Chapter 18: Acute Kidney Injury in the Elderly

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Acute kidney injury (AKI), as defined by the precipitous decline in GFR, is frequently encountered in the elderly. The effect of advancing age in decreasing renal reserve and the associated comorbid conditions of elderly patients increase the risk for the development of AKI. Although studies describing the incidence of AKI in this population are difficult to compare because the definitions of AKI vary dramatically from study to study, it is clear that the elderly are at the highest risk for the development of AKI. Indeed, Feest et al.\textsuperscript{1} showed that there is a three- to eight-fold, progressive, age-dependent increase in the frequency of development of community-acquired AKI in patients older than 60 yr of age. The mean age of patients with AKI has increased by 5 to 15 yr over the past 25 yr.\textsuperscript{2} Groeneweld et al.\textsuperscript{3} showed that the age-related yearly incidence of AKI rose from 17 per million in adults under age 50 yr to 949 per million in the 80 to 89 yr age group. Although all causes of AKI are encountered in this age group, the frequency of prerenal and postrenal etiologies is especially prevalent in the elderly.\textsuperscript{4} Furthermore, elderly patients are more frequently subjected to invasive procedures and exposure to multiple (and possibly nephrotoxic) medications and to radiocontrast agents, all of which increase the risk for AKI.

**STRUCTURAL AND FUNCTIONAL ALTERATIONS IN THE AGED KIDNEY**

In the absence of a specific disease, the kidney undergoes age-dependent structural and functional alterations leading to a significant decrease in renal mass, functioning nephron numbers, and baseline kidney function.\textsuperscript{5} Under normal conditions, these changes can be functionally compensated for by adaptations in renal hemodynamics to maintain a sufficient GFR. However, in the setting of pathophysiologic challenges, the older kidney lacks sufficient functional reserve and is more likely to develop clinically relevant damage.\textsuperscript{6} Although it has been proposed that parenchymal loss in the aging kidney directly confers a higher susceptibility to acute damage, this is not supported by experimental data in which the reduction in renal mass surprisingly protected against ischemia/reperfusion injury in a 5/6 nephrectomy model.\textsuperscript{7} Thus, cellular and molecular alterations that occur with aging may be more important than simply a loss in nephron numbers.

Lameire et al.\textsuperscript{8} showed that, in combination with dehydration, a disturbance in autoregulatory defense mechanisms that would normally preserve GFR and renal blood flow can, in the elderly kidney, lead to ischemia and AKI. One hypothesis links blunted nitric oxide (NO) production in the elderly kidney to an increased risk for AKI.\textsuperscript{9} For example, studies in a rat model of gentamicin-induced AKI show that an increased glomerular NO production seems to protect renal function through its vasodilatory effects.\textsuperscript{10} When old and young animals are treated with equivalent doses of gentamicin, older animals show more severe AKI that correlates with a blunted stimulation in NO production.\textsuperscript{10} Miura et al.\textsuperscript{11} have also hypothesized that, in addition to alteration autoregulation, aging tubular cells may be more vulnerable to ischemic damage because cellular antioxidant defenses decline with age as well as the fact that tubular cells have alterations in metabolism that render them more susceptible to injury (such as an accelerated rate of ATP depletion caused by mitochondrial alterations).

**CAUSES OF AKI IN THE ELDERLY**

In the elderly, AKI is often iatrogenic and multifactorial. Elderly patients show the same spectrum for the causes of AKI as the general population. How-
ever, specific differences in the incidences and presentation make this group unique. For example, elderly patients are more likely to have received multiple concurrent insults that result in AKI.

Prerenal AKI
Prerenal AKI is the second most common cause of AKI in the elderly, accounting for nearly one third of cases.12 The main cause of prerenal AKI is decreased perfusion to the kidney. Although many of the causes of renal hypoperfusion can be reversed with adequate fluid replacement, others progress to acute tubular necrosis (ATN). Interestingly, the evolution to ATN occurs more frequently in the elderly than in younger patients.6 Decreased perfusion to the kidney can develop from decrease in cardiac output or effective circulating volume (sepsis, cirrhosis, nephrotic syndrome) or hypovolemia (gastrointestinal losses, bleeding, diuretic use, poor oral intake).

