, this impairment is not associated with kidney damage. Drugs, most notably ACE inhibitors, have similar effects.

2 Kidney damage and dysfunction

It follows logically from the previous section that kidney damage and dysfunction are not the same nor should they occur in equal measure. **Figure 4** illustrates this relationship. Importantly, the damage/dysfunction paradigm is not only significant for determining etiology of AKI but also for prognosis. Damage or dysfunction by themselves have much better prognosis than both together.[37]

Figure 4. Conceptual framework for AKI based on functional and damage criteria.[38]

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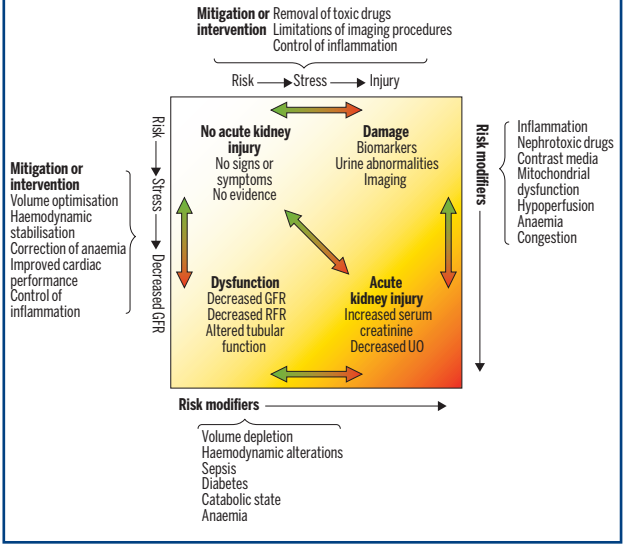


In the top left panel, no evidence of damage or dysfunction might identify a normal clinical condition; in the bottom left panel, a progressive decrease in GFR with increase in serum creatinine shows kidney dysfunction alone. This dysfunction might occur with the use of an angiotensin-converting-enzyme inhibitor, which can reduce GFR without damaging the kidney. In the top right panel, kidney damage is identified by specific biomarkers, but no dysfunction is present (normal serum creatinine). This condition has also been described as subclinical AKI. In the bottom right panel, both damage and dysfunction are present. Red arrows show progression, whereas green arrows show regression or recovery. Progression or regression can be affected by risk modifiers or by specific interventions. AKI: acute kidney injury; GFR: glomerular filtration rate; RFR: renal functional reserve; UO: urine output.

Similarly, when both functional markers, serum creatinine and urine output, are abnormal, prognosis is considerably worse than when either is affected alone.[39] However, as discussed in chapter 1, there are significant limitations to serum creatinine and urine output. These limitations have prompted a number of different alternatives for measuring kidney (glomerular) function.

3 Alternative markers of kidney function

Alternative markers of kidney function can be divided into two main categories: endogenous substances which are cleared from the plasma by the kidney, and techniques for measuring GFR directly. The first category theoretically includes numerous substances but, for practical purposes, only two require discussion - cystatin C and proenkephalin.

Cystatin C is a 13-kDalton (kDa) protein that is freely filtered at the glomerulus and not reabsorbed or secreted in the tubules. Its production is extremely constant, though it can be increased by corticosteroids. Thus, when measured in the plasma it can be used as a marker of GFR much the same as serum creatinine - only more accurately.[40] It has already been used for many years in patients with CKD and is unaffected by loss of muscle mass, making it a more useful marker in patients recovering from critical illness.[41]

Proenkephalin is an endogenous opioid polypeptide hormone which has been studied as a potential marker of GFR. Proenkephalin is freely filtrated at the glomerulus and thus plasma concentrations correlate with GFR.[42] However, as a hormone, production rates are not stable and are subject to various regulatory pathways. Little is known about the performance of the marker in different patient groups but existing evidence supports its utility in comparison to other filtration markers (creatinine, cystatin C).

The second category of filtration markers involve direct measurement of GFR. Timed urine collections allow for creatinine clearance measures and various approaches can be used including collection times as short as two hours. While these approaches may be superior to serum creatinine, they generally suffer from all of the same limitations. Other approaches involve exogenous substances (e.g. inulin, iohexol), but these are impractical for critically ill patients. Recent advances in technology to measure fluorescent compounds through the skin have opened the door for real-time monitoring of GFR. Using transdermal sensors, the plasma disappearance rate of an exogenous fluorescent compound eliminates the delay inherent in using an endogenous marker of filtration and permits continuous monitoring of GFR.[43] One or more technologies using this approach should soon be available for clinical use.

4 Markers of kidney damage

There are numerous molecules that are expressed differently in patients with kidney damage compared to healthy persons. Some are specific to certain parts of the nephron and a few can differentiate AKI from CKD. **Table 7** lists several such markers and their origins within the kidney and elsewhere.[44]

Table 7. The origin of biomarkers based on biological properties.[44]

Adapted from Srisawat, *et al. Crit Care Clin*. 2020;36(1):125-140.

Biology	Biomarkers
Filtered (impaired tubular reabsorption)	Albumin, Cystatin C, Beta 2 microglobulin, L-FABP
Up-regulation	NGAL, KIM-1, Clusterin, IL-18, Netrin-1
Down-regulation	Trefoil factor 3 (TFF3)
Preformed (released)	ALP, GGT, GST, NAG, L-FABP, TIMP-2, IGFBP-7

L-FABP: liver type fatty acid binding protein; NGAL: neutrophil gelatinase associated lipocalin; KIM-1: kidney injury molecule-1; ALP: alkaline phosphatase; GGT: gamma glutaryl transferase; GST: glutathione S-transferase; NAG: N-acetyl-beta-D-glucosaminidase; TIMP-2: tissue inhibitor of metalloproteinase-2; IGFBP-7: insulin-like growth factor-binding protein7.

The following biomarkers have been extensively studied and widely used as diagnostic tests of AKI.

→ Neutrophil Gelatinase Associated Lipocalin (NGAL)

NGAL is the most studied AKI biomarker. This 25 kDa protein was first discovered in the granules of neutrophils and later found in many organs, such as the kidney (proximal/distal tubular epithelial cells), lung, liver and large intestine. The thick ascending limb and the intercalated cells of the collecting duct are the main intrarenal production sites, and NGAL can also be detected at the proximal tubular epithelium because of the failure of filtered NGAL reabsorption in a megalin-dependent manner.[45]

An important caveat is that age, gender (female), urinary tract infection and impaired renal function (chronic kidney disease) may increase levels of urine NGAL.[46] Two recent meta-analyses found the AUC for urine NGAL to predict AKI was 0.82 and 0.72, respectively.[47,48] Recently, a meta-analysis by Klein et al, included 41 studies and showed the pooled AUCs for urine and plasma NGAL were 0.72 (95% CI 0.638-0.803) and 0.755 (0.706-0.803), respectively.[49]

NGAL is expressed in a severity-dependent fashion in AKI and is activated at the time of patient presentation, for example in the setting of post contrast exposure, post cardiac surgery, and kidney transplantation. It is also clear that dehydration alone does not trigger NGAL expression whereas kidney damage does. However, NGAL expression lacks specificity for AKI and the diversity of test kits on the market means that cut-offs are not standardized.

Liver-type Fatty Acid Binding Protein (L-FABP)

This biomarker has a molecular weight of 14 kDa and is a member of a superfamily of lipid-binding proteins, consisting of nine members named for the organ in which they were first identified, i.e. liver (L), intestine (I), muscle and heart (H), adipocyte (A), epidermal (E), ileum (IL), brain (B), testis (T), and myelin (MY).

L-FABP is critical for fatty acid uptake and facilitates the transfer of fatty acids between extracellular and intracellular membranes. L-FABP is not only found in the liver, but also in many organs, such as the intestine, stomach, lung, and kidney. L-FABP can be detected in urine and recently, urinary L-FABP has been approved as an AKI biomarker in Japan.

Ho J et al, analyzed the role of L-FABP to predict AKI after cardiac surgery by including 6 major studies and showed AUCs between 0.52 and 0.85 with a composite AUC of 0.72.[48] In critically ill patients, L-FABP was superior to other biomarkers including NGAL, interleukin-18, N-acetyl-beta-D-glucosaminidase (NAG), and albumin, for predicting AKI with an AUC 0.75.[50] Few studies have explored the role of L-FABP in predicting short or long-term renal outcomes or mortality.

Kidney Injury Molecule-1 (KIM-1)

KIM-1 is a 38.7 kDa protein that is markedly upregulated in proximal tubular epithelia after various exposures (e.g. ischemic/reperfusion, nephrotoxins). In response to injury, the extracellular component of KIM-1 is shed from the cell membrane into the tubular lumen in a matrix metalloproteinase (MMP)-dependent manner.[51] In clinical studies, KIM-1 has rather modest performance as a biomarker of AKI with AUCs of 0.70-75.[52,53] However, KIM-1 is very sensitive to injury and is approved for preclinical nephrotoxicity studies by the US FDA.

5 Second-generation AKI biomarkers

Unlike the damage biomarkers discussed above, newer biomarkers have been discovered by studying multiple cohorts of patients with diverse exposures that are known to cause AKI (e.g. sepsis, trauma, surgery) rather than starting from a model system. These markers have undergone qualification and verification using KDIGO criteria for AKI (Stage 2-3) which were not available when the first-generation biomarkers were discovered.

