Diagnostic approach to adult patients with subacute kidney injury in an outpatient setting

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INTRODUCTION

Patients with kidney disease may have a variety of different clinical presentations. Some have symptoms or signs that are directly referable to the kidney (such as hematuria) or to associated extrarenal manifestations (edema, hypertension, signs of uremia). Many patients are asymptomatic and are incidentally found to have an elevated serum creatinine concentration, abnormal urine studies (such as proteinuria or microscopic hematuria), or abnormal radiologic imaging of the kidneys.

Specific disorders generally cause acute, subacute, or chronic kidney injury. Acute kidney injury (AKI) develops over hours to days and is usually diagnosed in hospitalized patients or following a procedure. Subacute kidney injury describes a presentation that develops more slowly than AKI but generally results in worsening creatinine over the course of a few weeks. Chronic kidney disease (CKD) is defined by an elevated creatinine, or other evidence of kidney damage, that is present and relatively stable for greater than three months.

Although not all presentations fit within these narrowly defined categories, knowledge of the duration and acuity of onset of disease often narrows the differential diagnosis among patients who may present similar clinical findings related to the kidney.

This topic reviews the evaluation of patients who present with subacute kidney injury. Most patients are evaluated as outpatients, but, in some cases, the trend of gradually rising creatinine is recognized upon hospital admission. The evaluation of hospitalized patients who develop an increase in creatinine within hours to days is discussed elsewhere [1]. (See "Evaluation of acute kidney injury among hospitalized adult patients".)

The evaluation of patients with newly identified CKD is discussed elsewhere [1]. (See "Chronic kidney disease (newly identified): Clinical presentation and diagnostic approach in adults".)

OVERVIEW

Major components of evaluation — The major components to the evaluation of patients with an elevated creatinine involve:

- Careful history and physical examination. An important part of the history is the duration of the increased creatinine.
- Assessment of kidney function by estimation of the glomerular filtration rate (GFR). Estimation of the GFR requires that the patient is in steady state. (See 'Evaluation' below.)
- Careful examination of the urine by both qualitative chemical tests and microscopic examination. The urinary findings narrow the differential (table 1). (See 'Urinalysis' below.)
- Radiographic imaging of the kidneys. (See 'Radiologic studies' below.)
- Serologic testing and tissue diagnosis with kidney biopsy if noninvasive evaluation is not sufficient for diagnosis. (See 'Serologic testing and role of kidney biopsy' below.)

Determination of disease duration — The determination of disease duration is an important aspect of the evaluation. Making this determination accurately requires the availability of older data for comparison. Knowing the disease duration helps to narrow the differential diagnosis of cause and to provide prognostic information to guide management.

The distinction among acute kidney injury (AKI), subacute injury, and chronic kidney disease (CKD) is arbitrary, but the following definitions have been established by consensus panels:

- **Acute** – AKI is defined by a rise in the serum creatinine concentration or an abnormal urinalysis that has developed within hours to days. Consensus criteria for AKI include an increase in serum creatinine by ≥0.3 mg/dL (27 micromol/L) relative to a known baseline value within 48 hours, or an increase to ≥1.5 times the known or presumed baseline value within seven days, or a decrease in urine volume to <3 mL/kg over six hours (Kidney Disease: Improving Global Outcomes [KDIGO]-AKI) (table 2).

  AKI is most commonly diagnosed in hospitalized patients. (See "Definition and staging criteria of acute kidney injury in adults".)

- **Chronic** – The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) and the KDIGO CKD guidelines define CKD as being present if reduced GFR (ie, <60 mL/min/1.73 m^2) or evidence of kidney damage, such as albuminuria or abnormal findings on renal imaging, have been present for three months or more. (See "Definition and staging of chronic kidney disease in adults", section on 'Definition of CKD' and "Chronic kidney disease (newly identified): Clinical presentation and diagnostic approach in adults".)

- **Subacute** – KDIGO AKI guidelines in 2012 proposed the term "acute kidney diseases and disorders" (AKD) to encompasses any decrement in kidney function occurring in less than three months [1]. Disorders that evolve over more than 48 hours but generally in under three months are informally

referred to here as subacute kidney injury. AKD includes both AKI and subacute kidney injury, and there is considerable overlap in an acute and subacute presentation.

We emphasize that these categories may guide the urgency of evaluation but are less important than having a clear understanding of the natural history of the various underlying diseases. Many signs and symptoms of disease may be present before there is a decline in clearance function. As an example, glomerular diseases referred to as rapidly progressive glomerulonephritides (RPGNs) often cause subtle signs and symptoms for weeks to months before the patient develops overt manifestations of nephritic syndrome, including a decline in creatinine clearance. In two case-series reports of antineutrophil cytoplasmic antibody (ANCA) vasculitis, for example, an average time of ≥10 weeks elapsed between reported, initial symptoms and the diagnosis of glomerulonephritis [2,3].

The assessment of disease duration is best performed by comparing the current serum creatinine concentration and/or urinalysis with previous results. As an example, a patient with a current serum creatinine concentration of 4 mg/dL (354 micromol/L) and a creatinine of 0.6 mg/dL (53 micromol/L) one month previously has acute or subacute disease. In contrast, the same patient with a prior serum creatinine concentration of 3.5 mg/dL (309 micromol/L) two years ago almost certainly has slowly progressive CKD.

