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Acute Kidney Injury in the Elderly

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Synopsis

The aging kidney undergoes a number of important anatomic and physiologic changes that increase the risk of acute kidney injury (formerly acute renal failure) in the elderly. This article reviews these changes and discusses the diagnoses frequently encountered in the elderly patient with acute kidney injury. The incidence, staging, evaluation, management, and prognosis of acute kidney injury are also examined with special focus given to older adults.

Keywords

acute kidney injury; acute renal failure; elderly; geriatric

Acute renal failure (ARF) is the rapid loss of kidney function, occurring over hours or days and resulting in the accumulation of metabolic waste products and the dysregulation of extracellular volume and electrolyte homeostasis. ARF is common, especially among the elderly (≥ 65). It has been estimated that it occurs during 2–7% of all hospital admissions[1–3] and at even higher rates in elderly patients.[4–7] Until recently there was no generally accepted operational definition of ARF. As a result reported incidence rates varied greatly due to differences in the definitions used as well as the clinical settings studied. Despite this, acute kidney disease has consistently been associated with increased morbidity and mortality[8–16] and multiple studies as well as a recent meta-analysis have demonstrated worse outcomes in the elderly.[17–23] In light of recent findings that have established an association between even small (0.3 mg/dL) increases in serum creatinine and adverse outcomes, [24–26] the descriptive terminology of acute kidney disease has been modified to recognize the importance of even modest decrements in kidney function.[27, 28] For the remainder of this paper, we will use the term acute kidney injury (AKI) to refer to any sudden reduction in kidney function whereas the term ARF will be restricted to severe organ dysfunction, typically necessitating dialysis or other supportive interventions.

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Definition and Incidence

The definition of AKI in published studies has varied widely and this lack of standardization has been an impediment to a clear understanding of its epidemiology[29]. In 2002, the Acute Dialysis Quality Initiative (ADQI) group proposed the Risk, Injury, Failure, Loss, End-stage renal disease (RIFLE) criteria for diagnosis and stratification[30]. The RIFLE criteria (table 1) use increasing degrees of renal dysfunction (defined based on relative increases in serum creatinine from baseline or duration and severity of oliguria) and clinical outcome criteria (persistent ARF) to classify AKI.[30] Multiple studies have now demonstrated a clear association between RIFLE stage and clinical outcomes across patient care settings [31–39]. More recently, the Acute Kidney Injury Network (AKIN), convened by an international consortium of renal and critical care societies, proposed several refinements to the RIFLE criteria (table 1).[28] Modifications to the definition of AKI included the addition of an absolute increase in serum creatinine of ≥ 0.3 mg/dL and the specification that the decline in kidney function occur within a 48-hour period. The AKIN workgroup also advocated for the use of the term “acute kidney injury” with the goal of enhancing future patient outcomes by fully capturing the broad range of acute renal dysfunction.[28] The use of the term “kidney” in place of “renal” may also assist in patient communication. The AKIN workgroup additionally proposed that the more traditional term “acute renal failure” be restricted to the severe state of complete organ dysfunction. This new terminology emphasizes that regardless of etiology, AKI is characterized by functional and/or morphologic alterations in the kidney.[40]

Despite these recent advances in defining AKI, limitations remain. Both the RIFLE and AKIN criteria are predominantly based upon changes in serum creatinine concentration. Although creatinine remains the best clinical marker of kidney function, there are multiple limitations to its use as a marker of kidney function, especially in the non-steady states that characterize AKI. Elevations in creatinine are often delayed in relation to the onset of AKI,[41, 42] and serum creatinine levels are influenced by factors other than kidney function including muscle mass, volume of distribution, catabolic state, and medications.[43] For example, in the elderly or chronically infirm patient with reduced muscle mass, elevations in creatinine following even severe episodes of AKI may be relatively modest. Additionally, alterations in volume status can also affect creatinine values. Volume expansion in the setting of AKI can diminish the associated increase in serum creatinine or even result in a stable or fall in concentration as a result of hemodilution despite the decline in kidney function.[25] Due in part to these shortcomings, there has been recent emphasis on identifying and validating one or more biomarkers to assist in the early diagnosis of AKI and the differentiation between functional and structural kidney injury. Although multiple candidates have been identified,[44, 45] none have been adequately validated and their use in clinical practice cannot be recommended.

Not surprisingly in the absence of a well-accepted definition of AKI, researchers have used varying criteria. This coupled with diverse clinical study settings and varying methods of ascertainment of AKI has made it difficult to reliably characterize the epidemiology of AKI. Using the 5% random sample of Medicare Beneficiaries from 2000 and identifying AKI based on International Classification of Diseases Ninth Revision (ICD-9) coding, one recent study reported an incidence rate of AKI of 3.1% in a cohort of over 233,000 patients surviving to hospital discharge [18] In an analysis of data from the 5% Medicare Beneficiary Sample over the period 1992 to 2001, the AKI incidence rate based on ICD-9 coding was 2.4% in a sample that included over 5 million hospital discharges.[46] There was a progressive increase in the incidence of AKI over these 10 years, rising from 1.5% of hospital discharges in 1992 to 3.6% in 2001.[46] Similar increases in the incidence of AKI in hospitalized patients have also been reported by other researchers.[7, 47]

However, these findings are likely to underestimate the true incidence of AKI in hospitalized patients due to the limited sensitivity of ICD-9 coding.[29, 46, 48] Studies that have examined the accuracy of ICD-9 codes for AKI have demonstrated that while they are greater than 97% specific, their sensitivity is only approximately 20–35%,[3, 48] suggesting that these studies underestimate the true incidence of AKI. Despite these limitations, similar findings have also been noted in two often-cited studies conducted at two urban US tertiary care medical centers 17 years apart. AKI, as judged by a graded scheme of creatinine elevation, occurred in 4.9% of approximately 2,200 hospitalized patients in 1979 and 7.0% of approximately 4,600 hospitalized patients in 1996.[1, 7] These findings are also generally consistent with a community-based study using the Kaiser-Permanente of Northern California database that evaluated the period from 1996 to 2003 and found an overall incidence of non-dialysis requiring AKI of 384.1 per 100,000 person-years and of dialysis requiring AKI of 24.4 per 100,000 person years, with a progressive increase over the study period.[49]