→ Insulin-like growth factor-binding protein 7 (IGFBP-7) and tissue inhibitor of metalloproteinases-2 (TIMP-2)

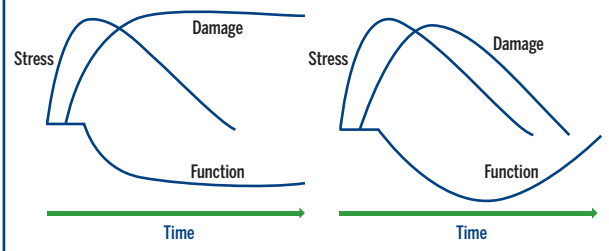
The first report of TIMP-2 and IGFBP-7 as markers of AKI came from Kashani et al.[52] This study included adult patients in ICUs in 35 centers across North America and Europe. The primary endpoint was moderate-severe AKI (KDIGO stage 2-3) within 12 hours of sample collection which occurred in 14% of subjects. Urinary [TIMP-2•IGFBP-7] demonstrated an AUC of 0.80 and was significantly superior to all existing markers of AKI ($p<0.002$), none of which achieved an AUC >0.72. In sensitivity analyses, [TIMP-2•IGFBP-7] remained significant and superior to all other markers regardless of changes in reference creatinine method.

Numerous subsequent studies have confirmed the initial results in various cohorts - however, cardiac surgery remains the most common.[54] In this area a total of 10 studies have enrolled 747 patients. Pooled sensitivity and specificity were found to be 0.77 (95% CI: 0.70-0.83) and 0.76 (95% CI: 0.72-0.79), respectively. Pooled positive likelihood ratio (LR), negative LR, and diagnostic odds ratio were 3.26 (95% CI: 2.51-4.23), 0.32 (95% CI: 0.24-0.41), and 10.08 (95% CI: 6.85-14.84), respectively. The AUC estimated by summary receiver operating characteristics was 0.83. There was no heterogeneity amongst the 10 studies from both threshold and non-threshold effects. As such, the first study implementing a care bundle for AKI using urinary [TIMP-2•IGFBP-7] as an enrollment criterion was in cardiac surgery (discussed above).[41]

Since its release into the market, [TIMP-2•IGFBP-7] has been shown to perform well in sepsis (AUC 0.85)[55], in surgery patients (AUC 0.84),[56] and in patients with underlying chronic conditions including CHF (AUC 0.89) and CKD (AUC 0.91).[57] The test has been shown to increase rapidly (within 4 hours) after various exposures, and has very distinctive response kinetics after exposure to various nephrotoxins - well before creatinine elevations.[58]

Importantly, both clinical[59] and laboratory[60] studies have shown that [TIMP-2•IGFBP-7] increases with sub-lethal stimuli such that (particularly at low levels) the test is marker of kidney "stress" rather than damage per se (see **Figure 5**).[61] Indeed, clinical experience with the test indicates that early treatment (e.g. discontinuation of a nephrotoxin) can result in rapid reversal of the stress response and avoidance of AKI, as has been seen by others.[62,63] Whereas, very high levels or persistently positive results are indicative of irreversible AKI.

Figure 5. Relation between kidney stress, damage and dysfunction.



Depicted is the relationship between acute kidney stress, damage and dysfunction. The right panel shows a reversible injury. Stress begins soon after an insult and rises quickly. Stress may abate as the insult is removed even as damage continues be incurred. Once a sufficient number of cells are damaged, function will begin to fall. However, such damage might be reversible (right panel) and as damage reverses, function can improve. Note, that function may also improve in the absence of reversal of damage by hyper-filtration in remaining nephrons.
The left panel shows an irreversible injury. Stress increases as in the right panel and falls as the insult is removed. However, the damage is not reversed and function does not recover. This irreversible damage results from cell death and dead cells are not replaced by normally functioning cell.

6 Other markers

Numerous other molecules have been studied as potential second-generation biomarkers for AKI including netrin-1, clusterin, calbindin, osteopontin,[64] fibroblast growth factor 23 and alpha Klotho.[65]

Furthermore, a third generation of biomarkers is emerging that can detect persistence of AKI.[66] As these markers become available for clinical use we will have a much better idea how they can be used.

Figure 6. Biomarkers for Acute Kidney Injury.[64]

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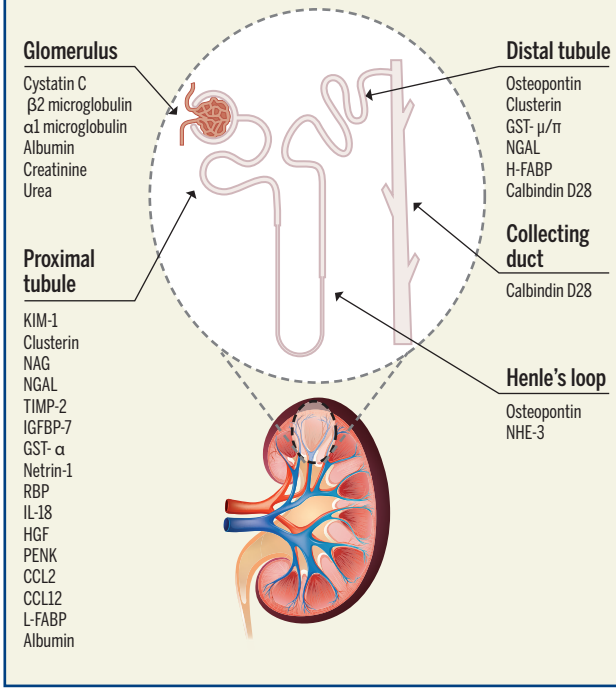


Shown is a nephron along which putative «biomarkers» are approximately located. It is hoped that these products arrive in the urine before clinical evidence of decreased glomerular filtration rate (increase in serum creatinine) is apparent. All are dependent upon urine production. Thus, oliguria is a strong confounder.

CCL: C-C motif chemokine ligand; GST: glutathione-S-transferase; HGF: hepatocyte growth factor; IGFBP: insulin-like growth factor binding protein; L-FABP: liver-type fatty acid binding protein; NAG: N-acetyl-beta-D-glucosaminidase; NGAL: neutrophil gelatinase associated lipocalin; PENK: proenkephalin; RBP: retinol binding protein; TIMP-2: tissue inhibitor of metalloproteinases-2.

7 Clinical application

The challenge for new biomarkers is that effective treatments will need to be paired with the test in order to show benefit. For AKI, two single-center studies have shown benefit associated with use of [TIMP-2•IGFBP-7] in patients after surgery.[62,63]

In the first study,[62] biomarker-positive patients were randomized to receive a care bundle which included a hemodynamic management algorithm based on mean arterial pressure and stroke volume variation. AKI was significantly reduced with the intervention compared to controls (55.1 vs. 71.7%; ARR 16.6% (95% CI 5.5–27.9%); p=0.004).

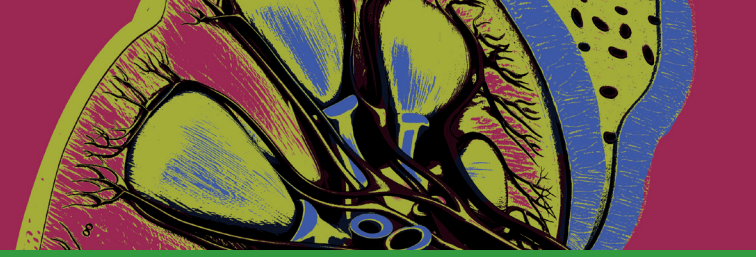
In the second study,[63] a similar care bundle including early optimization of fluids and maintenance of perfusion pressure, was applied to non-cardiac major surgery patients after testing positive for the biomarker. Overall, AKI rates were not statistically different between groups (19/60 (31.7%) in the intervention group vs. 29/61 (47.5%) in the standard care group, p=0.076). However, rates of moderate and severe AKI, a secondary endpoint, were reduced with the intervention (4/60 (6.7%) vs. 12/61 (19.7%), p=0.04), as were lengths of ICU stay (median difference 1 day, p=0.035, and hospital stay median difference 5 days, p=0.04).

Recently, a multicenter, multinational, RCT tested a KDIGO bundle consisting of optimization of volume status and hemodynamics, functional hemodynamic monitoring, avoidance of nephrotoxic drugs, and prevention of hyperglycemia in 278 high-risk patients identified by the urinary [TIMP-2•IGFBP-7] after cardiac surgery. Although overall AKI rates were not statistically different between groups, the occurrence of moderate and severe AKI was significantly lower in the intervention group as compared to the control group (14.0% vs 23.9%; ARR 10.0% [95% CI, 0.9-19.1]; p=0.034).[67]

Conclusions

Although the field of AKI has lagged behind other areas in the development of biomarkers, there are now multiple tests available in various parts of the world.

Both tests for [TIMP-2•IGFBP-7] and KIM-1 undergone regulatory review by the US FDA, the former for clinical use as an *in vitro* diagnostic and the latter in drug development. The recent studies showing clinical application are still few in number but will likely be starting points for larger trials. In addition, new questions concerning the evaluation of AKI etiology, prediction of outcomes including recovery and need for RRT are being asked and new biomarkers are being evaluated. The future will likely bring us many more tests.



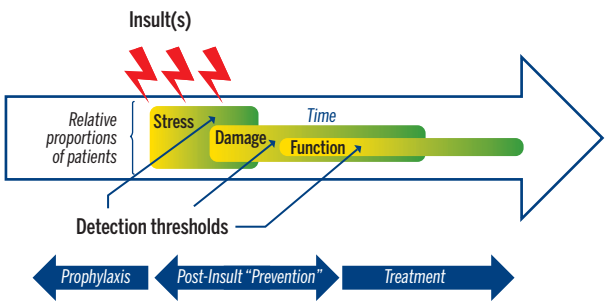
PREVENTION OF AKI

> *An ounce of prevention is worth a pound of cure.*
>
> *Benjamin Franklin*

1 Terminology and AKI time course

Obviously, it is better to prevent an episode of AKI than to try and treat it but all interventions, at least those that are effective, come with a price. Interventions have unintended effects and most also cost resources—whether monetary, non-monetary or both. Thus, all prevention strategies first consider who is at risk and when they are at risk. **Figure 7** illustrates the time course for AKI.

Figure 7. Time course for Acute Kidney Injury events.