When a previous urinalysis, serum creatinine concentration, and/or radiographic study are unavailable, certain findings from the history and physical examination may suggest the duration of disease. As examples [4]:

- The recent onset of symptoms or signs, such as sudden onset of anasarca, discolored urine, new skin lesions, altered mental status, rapidly rising blood pressure, or other systemic findings also suggest an acute or subacute process.
- Marked oliguria (urine output <500 mL/day) or anuria indicates an acute process since prolonged oliguria/anuria does not occur in slowly progressive CKD (even if advanced) prior to initiation of maintenance dialysis.
- A daily progressive increase in the serum creatinine concentration indicates an acute process, while a stable value over weeks to months suggests CKD.
- Imaging showing small kidneys relative to the patient's habitus provides definitive evidence of chronicity. However, the presence of normal-sized kidneys does **not** exclude chronic disease. Markedly increased renal echogenicity coupled with small, atrophic kidneys strongly suggest CKD [5-7]. (See "Radiologic assessment of renal disease".)

Other findings are less helpful. As an example, anemia due to erythropoietin deficiency is a common (though not absolute) finding in CKD, but many conditions can cause both hemolysis or bleeding and AKI or subacute injury. Hyperphosphatemia also does not distinguish acute from chronic disease. Although hyperphosphatemia commonly affects CKD patients, serum phosphorus levels can also rise quickly in AKI or subacute kidney injury.

MAJOR CAUSES AND PATHOGENESIS OF KIDNEY DISEASE

The traditional approach to kidney disease has been to categorize the clinical etiology as prerenal (decreased renal perfusion pressure), intrinsic renal (pathology of the vessels, glomeruli, or tubulointerstitium), or postrenal (obstructive).

However, diseases often cross these nosological boundaries. As examples, prolonged prerenal azotemia can lead to intrinsic acute tubular necrosis (ATN) and possibly to chronic fibrosis and progressive chronic kidney disease (CKD), and untreated urinary tract obstruction eventually causes fibrosis and atrophy of the obstructed kidney(s). In addition, many diseases that initially damage the glomeruli eventually result in tubulointerstitial fibrosis. Another example is cholesterol emboli syndrome, which affects both small vessels and the glomeruli and ultimately causes tubulointerstitial fibrosis.

Conditions that cause prerenal, intrinsic, or postrenal subacute kidney injury are discussed below.

Prerenal disease — Prerenal conditions that cause subacute kidney injury include overdiuresis, decreased oral intake, diarrhea, or unreplenished insensible losses. Renal perfusion pressure may also be low in hypervolemic states with low effective circulating (arterial) volume, such as heart failure with reduced ejection fraction or decompensated liver disease with portal hypertension. (See "Cardiorenal syndrome: Definition, prevalence, diagnosis, and pathophysiology" and "Hepatorenal syndrome".)

Alterations in renal vascular autoregulation, such as afferent arteriole vasoconstriction caused by nonsteroidal antiinflammatory drugs (NSAIDs), and inhibition of efferent vasoconstriction by renin-angiotensin system (RAS) blockade cause a propensity for prerenal kidney injury. (See "NSAIDs: Acute kidney injury (acute renal failure)".)

Intrinsic renal vascular disease — Intrinsic renal vascular diseases directly affect both large- and small-sized blood vessels within the kidneys.

Subacute intrinsic diseases that involve the vasculature include small vessel vasculitides affecting glomerular capillaries, atheroembolic disease, and diseases that cause microangiopathic hemolytic anemia (MAHA) and thrombotic microangiopathy (TMA) syndromes, such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and hypertensive emergencies (including in pregnant women). (See "Overview of and approach to the vasculitides in adults", section on 'Small-vessel vasculitis' and "Glomerular disease: Evaluation and differential diagnosis in adults" and "Clinical presentation, evaluation, and treatment of renal atheroemboli" and "Approach to the patient with suspected TTP, HUS, or other thrombotic microangiopathy (TMA)" and "Evaluation and treatment of hypertensive emergencies in adults" and "Renal disease in systemic sclerosis (scleroderma), including scleroderma renal crisis" and "Preeclampsia: Clinical features and diagnosis".)

Intrinsic renal vascular diseases that involve larger vessels include renal infarction from aortic dissection, systemic thromboembolism, or renal artery abnormalities (such as aneurysm or vasculitis). Renal vein thrombosis is most frequently associated with massive proteinuria in the setting of nephrotic syndrome. (See "Renal infarction" and "Overview of and approach to the vasculitides in adults", section on 'Medium-vessel vasculitis' and "Hypercoagulability in nephrotic syndrome".)

Intrinsic glomerular disease — Disorders that produce glomerular disease can be classified as being primary (idiopathic, not associated with systemic disease) or secondary (such as paraneoplastic, drug induced, or part of a systemic rheumatologic disease). Two general patterns are observed (with considerable overlap in some diseases) (table 1):

- A nephritic (proliferative) pattern produces an active urine microscopy with red blood cell (RBC) casts, dysmorphic red cells, and a variable degree of albuminuria [8,9]. (See "Glomerular disease: Evaluation and differential diagnosis in adults".)

