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Review: approach to the patient with presumed AKI

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INTRODUCTION

The first paper in this series on AKI described the definition and epidemiology of AKI focusing on sub-Saharan countries and Rwanda [1]. The present paper describes the diagnostic and differential diagnostic approach to classify AKI as prerenal, intrinsic renal, or postrenal AKI.

Pre-renal and post-renal AKI are the consequence of extra-renal diseases leading to a decline in glomerular filtration rate (GFR) while "intrinsic" AKI represents structural intrarenal damage, If the pre- and/or post-renal conditions persist, they will ultimately evolve to renal structural damage and hence intrinsic renal disease. The early diagnosis of AKI and the differentiation between prerenal, postrenal, and post renal AKI are very important because each cause not only requires a different therapeutic approach but is also associated with a different prognosis. This chapter describes the most important clinical, laboratory, and radiological techniques available in most academic renal units in Rwanda that could solve most causes of AKI.

HISTORY

Patients who develop AKI usually have an identifiable initiating event that can be found from review of vital signs, laboratory data, urine output records, and medications. Review of past medical records, including outpatient laboratory results, if available, can determine if there is any prior history of impaired renal function. Particular attention should be paid how well comorbid conditions like diabetes, hypertension, CHF, HIV and other tropical and non-tropical infections have been managed in the outpatient setting.

All these diseases are at higher risk for AKI even if they are correctly managed. Concurrent sepsis and gastrointestinal losses, such as diarrhea, nausea, vomiting, or changes in appetite suggested by weight loss, can help to establish important risk factors for pre-renal AKI. Review of hospital and outpatient records should also focus on medications, herbal or other potentially nephrotoxic remedies, vitamins, and analgesics. The review of records should also look for any recent diagnostic imaging where iodinated contrast medium was used.

Iodinated contrast administration in emergency circumstances, particularly to patients at risk (elderly > 70 years of age, hypovolemic patients, and patients with pre-existing chronic kidney disease) remains an important cause of AKI. However, incidence of contrast induced CI-AKI in patients without these risk factors and undergoing elective, non-emergent contrast administration is very low, < 1%) [2].

Previous documented allergies, especially of antibiotics, may help in diagnosing cases of acute allergic interstitial nephritis (AIN). Prerenal azotemia should be suspected in the setting of vomiting, diarrhea, glycosuria causing polyuria, and medications including diuretics, NSAIDs, ACE inhibitors, and ARBs. Physical signs of orthostatic hypotension, tachycardia, reduced jugular venous pressure, decreased skin turgor, and dry mucous membranes are often present in prerenal azotemia.

In any patient presenting with AKI, urinary tract obstruction (UTO) must be excluded as prompt intervention can result in improvement or complete recovery of renal function. UTO is more common among children than adults presenting with urinary tract symptoms or renal failure because of the contribution of congenital abnormalities. In the adult, UTO is more common among older men with prostatic disease and patients with a single kidney or intra-abdominal, particularly pelvic cancer [3]. Prostatic enlargement is also associated with enhanced risk for ureteral obstruction in presence of inflammatory aortic aneurysms [4]. Pain is frequently absent, even in acute obstruction (UTO), and, when present, usually results from bladder distension, secondary infection, or obstructing stones or masses.

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Hydronephrosis alone is almost always asymptomatic, and pain should prompt a consideration of additional diagnoses such as stones, papillary necrosis, or infection.
Relatively severe pain (renal or ureteral colic) may be seen with acute complete obstruction (as with a ureteral calculus). Renal colic with typical irradiation to the back or groin, with or without macroscopic hematuria can be present in stones as well as in papillary necrosis. However, with external ureteral compression leading to UTO, pain is usually absent because of the slowly progressive course of obstruction. Pyelonephritis presents mostly with flank pain but associated with symptoms of lower urinary tract infection as urgency, dysuria and general symptoms like nausea and fever [5].