Most acute kidney injury is due to multiple insults (either repeated similar insults such a nephrotoxic drug, or variable insults). Therefore, injury is rarely from a discrete event. Kidney stress increases prior to damage and damage prior to change in function when the change in function is being caused by damage. Note, function may decline early in the time course as some insults produce changes in function before damage (e.g. ischemia). Note also that detection thresholds for various measures of stress, damage and function do not begin immediately and require some accumulation of signal —see chapter 3 for details. The relative proportions of patients exhibiting stress, damage and dysfunction are illustrated by the vertical dimensions of each box.

This figure also illustrates the terminology used for AKI interventions. The term *Prevention*, or *Prophylaxis*, is often used for both pre-insult interventions, as well as for interventions provided after the insult but before the clinical manifestation of AKI using KDIGO criteria. The term *Treatment*, by contrast, is reserved for interventions provided after the diagnosis of AKI is made (again using KDIGO criteria). This terminology will likely evolve as diagnostics for AKI are further refined.

2 Clinical risk stratification

The concept of risk includes both susceptibilities and exposures. Susceptibility refers to what the patient brings to the risk equation. Typical susceptibility variables include age and comorbid medical conditions; whereas exposures include various clinical scenarios where AKI may occur, sepsis, major surgery, drugs etc.[1] **Table 8** lists several susceptibilities and exposures for AKI.

Table 8. Common susceptibilities and exposures for Acute Kidney Injury.[1]

Source: KDIGO. *Kidney Inter*., Suppl. 2012; 2: 1–138.

Exposures	Susceptibilities
Sepsis	Dehydration or volume depletion
Critical illness	Advanced age
Circulatory shock	Female gender
Burns	Black race
Trauma	CKD
Cardiac surgery (especially with CPB)	Chronic diseases (heart, lung, liver)
Major noncardiac surgery	Diabetes mellitus
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anemia
Poisonous plants and animals	

CKD: chronic kidney disease; CPB: cardiopulmonary bypass.

Risk stratification can be performed either before an insult (prophylaxis phase) or after the insult (post-insult prevention phase). If before the insult, only susceptibilities may be considered, whereas after the insult, exposures can be included as well. Clinical risk stratification works best when applied to very specific populations and therefore when the variables are also very specific. For example, the type of cardiac surgery (i.e. valve replacement vs. coronary artery grafting) is an important exposure criterion but it only applies to cardiac surgery.

3 Role of biomarkers

Even when specific to a given population and when including exposure variables, clinical risk prediction can be quite limited. While certain exceptions exist where results appear to validate across patient cohorts,[68] most risk prediction models have limited generalizability across institutions. Another concern is that in the context of a clinical study, ascertainment of a given variable may be much better than it is in the "real world".

Biomarkers can address many of the limitations of clinical risk prediction. However, as discussed in chapter 3, the only markers that can be used in the prophylaxis phase are markers that help clarify underlying chronic disease — especially CKD (e.g. baseline serum creatinine, urinary albumin). Emerging markers like urinary dickkopf-3 (DKK3) may have a role in identifying risk in this phase primarily because they can detect CKD before it meets the definition.[69]

Another approach is to stress the system with a protein load and see if the response is appropriate. Investigators have shown that failure to increase GFR in response to a protein load by at least 15 mL/1.73 m^2 resulted in an 11.8 times greater likelihood to experience AKI (95% CI 4.62 to 29.89 times, $p<0.001$) with subsequent cardiac surgery.[3]

Once the insult has occurred however, markers of kidney stress (e.g. TIMP-2, IGFBP-7) and damage (e.g. KIM-1, NGAL) can be used to identify patients before they manifest AKI by KDIGO criteria. However, as **Figure 7** illustrates, not all patients that develop kidney stress will develop damage and not all those with damage will manifest a decline in function that is needed to meet the (currently accepted) criteria for AKI diagnosis. Importantly, markers of kidney damage are inherently less useful compared to markers of kidney stress because damage may rapidly become irreversible. Nevertheless, early identification of damage is still much better than only identifying it when it begins to impair function.

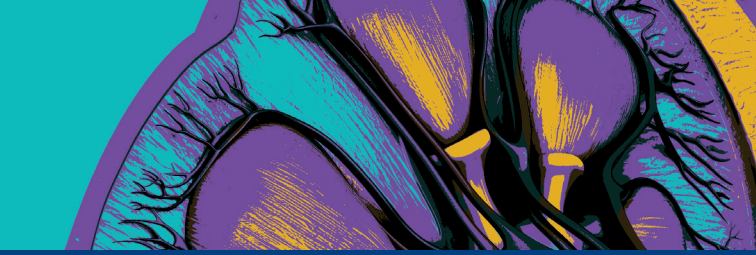
4 Prevention bundles

Given the complexities in risk stratification discussed above, prevention strategies for AKI can be challenging to develop and deploy. Some basic interventions like providing adequate hydration and avoiding certain medications can be applied in the prophylactic phase (**Table 9** lists some options for such interventions).

Table 9. Selected interventions for Acute Kidney Injury prevention.

Action	Prophy-laxis	Post-Insult	Comments
Ensure proper hydration	x	x	Hydration refers to water—volume status refers to total circulating blood volume. Although these two parameters are associated with each other they can be discordant.
Avoid unnecessary nephrotoxins and drugs that reduce kidney function	x	x	Common examples include non-steroidal anti-inflammatory drugs, various antibiotics such as vancomycin and piperacillin, angiotensin converting enzyme inhibitors.
Obtain/assess baseline kidney function	x	x	
Use functional hemodynamic monitoring to guide fluid management		x	This can be initiated in certain settings just prior to the insult (e.g. surgical procedures).
Subspecialist involvement		x	Can be tailored to the patient population but may involve nephrology, intensive care, cardiology, hematology and hepatology.

Two single-center[62,63] and one multicenter study[67] have shown benefit associated with the use of a KDIGO-based bundle in patients testing positive for [TIMP-2•IGFBP-7] after surgery.



EVALUATION AND MANAGEMENT

Evaluation and management of AKI go together because often it is the response to treatment that helps determine the nature of the disorder. For example, a patient with oliguria and fluid overload who improves with interventions that improve cardiac function (e.g. an inotrope) has a high probability of cardio-renal syndrome. Similarly, a patient whose renal function improves with discontinuation of a nephrotoxic drug is very likely to have a drug-induced AKI. Although some specific tests are available to help determine the cause of AKI, the response to treatment is a helpful clue.

1 Clinical approach to a patient with abnormal kidney function

Patients with reduced kidney function may be identified on routine laboratory testing or in the setting of an acute illness. Reduced kidney function in the context of acute illness, especially if it is an illness known to be associated with AKI (e.g. sepsis, trauma, heart failure) makes AKI more likely. However, various types of kidney disease and disorders may occur and often, they can be challenging to differentiate. **Table 10** lists the various conditions in which reduced kidney function may present.

The most important piece of information to obtain in the evaluation of patients with reduced kidney function is the level of kidney function they have had previously. A search for prior serum creatinine testing should be exhaustive. Establishing a patient's baseline kidney function will go a long way to determining what type of kidney dysfunction they have and will help guide the differential diagnosis (see **Table 10**). Baseline kidney function will also help establish the severity of AKI/AKD if present. For example, a patient with a GFR 50 has taken a much larger insult if their baseline GFR was 100 compared to 60. Determining the baseline is therefore critical in the evaluation of kidney disease.

Table 10. Classification of kidney diseases and disorders.

Type of Kidney Disease/ Disorder	Criteria	Meets criteria for AKI?	Examples
CKD	GFR <60 mL/kg/1.73m^2 for 90 days or more.	No	Diabetic nephropathy, hypertensive kidney disease.
CKD with AKD (AKI)	GFR <60 mL/kg/1.73m^2 for 90 days or more with superimposed AKI.	Yes	Cardiac surgery associated AKI in a patient with CKD.
CKD with AKD (no AKI)	GFR <60 mL/kg/1.73m^2 for 90 days or more with a decrease in GFR of 35% or greater within 90 days but does not meet AKI criteria.	No	Drug associated AKD in a patient with underlying CKD—drugs may accumulate as kidney function declines.
AKI	Increase in serum creatinine 50% or more within 1 week OR increase by 0.3 mg/dL or more within 48h OR urine output <0.5 mL/kg/hr for 6 hours or longer.	Yes	Sepsis is the leading cause, followed by drugs, cardiorenal syndrome and surgery associated AKI.
AKD (no AKI)	GFR <60 mL/kg/1.73m^2 for <90 days or increase in serum creatinine 50% or more over greater than 1 week but <90 days.	No	Drugs, glomerular disease.

Chronicity can also be supported by kidney size (small kidneys are characteristic of CKD) and by elevated parathyroid hormone. Bone loss may also be evident on X-ray. Conversely, acuity is supported by oliguria, active urine sediment (granular casts, red and white blood cells) and presence of stress or damage biomarkers (see **Table 2**).[2]

2 Evidence of kidney damage

Evidence of kidney damage should always be sought in patients with decreased kidney function (see **Figure 4**). However, kidney damage may also occur in the absence of change in kidney function and should therefore be considered if the clinical context is appropriate—generally when an exposure has occurred in the acute setting (e.g. sepsis, chemotherapy) or when underlying disease makes kidney damage likely in the chronic setting (diabetes, hypertension).

Typical markers of kidney damage in the chronic setting include albuminuria and hematuria. Markers of damage in the acute setting include granular casts and various urinary biomarkers (see Chapter 3). The presence or absence of kidney damage can also help elucidate the causes of changes in kidney function.

3 Identifying the cause of AKI

Once AKI is suspected or diagnosed, the next step is to determine the cause or causes. The most common conditions leading to AKI are listed in **Table 5**. While this broad differential should always be kept in mind, the diagnostic approach is not to address each one as being equally likely in every case. A "general workup" is usually appropriate to quickly narrow the differential diagnosis.