- A nephrotic (nonproliferative) pattern is associated with proteinuria, usually in the nephrotic range (>3.5 g per 24 hours or on spot protein-to-creatinine ratio), and an inactive urine microscopy with few cells or casts. (See "Glomerular disease: Evaluation and differential diagnosis in adults".)

  The quantification of protein excretion is discussed elsewhere. (See "Assessment of urinary protein excretion and evaluation of isolated non-nephrotic proteinuria in adults".)

Both patterns can present with an acute or more chronic time course, and elements of both may be observed simultaneously or sequentially in the same patient. The differential diagnosis of glomerular disease is discussed elsewhere. (See "Glomerular disease: Evaluation and differential diagnosis in adults".)

Intrinsic tubular and interstitial disease — Subacute tubulointerstitial diseases include interstitial nephritis (which is often drug induced and commonly called acute interstitial nephritis), cast nephropathy in multiple myeloma, and acute phosphate nephropathy following a phosphate-containing bowel preparation [10]. (See "Etiology and diagnosis of prerenal disease and acute tubular necrosis in acute kidney injury in adults" and "Clinical manifestations and diagnosis of acute interstitial nephritis" and "Kidney disease in multiple myeloma and other monoclonal gammopathies: Etiology and evaluation" and "Clinical manifestations of hypercalcemia", section on 'Renal insufficiency' and "Tumor lysis syndrome: Definition, pathogenesis, clinical manifestations, etiology and risk factors" and "Acute phosphate nephropathy".)

ATN never causes subacute kidney injury but rather always presents as AKI. However, AKI, especially if severe or frequently recurrent, may not recover completely, resulting in irreversible CKD. In such patients, if the elevated creatinine is identified within three months, it may be erroneously "classified" as subacute kidney injury. Causes of AKI are often easily identified in the history, such as cardiac surgery, severe sepsis, or severe diarrheal disease, and chronicity can be established by close follow-up of the patient's creatinine trend over time.

Obstructive nephropathy — Obstruction may occur anywhere in the urinary tract. A substantial reduction in glomerular filtration rate (GFR) suggests bilateral obstruction (or unilateral obstruction of a single functioning kidney). This is most commonly due to prostatic disease or intraabdominal cancer. Retroperitoneal fibrosis is a rare cause of chronic ureteral obstruction. (See "Clinical manifestations and diagnosis of retroperitoneal fibrosis".)

Acute obstruction of the urinary tract usually causes symptoms of pain (renal colic or suprapubic fullness), but gradual, severe obstruction may cause kidney dysfunction without obvious symptoms. If untreated,

obstructive nephropathy leads to irreversible tubulointerstitial fibrosis (ie, intrinsic disease). (See "Clinical manifestations and diagnosis of urinary tract obstruction and hydronephrosis".)

CLINICAL MANIFESTATIONS

Patients with subacute kidney injury may present with symptoms and signs resulting directly from diminished kidney function. These include edema, hypertension, and/or decreased urine output. Patients with rheumatologic diseases affecting the kidney may have subtle joint or skin manifestations. However, many patients have no clinical symptoms. In such patients, kidney injury is detected by laboratory tests that are obtained, potentially as part of an evaluation of an unrelated disorder.

Symptoms and/or signs of prolonged kidney failure, including weakness and easy fatigability, anorexia, vomiting, mental status changes, and seizures, are generally not present in patients with subacute injury, although exceptions may occur. Such symptoms suggest severe acute kidney injury (AKI) or advanced chronic kidney disease (CKD).

The total absence of urine (anuria) is never observed with subacute or chronic injury and always indicates at least some component of AKI. (See "Evaluation of acute kidney injury among hospitalized adult patients".)

The major, and occasionally the only, laboratory finding in patients with subacute kidney injury is an increased serum creatinine concentration. Increased urea (blood urea nitrogen [BUN]) and hyperkalemia may also be present. Albuminuria and/or abnormal urine microscopy may be present. (See 'Urinalysis' below.)

Radiographic imaging may point to a cause of subacute kidney injury, revealing hydronephrosis or large kidneys as may be seen with infiltrative diseases. (See "Radiologic assessment of renal disease".)

EVALUATION

Overview — Once kidney disease is discovered and determined to be subacute in onset, the underlying cause should be identified, if possible. Frequently helpful are a careful history, review of medications, and physical examination (eg, signs of volume contraction).

The presence of certain symptoms or signs may suggest an underlying diagnosis. As examples:

- Systemic symptoms and findings, such as fever, arthralgias, and pulmonary lesions, are suggestive of a systemic disease such as vasculitis or lupus. (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults".)
- Livedo reticularis and distal microemboli suggest atheroembolic disease. (See "Embolism from atherosclerotic plaque: Atheroembolism (cholesterol crystal embolism)".)
- Unilateral flank pain is most consistent with obstruction, renal infarction, or infection. (See "Renal infarction", section on 'Differential diagnosis'.)