In addition to the rising incidence of AKI, the median age of patients with AKI also appears to be increasing.[20, 50] This in part reflects improvements in life expectancy with a resultant aging population.[17, 50, 51] Indeed, recent estimates show that significant proportions of the US and western European population are greater than 65 years of age (e.g., approximately 17.5% of the Italian population, 16% of the British population, 16% of the Spanish population, and 12.5% of the US population).[39, 50] The elderly also represent the fastest growing age group in the western world with more than 395 million people expected to be over the age of 60 by the year 2050.[51]

Multiple studies have demonstrated that the elderly are more susceptible to developing AKI.[4, 17, 50, 52–55] In a Spanish hospital cohort, the incidence of AKI was 3.5-times higher in patients older than 70 years than in their younger counterparts.[4] A subsequent study in the same population and setting revealed that patients aged >80 years were 5-times more likely to develop AKI than the general population.[52] In an Italian hospital cohort, the elderly (≥ 65 years) had 10 times the incidence rate of AKI compared to those < 65 years of age.[50] In the Medicare 5% Beneficiary Sample, the incidence of AKI progressively increased with age from 1.9% in those younger than 65 years as compared to 2.9% in those older than 85 years.[46] Similarly, in the Kaiser-Permanente of Northern California community-based cohort, the incidence rate of non-dialysis requiring AKI increased from 78 per 100,000 person-years in patients younger than 50 years to 3,545 per 100,000 person-years in those ≥ 80 years. The increased incidence of AKI in the elderly is thought to be multifactorial, attributable in part to anatomic and physiologic changes in the aging kidney, to an increased burden of comorbidities impacting kidney function, to more frequent exposure to medications and interventions that alter renal hemodynamics or are nephrotoxic, and to alterations in drug metabolism and clearance associated with aging.[6, 17, 43]

The Aging Kidney

The kidney undergoes a number of important age dependent changes (Table 2). Renal mass decreases with aging, reaching approximately 75–80% of young adulthood weight by the age of 80 to 90 years.[56–58] At age 70 years, the kidneys have lost between 30% to 50% of their cortical glomeruli due to ischemic changes and a significant number of the remaining glomeruli manifest some degree of sclerosis.[59–62] Some have posited that the glomerulosclerosis of aging is dependent on subclinical injury to the kidney from comorbidities, including hypertension and vascular disease.[63] Other morphologic changes that occur with aging include a reduction in the number and size of tubules, increasing tubulointerstitial fibrosis, a decrease in glomerular filtering surface area due to an increasing proportion of meansangial cells, thickening of glomerular and tubular basement membranes, arteriosclerosis (even in healthy non-hypertensive elderly patients), and decreased afferent arteriolar luminal area.[64–67]

The structural changes that occur with aging contribute to functional alterations (Table 2). The most salient of these include a reduction in renal blood flow (RBF) of up to 50% from age 20 to age 80[68, 69] and a progressive decline in glomerular filtration rate (GFR).[70, 71] Based on longitudinal studies of healthy patients without hypertension, diabetes, heart disease, or clinically apparent atherosclerosis, a progressive decline in GFR of 0.75 ml/min/1.73m^2 per year was observed after the age of 30. However, approximately 30% of patients did not manifest this age-related GFR decline, making it unclear whether genetic, dietary, metabolic, or other factors contribute to this process. Taken together, the decrease in RBF and GFR represent a loss of renal functional reserve in the elderly and contribute to an increased risk for development of AKI.[65]

Other important renal physiologic changes noted in the elderly, are the loss of urinary concentrating and diluting ability, diminished sodium conservation, decreased plasma renin and aldosterone levels, decreased prostaglandin production, and an enhanced response to vasoconstrictive stimuli.[57, 58, 64, 71–80] These changes have significant clinical implications. The reduced capacity to retain salt and water increases the propensity to develop volume depletion and dehydration.[6] The presence of an increased renal vasoconstrictive response and decreased production of vasodilatory prostaglandins may heighten sensitivity to pathological stressors (e.g., blood loss) and medications (e.g., nonsteroidal anti-inflammatory drugs).

These changes partially explain the susceptibility of the elderly to AKI.[72] Additionally, the aged have a higher prevalence of systemic diseases that contribute to their predisposition to developing AKI including diabetes mellitus (DM), hypertension (HTN), cardiovascular and peripheral vascular disease, congestive heart failure (CHF), benign prostatic hypertrophy (BPH), and malignancies such as prostate cancer and multiple myeloma. Further, treatment of these and a myriad of other disorders in the elderly leads to greater exposure to potentially nephrotoxic medications. In addition, changes in volume of distribution of these medications and decreased renal and hepatic clearance may increase the risk of nephrotoxicity. Nonetheless, the kidneys of the healthy elderly patient are able to compensate and maintain homeostasis under normal conditions despite these age-related alterations. However, in the setting of significant renal stressors, renal adaptive capacity is limited and AKI may result.[6, 72]

Etiologies of Acute Kidney Injury

Although there may be significant pathophysiologic overlap, the clinical assessment of AKI generally begins with categorization into prerenal, intrinsic, and postrenal etiologies. This classification has significant clinical utility, however it should be recognized that there may not be a clear demarcation between prerenal and intrinsic causes of AKI and that the elderly frequently have multiple contributing etiologies.[81, 82]

Prerenal AKI

Prerenal azotemia is defined as a functional decline in glomerular filtration associated with renal underperfusion and is a leading cause of AKI in the general and geriatric populations.[12, 52, 83] Although classically associated with hypovolemia and resulting from failure of normal adaptive responses to maintain GFR, prerenal AKI also commonly develops in the setting of effective intravascular volume depletion associated with congestive heart failure (cardiorenal syndrome) and liver disease.