This workup should focus on six broad areas:
i. Fluid status; ii. Hemodynamics; iii. Infections; iv. Medications and other toxins; v. Urinalysis; vi. Imaging.[70]

Assessing fluid status

Perhaps one of the most over-diagnosed and misunderstood conditions responsible for kidney impairment is dehydration. Clinicians often assume that any increase in serum creatinine is due to volume depletion and treat all cases with fluids first. While volume depletion will result in retained solute, its rarely the sole cause of AKI in hospitalized patients. Typically, patients in the ICU are in positive fluid balance, not negative, and profound and sustained dehydration in a hospitalized patient is tantamount to mismanagement.

However, patients will often present to medical attention with dehydration and this state contributes to a decrease in kidney function in many patients. Furthermore, impaired kidney function due to dehydration may signal life-threatening hypovolemia or it may simply mean that the patient requires oral rehydration. Assessment of this condition therefore requires a graded approach.[38] **Figure 8** illustrates some of the clinical features that should be considered in the assessment of fluid status.

Figure 8. Assessing risk for fluid imbalance.[38]

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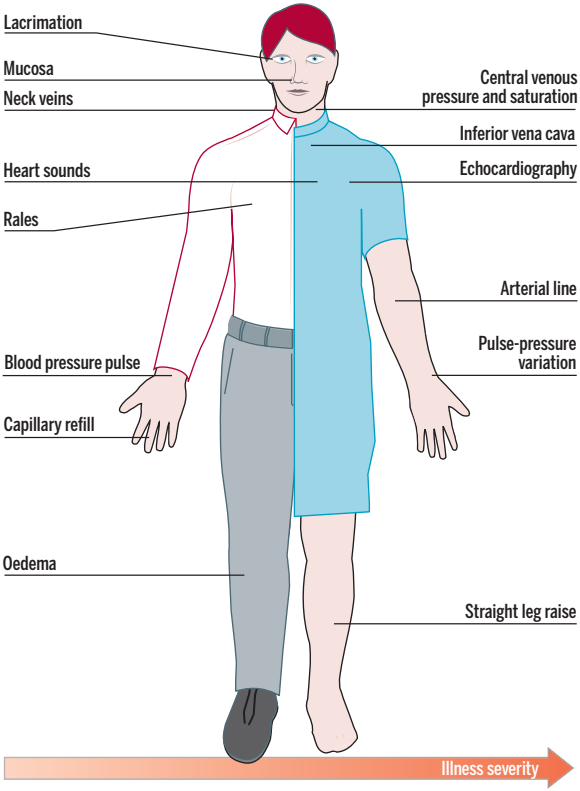

In a non-critically ill patient (left) fluid status is assessed by history and physical examination. In the proper context (e.g. diarrheal illness) with consistent signs and symptoms (e.g. dry mucous membranes, increased thirst), physical examination findings will often suffice. In more complex patients (e.g. underlying congestive heart failure) or in those with critical illness (e.g. septic shock), more invasive methods will often be required (illustrated by the right side of the figure). Little evidence exists that one form of functional hemodynamic monitoring is superior to another but dynamic measures (e.g. pulse-pressure variation) are superior to static measures (central venous pressure).

It is important to recognize that the relationship between fluid balance and AKI complications is a "U-shaped" curve (**Figure 9**). When fluid balance is too negative, hypotension and organ hypoperfusion perpetuating the damage to the kidney may occur. A complementary problem can occur when fluid balance is too positive—venous congestion might impair kidney function and cause severe clinical complications.

Figure 9. Relationship between hemodynamic status and Acute Kidney Injury.[38]

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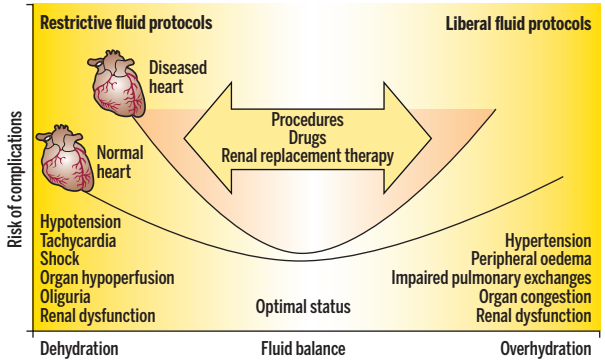

The relationship between hemodynamics and AKI complications is a U-shaped curve. In the case of fluid restrictive protocols, the patient might experience hypotension and organ hypoperfusion perpetuating the damage to the kidney. The same problem can occur in case of too liberal policies where the congestive state might impair kidney function and cause severe clinical complications.

Hemodynamic monitoring

In addition to fluid status, "hemodynamics" includes cardiac performance and vascular tone. In patients where these variables are likely to be impacted (e.g. sepsis, cardiac surgery, heart failure), it is important to monitor them. Functional hemodynamics aims at increasing cardiac output, and variability of stroke volume or pulse pressure is measured in response to various challenges. These variables have become common place in modern ICUs. Typical challenges include positive pressure ventilation, straight leg raise or fluid bolus infusion. These maneuvers alter central vascular blood volume, if only transiently, and can be used to gauge cardiac output response. For example, a pulse pressure variation >13% is usually predictive of an increase in cardiac output with fluids.

Management of impaired cardiac function is critical to the management of AKI in such patients and treatment of vasomotor paralysis (e.g. septic shock, post-cardiac surgery etc.) with vasopressors is similarly critical. Norepinephrine is usually first-line therapy but vasopressin, epinephrine and angiotensin II are used as second-line therapy with variation in practice around the world and no clear advantage for AKI across the various drugs.

Infections

Sepsis is the most common cause of AKI in critically ill patients and is common even outside the ICU - one third of community-acquired pneumonia patients develop AKI.[71] Similar rates have been reported with COVID-19.[72] Furthermore, many large multicenter studies over more than 15 years have shown that sepsis is a cause of AKI in 40-50% of patients.[9,10,73] Thus, sepsis should always be considered in patients presenting with or developing AKI. This is particularly important when AKI occurs in a setting where it is common but with a presentation which is uncommon. For example, patients undergoing cardiac surgery typically develop AKI within 72 hours of surgery; those developing AKI later in their course are more likely to have a different etiology such as infection.

Finally, the presence of AKI in the setting of infection is a common way to define sepsis (infection plus organ failure). Unfortunately, this relationship is often missed.[74] This may be due to lack of appreciation for the impact of AKI on mortality in patients with sepsis. Even in patients with septic shock, patients developing AKI were four times as likely to die within 60 days compared to patients without AKI in a large multicenter clinical trial.[75]

Medications and other toxins

Medications are perhaps the most important factors in the development of AKI and/or its consequences for patients. This is because many drugs can injure the kidney in many different ways and also most drugs are excreted by the kidney so that AKI can result in accumulation of drugs leading to adverse events. Of course, some drugs are on both lists. **Table 11** lists several of the most common nephrotoxic drugs and **Table 12** lists drugs that are cleared by the kidney and are common causes of adverse drug events due to changes in kidney function.

Table 11. Common potentially nephrotoxic drugs.[76]

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Acyclovir	Enalaprilat	Mesalamine
Ambisome[a]	Foscarnet	Methotrexate
Amikacin	Gadopentetate dimeglumine[a]	Nafcillin
Amphotericin B	Gadoxetate disodium[a]	Piperacillin/tazobactam
Captopril	Ganciclovir	Piperacillin
Carboplatin	Gentamicin	Sirolimus
Cefotaxime	Ibuprofen	Sulfasalazine
Ceftazidime	Ifosfamide	Tacrolimus
Cefuroxime	Iodixanol[a]	Ticarcillin/clavulanic acid
Cidofovir[a]	Iohexol[a]	Tobramycin
Cisplatin	Iopamidol[a]	Topiramate
Colistimethate	Ioversol[a]	Valacyclovir
Cyclosporine	Ketorolac	Valganciclovir
Dapsone	Lisinopril	Vancomycin
Enalapril	Lithium	Zonisamide

[a] Medications counted for 7 days after administration toward exposure.

Table 12. Drugs with a high risk for adverse events when kidney function is impaired.

ACE Inhibitors and ARBs	**Anti-tuberculosis drugs**
Allopurinol	**Antivirals** • Nucleoside analogues (e.g. acyclovir) • Most HIV and hepatitis drugs
Antibiotics • Aminoglycosides • Aztreonam • Carbapenems • Cephalosporins* • Colistin • Daptomycin • Penicillins • Quinolones • Sulfamethoxazole-Trimethoprim • Tetracycline • Vancomycin	**Calcineurin inhibitors** **Chemotherapy agents** **Colchicine** **Hydralazine** **Lithium** **Methotrexate** **Methylprednisolone** **Meperidine** **Metformin**
Antifungals • Amphotericin-B • Azoles • Flucytosine	**NSAIDs** **Proton pump inhibitors** **Statins**

*Renally cleared cephalosporins include Cefazolin, Cefepime, Cefotaxime, Cefotetan, Cefoxitin, Ceftazidime, and Cefuroxime.

ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers; NSAIDs: nonsteroidal anti-inflammatory drugs.