Dehydration is a common occurrence in the elderly, affecting nearly 1% of hospital admissions in the elderly.13 Risk factors for dehydration include acute febrile illnesses, polypharmacy (diuretics, laxatives, drugs that decrease appetite or level of consciousness), and being bedridden. These patients often present in AKI with significant hypernatremia and, if untreated, the condition has a very high mortality rate.14 It may be difficult to make the diagnosis of hypovolemic AKI in the elderly because the clinical signs and symptoms of dehydration (such as tachycardia, skin tenting) are unreliable. Furthermore, the traditional urinary parameters for differentiating prerenal from intrinsic renal failure may simply reflect age-related disturbances in tubular handling of sodium and water as well as drug effects (diuretics). Thus, a high degree of suspicion for prerenal etiologies must be entertained, and a cautious trial of fluid therapy may be warranted. Because of the high incidence of urinary incontinence, a foley catheter should be placed to closely monitor urine output.

RENNAL AKI
Numerous intrarenal causes of AKI can affect the elderly, of which ATN is the most common. An exhaustive description of these causes is beyond the scope of this chapter; however, those causes that are more specifically relevant to the elderly population are discussed below.

Renovascular Diseases
This group of etiologies includes any cause of acute obstruction of the renal vasculature. Thus, cholesterol embolization after intravascular procedures or surgery or rarely acute renal artery thrombosis may lead to this syndrome of AKI. Elderly patients, by virtue of their increased burden of atherosclerotic vascular disease and increased need for invasive procedures, are at heightened risk.

Hemodynamically Mediated AKI
Direct interference with the protective autoregulatory mechanisms of renal blood flow and GFR may precipitate AKI. Drugs commonly prescribed to the elderly and known to impair renal autoregulation or to interfere with the vasodilatory capacity include nonsteroidal anti-inflammatory agents (NSAIDs), angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor antagonists (ARB).

Well-known risk factors for NSAID-induced AKI include age >60 yr, atherosclerotic cardiovascular disease, pre-existing chronic kidney disease (CKD), and renal hypoperfusion states (sodium depletion, diuretic use, cirrhosis, congestive heart failure, hypotension, volume depletion).15 In one study, NSAIDs accounted for 15.3% of all cases of drug-induced AKI but accounted for >25% of cases in those age >65 yr.16 It should be recognized that there is little evidence of NSAIDs impairing renal function in otherwise healthy elderly individuals.

In the elderly, the frequency of AKI secondary to ACEi has been estimated to vary between 6 to 38%.17 In part, this may be to the greater incidence of significant renovascular disease in the elderly (either bilateral renal artery stenosis, or unilateral stenosis in a solitary functioning kidney).

Acute Tubular Necrosis
Acute tubular necrosis is the most frequent cause of AKI in the elderly, with an incidence ranging from 25 to 87%.18 The insults that lead to this condition include nephrotoxins (aminoglycosides, radiocontrast agents), pigment-induced (rhabdomyolysis), and ischemia (sepsis, surgery). In older patients with ATN, several chronic premorbid conditions such as congestive heart failure, hypertension, and diabetes predispose to the development of severe tubular injury. Elderly patients more frequently undergo significant cardiovascular surgery (aortic aneurysm repair, bypass surgery) that is associated with a high risk for ATN. Elderly patients are more susceptible to serious infections and the development of sepsis and multisystem organ failure. In this setting, the development of AKI requiring dialysis has an attendant mortality of >80%.19

Prevention of ATN requires careful attention to baseline GFR. In the elderly, serum creatinine values may appear normal yet be associated with a significant decline in GFR. This reliance on serum creatinine as a marker of renal function can easily lead to inappropriate dosing of antibiotics and other nephrotoxins. Thus, use of either the Cockroft-Gault or Modification of Diet in Renal Disease (MDRD) equation to estimate renal function is mandatory. When available, preventative strategies such as intravenous hydration before radiocontrast administration should be undertaken.20

Acute Interstitial Nephritis
Elderly patients are at increased risk secondary to the large number of medications that they may be taking. This may include herbal supplements and other over-the-counter medications. Given the complex comorbidities of elderly patients, it
may be difficult to make the diagnosis of acute interstitial nephritis (AIN) as the cause of AKI, and renal biopsy may be required.