The normal adaptive response to volume depletion includes activation of the renin-angiotensin-aldosterone axis (RAAS), upregulation of the sympathetic nervous system, and stimulation of vasopressin secretion. Activation of the RAAS increases angiotensin II levels. Angiotensin II, a potent vasoconstrictor, acts on both the afferent (pre-glomerular) and efferent (post-glomerular) arterioles; however its afferent vasoconstrictive effects are normally balanced by

secretion of vasodilatory prostaglandins. The net effect is predominant efferent arteriolar vasoconstriction. While the overall increase in arteriolar resistance results in a fall in renal blood flow, the predominance of postglomerular vasoconstriction allows restoration of a near-normal intraglomerular pressure and maintenance of GFR, albeit at the expense of an increased filtration fraction (the ratio between GFR and renal plasma flow). Changes in intrarenal hemodynamics and upregulation of angiotensin II, aldosterone, vasopressin and the sympathetic nervous system modulate renal tubular function increasing sodium, water, and urea conservation.

Prerenal AKI ensues if the fall in renal perfusion exceeds the ability of these counter-regulatory systems to maintain a near-normal GFR Nonetheless, the adaptive responses maximizing reabsorption of sodium, water, and urea continue to operate, leading to a reduced urine volume, decreased urine sodium concentration and increased urine osmolality. Hence, the features of prerenal AKI (Table 3): low urine sodium concentration (U_{Na} <20meq/L), low fractional excretion of sodium (F_ENa; <1%), low fractional excretion of urea (F_EUrea <35%), high urine osmolality (U_{Osm} >500 mosm/kg), and an elevated blood urea nitrogen (BUN):serum creatinine ratio (>20:1).

In the elderly, these indices may be less useful due to age-associated defects in sodium and water conservation.[84] Urine sodium may be > 20 mEq/L and U_{Osm} < 500 mosm/kg despite effective intravascular volume depletion. In addition, an inability to maximally concentrate the urine may result in prerenal AKI with urine volumes in excess of 500 mL/day. Similarly, diuretics, which may also predispose to prerenal AKI, may diminish the utility of these indices through their effects on renal salt and water handling. Since the hallmark of prerenal azotemia is the rapid restoration of renal function following normalization of kidney perfusion, a therapeutic trial of intravenous fluids may be required to confirm the etiology when diagnostic indices are ambiguous or inconsistent with the clinical setting.

Although frequently regarded as benign, prerenal AKI is associated with an increased mortality risk,[7] most likely related to underlying comorbidities that contribute to its development. It should also be appreciated that prerenal states are a significant risk factor for the development of intrinsic AKI. Pre-existing prerenal states increase the risk of both ischemic and nephrotoxic insults. In addition, prolonged or severe renal hypoperfusion that is initially manifest as functional prerenal AKI may develop into intrinsic AKI (i.e., ischemic acute tubular necrosis) with structural injury to the renal tubules.

Causes of prerenal AKI (Table 4) include states of true volume depletion as well as conditions in which decreased effective arterial blood volume causes renal underperfusion. Common etiologies of true volume depletion include vomiting and diarrhea, blood loss due to hemorrhage, third-spacing of fluids following surgery or pancreatitis and increased renal losses associated with diuretics. Elderly patients may be at increased risk for true volume depletion due to changes in body composition with aging, leading to decreased total body water as a fraction of body weight, and from an increased burden of comorbid disease. Treatment of prerenal AKI associated with true volume depletion requires volume resuscitation with isotonic crystalloid. Prerenal AKI arises from decreased effective arterial blood volume in CHF, cirrhosis, and in select patients with nephrotic syndrome, often exacerbated by diuretic therapy. Treatment in these situations will usually require volume resuscitation and/or treatment of the underlying disease process.

Medication use may also play a significant role in the development of prerenal AKI. Diuretic use exacerbates the underlying predisposition to volume depletion and may contribute in up to 25–40% of cases of prerenal AKI in elderly patients.[85] Medications that alter renal hemodynamics also contribute to the development of prerenal AKI. Nonsteroidal anti-

inflammatory drugs (NSAIDs), which are used by approximately 10–25% of the elderly,[86–89] inhibit production of vasodilatory prostaglandins. NSAID use has been associated with a threefold higher risk of AKI in the general population[90] and an absolute risk of prerenal AKI of 13% in a very old (mean age 87 years) nursing home cohort.[91] The simultaneous presence of chronic kidney disease, CHF, DM, HTN, diuretic or angiotensin converting enzyme inhibitor (ACEI) use further increases this risk.[90–92] The elderly are believed to have a higher baseline risk of AKI from NSAID use due to prolonged NSAID half-life, decreased body mass, and the previously outlined age-related physiologic changes that make them more reliant on prostaglandin dependent afferent arteriolar vasodilation.[55, 93] Judicious use of these medications and close patient follow-up are recommended in the aged, especially in those with reduced GFR. If prerenal AKI occurs, timely discontinuation of NSAIDs and volume repletion may help restore renal function before the onset of ischemic acute tubular necrosis (ATN). Patient education is also warranted given the wide non-prescription availability of NSAIDs and findings that suggest many patients would be willing to switch to other safer, albeit less effective, analgesics.[94]

Two other classes of agents frequently used by the elderly that carry a significant risk of prerenal AKI are angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB).[85] The use of these medications has increased in the setting of CHF and HTN. Risk factors associated with the development of AKI due to ACEI or ARB include volume depletion, underlying chronic kidney disease, bilateral renal artery stenosis (or unilateral renal artery stenosis with a solitary kidney), CHF, and concomitant diuretic use.[55] While these agents are not contraindicated in the elderly, they must be used with caution. Follow-up serum chemistries should be obtained 1 to 2 weeks after initiating or increasing the dose of these medications to monitor for AKI or hyperkalemia. A creatinine increase of greater than 30% from baseline should prompt discontinuation or dose reduction of the medication.[95] Although evaluation for renal artery stenosis may be considered,[95] most cases of ACEI or ARB induced AKI are not associated with renal artery stenosis.[96] Prompt volume repletion and cessation of the medication usually restore kidney function.