Urinalysis

Urine can provide multiple clues on the cause of kidney disease. Urine chemistries, cells, casts and crystals can all help point to the type and chronicity of kidney disease. Urinalysis can also help identify infection. **Table 13** describes the interpretation of findings on urinalysis. Granular casts (**Figure 10**) are suggestive of tubular injury, while red cell casts are highly specific for glomerular disease. Granular casts (also called muddy brown casts) have limited sensitivity for tubular injury and can easily be missed, especially in dilute urine. Their identification requires experience and so interobserver variation exists.[36]

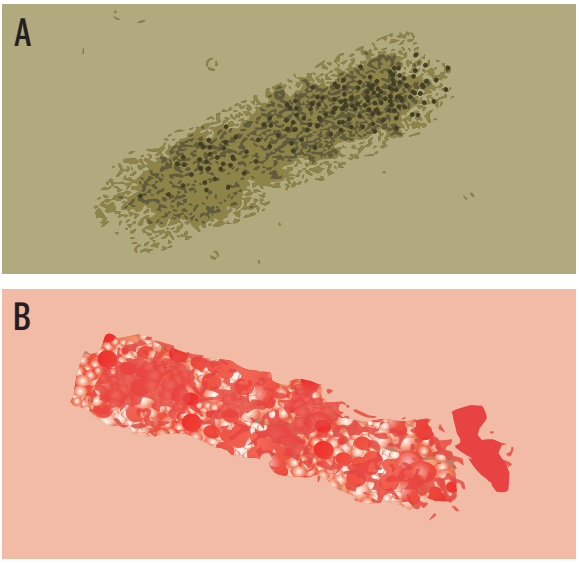
Table 13. Interpretation of findings on urinalysis.

Results	Interpretation
Albumin without hematuria	May be normal if urine is concentrated. Large amounts of albumin indicate glomerular disease (e.g. diabetic nephropathy, FSGS, membranous glomerulopathy, amyloidosis).
Albumin with hematuria	Concerning for glomerulonephritis.
Dysmorphic red cells/red cell casts	VERY concerning for glomerulonephritis.
Granular casts	Tubular injury; free tubular epithelial cells may also be seen.
White cells	In isolation can be seen with infection or tubulointerstitial disease. Together with granular casts, increases likelihood of tubulointerstitial nephritis.
Crystals	Calcium phosphate, uric acid, cystine, may be indicative of renal calculi. Calcium oxalate in the setting of AKI should raise concern for ethylene glycol toxicity. Heavy uric acid crystals and AKI can be seen in tumor lysis syndrome.
Normal	Normal; can also be seen obstruction, hypertensive nephrosclerosis, hepatorenal and cardiorenal disease.

FSGS: Focal segmental glomerulosclerosis

Figure 10. Casts seen in spun urine.

Reproduction of granular and red cell casts seen in spun urine.



A. Granular casts (also known as muddy brown casts) are strongly suggestive of acute tubular injury.
B. Red blood cell casts are seen with glomerulonephritis.

Urine sodium has been used for centuries to test renal tubular function. When plasma volume is reduced, the kidney becomes sodium avid and urine sodium falls. To account for differences in urine concentration, the fractional excretion of sodium (FENa) has been used. In the setting of oliguria, a FENa of less than 1% indicates that tubular function is intact whereas a value of greater than 1% generally suggests a loss of tubular function and AKI. However, use of diuretics, agents interfering with renin-angiotensin-adosterone system or osmotic agents such as mannitol interfere with sodium excretion and FENa.

$$\text{FENa} = \frac{\text{urinary sodium X plasma creatinine}}{\text{urinary creatinine X plasma sodium}} \text{ X 100}$$

In patients who have received diuretics, fractional excretion of urea (FEUrea) may be useful. A low FEUrea (≤35%) is a more sensitive and specific index than FENa in identifying intact tubular function especially if diuretics have been administered.[77]

$$\text{FEUrea} = \frac{\text{urinary urea nitrogen X plasma creatinine}}{\text{urinary creatinine X blood urea nitrogen}} \text{ X 100}$$

Urinary indices have not been validated in critically ill patients and have shown disparate results in patients with septic AKI. Systemic inflammation secondary to sepsis has been shown to cause conformational changes in the Na/H, chloride and urea channels, thereby independently affecting their excretion. Recent studies have consistently demonstrated the limited diagnostic and prognostic utility of urine biochemistry in AKI[78] and the routine use of these indices in patients with oliguria is not recommended.

Imaging and histology

Kidney ultrasonography is widely used for evaluation of kidney disease. Kidney size (small kidneys are seen in CKD, although it may take years for this to develop) and echogenicity can provide clues to the chronicity of disease. Obstruction will result in hydronephrosis - though caution is needed here as obstruction can be missed early on. Renal vascular disease can also be identified, although angiography may be required to confirm. CT scans can also be useful in evaluating kidney disease and can help identify other conditions, such as retroperitoneal fibrosis. Kidney histology obtained by biopsy is often used in AKI when the diagnosis is uncertain or when glomerular disease is suspected.

4 Non-specific management of AKI

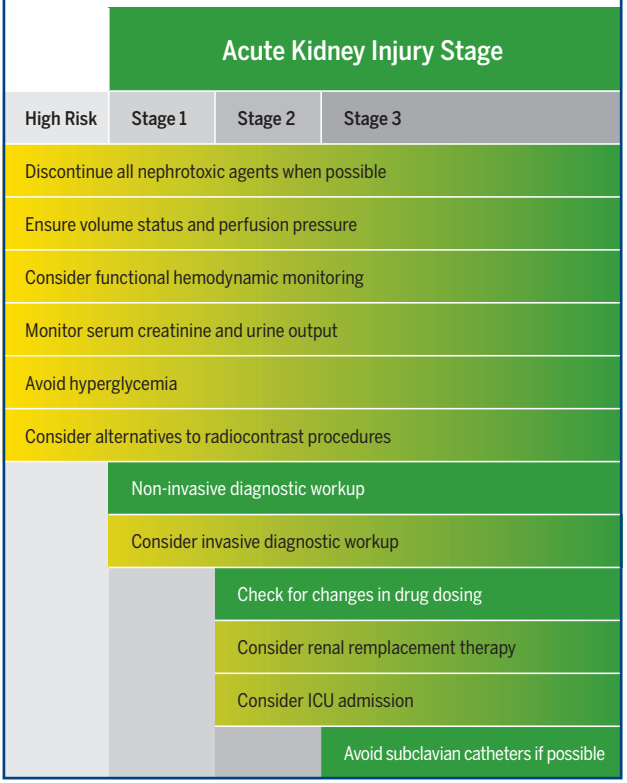
Most cases of AKI have multi-factorial causes and even for cases due to a single inciting event, it is important to avoid further injury. Thus, management of AKI is predicated on three principles:

- *i.* avoid further insults;
- *ii.* monitor for recovery/progression;
- *iii.* identify and manage/prevent complications.

The 2012 KDIGO guideline on AKI is an excellent resource for the application of these principles (see **Figure 11**).

Figure 11. Stage-based management of AKI.[1]

Source: KDIGO. Acute Kidney Injury Work Group. *Kidney Inter Suppl* 2012, 2(1):1–138.



Shading of boxes indicates priority of action; solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases.
AKI: acute kidney injury; ICU: intensive care unit.

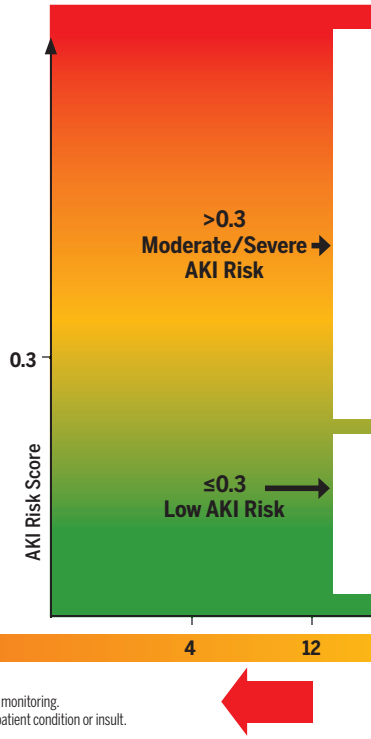
Avoidance of further insults usually takes the form of careful attention to medications and avoiding radiocontrast when possible. It is also important to avoid both fluid overload and underfilling as discussed above. Common complications from AKI are listed in **Table 6** and include fluid overload, adverse drug events, acid-base and electrolytes abnormalities, increased bleeding, infection risks and encephalopathy. Detailed recommendations for management of these complications are beyond the scope of this monograph but the reader is referred to other reviews

Figure 12. Biomarker-guided management of patients at risk for AKI.[70]

Reproduced from Guzzi, *et al.*, Critical Care. 2019;23 p.225 under Creative Commons License BY-NC.

Potential AKI Risk Patients

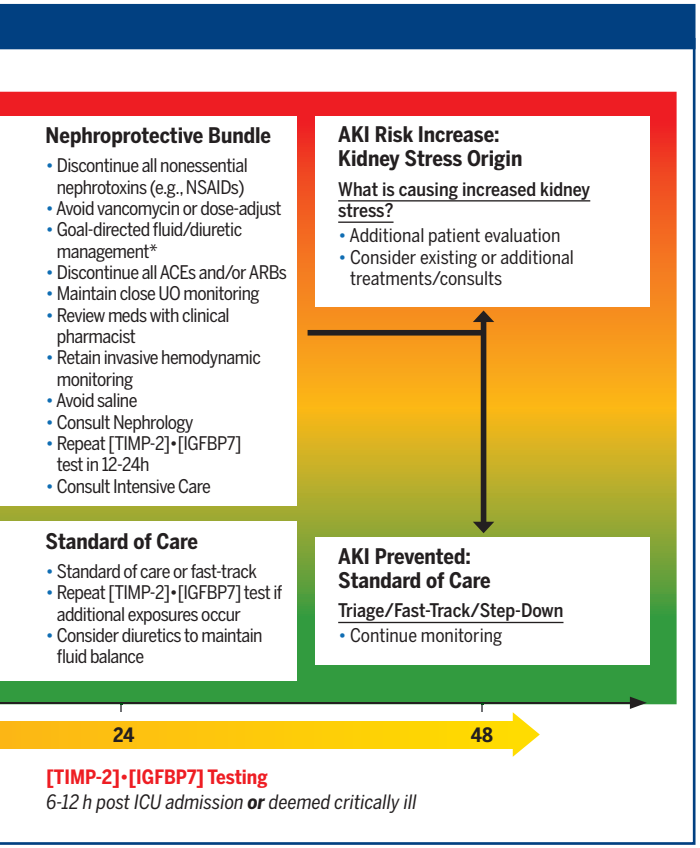
- Cardiovascular/respiratory compromise <24 h (≥21 y)
- Shock
- Sepsis (suspicion/confirmation)
- Post-operative major/cardiac surgery
- Trauma with cardiac/respiratory compromise
- Other



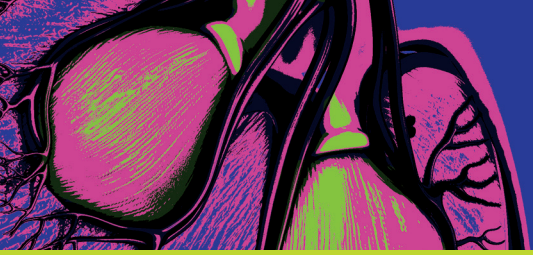
* Includes bedside ultrasound and functional hemodynamic monitoring.
†Consider additional testing with any significant change in patient condition or insult.

on the topic (see Kellum JA, Cerda J. Renal and Metabolic Disorders; Oxford University Press, 2012 ISBN-13: 978-0199751600).