In patients with sickle cell disease, the aggregation of sickle shaped red blood cells can cause the micro-circulation to become obstructed, which results in ischemic necrosis. These vaso-occlusive crises are very painful. The renal medulla and papillae are particularly susceptible to this ischemic necrosis which can present as severe colic pain, often with macroscopic hematuria and, in presence of bilateral involvement or an obstructed solitary kidney, may lead to post renal AKI.

Most causes of obstructive uropathy are amenable to therapy and the prognosis is generally good, depending on the underlying disease.

PHYSICAL EXAMINATION

Physical examination should focus on vital signs, including fever, changes in blood pressure, and urine output measurements during hospitalization. Clinicians should carefully monitor a patient's hemodynamic status upon admission and during hospitalization, especially with regard to blood pressure medication dose adjustments to avoid hypotension.

This is most problematic in acutely ill patients who are admitted with hypovolemia and are medicated with angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), diuretics, or nonsteroidal anti-inflammatory drugs (NSAIDs) which can further reduce renal perfusion pressures resulting in subsequently greater risk of developing AKI.

Many patients with AKI may have a low systemic blood pressure and low systemic perfusion, sometimes caused by volume depletion. However, at the moment of assessment, the blood pressure may not be dramatically low. In the absence of frank hypotension, the clinician may speculate that an unobserved drop in blood pressure must have caused the fall in GFR. This type of AKI has been called 'normotensive', because the patient's blood pressure is, at least temporarily, within the normal range [6]

INTERPRETATION OF THE SERUM CREATININE (SCR)

In the hospital setting, serum creatinine is an important and convenient laboratory marker for identifying AKI and chronic kidney diseases [7]. Serum creatinine alone is not the most accurate way of evaluating a patient's true renal function, because factors such as age, sex, dietary intake, and muscle mass influence the baseline level of serum creatinine production. Therefore, for the same degree of renal failure, serum creatinine measurements will tend to be lower in specific patient populations like the elderly, malnourished patients with terminal conditions, and those with cirrhosis. Critically ill patients will also tend to have decreased creatinine production because of prolonged immobilization, malnutrition, decreased muscle mass, or hemodilution from intravenous (IV) fluid administration. In critically ill patients and sepsis, the production of creatinine is decreased due to the accompanying inflammation and the rapid loss of muscle mass which may persit a long time after hospital discharge [8].

DIFFERENTIATING PRERENAL, RENAL AND POSTRENAL AKI

For many years the diagnosis and management of AKI was based on a concept where the etiologies were divided into three categories: pre-renal, intrinsic renal and post-renal AKI.

The term "pre-renal" suggests that GFR is decreased as a consequence of renal hypo-perfusion in relation to events "outside" the kidney. The renal hypo-perfusion is either due to "true" hypovolemia (a fall in the absolute circulating volume) like in diarrhea or vomiting, or a decreased "effective" circulating volume seen in heart failure, cirrhosis, nephrotic syndrome or in vasoplegia during sepsis or septic shock. In prerenal AKI, the decline in GFR is not based on primary structural damage of the kidney parenchyma, but is an appropriate vasoconstrictive response of the renal circulation to external insults. These insults are also reversible meaning that when the "external" causes are reversed, kidney function would also be reversible [9]. It is presumed that in prerenal AKI there is very little to no structural damage to the kidney. "Rapid" reversibility of kidney function (within 24-72 hours) after acute insult has been called transient AKI. Although rapid reversibility might imply structural integrity, there is little evidence that it can confirm or deny structural damage in pre-renal AKI. Presence or absence of damage cannot be excluded unless a biopsy is performed, and a biopsy cannot be justified in such situations. Furthermore, several cohort studies have identified that "transient AKI" was associated with adverse outcomes (need for dialysis and death) even when AKI is resolved within 24 hours [10-13]. For patients whose renal function returns to baseline within 48 hours, the Acute Disease Quality Initiative (ADQI) 16 conference recently proposed to use the term "rapid reversal" of AKI, while "persistent AKI" is characterized by a duration beyond 48 hours [14]