Intrinsic AKI

Intrinsic AKI is differentiated from prerenal states by the presence of structural injury to the kidneys that persist after withdrawal of the inciting factors. It is useful to categorize the etiologies of intrinsic AKI based on the histologic compartment of the kidney that is predominantly injured. Thus, we differentiate between primary damage to the tubular epithelium (acute tubular necrosis, ATN), inflammatory diseases of the interstitium (acute interstitial nephritis, AIN), glomerular disease (acute or rapidly progressive glomerulonephritis), and acute vascular disorders as their treatment and outcomes differ significantly.

Acute Tubular Necrosis—ATN is the most common form of intrinsic AKI. It accounts for nearly half of all cases of AKI in hospitalized patients[12, 52, 97] and is the predominant cause of AKI in critical illness.[98] Although ATN is classified as ischemic or nephrotoxic, these etiologies frequently coexist and many cases are multifactorial. Ischemic ATN may develop in approximately 50% of critically ill patients.[9, 99] Septic ATN, although previously considered a subset of ischemic ATN, has a more complex pathophysiology than exclusive renal ischemia.[99] Sepsis has been linked to 30% of ATN cases in the elderly[100–102] and endotoxemia triggered renal vasoconstriction may heighten the elderly patient's susceptibility to ATN.[64] Recent studies also indicate that endotoxemia may independently activate inflammatory mediators and incite endothelial damage that potentiates the renal injury due to hypoperfusion.[99, 103–105] Prerenal AKI can lead to ischemic ATN if volume repletion is delayed and this progression appears to be more common in the aged.[83] Surgical interventions are associated with almost

one-third of cases of ischemic ATN in the elderly with cardiac surgery and aortic aneurysm repair as the most common precipitants.[21, 106] Perioperative hypotension, blood loss, gastrointestinal drainage, and preoperative cardiac complications account for many of these cases of ATN.[4, 5]

The development of ischemic ATN involves multiple pathways including ischemia-reperfusion injury to the tubular epithelial cells, endothelial injury with disruption of microvascular flow, and activation of inflammatory pathways.[107–113] Clinically, ischemic ATN can follow a highly variable course, however, four characteristic stages have been identified: initiation, extension, maintenance, and recovery.[107, 111]

In the initiation phase, ischemia-reperfusion injury causes a loss of tubular epithelial cell polarity, cellular detachment, and triggers apoptosis and necrosis.[114, 115] The combination of renal vasoconstriction, sloughed tubular debris forming obstructing intratubular casts, and backleak of glomerular filtrate across the denuded epithelial surface leads to a loss of renal function[114] Clinically, BUN and creatinine levels increase. Urine output can vary; although oliguria or anuria may be present, some patients remain nonoliguric throughout their course. The initiation phase rapidly transitions into the extension phase. Although the inciting insult may have resolved, this phase is characterized by continued renal ischemia and hypoxia that is mediated by microvascular endothelial injury and inflammatory processes.[107] In the maintenance phase, renal function remains suppressed despite resolution of renal ischemia. During this stage, endothelial cells and tubular epithelial cells have an opportunity to repair, proliferate, and redifferentiate to help restore previous structure and function.[114, 116] However, superimposed insults including recurrent hypotension, nephrotoxin administration, and intravascular volume depletion may prolong this phase and delay recovery. The maintenance phase is followed by recovery of kidney function. In the recovery phase, urine output may increase briskly as persistent tubular dysfunction results in impaired salt and water homeostasis despite recovery of GFR, necessitating careful monitoring of volume and electrolyte status.

Risk factors for ischemic ATN include pre-existing chronic kidney disease, diabetes, atherosclerosis, active malignancy, and low serum albumin[117]; conditions that are more prevalent among the elderly. Patients with impaired renal autoregulation are also at increased risk for developing ATN even in the absence of frank hypotension. This is generally seen in patients with advanced age, hypertension, atherosclerosis, chronic kidney disease, or renal artery stenosis.[118]

The treatment of ATN is primarily supportive, as no specific therapeutic interventions have been found to hasten recovery of kidney function. In elderly patients with ATN, very careful attention must be paid to medication dosing, using pharmacokinetic monitoring to minimize the risk of drug toxicity. Although dopamine has been tried as a therapeutic agent, based on its renal vasodilatory properties, it has not been demonstrated to provide clinical benefit, is associated with an increased risk of cardiac arrhythmias and has no role in the treatment of ATN.[119, 120] The role of diuretic therapy in established ATN is less clear. Although nonoliguric ATN is associated with a better prognosis, use of diuretics to convert patients from oliguric to nonoliguric ATN is not associated with improved outcomes. Rather, diuretic response identifies a subset of patients with a better prognosis. Nevertheless, diuretics may be helpful in volume management, although high doses of loop diuretics (160 mg of furosemide) are often required. If the patient fails to respond, further doses are generally not helpful or indicated. Initiation of renal replacement therapy, if otherwise indicated, should not be deferred for a trial of diuretics, as doing so may be associated with worsened outcomes.[121, 122]

Nephrotoxic ATN results from direct tubular injury from endogenous or exogenous renal toxins. Myoglobin, hemoglobin, and light chains are frequently encountered endogenous

substances associated with tubular toxicity. Heme-pigment nephrotoxicity can be seen in the setting of severe hemolysis or rhabdomyolysis. The AKI seen in myeloma kidney is in part attributable to the renal toxicity of light chains. Antibiotics, particularly aminoglycosides and amphotericin B, and chemotherapeutic agents such as cisplatinum remain important causative agents of nephrotoxic ATN in the elderly. Age is a well-described risk factor for the development of aminoglycoside nephrotoxicity.[123] The often inappropriate dosing of medications as the result of overestimation of the level of renal function and loss of lean body mass place the elderly at increased risk of nephrotoxicity from other medications as well.[55]