As depicted in **Figure 11**, management of AKI begins with "high-risk". Determining which patients are at high risk can be challenging and it is the main rationale for the development of AKI biomarkers. **Figure 12** provides an approach to AKI management based on biomarkers.



Protocol early management of AKI based on [TIMP-2•IGFBP-7] testing.
ACEs: angiotensin-converting enzymes;
AKI: acute kidney injury;
ARBs: angiotensin-receptor blockers;
ICU: intensive care unit;
NSAIDs: nonsteroidal anti-inflammatory drugs;
UO: urinary output.



RENAL REPLACEMENT THERAPY

Extracorporeal kidney support, otherwise known as renal replacement therapy (RRT), in the form of dialysis or hemofiltration (or both) is provided to a minority of patients with AKI. In the worldwide AKI-EPI study, 23.5% of patients with AKI underwent RRT.[10] A somewhat lower rate of 15% was seen in the Southeast Asia AKI study.[11] However, both of these studies focused on patients with AKI being cared for in the ICU. In a recent multicenter study in the US, about 5% of patients hospitalized with AKI (not limited to the ICU) received RRT.[79]

1 Indications

Traditionally, indications for RRT for AKI have been grouped into 'emergent' and 'non-emergent' indications. Emergent indications include severe cases of hyperkalemia, fluid overload, acidosis or manifestations of uremia (e.g. pericarditis). Both severity of these conditions and their refractoriness to medical management have been included in the classification of an emergent indication.

For example, a patient presenting with a serum potassium of 9 mmol/L and cardiac irritability requires emergent dialysis whereas for a patient with a level of 7 mmol/L and no EKG changes, medical management might be attempted first. Determining the degree of severity and refractoriness is always a matter of clinical judgment and continues to be an area of significant heterogeneity. In recent trials testing alternative strategies for initiation of RRT in AKI, a series of clinical criteria were used as exclusion criteria and thus were thought to represent the standard of care as to when to initiate (see **Table 14**).[80,81]

Conversely, anything judged to not be emergent is classified as a non-emergent indication. Most commonly, non-emergent indications include fluid overload that is less severe than what is judged to be emergent and metabolic/solute imbalances.

Table 14. Emergent Criteria for RRT in the setting of Stage 3 AKI.

Parameter	STARRT-AKI[81]	AKIKI[80]
BUN	NA	>112 mg/dL (>40 mmol/L)
K	≥6 mmol/L	>6 mmol/L (>5.5 mmol/L despite treatment)
Acidosis	pH ≤7.20 (or serum bicarbonate ≤12 mmol/L)	pH <7.15 in the setting of metabolic acidosis
Pulmonary edema	Ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen of ≤200	Requiring >5L/min or 50% O_2 to maintain O_2 saturation >95%
Persistent AKI	Stage 2-3 AKI ≥72 hours	Stage 3 AKI with oliguria >72 hours

Criteria used for emergent RRT in recent larger clinical trials.[80,81]

In the chronic setting, dialysis is usually started to manage retention of solutes (e.g. urea, beta-2 microglobulin) that lead to variety of pathologic disturbances (e.g. platelet dysfunction, arthralgia, loss of appetite) and metabolic acidosis which leads to bone demineralization.

In the acute setting, concerns are more focused on the effects of kidney failure on fluid balance, platelet and neutrophil dysfunction and the contribution of uremia to encephalopathy. Judging the relative impact of these disturbances on outcomes and balancing the risks inherent in providing acute RRT with the risks attributable to these disturbances can be difficult.

Furthermore, the effect of these abnormalities is variable between individuals and over time. If one conceptualizes the potential for adverse effects from kidney dysfunction as a 'demand' for kidney function and the residual kidney function as 'capacity' then it is possible to consider a demand-capacity relationship that changes over time and is unique to the patient.[82]

Thus, a demand-capacity imbalance may exist because demand is high and capacity is only marginally reduced or demand is only marginally increased but capacity is significantly compromised (**Figure 13**). Alternatively, both high demand and low capacity may co-exist. The nature of the demand-capacity imbalance for a given patient and the expectation as to how this relationship will change over time guides decision-making about the timing of RRT (see **Figure 14**).

In general, when a given patient's demand-capacity imbalance is not expected to resolve before they begin to be adversely affected by it, they should be started on RRT without delay.

Figure 13. Demand and capacity - a conceptual model.

Source: Acute Dialysis Quality Initiative 17. www.adqi.org. Used with permission.

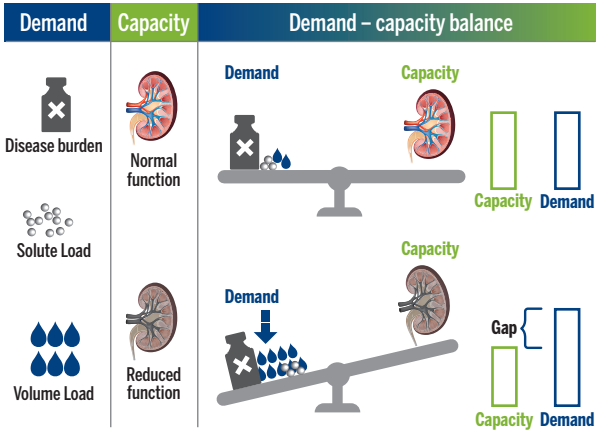
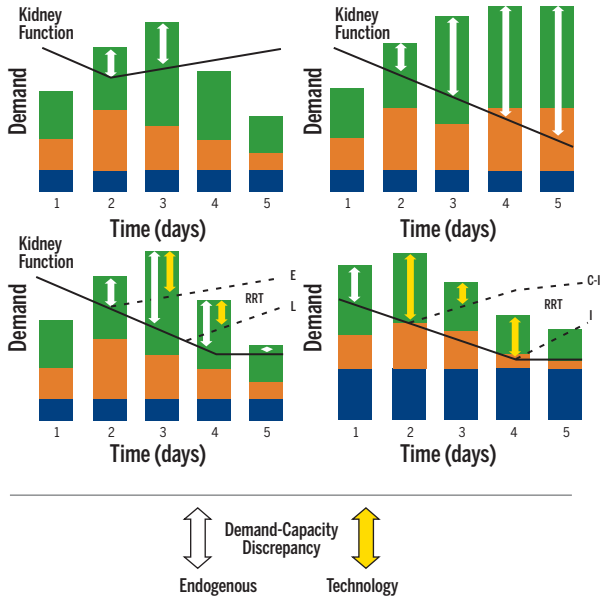


Figure 14. Four patient scenarios.

Source: Acute Dialysis Quality Initiative 17. www.adqi.org. Used with permission.



The bars represent total demand including chronic disease (blue), acute illness (orange) and solute/fluid excess (green).

Figure 14 continued

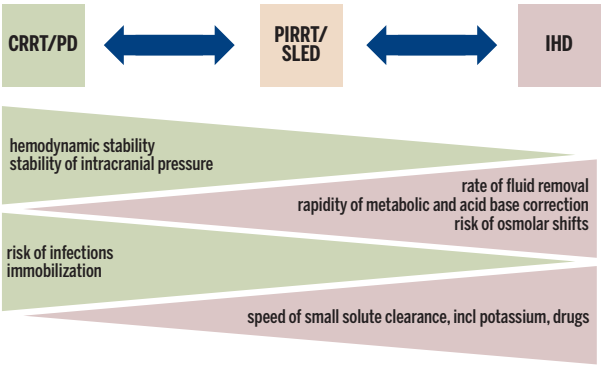
The top two panels represent no RRT—the left illustrates early reversal of AKI and the right shows progressive renal failure and increasing discrepancy between renal function capacity and physiological demands.
The two bottom panels illustrate the effect of RRT (dashed lines) with (left) early (E) or later (L) initiation and two different demand-capacity discrepancy patterns. On the right the patient scenario illustrated is different with high underlying disease burden and either initiation of continuous RRT on day 2 transitioning to intermittent RRT on day 4 (dashed line marked as C-I) or initiation of intermittent therapy on day 4 (I).

2 Modalities

The various types of RRT available can be classified according to whether they are applied, or intended for application, 24 hours a day—known as continuous therapies; or whether their application is for short treatments, often lasting 3-4 hours—known as intermittent therapy (**Figure 15**). In recent years, a variety of hybrid therapies (with a variety of terms to describe them) have emerged. These therapies are provided for longer durations and often more frequently than traditional intermittent RRT but are not continuous therapies. **Figure 15** depicts characteristics and advantages/disadvantages of each of the RRT modalities.

Figure 15. Characteristics and risks of different RRT modalities.