It should be reminded that the discrimination between prerenal and renal AKI is not sufficient to guide fluid therapy. In cases like dehydration, rapid hydration is indicated, whereas in conditions with the same "prerenal" presentation, like hepatorenal, nephrotic or cardiorenal syndrome, hydration could have deleterious consequences (like pulmonary edema). In cardiorenal syndrome, it is the improvement of cardiac output, not the fluid administration, that will improve renal function [15, 16]. Fluid responsiveness is thus not synonymous with "pre-renal" AKI.

A recent study that involved patients with septic AKI provides evidence on the concepts of intrinsic and pre-renal AKI [17]. In this study, 77% of septic patients with AKI were found to have focal features of ATN on light microscopy, but only a small number of the renal tubules showed histopathological findings with most of the microscopic fields appearing normal. These findings have led to the hypothesis that transient and persistent AKI in critically ill patients might share similar pathophysiological

mechanisms and that the duration of AKI might reflect its severity rather than its mechanism [18].

As discussed above, postrenal AKI should always be considered in the differential diagnosis of AKI because treatment is usually successful if instituted early. Simple bladder catheterization can rule out urethral obstruction. Imaging of the urinary tract with renal ultrasound or CT should be undertaken to investigate obstruction in individuals with AKI unless an alternate diagnosis is apparent (see below).

ROUTINE URINARY EXAMINATION

Oligo-anuria

Anuria is seen with cessation of glomerular filtration (e.g., rapidly progressive glomerulonephritis, acute cortical necrosis, or total renal arterial or venous occlusion) or complete urinary tract obstruction. Brief (<24–48 hours) episodes of oligo-anuria occur in some cases of ATN, such as in severe septic shock [7]. A reduction in urine output (oliguria, defined as <400 mL/24 h) usually denotes more severe AKI (lower GFR) than when urine output is preserved.

A normal urine output does not rule out UTO. Urine output in UTO may be quite variable, ranging from anuria with complete bilateral ureteral or complete urethral obstruction to oliguria, normal volume, or even polyuria. Polyuria, even in the presence of reduced glomerular filtration rate (GFR), may result from tubular injury with impairment of the ability of tubules to retain salt and concentrate the urine. In addition, urethral obstruction may lead to bladder distention and overflow incontinence, which may result in frequency, urgency, nocturia, and a sensation of polyuria. In this setting, an enlarged bladder can often be detected by careful percussion of the pelvis and lower abdomen. In severe cases, there may be abdominal distension and pain.

Oliguria requires a diagnostic work-up that should minimally include an evaluation of kidney function (short-term creatinine clearance), volume status, cardiac output, perfusion pressure, and identification of other potentially reversible causes (e.g., post-renal causes or nephrotoxic drugs). However, many short episodes of oliguria are not followed by SCr-defined AKI and more stringent urine output [7]. Criteria to predict the subsequent development of SCr- defined AKI have been suggested [19].

In most critically ill patients, who are often admitted in an Intensive Care Unit (ICU), the development of oliguria is a bad prognostic sign. Oliguria is indeed part of many illness severity and prognostic scores. Oliguria without AKI-Cr has a higher mortality than the absence of any AKI. Additionally, Prowle et al [20] found that only oliguria lasting for more than 12 hours provides significant prediction of the development of Stage 2 AKI. However, creatinine-defined Stage 2 AKI frequently occurred without this duration of oliguria, while shorter duration of oliguria was common and often did not lead to the development of biochemical AKI. Moreover, the prediction of AKI by urinary output varied by the patient cohort with a better performance in medical patients than in surgical patients. However, the addition of oliguria to the creatinine criteria increases prognostic accuracy, possibly because the patients either die or receive RRT before the creatinine criteria are reached. Both severity and duration of oliguria are associated with mortality and need for RRT. The worst outcomes are seen when both UO and SCr criteria are met [19].