Contrast-induced nephropathy (CIN) is a major cause of AKI in hospitalized elderly patients.[82, 124] Older adults may also have an elevated risk of developing contrast-induced nephropathy due to a higher prevalence of chronic kidney disease,[125, 126] an important risk factor for contrast nephropathy.[127–129] However, age *per se* has not been consistently identified as an independent predictor of contrast nephropathy. Other risk factors include diabetic nephropathy, volume depletion, volume of contrast administered, and use of high osmolar (as compared to low or iso-osmolar) contrast agents.[127–129] Clinically, CIN is characterized by an acute rise in the creatinine within 24 to 48 hours after contrast administration that subsequently peaks after 3 to 5 days followed by a return to baseline within 7 to 10 days. The patient usually remains non-oliguric and the urinary sediment may reveal granular casts and renal tubular epithelial cells.

The primary means of preventing CIN is the avoidance of the unnecessary administration of contrast to high risk patients. If contrast administration is indicated, a low osmolarity or iso-osmolar agent should be used and the volume of contrast administered should be minimized. The primary intervention for prevention of CIN is adequate administration of isotonic intravenous fluids prior to and following contrast administration.[130–132] The optimal regimen for fluid administration is uncertain, however the use of at least 1 mL/kg of isotonic saline for 4 to 12 hours pre- and post-procedure are generally recommended.[133] Although several studies have suggested added benefit with the use of sodium bicarbonate rather than saline,[134] the actual benefit is uncertain.[135, 136] The role of the antioxidant N-acetylcysteine in preventing CIN remains unclear. Multiple large studies have yielded conflicting results and multiple meta-analyses have similarly produced contradictory findings.[137–143] Based on these inconsistent results, it seems unlikely that N-acetylcysteine exerts a large protective effective. However, given the safety profile and minimal cost of oral N-acetylcysteine as well as the significant morbidity associated with CIN, its continued use is not inappropriate.

Acute Interstitial Nephritis—Acute interstitial nephritis (AIN) is a less common cause of intrinsic AKI accounting for less than 5% of cases, although the reported incidence in biopsy series of unexplained AKI is much higher at approximately 20–25%.[144, 145] Pathologically, AIN is characterized by an acute lymphocytic infiltrate of the renal interstitium, often with accompanying eosinophils. Although the classic presentation consists of AKI accompanied by the triad of fever, rash, and eosinophilia, the complete triad is observed only in approximately 15% of patients.[146, 147] Typical urinary abnormalities include sterile pyuria, white blood cell casts, hematuria, and sub-nephrotic proteinuria. Although eosinophiluria has been considered a hallmark finding it is not specific[148–150], as it may be seen in pyelonephritis, prostatitis, cystitis, and atheroembolic disease. Although the diagnosis is often made on the basis of the clinical presentation, renal biopsy may be necessary to confirm the diagnosis.

Hypersensitivity to medications is the most frequent cause of AIN, accounting for 60 to 70% of cases.[146, 147] Antibiotics, particularly penicillins, cephalosporins and sulfonamides, are the most commonly implicated drugs. The onset of AIN is usually within 3 weeks of initiation of the inciting medication although this is highly variable. Infections are the second leading cause, followed by systemic collagen vascular diseases. AIN appears to be more common in the

elderly, perhaps related to the more frequent use of prescription and over-the-counter medications including NSAIDs.[146]

Treatment consists of discontinuation of the offending agent or treatment of the underlying infection or systemic disorder. Renal recovery is variable and often takes days to weeks. The role of corticosteroids is controversial although they have been used in small, uncontrolled trials to accelerate kidney recovery.[151] While it has been suggested that early initiation of corticosteroids is associated with more complete recovery of kidney function,[152] results have not been consistent[153] and have not been validated in randomized studies.

The presentation and course and NSAID-induced AIN differs considerably from other forms of medication-induced AIN. The onset of NSAID-induced AKI is often delayed months after the initiation of the medication and classic hypersensitivity symptoms are seldom present.[154] Frequently, the patient exhibits nephrotic range proteinuria and minimal change disease or membranous nephropathy is commonly found on kidney biopsy.[154, 155] Prompt cessation of NSAID use is required and renal recovery, including resolution of proteinuria, usually occurs within 2 months.[154]

Acute Renal Vascular Disease—Vascular diseases associated with AKI can be divided into large vessel or small vessel processes. The large-vessel processes that can produce AKI include renal artery thromboembolism, renal artery dissection, and renal vein thrombosis. Their incidence in the elderly may be increased.[97] Although all of these may cause renal infarction, AKI will only result if the lesions are bilateral, occur unilaterally in a solitary kidney, or occur in a patient with significant pre-existing chronic kidney disease. Clinically, these disorders present with sudden flank pain, hematuria, and oligoanuria depending on severity and are associated with elevations in serum lactate dehydrogenase (LDH). Risk factors include trauma, nephrotic syndrome, and atrial fibrillation. Confirmation of the diagnosis requires imaging with contrast-enhanced CT scan, MRI, radionuclide renal scan, or angiography to demonstrate the vascular lesion or renal perfusion defect. The lesions are typically not amenable to fibrinolytic therapy or interventional approaches and therapy usually consists of anticoagulation and supportive care.