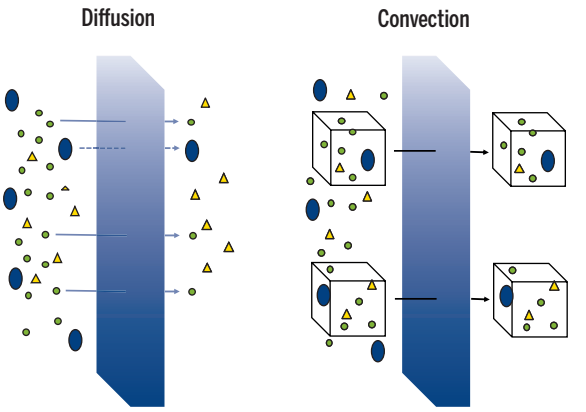
Source: Acute Dialysis Quality Initiative 17. www.adqi.org. Used with permission.



CRRT: continuous renal replacement therapy; IHD: intermittent hemodialysis; PIRRT: prolonged intermittent renal replacement therapy; SLED: slow efficiency dialysis; PD: peritoneal dialysis.

The second aspect of modality to understand concerns the solute transport principles that are used to achieve clearance. There are two distinct forms, diffusion and convection (**Figure 16**).

Figure 16. Solute transport principles used in renal replacement therapy.



With diffusion, solute transport is determined by concentration gradients between plasma and dialysate and is limited by solute size with larger molecules diffusing less well compared to smaller molecules. With convection, there is bulk flow of water with solute driven by a pressure gradient. Molecular size has far less impact on clearance when convection is used.

Diffusion is the movement of molecules from an area of high concentration (e.g. plasma) to an area of low concentration (e.g. dialysate). When dialysate is run countercurrent to the blood flow, a maximum concentration gradient will exist along the dialyzer. Larger molecules, up to the pore size cutoff of the membrane, will still diffuse down their concentration gradient but this will occur more slowly as the molecule size increases. Thus, diffusion favors smaller molecules.

Convection, by contrast, involves bulk flow of plasma water across the membrane driven by a pressure gradient. Solutes are dragged across the membrane with the water as long as they are smaller than the pore size cutoff. Convection does not depend on molecule size and there is no concentration gradient per se because there is no dialysate.

Clearance is achieved by replacing the removed plasma water and solute with sterile fluid that has a lower (or zero) concentration of the solute of interest.

Thus, a "dose" of RRT can be measured by the amount of ultrafiltrate produced and replaced using convection. The dose using diffusion is similarly estimated by the volume of dialysate as long as the dialysate is fully saturated (i.e. equilibrium between the concentration of the solute in the plasma and spent dialysate is reached). In practice, this is achieved by regulating the dialysis flow rate relative to the blood flow.

Continuous RRT (CRRT) may be either diffusive (continuous hemodialysis) or use convection (continuous hemofiltration) or both (continuous hemodiafiltration). Although hemofiltration can be delivered intermittently, for practical reasons, intermittent therapies are mainly diffusive.

3 Management considerations

A detailed discussion of application of RRT is beyond the scope of this document. For a handbook reference on CRRT the reader is referred to:

→ Continuous Renal Replacement Therapy (2nd ed.)
Edited by John A. Kellum, Rinaldo Bellomo, and Claudio Ronco
Oxford University Press. Feb 2016; ISBN-13: 9780190225537

While a more comprehensive treatment of the subject can be found in:

→ Critical Care Nephrology (3rd ed.)
Edited by Claudio Ronco, Rinaldo Bellomo, John A. Kellum, and Zaccaria Ricci
Elsevier, 2019; ISBN-13: 978-0323449427

However, two specific management considerations will be discussed here - net ultrafiltration rate and modality transition.

→ Net ultrafiltration rate

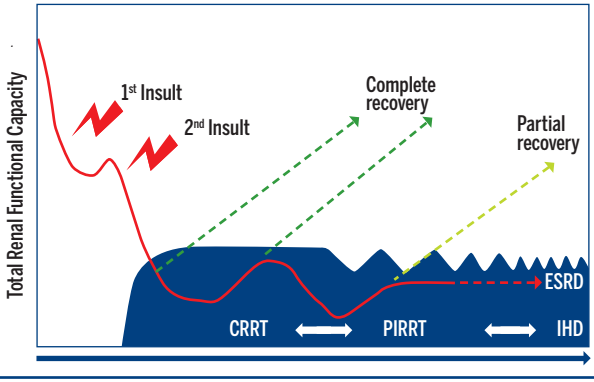
Net ultrafiltration (NUF) rate is defined as the total effluent rate minus the sum of replacement fluid and spent dialysate. When NUF rate exceeds 1.75 mL/kg/hr, there is an association with increased mortality.[83,84] The mechanisms responsible for this relationship are unclear but likely include an effect on organ perfusion which can be jeopardized by rapid removal of fluids from the intravascular space.[85] These findings support the practice of ordering NUF in relation to body weight (rather than just mL/hr) and limiting NUF rate to <1.75 mL/kg/hr except when required to reverse life-threatening fluid overload.

→ Modality transition

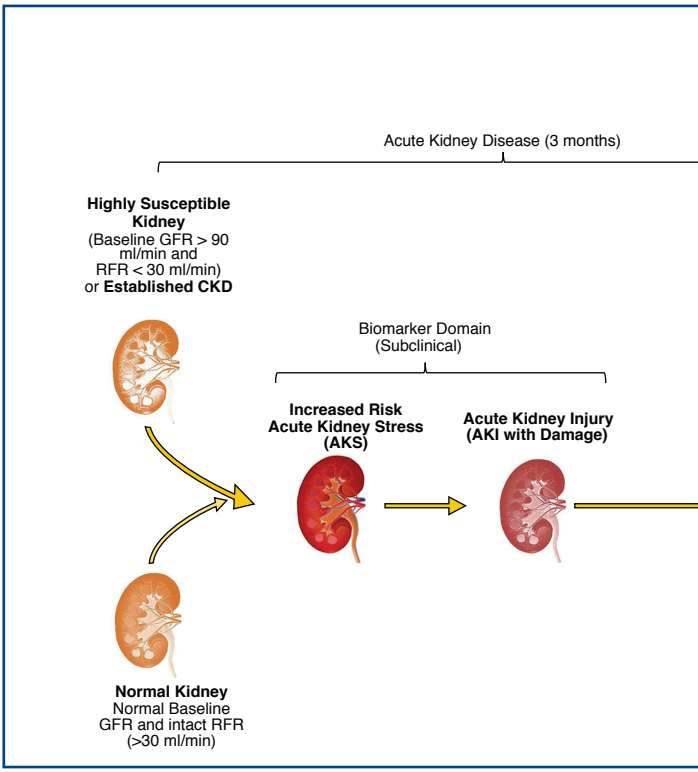
Over time, many patients will recover kidney function after AKI and will be able to be liberated from RRT. Other patients may require transition to more chronic modes of therapy. **Figure 17** illustrates the modality of transition across different patient experiences.

Figure 17. Potential pathways following an episode of AKI, including transition.

Source: Acute Dialysis Quality Initiative 17. www.adqi.org. Used with permission.



ESRD: end stage renal disease; CRRT: continuous renal replacement therapy; PIRRT: prolonged intermittent renal replacement therapy; IHD: intermittent hemodialysis.



FOLLOW-UP FOR PATIENTS WITH ACUTE KIDNEY INJURY

As discussed in Chapter 1, AKI is by definition, an abrupt event resulting in a loss of kidney function. However, injury to the kidney may result in various patterns of functional change over time. **Figure 18** illustrates the various patient trajectories following an injurious event (e.g. nephrotoxic medication, sepsis, surgery).[33,86] Importantly, some events never result in measurable changes in kidney function - they remain subclinical. Other cases produce clinical evidence of AKI and then either resolve or persist. Unfortunately, some cases of AKI only appear to resolve while underlying injury leads to subsequent progression to chronic kidney disease.

Figure 18. Clinical trajectories following AKI.[86]

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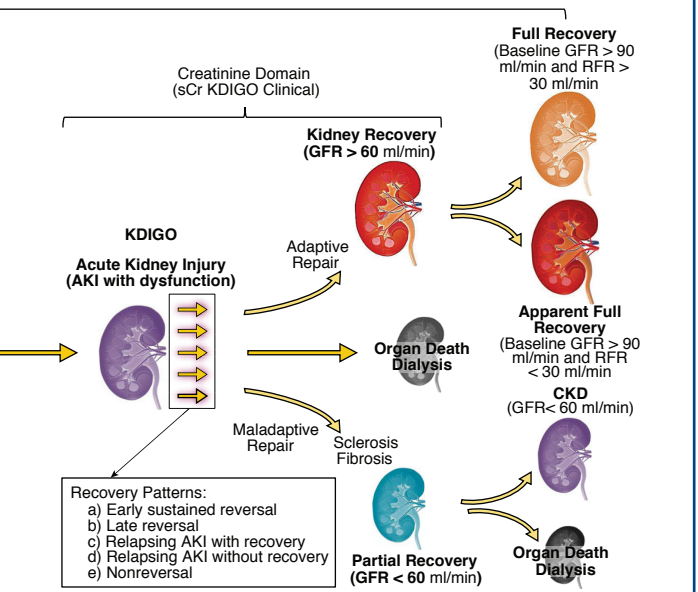


1 Post-AKI Phenotypes

For patients sustaining AKI, a variety of recovery phenotypes have been identified with profound implications for health.[33] For most patients, their clinical state at hospital discharge dictates long-term outcomes. **Table 15** list the various recovery phenotypes, their definitions and effect on survival for critically ill patients.

Table 15. Recovery after Acute Kidney Injury.[33]

Adapted from Kellum, *et al. Am J Respir Crit Care Med*. 2017;195:784-791.