AKI with preserved urine output can be seen in nephrogenic diabetes insipidus with characteristics of longstanding urinary tract obstruction, tubulointerstitial disease, or nephrotoxicity from cisplatin or aminoglycosides, among other causes. Red or brown urine may be seen with or without gross hematuria. If the color persists in the supernatant after centrifugation, then pigment nephropathy from rhabdomyolysis or hemolysis should be suspected.

Proteinuria

In the absence of preexisting proteinuria from CKD, AKI from ischemia or nephrotoxins leads to mild proteinuria (<1 g/d). Greater proteinuria in AKI suggests damage to the glomerular ultrafiltration barrier or excretion of myeloma light chains; the latter are not detected with conventional urine dipsticks (which detect albumin) and require immunoelectrophoresis. Atheroemboli can cause a variable degree of proteinuria. Extremely heavy proteinuria ("nephrotic range," >3.5 g/d) can occasionally be seen in glomerulonephritis, vasculitis, or interstitial nephritis (particularly from NSAIDs). AKI can also complicate cases of minimal change disease, a cause of the nephrotic syndrome.

Urinanalysis and Urine Sediment

Evaluation of the urine sediment is an underutilized tool and may prove very useful in discriminating prerenal AKI from many etiologies of "intrinsic" renal AKI. In addition, it is inexpensive and available in most clinical laboratories in low income countries. Although these examinations are invaluable tools, they require clinical correlation because they are of generally limited sensitivity and specificity. However, careful urine sediment examination performed by skilled nephrologists can point to the cause of AKI.

Prerenal AKI may present with either hyaline casts or an unremarkable urine sediment. Postrenal AKI may also lead to a normal sediment, but hematuria and pyuria may be seen depending on the cause of the obstruction. AKI from ATN due to ischemic injury, sepsis, or certain nephrotoxins has characteristic urine sediment findings like pigmented (muddy brown), granular casts and tubular epithelial cell casts. However, these findings may be absent in more than 20% of cases [7].

Perazella et al [21] examined the utility of urine microscopy and a urine sediment score based on the number of renal tubular epithelial cells (RTECs) and granular casts in patients with hospital-acquired AKI caused by prerenal AKI or ATN. This urinary scoring system was able to differentiate acute tubular necrosis (ATN) from prerenal AKI. The higher the number of RTECs and granular casts were found in the urinary sediment the higher was the likelihood for diagnosis of ATN, while the lower the number of RTECs and casts was the likelihood higher for prerenal AKI. Thus, critical performance of urine microscopy appears to be useful to differentiate the most common causes of hospital-acquired AKI.

Glomerulonephritis may lead to dysmorphic red blood cells or red blood cell casts. Interstitial nephritis may lead to white blood cell

casts. The urine sediment findings overlap somewhat in glomerulonephritis and interstitial nephritis, and a diagnosis is not always possible on the basis of the urine sediment alone. Urine eosinophils have a limited role in differential diagnosis; they can be seen in interstitial nephritis, pyelonephritis, cystitis, atheroembolic disease, or glomerulonephritis. Crystalluria may be diagnostically important. The finding of oxalate crystals in AKI should prompt an evaluation for ethylene glycol toxicity. Abundant uric acid crystals may be seen in the tumor lysis syndrome.

The urinary sediment may thus indicate the presence of a primary renal disease or urinary tract infection, but results should always be interpreted alongside the clinical picture [18]. Table 1 summarizes the most relevant urinary parameters that are helpful in the differential diagnosis between pre-renal AKI and established acute tubular necrosis.