A constellation of symptoms and signs may suggest a particular set of disorders. As examples, hypertension, hematuria with red cell casts, and a rapidly rising serum creatinine concentration are almost certainly due to acute glomerulonephritis or renal vasculitis. Edema, heavy proteinuria, and little or no hematuria are indicative of a nonproliferative (nephrotic) glomerular disease such as diabetic glomerulosclerosis, membranous nephropathy, focal segmental glomerulosclerosis, or minimal change disease. Some other urinary findings are relatively nonspecific (eg, a normal or near-normal urinalysis) and can be observed in a variety of disorders (table 1). (See "Urinalysis in the diagnosis of kidney disease", section on 'Correlation of urinary findings with kidney diseases'.)

The approach to evaluation varies among clinicians and depends on the degree of creatinine change and the corresponding change in the glomerular filtration rate (GFR), which is estimated from the serum creatinine. Kidney injury can be considered mild if the serum creatinine has increased <0.5 mg/dL above baseline; injury is moderate to severe if the serum creatinine has increased ≥0.5 mg/dL above baseline. However, the absolute change in creatinine should be evaluated in the context of the baseline creatinine. For patients with chronic kidney disease (CKD) and thus a higher creatinine at baseline, small fluctuations in creatinine are common. For such patients, mild injury may be better operationalized as a less than 50 percent change in creatinine and moderate to severe injury operationalized as a greater than 50 percent change in creatinine. Among patients with a relatively low baseline serum creatinine, smaller changes may reflect a significant reduction in kidney function. For example, if a patient has a baseline serum creatinine of 0.6 mg/dL, an increase of 0.3 mg/dL is significant.

For most patients with mild injury, we follow a stepwise approach that begins with assessment of volume status and the exclusion of drugs that are nephrotoxins or cause prerenal azotemia (algorithm 1). Common examples of such agents are nonsteroidal antiinflammatory agents (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and diuretics. We repeat the serum creatinine in one to two weeks. If new systemic symptoms or blood pressure changes are present, more rapid evaluation is warranted.

If, on repeat testing, the creatinine remains elevated, we perform laboratory and radiographic tests as described below. (See 'Initial testing' below.)

For patients who have moderate or severe injury, we initiate the laboratory and radiographic evaluation immediately (ie, concurrent with holding potential nephrotoxins and restoring euvolemia). (See 'Initial testing' below.)

Initial testing — Initial testing should include a reagent strip urinalysis (dipstick) with automated urine microscopy, the quantification of urine protein or albumin (by random [or "spot"] protein-to-creatinine ratio or albumin-to-creatinine ratio), and a kidney ultrasound. Some clinicians also send a serum and urine protein electrophoresis (SPEP and UPEP) at the time of the initial evaluation and, if these are abnormal, a serum free light chain assay.

Among all patients who are considered at higher risk for multiple myeloma based on key clinical features, we obtain a SPEP and UPEP, with immunofixation, and a serum light chain assay at the time of the initial evaluation. Patients who are considered at higher risk for myeloma include all patients who are >40 years of

age who have a documented increase in the serum creatinine within three to six months and no other obvious cause for increased creatinine, such as NSAID use. Patients who have other manifestations consistent with myeloma are also considered at high risk regardless of whether the creatinine increase is documented to be within three to six months; such manifestations include hypercalcemia, bone pain or radiographic lesions, or anemia that is disproportionate to CKD and otherwise unexplained. (See "Kidney disease in multiple myeloma and other monoclonal gammopathies: Etiology and evaluation", section on 'Patients with acute or subacute kidney injury'.)

The utility of measuring total urine protein versus albumin is debatable. A more detailed discussion is presented elsewhere (see "Assessment of urinary protein excretion and evaluation of isolated non-nephrotic proteinuria in adults"). Manual urine microscopy for the assessment of urine sediment is best performed by an experienced operator.

We perform imaging in all patients with subacute injury and in those with an increased serum creatinine of unclear duration. In most patients, we perform a kidney ultrasound rather than other imaging modalities. However, patients who are suspected of renal or ureteral calculi often undergo non-contrast computed tomography (CT) as an initial imaging test. (See 'Clinical manifestations' above and "Kidney stones in adults: Diagnosis and acute management of suspected nephrolithiasis", section on 'Noncontrast CT'.)

The urgency with which the kidney imaging is performed depends upon the rate of creatinine rise or onset of clinical symptoms. Among patients with a rapid rate of creatinine rise or marked symptoms, a referral to the emergency department may be warranted for measurement of post-void residual by ultrasound, placement of a bladder catheter for strict urine volume monitoring, and further evaluation (see "Clinical manifestations and diagnosis of urinary tract obstruction and hydronephrosis"). Even patients with a subjectively normal amount of urine production at home may have severe bladder outlet obstruction, as is observed among patients with slowly progressive prostatic hypertrophy.