Phenotype	Definition	Frequency	Survival at 1 year
Early sustained reversal	Reversal of AKI within 1-week and sustained through hospital discharge	26.6%	90%
Late recovery	No reversal within 1 week but recovery prior to discharge	9.7%	75%
Relapse-recovery	Early reversal but relapse of AKI with recovery prior to discharge	22.5%	69%
Relapse-no recovery	Early reversal but relapse of AKI *without* recovery prior to discharge	14.7%	42%
No reversal	AKI is persistent throughout hospital stay	26.5%	40%

Frequency and hazard ratios are based on data from a study of just under 17,000 critically ill patients with stage 2-3 AKI.[33] Reversal was defined as the absence of AKI criteria for at least 24-hours. Recovery was ascertained at hospital discharge and required survival and absence of renal replacement therapy in addition to no evidence of AKI.

2 Post-discharge monitoring and management

Since post-discharge complications are more common among patients who do not recover renal function by hospital discharge, this group represents the highest priority for follow-up. In general, such patients should be seen within 1-2 weeks of discharge.

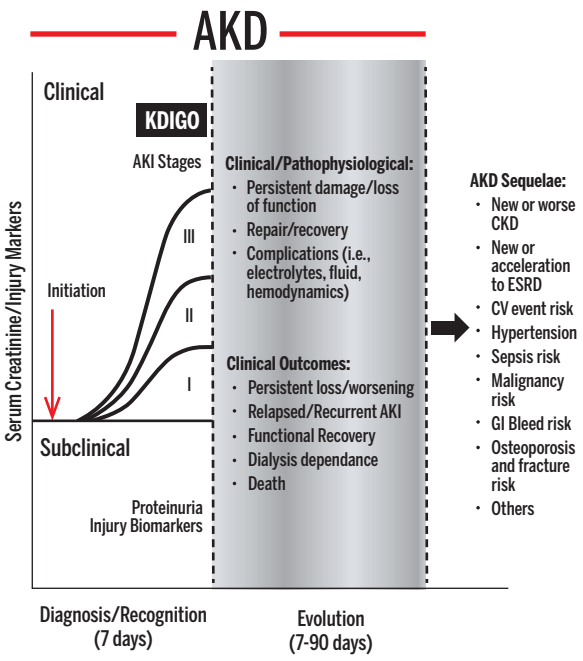
Patients with late recovery or those having relapse of AKI with subsequent recovery are the next highest risk category and should receive follow-up soon after discharge - by day 30 at the latest. The lowest risk group are patients with early sustained reversal. These patients might not require specific post-discharge follow-up but should have their renal function checked along with other outpatient monitoring.

Patients who sustained an episode of AKI are at risk for subsequent CKD. As such, monitoring kidney function as well as management of CKD risk-factors (hypertension, diabetes, etc.) is critical.

Furthermore, patients with unstable kidney function at hospital discharge are at particularly high risk for adverse drug events. This can occur both because kidney function worsens and drug accumulation causes toxicity, but also because kidney function may improve and result in treatment failures if drug dosing is not adjusted. As such, careful attention to drug selection and dosing on follow-up visits is vital. **Figure 19** provides a framework for management of patients post-AKI based on the AKD stage they are in after the first week.

Figure 19. Evolution of AKI into AKD.

Source: Acute Disease Quality Initiative 16. www.adqi.org. Used with permission.

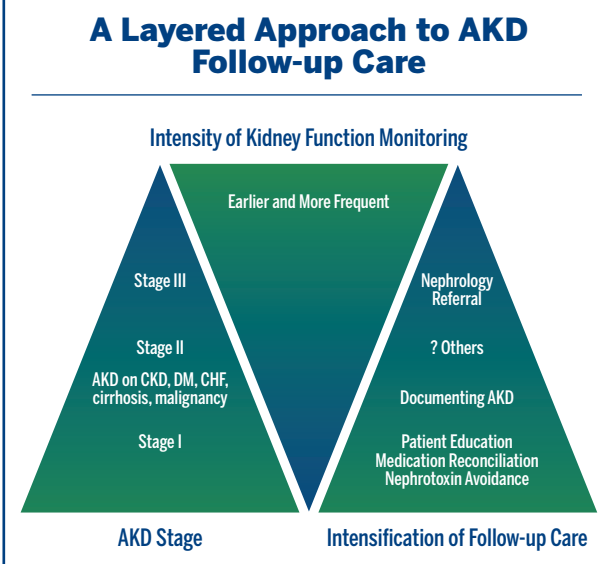


Patients with AKI can recover and can evolve into AKD. Subjects who recover from AKI and/or AKD may still be at risk for long-term sequelae.

Although many patients who are hospitalized with AKI or developing AKI in hospital will have a protracted length of stay, others may be discharged early, often before renal function has stabilized. Close follow-up for these patients is critical for the reasons discussed above. Classifying patients according to their AKD stage and then using the stage to guide the intensity of follow-up has been proposed by the ADQI 16 workgroup (**Figure 20**).[87]

Figure 20. Layered Approach to AKD Follow-Up.

Source: Acute Disease Quality Initiative 16. www.adqi.org. Used with permission.

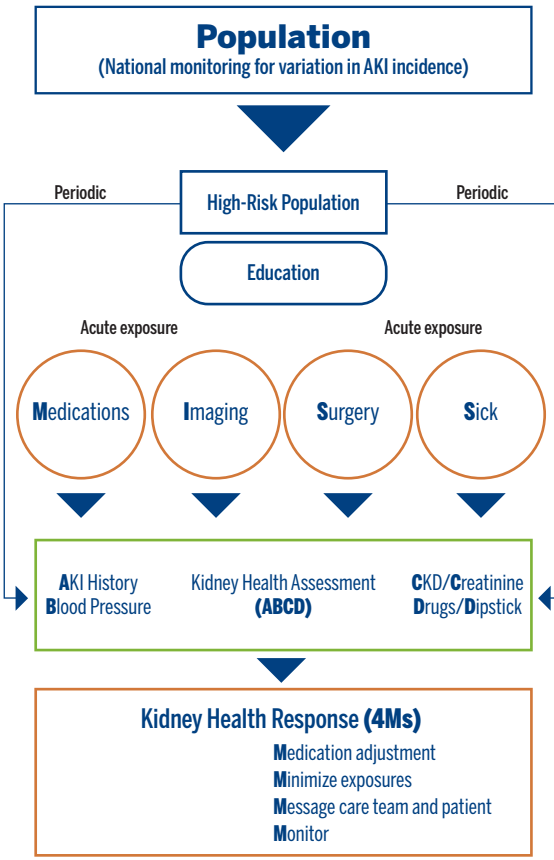


Based on the stage of AKD, different levels of follow-up may be appropriate for patients with AKD.

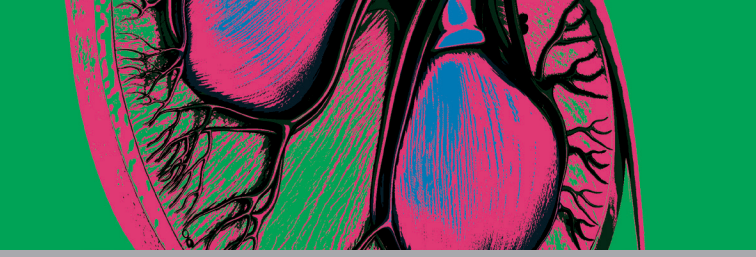
Finally, anyone developing AKI is at subsequent risk for another episode of AKI, in addition to development of CKD. Frequent kidney health assessments and appropriate responses may help mitigate these risks.[88-90] **Figure 21** illustrates this approach. This approach has also been adapted for pediatrics[91] and neonates.[92]

Figure 21. Kidney Health Assessment and Response.

Source: Acute Disease Quality Initiative 22. www.adqi.org. Used with permission.



Kidney Health Assessment includes AKI history, Blood pressure, CKD, serum Creatinine level, Drug list, and urine dipstick. Exposures (MISS) include Nephrotoxic Medications, Imaging, Surgery, Sickness. Kidney Health Response (4Ms) that encompasses Medication review to withhold unnecessary medications (e.g. non-steroidal anti-inflammatory drugs), the Minimization of nephrotoxic exposures (e.g. intravenous contrast), Messaging the healthcare team and patient to alert the high-risk of AKI, and Monitoring for AKI and its consequences.



LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme
AIN	Allergic interstitial nephritis
AKD	Acute kidney disease
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ARBs	Angiotensin receptor blockers
CCL	C-C motif chemokine ligand
CKD	Chronic kidney disease
CPB	Cardiopulmonary bypass
CRRT	Continuous renal replacement therapy
DAMPS	Damage-associated molecular patterns
DKK3	Dickkopf-3
eGFR	Estimated GFR
ESRD	End stage renal disease
FENa	Fractional excretion of sodium
FEUrea	Fractional excretion of urea
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GST	Glutathione S-transferase
HGF	Hepatocyte growth factor
HUS	Hemolytic uremic syndrome
ICU	Intensive care unit
IGFBP-7	Insulin-like growth factor-binding protein7
IHD	Intermittent haemodialysis
kDa	Kilodalton

KDIGO	Kidney disease: improving global outcomes
KIM-1	Kidney injury molecule-1
L-FABP	Liver type fatty acid binding protein
MMP	Matrix metalloproteinase
NAG	N-acetyl-beta-D-glucosaminidase
NGAL	Neutrophil gelatinase associated lipocalin
NKD	No known kidney diseases or disorders
NSAIDs	Nonsteroidal anti-inflammatory drugs
NUF	Net ultrafiltration
PAMPs	Pathogen-associated molecular patterns
PRRs	Pattern recognition receptors
RFR	Renal functional reserve
RRT	Renal replacement therapy
S-AKI	Sepsis associated AKI
SCr	Serum creatinine
TIMP-2	Tissue inhibitor of metalloproteinase-2
TLRs	Toll-like receptors
TTP	Thrombotic thrombocytopenic purpura
PD	Peritoneal dialysis
PENK	Proenkephalin
PIRRT	Prolonged intermittent renal replacement therapy
RBP	Retinol binding protein
ROS	Reactive oxygen species
SLED	Slow low efficiency dialysis
UO	Urine output

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