Table 1: Urinary parameters

	Prerenal AKI	Acute tubular necrosis
Urinalysis	Hyaline casts	Renal tubular cells, (RTC), granular 'brown" casts
Specific gravity	1020	1010
Osmolality (mosm/kg)	>500	~300
Sodium (mmol/L)	<20	>40
Fractional excretion sodium (%)	<1	>3
Fractional excretion urea (%)	<35	>35
Fractional excretion uric acid (%)	<7	>15

*RTC: Renal Tubular Cells

RENAL FAILURE INDICES

Several indices have been used to help differentiate prerenal azotemia from intrinsic AKI when the tubules are malfunctioning [22]. The low tubular flow rate and increased renal medullary recycling of urea seen in prerenal azotemia may cause a disproportionate elevation of the blood urea compared to creatinine. Other causes of disproportionate blood urea elevation need to be kept in mind, however, including upper gastrointestinal bleeding, hyper-alimentation, increased tissue catabolism, and glucocorticoid use.

In 'prerenal' AKI, tubular function is presumably intact and augmented activity of the sympathetic nervous system, the renin–angiotensin–aldosterone system, and vasopressin secretion as reaction to the presence of absolute or relative hypovolemia due to a decrease in effective circulating blood volume provoke renal vasoconstriction which is associated with a concentrated urine with high urinary osmolality, and enhanced tubular sodium reabsorption with low urinary sodium concentration [7]

The FeNa (Fraction of excreted sodium) is calculated as the ratio of urine to plasma sodium concentration divided by urine to plasma creatinine concentrations times 100.

$$FE_{Na} = 100 \times \frac{\text{sodium}_{\text{urinary}} \times \text{creatinine}_{\text{plasma}}}{\text{sodium}_{\text{plasma}} \times \text{creatinine}_{\text{urinary}}}$$

As such, FENa depends on sodium intake, effective intravascular volume, GFR, diuretic intake, and intact tubular reabsorptive mechanisms. With prerenal AKI, the FeNa may be below 1%, suggesting avid tubular sodium reabsorption.

In patients with CKD, a FeNa significantly above 1% can be present despite a superimposed prerenal state. The FeNa may also be above 1%, despite hypovolemia due to treatment with diuretics. Low FeNa is often seen early in glomerulonephritis and other disorders and should not be taken as *prima facie* evidence of prerenal azotemia. Low FeNa is therefore suggestive, but not synonymous, with effective intravascular volume depletion and should not be used as the sole guide for volume management. The response of urine output to crystalloid or colloid fluid administration may be both diagnostic and therapeutic in prerenal azotemia. In ischemic AKI, the FeNa is frequently above 1% because of tubular injury and resultant inability to reabsorb sodium.

However, several causes of ischemia-associated and nephrotoxin-associated AKI can present with FeNa below 1% including sepsis (often early in the course), rhabdomyolysis, and contrast nephropathy.

The ability of the kidney to produce a concentrated urine is dependent on water intake, integrity of the corticomedullary osmotic gradient and function of the collecting duct and the intact physiology of vasopressin [23]. In patients not taking diuretics who have good baseline kidney function, urine osmolality may be above 500-600 mOsm/kg in prerenal AKI. This is consistent with an intact medullary gradient and elevated serum vasopressin levels causing water reabsorption resulting in concentrated urine. In elderly patients and those with CKD, however, baseline concentrating defects may exist, making urinary osmolality unreliable in many instances [24]. In ischemic, septic or toxic AKI, the strucural damage of the tubules results in loss of the concentrating ability resulting in urine osmolality below 300-350 mOsm/kg even in presence of hypovolemia [7].

Routine Blood Laboratory Findings (for more detailed review see [25].

Certain forms of AKI are associated with characteristic patterns in the rise and fall of SCr. Prerenal azotemia typically leads to modest rises in SCr that return to baseline with improvement in hemodynamic status. Contrast nephropathy leads to a rise in SCr within 24–48 hours, a peak within 3–5 days, and resolution within 5–7 days (for review see [26]). After contrast media administration in the abdominal arterial circulation, renal atheroembolic disease usually manifests with more subacute rises in SCr, although severe AKI with rapid increases in SCr can occur in this setting. With many of the epithelial cell toxins such as aminoglycoside antibiotics, the rise in SCr is characteristically delayed anywhere from 3–5 days to 2 weeks after initial exposure.