The results of the urinalysis and ultrasound generally direct the remainder of the diagnostic evaluation (algorithm 1):

- Patients who have evidence of obstruction on ultrasound require further investigation and usually intervention to relieve the obstruction and determine the cause. (See "Clinical manifestations and diagnosis of urinary tract obstruction and hydronephrosis".)
- Patients who have a urinalysis and/or albumin-to-creatinine ratio that suggests a glomerular or interstitial lesion should be further evaluated based upon the specific finding on urinalysis or based upon determination of abnormal proteinuria. Among patients with evidence of glomerular bleeding (ie, red blood cell [RBC] casts or dysmorphic RBCs), it is important to perform an expedient evaluation, even if this requires an inpatient work-up. Some glomerular diseases may be rapidly progressive, and timely serology and biopsy evaluations followed by appropriate immunosuppression can drastically improve morbidity associated with them. (See "Urinalysis in the diagnosis of kidney disease" and "Overview of the classification and treatment of rapidly progressive (crescentic) glomerulonephritis".)
- Patients with granular casts and renal tubular epithelial cells should be evaluated for acute tubular necrosis (ATN). (See "Etiology and diagnosis of prerenal disease and acute tubular necrosis in acute

kidney injury in adults".)

- Patients with sterile pyuria should be evaluated for interstitial nephritis. (See "Clinical manifestations and diagnosis of acute interstitial nephritis".)

- Patients who have normal renal imaging (no obstruction or other apparent intrinsic process such as polycystic kidney disease [PKD]), minimal proteinuria, and benign urinalysis and microscopy should be evaluated with a SPEP and UPEP, if this has not yet been performed. If either the SPEP or UPEP is abnormal, we obtain immunofixation and a serum free light chain assay. Because of its improved sensitivity over spot UPEP in detecting light chain disease, some clinicians obtain a serum free light chain assay initially rather than SPEP or UPEP [11,12].

The recognition of monoclonal gammopathy by serum or urine electrophoresis or by abnormal ratio of light chains in a patient with kidney disease of uncertain etiology may prompt kidney biopsy for definitive diagnosis. Discussion of monoclonal gammopathy of undetermined significance (MGUS) or monoclonal gammopathy of renal significance (MGRS), myeloma, and amyloidosis are presented elsewhere. (See "Kidney disease in multiple myeloma and other monoclonal gammopathies: Etiology and evaluation" and "Renal amyloidosis".)

For patients with an unremarkable initial work-up (including benign urinalysis and absent abnormal proteinuria), further evaluation is determined by the severity of disease and rate of further decline of kidney function. Among patients who have mild injury, the serum creatinine may be repeated in one to two weeks. If the creatinine remains stable, we generally continue to follow it intermittently, until a clear temporal pattern is established. Among patients who have signs and symptoms of rapidly progressive or unexplained systemic disease, a kidney biopsy may be warranted, even if the estimated GFR (eGFR) is near normal.

If the creatinine is markedly elevated on initial evaluation without a clear explanation or if an initially mild increase in the creatinine worsens over the course of weeks to months, then a kidney biopsy should be performed, providing there is no clear evidence of chronicity on imaging. A biopsy generally provides more definitive tissue diagnosis and may allow a therapeutic intervention to stave off progression to end-stage kidney disease (ESKD).

In some cases, even without kidney biopsy, the etiology of kidney disease can be ascertained with reasonable certainty with tissue diagnosis from other sites. As an example, a bone marrow biopsy among patients with monoclonal gammopathy or a fat pad biopsy among those with amyloidosis may avert the need for a kidney biopsy. Kidney biopsy is discussed below and in more detail elsewhere (see "The kidney biopsy"). Additional testing prior to biopsy may also be suggested by the history. As an example, determining lead levels may be indicated among patients with a history of lead exposure. (See "Lead nephropathy and lead-related nephrotoxicity".)

Estimation of glomerular filtration rate — The most common methods utilized to estimate the GFR in adults are the serum creatinine concentration, the creatinine clearance, and GFR estimation equations based upon the serum creatinine concentration and variables such as age, sex, and race. (See "Assessment of kidney function", section on 'Estimation of GFR'.)

The equations that use serum creatinine concentration to estimate GFR were derived in patients with stable kidney function. The use of these equations may lead to errors in estimation of kidney function among patients who are not in steady state, such as those with acute kidney injury (AKI), in whom the GFR is often markedly reduced upon presentation, but there has not yet been adequate time for creatinine concentration to equilibrate. Measuring the serum creatinine over time often allows one to determine whether there is sufficient stability to use estimation equations.

Urinalysis — The urinalysis involves both use of a urine dipstick and microscopic examination of the urine sediment. The dipstick can test for protein (albumin), pH, glucose, hemoglobin (or myoglobin), leukocyte esterase and nitrites (reflecting pyuria), and specific gravity. (See "Urinalysis in the diagnosis of kidney disease", section on 'Urine dipstick'.)

Microscopic examination of the urine sediment by an experienced operator is an important component of the diagnostic evaluation since characteristic findings strongly suggest certain diagnoses (table 1). (See "Urinalysis in the diagnosis of kidney disease", section on 'Urine sediment' and "Etiology and diagnosis of prerenal disease and acute tubular necrosis in acute kidney injury in adults", section on 'Urinalysis'.)

Urine volume — The absolute volume of urine production is most helpful in evaluation if it is very low or if it is significantly changing in a single direction (increasing or decreasing). Normal urine output can be maintained even with an abnormally low GFR, as in nonoliguric ATN or in many patients with CKD. As noted above, clear evidence that a patient has become oliguric or anuric, whether by reliable history or by physical exam of volume overload, should prompt more urgent or emergency evaluation since oliguria and certainly anuria suggest an AKI or the late stages of a subacute kidney injury. (See 'Overview' above and "Evaluation of acute kidney injury among hospitalized adult patients", section on 'Urine volume'.)