Small vessel involvement with atheroembolic disease is more common. Atheroembolic disease is largely a disorder of the elderly, with a mean age of 71 in one series,[156] and is associated with diffuse atherosclerosis. Although atheroembolism can occur spontaneously, it is more commonly triggered by vascular surgery or angiographic procedures, anticoagulation or thrombolytic agents. Destabilized atheromatous plaques shower cholesterol crystals into the small arteries of the skin, central nervous system, extremities, gastrointestinal system and kidneys, with the kidneys being a frequently involved organ due to the high renal blood flow. The cholesterol emboli are usually non-obstructing; however they incite a vigorous inflammatory response that eventually occludes the vascular lumen. Although the presentation may occur immediately after vascular surgery or angiography, patients often present days to weeks after the procedure with worsening renal function, *livedo reticularis*, and ischemic necrosis of the toes. Eosinophilia, eosinophiluria, proteinuria, and hypocomplementemia are often documented. The renal course is highly variable but often manifests as subacute kidney injury with a progressive or stuttering deterioration in renal function over a period of days to weeks. Although atheroembolic disease carries a poor prognosis, renal functional recovery can occur.[157] There is no specific treatment for atheroembolic disease. Care is supportive including nutritional support, especially if there is concomitant gastrointestinal involvement, and aggressive management of hyperlipidemia. Anticoagulation is contraindicated as it may precipitate further cholesterol embolization.

Acute Glomerulonephritis—AKI can also develop from acute or rapidly-progressive glomerulonephritis. Timely diagnosis and treatment of these conditions is critical in order to preserve renal function and avoid life-threatening complications. Diffuse proliferative forms of glomerulonephritis can be associated with infections and generally carry a good prognosis both in the elderly and young.[158–161] Rapidly progressive (crescentic) glomerulonephritis is a fulminant presentation of glomerular disease that will lead to renal failure over days to weeks if left untreated. Evidence suggests that rapidly progressive glomerulonephritis may be more common among the elderly and carries a poorer prognosis.[158, 159, 162–166] Clinically, patients often present with AKI, hypertension, hematuria, and proteinuria. Characteristically, the urinary sediment demonstrates dysmorphic red blood cells and red blood cell casts. Serologic studies including complement levels, antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane antibodies, cryoglobulin levels, and hepatitis B and C antibodies can be useful in suggesting an etiology, although kidney biopsy is nearly universally required for specific diagnosis. Treatment, including high-dose glucocorticoids, immunosuppressive therapy and plasmapheresis, will be dependent on the specific etiology. Despite the potential for treatment associated toxicities, case series have demonstrated that elderly patients with limited comorbidities may tolerate and respond well to therapy.[167]

Postrenal AKI

Post renal or obstructive AKI is a more common entity in the aged than in the young,[52] accounting for 9% to 30% of cases.[54, 97, 100, 168] Postrenal AKI can be categorized as affecting either the upper urinary tract (proximal to the bladder) or lower urinary tract (obstruction occurring at the bladder outlet or urethra). Obstruction of the lower tract will affect both kidneys and diminish renal function. In contrast, unilateral upper tract obstructing processes may cause renal colic and unilateral hydronephrosis, but will not cause deterioration in renal function if the contralateral kidney can compensate. However, if the obstruction is bilateral, is of a unilateral functioning kidney, or if there is significant underlying chronic kidney disease, upper tract obstruction can also cause AKI.

The most frequent causes of postrenal AKI (Table 5) in the elderly include benign prostatic hypertrophy (BPH) or prostate cancer, retroperitoneal adenopathy or malignancies, pelvic neoplasms, and neurogenic bladder. Though BPH and prostate cancer are common in older men, they fortunately cause obstruction in only a minority of cases. In elderly women, pelvic and retroperitoneal malignancies are the most frequent causes of postrenal AKI.[6]

Postrenal AKI may present with either complete or partial obstruction. Complete obstruction is characterized by anuria. The patient may also report flank and abdominal pain or suprapubic fullness. In contrast, the patient with partial obstruction may remain completely asymptomatic or may report similar pain symptoms as well as voiding complaints including frequency, urgency, hesitancy, hematuria, and nocturia. Urine output can be variable, ranging from oliguria to polyuria, or fluctuating between the two.

Due to its increased incidence in the elderly and varying presentation, the clinician must maintain a high index of suspicion for postrenal AKI. The diagnosis should especially be considered in patients with BPH or lower urinary tract symptoms; diabetes; kidney stones; abdominal or pelvic malignancies, surgeries, or radiation; retroperitoneal adenopathy or neoplasms; and medication use associated with urinary retention. Lower tract obstruction is diagnosed by confirmation of urinary retention using ultrasonographic bladder scans or placement of a bladder catheter. An elevated residual bladder volume (>100–150 ml) after voiding is highly suggestive of postrenal AKI; although, some elderly patients may suffer from chronic urinary retention with elevation in the postvoid residual bladder volume in the absence of kidney dysfunction. [169, 170] Radiographic workup for upper tract obstruction usually begins

with ultrasound imaging, which is both sensitive and specific in detecting obstruction.[171] However, ultrasonography may appear normal in patients presenting with early obstruction or with retroperitoneal processes encasing the kidneys and ureters, preventing ureteral dilation.[172] Computed tomography (CT) can be valuable in determining the cause and level of obstruction if ultrasound fails to identify the lesion. Together, ultrasound, abdominal plain films, and CT scanning are diagnostic in the vast majority of cases.[173, 174] Intravenous pyelography has been supplanted by CT imaging and is now only rarely required. Antegrade or retrograde pyelography, however, can be valuable in identifying the site and cause of obstruction and provides an opportunity for therapeutic intervention. Laboratory findings are nonspecific in postrenal AKI often mimicking prerenal AKI in the early phase and intrinsic AKI later.[175, 176]

Treatment of postrenal AKI consists of the rapid detection and relief of obstruction. This can be accomplished by placement of a bladder catheter in lower tract disease or ureteral stents or percutaneous nephrostomy tubes for upper tract disease. A brisk post-obstructive diuresis frequently ensues due to water and sodium reabsorptive deficits as well as an osmotic diuresis attributable to previously retained solutes including urea.[64] Careful monitoring of the patient's volume status and electrolytes is essential to avoid the development of volume depletion or serious electrolyte disturbances. Although use of intravenous fluids may be required, it is important to avoid overly aggressive fluid replacement that can drive further diuresis. If the obstruction has been quickly diagnosed and reversed, renal function will improve. However, in patients with a longer duration and higher-grade of obstruction, renal functional recovery may be delayed, incomplete, or absent.[177] Brisk urine output following correction of the obstruction does not always correlate with renal recovery and hence close laboratory monitoring remains necessary.