A complete blood count may provide diagnostic clues. Anemia is common in AKI and is usually multifactorial in origin. It is not

related to an effect of AKI solely on production of red blood cells because this effect in isolation takes longer to manifest. Peripheral eosinophilia can accompany interstitial nephritis, atheroembolic disease, polyarteritis nodosa, and Churg-Strauss vasculitis. Severe anemia in the absence of bleeding may reflect hemolysis, multiple myeloma, or thrombotic microangiopathy (Hemolytic uremic syndrome (HUS) or Thrombotic thrombocytopenic purpura (TTP)).

Other laboratory findings of thrombotic microangiopathy include thrombocytopenia, schistocytes on peripheral blood smear, elevated lactate dehydrogenase level, and low haptoglobin content. If possible, evaluation of patients suspected of having TTP-HUS includes measurement of levels of the von Willebrand factor cleaving protease (ADAMTS13) and testing for Shiga toxin–producing Escherichia coli. "Atypical HUS" constitutes the majority of adult cases of HUS. Genetic testing is also important because it is estimated that 60–70% of atypical HUS patients have mutations in genes encoding proteins that regulate the alternative complement pathway. Extensive reviews on the thrombotic microangiopathies have recently been published [27, 28]

AKI often leads to hyperkalemia, hyperphosphatemia, and hypocalcemia. Marked hyperphosphatemia with accompanying hypocalcemia, however, suggests rhabdomyolysis or tumor lysis syndrome. Creatine phosphokinase levels and serum uric acid are elevated in rhabdomyolysis, while tumor lysis syndrome shows normal or marginally elevated creatine kinase and markedly elevated serum uric acid. The anion gap may be increased with any cause of uremia due to the retention of anions such as phosphate, hippurate, sulfate, and urate. The co-occurrence of an increased anion gap and an osmolal gap may suggest ethylene glycol poisoning, which also may cause oxalate crystalluria. Low anion gap may provide a clue to the diagnosis of multiple myeloma due to the presence of unmeasured cationic proteins.

Laboratory blood tests are helpful in the diagnosis of glomerulonephritis and vasculitis, which include depressed complement levels and high titers of antinuclear antibodies (ANAs), antineutrophilic cytoplasmic antibodies (ANCAs), antiglomerular basement membrane (AGBM) antibodies, and cryoglobulins. Table 2 summarizes some of the most relevant blood and serum tests that are useful in the differential diagnosis of AKI.