Radiologic studies — A number of radiologic studies are used to evaluate the patient with kidney disease.

Because of safety, ease of use, and the information provided, the most commonly used radiographic technique in patients presenting with kidney disease is kidney ultrasonography. Increasing emphasis on controlling catheter-associated urinary tract infections has led to lower utilization of bladder catheters and more common use of bedside bladder scans. (See "Radiologic assessment of renal disease".)

Intravenous contrast agents should be avoided, if possible, in patients with kidney injury of any duration because these contrast media are known to be potentially nephrotoxic. This issue is discussed separately. (See "Prevention of contrast-induced acute kidney injury associated with angiography".)

Among patients with moderate to advanced kidney disease with eGFR <30 mL/min/1.73 m^2, the administration of gadolinium has been associated with the potentially severe syndrome of nephrogenic systemic fibrosis (NSF). Most reported cases have been in chronic dialysis patients, but the syndrome may also occur in those with acute or subacute injury. In such patients, gadolinium-based imaging should be avoided, if possible. This issue is discussed separately. (see "Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy in advanced kidney disease")

Serologic testing and role of kidney biopsy — Depending on the history, physical, radiographic, and urine findings, particularly those which suggest nephritic or nephrotic glomerular disease, serologic testing is

ordered to further characterize the etiology of kidney disease (see "Glomerular disease: Evaluation and differential diagnosis in adults"). A native (nontransplanted) kidney biopsy is most commonly obtained when noninvasive evaluation of subacute kidney injury has been unable to establish the correct diagnosis [13,14].

Biopsy may be deferred if other findings and serologic testing strongly support diagnostic and therapeutic decision making and the risk outweighs the benefit. A pregnant woman with nephritic syndrome, positive serologic markers for lupus, and hypocomplementemia, for example, may be treated with immunosuppression for lupus nephritis and the biopsy reconsidered postpartum.

Biopsy may also be deferred if the duration of the increased creatinine is not known and may have been present for longer than three months duration, particularly if imaging suggests chronicity (see 'Overview' above). In addition, as noted above, some patients who have stable CKD resulting from an episode of AKI may be erroneously classified as having subacute kidney injury just because an increased creatinine is detected within three months from a previously normal baseline. Such patients almost always have a history of intervening illness and hospitalization. Such patients should not necessarily undergo biopsy, since the biopsy would be unrevealing and specific intervention is not required.

Issues related to kidney biopsy, including indications, when biopsy may not be necessary, prebiopsy evaluation, technique, and complications, are discussed separately. (See "The kidney biopsy".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Acute kidney injury in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Chronic kidney disease (The Basics)" and "Patient education: Acute kidney injury (The Basics)")

- Beyond the Basics topics (see "Patient education: Chronic kidney disease (Beyond the Basics)" and "Patient education: Dialysis or kidney transplantation — which is right for me? (Beyond the Basics)" and "Patient education: Hemodialysis (Beyond the Basics)" and "Patient education: Peritoneal dialysis (Beyond the Basics)" and "Patient education: Protein in the urine (proteinuria) (Beyond the Basics)" and "Patient education: Split urine collection for orthostatic proteinuria (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Knowledge of the duration of kidney disease often narrows the differential diagnosis of the underlying cause. Subacute kidney injury generally develops over more than 48 hours but in under three months. (See 'Introduction' above and 'Overview' above.)
- Subacute kidney injury may be categorized as prerenal (decreased renal perfusion pressure), intrinsic renal (pathology of the vessels, glomeruli, or tubules-interstitium), or postrenal (obstructive). However, diseases often cross these nosologic boundaries. (See 'Major causes and pathogenesis of kidney disease' above.)
- Once kidney disease is discovered and duration determined, the underlying cause should be identified. Review of medications and physical examination are very helpful. Initial testing should include reagent strip urinalysis (dipstick) with automated urine microscopy and the quantification of urine protein or albumin (by random or "spot" protein-to-creatinine ratio or albumin-to-creatinine ratio) and a kidney ultrasound. The results of the urine studies and ultrasound generally direct the remainder of the diagnostic evaluation (algorithm 1). (See 'Evaluation' above.)

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GRAPHICS

Urinary patterns associated with different kidney diseases

Urinary pattern	Kidney disease suggested by pattern
Hematuria with dysmorphic red blood cells, red blood cell casts, varying degrees of albuminuria	Proliferative glomerulonephritis (eg, IgA nephropathy, ANCA-associated vasculitis, lupus nephritis)
Heavy albuminuria with minimal or absent hematuria	Nonproliferative glomerulopathy (eg, diabetes, amyloidosis, membranous nephropathy, focal segmental glomerulosclerosis, minimal change)
Multiple granular and epithelial cell casts with free epithelial cells	Acute tubular necrosis in a patient with underlying acute kidney injury
Isolated pyuria	Infection (bacterial, mycobacterial) or tubulointerstitial disease
Normal urinalysis with few cells, no casts, and no or minimal proteinuria	In presence of acute kidney injury: prerenal disease, urinary tract obstruction, hypercalcemia, acute phosphate nephropathy, myeloma cast nephropathy
	In presence of chronic kidney disease: ischemic nephropathy, hypertensive nephrosclerosis, urinary tract obstruction, hepato renal disease, cardiorenal disease

IgA: immunoglobulin A; ANCA: antineutrophil cytoplasmic antibody.