Diagnostic Approach to the Patient with AKI

A detailed history and physical examination is critical in differentiating the etiologies of AKI. Questions identifying previously mentioned symptoms or risk factors for hypovolemia, obstruction, ATN, AIN, heme-pigment nephropathy, myeloma, and atheroembolic disease are portions of the requisite thorough history. An examination must also include careful assessment of volume status, evidence of systemic vasculitis, atheroembolic disease and extra-renal manifestations of systemic diseases, and signs of uremia. Initial diagnostic studies (Table 6) should include a urinalysis including urine sediment examination, urine chemistries (urine sodium and creatinine), a bedside postvoid bladder sonogram or placement of a bladder catheter to rule out lower urinary tract obstruction, and renal ultrasound. The urinary sediment exam remains important as the presence of cellular elements and casts may confirm the previous clinical impression or force the clinician to re-examine the original working diagnosis. If the etiology of AKI remains unclear following a careful history, physical examination, and laboratory work-up, or if the work-up suggests the presence of acute glomerular disease, consideration of a kidney biopsy is warranted. A kidney biopsy is a relatively low risk procedure that is well tolerated by patients, even among the elderly. Approximately 30% of diagnoses were altered in one case series of kidney biopsies for AKI in older adults (age > 60 years).[145]

Treatment

The therapeutic modalities available for specific causes of AKI have been reviewed under each respective etiology. All patients with significant AKI also require attentive management of volume, electrolyte and acid-base status, and nutrition. Prompt reversal of fluid deficits is critical in preventing further exacerbation of AKI. Once deficits have been corrected, the clinician must continue to carefully assess volume status to ensure the patient does not develop

excessive volume expansion that may lead to pulmonary edema. Sodium and fluid restriction may be necessary. Similarly, electrolytes should be monitored closely. Potassium, phosphorus, and magnesium intake can be restricted as appropriate and phosphate binders may be necessary to treat hyperphosphatemia. Although mild hypocalcemia and hyperuricemia may be seen, if asymptomatic, these often do not require correction. If significant acidosis develops (pH<7.2), supplemental bicarbonate may be provided to maintain pH within a safe range. Additionally, medication doses should be adjusted for the impairment in kidney function. Serum creatinine values may not adequately reflect the true level of kidney function, and drug levels should be monitored, if possible. Nutritional support must not be overlooked as nutritional status is an important predictor of prognosis in AKI[178] and the elderly are particularly at risk for developing malnutrition.

In addition to the above supportive measures, renal replacement therapy (RRT) may be required in severe AKI. Indications for RRT in the setting of AKI include hyperkalemia, volume overload especially if associated with pulmonary edema, severe acidosis, or overt uremia. However, RRT is frequently started prophylactically, before the development of these complications. To date, studies have been unable to delineate the ideal timing for initiation of RRT.[179–181] Options for RRT include conventional intermittent hemodialysis, peritoneal dialysis, the various modalities of continuous renal replacement therapy including continuous hemodialysis and continuous hemofiltration, and the newer hybrid therapies, such as sustained low efficiency dialysis. Recent studies indicate that the specific modality of RRT does not affect outcomes, [182–184] and that the resources and expertise available at the local institution should guide the choice of dialysis modality. A recent, large multi-center randomized trial demonstrated that in the setting of critical illness, higher intensities of RRT did not improve morbidity or mortality over more conventionally dosed RRT.[185] In older adults with AKI, age alone should not be a contraindication to RRT as many elderly patients with AKI will recover renal function and do well.[6]

Prognosis

AKI has been consistently associated with increased morbidity and mortality, although outcomes appear to be improving.[8–16, 47, 186] Most patients with AKI recover renal function. Yet, one recent study revealed that among surviving intensive care unit patients with AKI, only approximately 55% exhibited complete recovery.[187] Growing evidence also indicates that AKI is a significant risk factor for chronic kidney disease and dialysis dependence in the elderly,[4, 17, 18, 54, 168, 188] with a recent meta-analysis revealing that 31% of elderly patients failed to recover renal function after an episode of AKI as compared to 26% of younger patients.[17] In one recent analysis following multivariate adjustment, the risk of end-stage renal disease was 13 times higher in hospitalized elderly patients with AKI than in elderly patients without AKI.[18] In that study, the risk of new dialysis dependence in elderly AKI patients steadily increased from 1% at 30 days following discharge to 7% at 2 years.[18] This risk was further elevated in the presence of pre-existing chronic kidney disease.[18] These findings imply that hospitalized elderly patients with AKI require close follow-up of their renal function upon discharge as a significant proportion will have residual functional defects and many may eventually require RRT. The same study also documented an absolute 2-year mortality risk increase of 29% for elderly patients with AKI compared to their elderly counterparts without AKI.[18] These findings are consistent with other recent studies that have demonstrated an increased mortality in older patients with AKI.[187, 189] Hence, AKI should not be viewed as a self-limited disease process from which most patients eventually recover but rather as a significant risk factor for long-term morbidity and mortality following hospital discharge.

Conclusion

The incidence of AKI is increasing, especially among the elderly. Anatomic and physiologic changes related to aging coupled with increased comorbidities appear to elevate the risk of developing AKI in older adults. A multitude of etiologies may cause or contribute to AKI and a careful assessment aided by serum, urinary, and radiologic tests will often arrive at the appropriate diagnosis. Studies reveal that the elderly suffer higher morbidity and mortality from AKI. However, reasonable outcomes are obtained in most elderly patients with AKI and age alone should not be a criterion for withholding supportive therapies. A standardized staging system for AKI coupled with a growing knowledge of its pathophysiology may allow for the identification of future treatments and consequent improvements in outcomes in the coming years.