Table 2. Blood and serum findings pointing to specific causes of ARF

LABORATORY FINDING	OBSERVED IN AKI DUE TO:
Anemia	Pre-existent chronic renal failure, hemorrhage, hemolysis
Anemia with rouleaux formation	Plasma cell dyscrasia
Eosinophilia	Atheroemboli, acute interstitial nephritis or polyarteritis nodosa
Leukopenia	SLE
Thrombocytopenia	SLE, Hantavirus infection, DIC, rhabdomyolysis, advanced liver disease with hypersplenism, 'white clot syndrome' due to heparin administration
Thrombocytopenia, reticulocytosis, elevated LDH, schistocytes on peripheral smear, low ADAMTS13 levels	Thrombotic microangiopathy
Coagulopathy	Liver disease, DIC, antiphosholipid antibody syndrome
Hyperkalemia <5.5 mEq/l Marked hyperkalemia	Various causes, including; Tumor lysis syndrome, hemolysis, use of NSAIDs, ACEi or ARB
Marked hyperkalemia, hyperphosphatemia, hypocalcemia, elevated serum uric acid and CK, AST, and LDH	Rhabdomyolysis
Marked hyperkalemia, hyperphosphatemia, hypocalcemia, very high serum uric acid, normal or marginally elevated CK	Acute uric acid nephropathy, tumor lysis syndrome, heat stroke
Hypercalcemia	Malignancy, sarcoidosis, vitamin-D intoxication etc.
Widening of serum anion and osmolar gap*	Ethylene glycol or methanol intoxication
Marked acidosis, anion gap > 5-10mEq/l	ethylene glycol poisoning, rhabdomyolysis, lactic acidosis from sepsis
Hypergammaglobulinemia	SLE, bacterial endocarditis and other chronic infections
Paraprotein (M-gradient), hypergammaglobulinemia	Myeloma
Urine electrophoresis showing free light chains	Myeloma, low-grade plasma cell dyscrasias (even in the absence of serum abnormalities)
Elevated serum IgA	IgA nephropathy
Elevated antinuclear antibodies	Autoimmune diseases including SLE, scleroderma, mixed connective tissue disease, Sjögren 's syndrome etc.
Elevated anti-double stranded DNA antibodies	SLE
Elevated anti-C1q antibodies	SLE, MPGN, some cases of IgA nephropathy
Elevated ANCA titer	Wegener's granulomatosis, microscopic polyangiitis
Antiglomerular basement membrane antibodies	Anti-GBM nephritis, Goodpasture syndrome
Cryoglobulins	Hepatitis C, lymphoproliferative disorders

*DIC – disseminated intravascular coagulation, LDH – lactic dehydrogenase, CK – creatinine kinase, AST - asparagine aminotransferase,SLE-systemic lupus erythematodes, NSAID-non steroidal anti-inflammatory drugs, ACEi- angiotensin converting enzyme inhibitors, MPGN-membrano proliferative glomerulonephritis; * Mild metabolic acidosis occurs frequently as a consequence of AKI and is often associated with a modest (5-10 mEq/l) increase in the anion gap.*

NOVEL BIOMARKERS

Recently, several novel biomarkers have been proposed for the diagnosis of AKI. They are in various stages of development and validation [29-32]. Not only is the analysis of these biomarkers expensive, but it is also not clear if a single or multiple biomarker approach is necessary to diagnose the complicated and multifactorial aspects of AKI [30, 32, 33]

The Furosemide Stress Test (FST)

The FST is based on the tubular handling of furosemide. As an organic acid, furosemide is tightly bound to serum proteins and appears in the tubular lumen by active secretion via the human organic anion transporter system in the proximal convoluted tubule. Once in the tubular lumen, furosemide inhibits luminal active chloride transport throughout the thick ascending limb of Henle. To prevent sodium reabsorption and to increase urine flow, furosemide requires thus two distinct tubular nephron segments to be functioning making it a physiologic and clinical tool for tubular functional testing [34].

It was recently demonstrated that the 2-hour urine output after a standardized high-dose FST (1mg/kg of furosemide in furosemide- naive patients or 1.5 mg/kg in those with prior exposure to furosemide) in clinically euvolaemic patients with early AKI has the predictive capacity to identify those with severe and progressive AKI [35]. In the prediction of progression to the Acute Kidney Injury Network (AKIN) classification (stage 3) in patients with AKIN stages 1 or 2, the area under the receiver-operating characteristic curve (AUC) for the urine output 2 hours after furosemide administration was 0.87 ± 0.09 (p=0.001). The ideal cut-off for predicting progressive AKI during these first 2 hours was a urine volume of 200 mL (100 mL/hr) with a sensitivity of 87.1% and a specificity of 84.1%.

In view of the relatively technical simplicity of this test, we recommend this test to predict the severity and progression of AKI [36], provided the correct indication of this test is respected, i.e. only applied in an euvolemic or hypervolemic patient. The FST is absolutely useless when furosemide is given to a hypovolemic patient with prerenal AKI.