Graphic 56160 Version 10.0

Criteria for acute kidney injury

	RIFLE[1]	AKIN[2]	KDIGO[3]
Diagnostic criteria*			
		Increase in serum creatinine of ≥0.3 mg/dL or ≥50% within 48 hours OR Urine output of <0.5 mL/kg/hour for >6 hours	Increase in serum creatinine of ≥0.3 mg/dL within 48 hours or ≥50% within 7 days OR Urine output of <0.5 mL/kg/hour for >6 hours
Staging criteria			
Risk (RIFLE) or stage 1 (AKIN/KDIGO)	Increase in serum creatinine to 1.5 times baseline OR Urine output of <0.5 mL/kg/hour for 6 to 12 hours	Increase in serum creatinine of ≥0.3 mg/dL or to 150 to 200% baseline OR Urine output of <0.5 mL/kg/hour for 6 to 12 hours	Increase in serum creatinine of ≥0.3 mg/dL or 1.5 to 1.9 times baseline OR Urine output of <0.5 mL/kg/hour for 6 to 12 hours
Injury (RIFLE) or stage 2 (AKIN/KDIGO)	Increase in serum creatinine of to 2 times baseline OR Urine output of <0.5 mL/kg/hour for 12 to 24 hours	Increase in serum creatinine to 200 to 300% baseline OR Urine output of <0.5 mL/kg/hour for 12 to 24 hours	Increase in serum creatinine to 2.0 to 2.9 times baseline OR Urine output of <0.5 mL/kg/hour for 12 to 24 hours
Failure (RIFLE) or stage 3 (AKIN/KDIGO)	Increase in serum creatinine to 3 times baseline OR Increase in serum creatinine by >0.5 mg/dL to >4.0 mg/dL OR Urine output of <0.3 mL/kg/hour for >24 hours or anuria for >12 hours OR Initiation of renal replacement therapy	Increase in serum creatinine to >300% baseline OR Increase in serum creatinine by >0.5 mg/dL to ≥4.0 mg/dL OR Urine output of <0.3 mL/kg/hour for >24 hours or anuria for >12 hours OR Initiation of renal replacement therapy	Increase in serum creatinine to ≥3.0 times baseline OR Increase in serum creatinine of ≥0.3 mg/dL to ≥4.0 mg/dL ¶ OR Urine output of <0.3 mL/kg/hour for ≥24 hours or anuria for ≥12 hours OR Initiation of renal replacement therapy
Loss (RIFLE)	Need for renal replacement therapy for >4 weeks		
End stage (RIFLE)	Need for renal replacement therapy for >3 months		

RIFLE: risk, injury, failure, loss, ESRD; AKIN: Acute Kidney Injury Network; KDIGO: Kidney Disease: Improving Global Outcomes; ESRD: end-stage renal disease.

* AKIN and KDIGO provided both diagnostic and staging criteria. RIFLE provided a graded definition of AKI that is implicit in the staging criteria.