**Glomerulonephritis**

Elderly patients have a higher incidence of p-anti-neutrophil cytoplasmic antibody (ANCA) and anti-glomerular basement membrane (GBM) associated with rapidly progressive glomerulonephritis (RPGN). Although the same principles apply to treatment of older adults with RPGN as with younger individuals, caution in the use of immunosuppressant medications such as corticosteroids, cytotoxic drugs, and plasmapheresis is warranted given a much higher risk of opportunistic infections and complications. The relative risk of death is 5.3 times higher in patients >60 yr compared with younger patients after aggressive immunosuppression in the treatment of RPGN. However, because of the potential for reversing AKI in some forms of glomerulonephritis, one should not hesitate to perform a renal biopsy if indicated. The procedure does not carry a higher risk in the elderly. The presence of significant glomerulosclerosis and arteriosclerosis in biopsy tissue may render the interpretation of histologic findings more difficult.

**POSTRENAL AKI**

In two major series, the incidence of postrenal obstructive AKI was 7.9 and 9% in patients over 65 and 70 yr, respectively. The obstruction may be either intrinsic or extrinsic and can occur at any level of the urinary tract. Among the causes of lower urinary tract obstruction, the most common in males is prostatic enlargement caused by benign prostatic hypertrophy or carcinoma. The second most common cause in males is urethral stricture disease often secondary to trauma. In females, the most common cause of postrenal failure is ureteral obstruction caused by pelvic malignancy (invasive carcinoma of the cervix). An uncommon cause of obstruction seen in the elderly is caused by an inflammatory aortic aneurysm and can be identified through proper imaging studies.

All elderly patients presenting with AKI require urethral catheterization and ultrasonography to identify possible obstructive etiologies. False-negative ultrasonography is usually only seen in those with very early obstruction or in those patients with significant retroperitoneal fibrosis that encases the ureters and renal pelvis preventing dilation.

**LABORATORY EVALUATION OF AKI IN THE ELDERLY**

The laboratory evaluation of AKI in the elderly patient is no different than for other patients. Attention to the history and physical examination is critical in narrowing the differential diagnosis to potential etiologies and to specific laboratory or imaging tests. As stated above, given the high prevalence of obstructive causes for AKI in this group, ultrasonography is mandatory. Microscopic examination of the urine for cellular elements, casts, and crystals is also mandatory and can lead to a proper diagnosis in a rapid, efficient manner. The finding of pigmented granular casts in the urine is indicative of tubular damage and supports the diagnosis of ATN. The appearance of red blood cell casts in the urine indicates active glomerular damage (glomerulonephritis) and warrants consideration of whether a renal biopsy should be performed. Urine electrolytes, urine eosinophils, and serologic testing for glomerulonephritis should be used when appropriate. There are no specific caveats for the elderly patient in this regard.

**TREATMENT OF THE ELDERLY WITH AKI**

In general, the treatment of AKI in the elderly follows the same principles as for the general population. However, the decision to initiate dialytic support in the very elderly with multiple comorbidities and a very poor prognosis may be difficult. This is especially true for those individuals with significant baseline renal impairment where the likelihood of renal recovery may be low. The decision to initiate dialysis in these patients requires a coordinated discussion with family members, consulting physicians and other care providers.

**PREVENTION OF AKI IN THE ELDERLY**

Given the morbidity and mortality associated with AKI, preventative strategies are clearly important. Tables 1 and 2 list both general preventative strategies and exposure-specific strategies that can be used in patients at risk for AKI.

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**Table 1. General approaches for the prevention of AKI**

<table>
<thead>
<tr>
<th>Approach</th>
<th>Details</th>
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<tr>
<td>Avoidance of nephrotoxins</td>
<td>Recognition of potential nephrotoxic agents&lt;br&gt;Recognition of high risk patients and clinical settings&lt;br&gt;Avoidance of concomitant use of multiple nephrotoxins&lt;br&gt;Use of lowest dose and for shortest time possible&lt;br&gt;If applicable, monitoring of drug dose&lt;br&gt;Frequent monitoring of renal function&lt;br&gt;Maintain euvelemia&lt;br&gt;Minimization of nosocomial infection&lt;br&gt;Extracellular fluid expansion&lt;br&gt;(maintain good urine output, stable hemodynamics)&lt;br&gt;Avoid agents that impair renal blood flow autoregulation&lt;br&gt;(NSAIDs, ACE inhibitors, ARBs)&lt;br&gt;Pharmacologic interventions if applicable&lt;br&gt;Use of computer surveillance systems&lt;br&gt;Identify high risk patients and medications&lt;br&gt;Determine correct dose for GFR</td>
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Table 2. Examples of specific renal protective strategies