RADIOLOGIC EVALUATION

Ultrasound (US) Imaging of the Kidney in AKI

Conventional ultrasound (B-mode) generates grey-scale images based on the property of sound waves to reflect at interfaces of media of different densities. This mode permits the evaluation of longitudinal size and parenchyma echogenicity and demonstrates (or rules out) the presence of hydronephrosis or cysts. An excellent recent review on the relevance of renal ultrasound and renal Doppler ultrasonography in AKI summarizes the strengths and limitations of both techniques [37].

Kidney size is typically measured on its long axis (bipolar length). Normal values range from 10-12 cm according to patient size and gender. In healthy individuals the left kidney is longer than the right by 0.3 cm; women have smaller kidneys than men by 0.5 cm; kidney sizes <10 cm are unusual in people younger than age 60 years, and kidney length decreases with age beginning at age 60 [37]. Small kidney size is suggestive of underlying CKD, while enlarged kidneys might be observed in infiltrative diseases, renal vein thrombosis, acute rejection in transplanted kidneys, in early stages of pregnancy and diabetic nephropathy.

It is long established that renal hypertrophy with ~30% higher than normal kidney size and the associated hyperfiltration are predictors of poor prognosis for developing albuminuria and CKD in both type 1 and type 2 diabetes mellitus, from recent review [38].

Renal echogenicity is evaluated by comparison with that of adjacent tissues (liver or spleen). Decreased echogenicity can be physiologic but might be associated with pathological processes such as edema. Hyper echogenicity almost always indicates diffuse kidney parenchymal pathology (infiltrative diseases, inflammatory states). Chronic kidney disease is often associated with increased brightness since fibrous tissues increase echogenicity.

Urinary tract obstruction represents a relatively easily reversible cause of AKI and should be ruled out in all patients with AKI with suggestive history or lack of clear cause of AKI. On US imaging, the collecting system of the kidney is not normally visible unless significant hydronephrosis is present. Hypovolemia, early obstruction, retroperitoneal tumors or fibrosis may lead to false negative results. False positive findings can be observed in pregnancy and in patients with diabetes insipidus, vesicoureteral reflux, megacystis-megaureter syndrome, full bladder and urinary tract infection [37].

If a high clinical index of suspicion for obstruction persists despite normal imaging and the patient is hypovolemic, the renal ultrasound should be repeated after correction of the hypovolemia. It is relatively rare that antegrade or retrograde pyelography are necessary for diagnosis of urinary tract obstruction.

Normal sized kidneys are expected in AKI. Enlarged kidneys in a patient with AKI suggests the possibility of acute interstitial nephritis. Vascular imaging may be useful if venous or arterial obstruction is suspected, but the risks of contrast administration should be kept in mind. Magnetic resonance imaging (MRI) with gadolinium-based contrast agents should be avoided if possible in severe AKI because of the possibility of inducing nephrogenic systemic fibrosis, a rare but serious complication seen most commonly in patients with end-stage renal disease.

KIDNEY BIOPSY

If the cause of AKI is not apparent based on the clinical context, physical examination, laboratory studies, and radiologic evaluation, kidney biopsy should be considered, provided the pathological knowledge, technical skills and equipment are present.

Kidney biopsy can provide definitive diagnostic and prognostic information about acute kidney disease and CKD. The procedure is most often used in AKI when prerenal azotemia, postrenal AKI, and ischemic or nephrotoxic AKI have been deemed unlikely.

Kidney biopsy can be considered when glomerulonephritis, vasculitis, interstitial nephritis, myeloma kidney, HUS-TTP, and allograft dysfunction are part of the differential diagnosis.

Kidney biopsy is associated with a risk of bleeding, which can be severe and organ or life-threatening in patients with thrombocytopenia or coagulopathy. Excellent summaries of recommendations for early detection and management of AKI in low- and middle income countries have recently been published by the 18th Acute Dialysis Quality Initiative [39, 40].

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