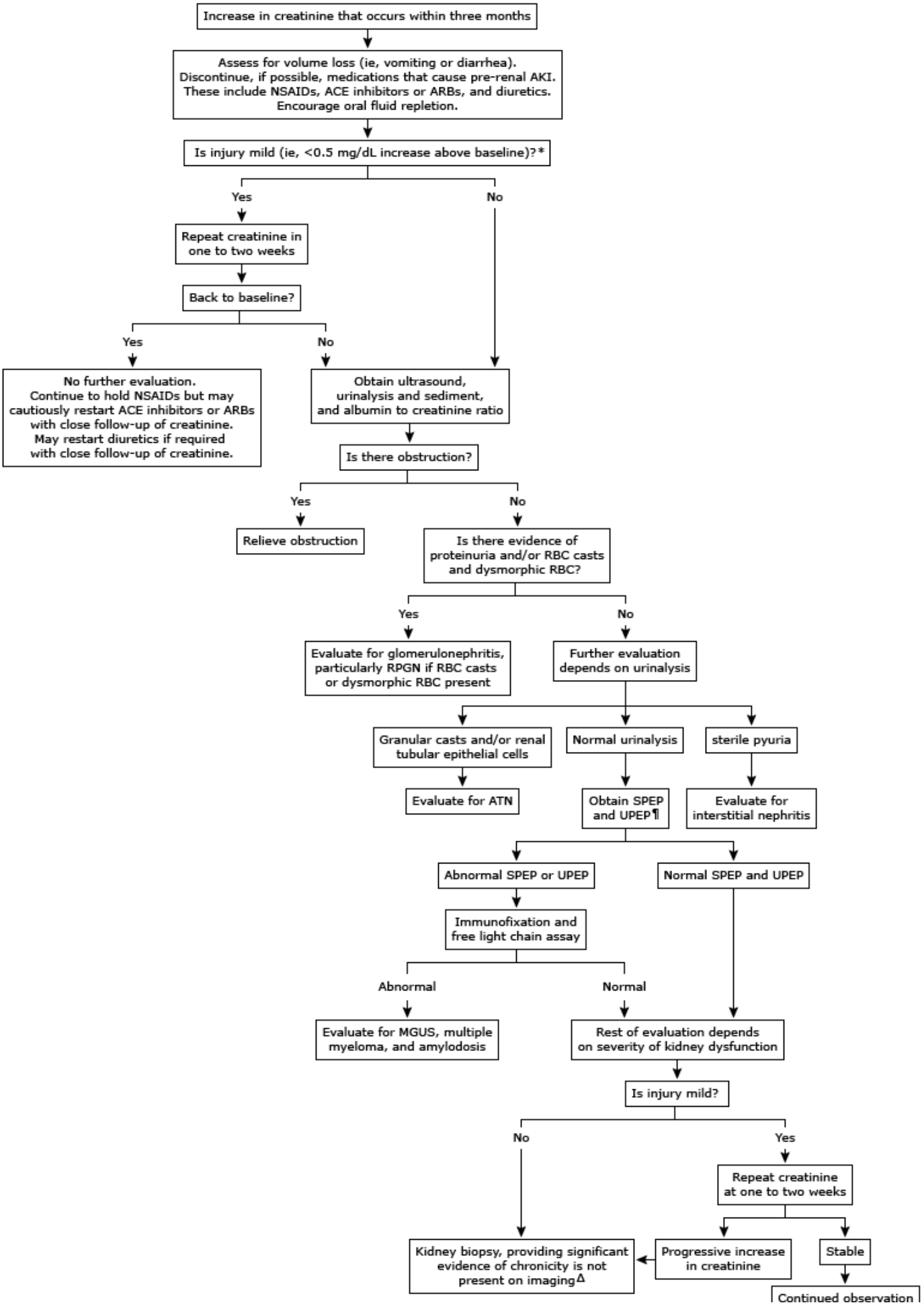
¶ In patients <18 years, stage 3 AKI is also defined by KDIGO as a decrease in estimated glomerular filtration rate (eGFR) to <35 mL/min/1.73 m^2.

References:

1. *Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8:B204. Copyright © 2004 BioMed Central Ltd.*
2. *Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11:R31. Copyright © 2007 BioMed Central Ltd.*
3. *Kidney Disease: Improving Global Outcomes (KDIGO). Acute Kidney Injury Work Group. KDIGO clinical practice guidelines for acute kidney injury. Kidney Int Suppl 2012; 2:1.*

Graphic 83168 Version 12.0

Evaluation of subacute kidney injury


Increase in creatinine that occurs within three months
Assess for volume loss (ie, vomiting or diarrhea). Discontinue, if possible, medications that cause pre-renal AKI. These include NSAIDs, ACE inhibitors or ARBs, and diuretics. Encourage oral fluid repletion.
Is injury mild (ie, <0.5 mg/dL increase above baseline)?*
Yes
No
Repeat creatinine in one to two weeks
Back to baseline?
Yes
No
No further evaluation. Continue to hold NSAIDs but may cautiously restart ACE inhibitors or ARBs with close follow-up of creatinine. May restart diuretics if required with close follow-up of creatinine.
Obtain ultrasound, urinalysis and sediment, and albumin to creatinine ratio
Is there obstruction?
Yes
No
Relieve obstruction
Is there evidence of proteinuria and/or RBC casts and dysmorphic RBC?
Yes
No
Evaluate for glomerulonephritis, particularly RPGN if RBC casts or dysmorphic RBC present
Further evaluation depends on urinalysis
Granular casts and/or renal tubular epithelial cells
Normal urinalysis
sterile pyuria
Evaluate for ATN
Obtain SPEP and UPEP¶
Evaluate for interstitial nephritis
Abnormal SPEP or UPEP
Normal SPEP and UPEP
Immunofixation and free light chain assay
Abnormal
Normal
Evaluate for MGUS, multiple myeloma, and amylodosis
Rest of evaluation depends on severity of kidney dysfunction
Is injury mild?
No
Yes
Repeat creatinine at one to two weeks
Kidney biopsy, providing significant evidence of chronicity is not present on imaging Δ
Progressive increase in creatinine
Stable
Continued observation

AKI: acute kidney injury; NSAID: nonsteroidal anti-inflammatory drug; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; RBC: red blood cell; RPGN: rapidly progressive glomerulonephritis; ATN: acute tubular necrosis; SPEP: serum protein electrophoresis; UPEP: urine protein electrophoresis; MGUS: monoclonal gammopathy of undetermined significance; GFR: glomerular filtration rate.

* For patients with chronic kidney disease, in whom small fluctuations in creatinine are common, mild injury may be better defined as <50% change in creatinine.

¶ For patients at higher risk for multiple myeloma (ie, age >40 years, and no other obvious cause of reduced GFR), SPEP, UPEP, immunofixation, and serum free light chains are obtained at time of initial evaluation. Some clinicians follow this approach for all adult patients.

Δ Irreversible kidney is suggested by the combination of increased echogenicity and kidney length <10 cm.

Graphic 105741 Version 2.0