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Table 1

Acute Kidney Injury Staging Criteria

Stage	Creatinine Criteria	Urine Output Criteria
	RIFLE Criteria	
Risk	Creatinine increase of 1.5–2 times baseline value	<0.5mL/kg/hr x 6hr
Injury	Creatinine increase of 2–3 times baseline value	<0.5mL/kg/hr x 12hr
Failure	Creatinine increase of ≥ 3 times baseline value or a creatinine value > 4mg/dl with an acute rise of ≥ 0.5mg/dL*	<0.3mL/kg/hr x 24hr or anuria x 12hr
Loss	Persistent acute renal failure (complete loss of kidney function) for > 4 weeks	
End-stage kidney disease	Persistent acute renal failure (complete loss of kidney function) for > 3 months	
	AKIN Criteria†	
1	Creatinine increase of 1.5–2 times baseline value **or increase in creatinine of ≥ 0.3* mg/dL**	<0.5mL/kg/hr x 6hr
2	Creatinine increase of 2–3 times baseline value	<0.5mL/kg/hr x 12hr
3	Creatinine increase of ≥ 3 times baseline value or a creatinine value > 4mg/dl with an acute rise of ≥ 0.5mg/dL*	<0.3mL/kg/hr x 24hr or anuria x 12hr

*To convert creatinine from mg/dL to μmol/L, multiply by 88.4.

†Reduction in renal function must occur within 48 hours.

Table 2

Anatomic and Physiologic Changes in the Aging Kidney

Anatomic
Loss of renal mass
Glomerular drop out and glomerulosclerosis
Diminished glomerular filtering surface area
Decreased tubular size and number
Increased tubulointerstitial fibrosis
Thickened glomerular and tubular basement membranes
Decreased afferent arteriolar luminal area
Increased arteriosclerosis
Physiologic
Decreased renal blood flow
Decreased glomerular filtration rate
Diminished urinary concentrating and diluting capacity
Diminished capacity for sodium conservation
Decreased plasma renin and aldosterone levels
Decreased prostaglandin production
Increased vasoconstrictive response to stimuli (e.g., volume depletion)

Table 3

Comparison of Laboratory Findings in Prerenal AKI and Acute Tubular Necrosis

Laboratory Measure	Prerenal	Intrinsic
BUN:Creatinine	>20:1	<15:1
Urine osmolality (mosm/kg)	>500	<350
Urine sodium (meq/L)	<20	>40
Fractional excretion of sodium	<1%	>2%
Fractional excretion urea	<35%	>50%
Urine microscopy	nonspecific, may include hyaline casts	renal tubular epithelial cells or casts, granular casts (“muddy brown”)

Table 4
Etiologies of Prerenal Acute Kidney Injury

True volume depletion
Blood loss
Insensible losses
Adrenal insufficiency
Gastrointestinal losses
Vomiting
Diarrhea
Genitourinary losses
Diuretics
Osmotic diuresis (hyperglycemia)
Third spacing
Decreased effective arterial blood volume
Heart failure
Cirrhosis
Nephrotic syndrome
Medications
Nonsteroidal anti-inflammatory drugs
ACEI/ARB
Calcineurin inhibitors
Hypercalcemia

Table 5
Causes of Postrenal Acute Kidney Injury

Upper tract obstruction
Nephrolithiasis
Blood clots
Papillary tissue
Pelvic neoplasms
Endometriosis
Retroperitoneal processes
Neoplasms
Adenopathy
Fibrosis
Hematoma
Gastrointestinal neoplasms
Radiation treatment
Lower tract obstruction
Urethral strictures
Nephrolithiasis
Blood clots
Phimosis/Paraphimosis
Prostatic processes
Benign hypertrophy
Carcinoma
Calculi
Bladder processes
Carcinoma
Calculi
Neurogenic bladder

Table 6

Urinary findings in Acute Kidney Injury

Test	Associated disorders	Miscellaneous notes
Urine sodium		
<20 meq/L	prerenal, hepatorenal syndrome, postrenal	Rhabdomyolysis can be associated with low urine sodium but usually with superimposed intravascular volume depletion
>40 meq/L	ATN, AIN, postrenal	Postrenal AKI can mimic either prerenal AKI or ATN in its urinary findings.
Fractional excretion of sodium		
<1%	prerenal, hepatorenal, acute glomerulonephritis, rhabdomyolysis, postrenal	
2%	ATN, AIN, postrenal	
Urine specific gravity		
≥1.020	prerenal, hepatorenal, contrast nephropathy, postrenal	Contrast agents with increased osmolality will increase the urinary specific gravity
1.010	ATN, AIN, postrenal	
Urine dipstick		
Proteinuria	glomerulonephritis, AIN, renal artery thromboembolism, renal vein thrombosis, atheroembolic disease, TTP/HUS, malignant hypertension, pyelonephritis/urinary tract infection	
Blood	glomerulonephritis, AIN, renal artery thromboembolism, renal vein thrombosis, atheroembolic disease, TTP/HUS, malignant hypertension, rhabdomyolysis, postrenal	Rhabdomyolysis will generate a positive dipstick response for heme but microscopy usually reveals no red blood cells. Postrenal AKI may be associated with hematuria depending on the etiology
Urine sediment		
WBCs	AIN, pyelonephritis/urinary tract infection, atheroembolic disease, glomerulonephritis,	AIN, atheroembolic disease, and pyelonephritis may all be associated with eosinophiluria
RBCs	glomerulonephritis, AIN, renal artery thromboembolism, renal vein thrombosis, atheroembolic disease, TTP/HUS, malignant hypertension, postrenal,	
RBC casts	glomerulonephritis, malignant hypertension	
WBC casts	AIN, pyelonephritis, rarely atheroembolic disease	
Granular casts	ATN, occasionally seen in a variety of other etiologies	Marked hyperbilirubinemia may be associated with casts that appear granular