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Strategy</th>
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<tr>
<td>Radiocontrast agents</td>
<td>Intravenous hydration (normal saline)</td>
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<td></td>
<td>Intravenous sodium bicarbonate (7)</td>
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<td></td>
<td>N-acetylcysteine</td>
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<td></td>
<td>Vitamin C</td>
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<td></td>
<td>Iso-osmolar contrast</td>
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<tr>
<td>Aminoglycoside antibiotics</td>
<td>Once-daily dosing</td>
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<tr>
<td>Tumor lysis (uric acid)</td>
<td>Monitoring of drug levels</td>
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<tr>
<td>Ethylene glycol ingestion</td>
<td>Intravenous hydration/urine alkalinization</td>
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<tr>
<td>Rhabdomyolysis</td>
<td>Intravenous hydration/urine alkalinization + mannositol</td>
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<tr>
<td>Methotrexate</td>
<td>Intravenous hydration/urine alkalinization</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Intravenous hydration</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>Monitor drug levels ± calcium-channel blockers</td>
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<tr>
<td>Amphotericin B</td>
<td>Use of lipid formulation</td>
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TAKE HOME POINTS

- Elderly patients are at higher risk for the development of AKI.
- Specific hemodynamic, metabolic, and molecular changes lead to increased susceptibility to injury in the aged kidney.
- Certain causes of AKI are more common in the elderly: postrenal obstructive disease, ischemic ATN, and hemodynamically mediated AKI.
- Multiple etiologies are often operative in the development of AKI.
- Diagnostic and therapeutic issues in AKI are no different for the elderly patient as for the general population.
- The outlook for renal recovery is likely impaired in the elderly patient.

DISCLOSURES

None.

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REVIEW QUESTIONS: ACUTE KIDNEY INJURY IN THE ELDERLY

1. Which one of the following statements is true?
   a. Serum creatinine in the elderly patient (age >65 yr) is an accurate reflection of GFR and can be used to predict the risk for acute kidney injury
   b. Aggressive immunosuppression for elderly patients with glomerulonephritis is associated with a five-fold higher risk of death than in younger patients
   c. Acute interstitial nephritis is less commonly seen in elderly patients than in younger cohorts.
   d. The likelihood of complete renal recovery after acute kidney injury in the elderly is similar to that in the general population
   e. The diagnostic ability of granular, pigmented casts for acute tubular necrosis is poor in the elderly patient

2. A 76-yr-old male presents to the emergency department with complaints of lethargy and fatigue. Laboratory work reveals a serum creatinine of 6.5 mg/dl, blood urea nitrogen of 104 mg/dl, and serum electrolytes are within normal limits. Recent history reveals that he just began furosemide 40 mg daily for complaints of dyspnea on exertion. Prior laboratory work 1 wk ago was notable for a serum creatinine of 1.9 mg/dl (baseline value). Which one of the following steps is indicated in the further evaluation of acute kidney injury in this patient?
   a. Renal biopsy
   b. Urine electrolytes and calculation of fractional excretion of sodium
   c. Urgent initiation of hemodialysis
   d. Intravenous hydration with normal saline at a rate of 500 ml/h
   e. Placement of a foley catheter and urgent renal ultrasound

3. Which statement regarding recovery of renal function after acute kidney injury in the elderly is correct?
   a. The prognosis for renal recovery in the elderly is similar to that of the general population
   b. Renal function never recovers to baseline after an episode of acute kidney injury in the elderly
   c. The capacity for renal epithelial cell proliferation declines with aging as does the function of progenitor and stem cells that are critical for tubular repair
   d. Elderly patients with acute kidney injury have a 60% higher rate than the general population of requiring long-term dialysis