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Acute Kidney Injury in Older Adults

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ABSTRACT

Aging kidneys undergo structural and functional changes that decrease autoregulatory capacity and increase susceptibility to acute injury. Acute kidney injury associates with duration and location of hospitalization, mortality risk, progression to chronic kidney disease, and functional status in daily living. Definition and diagnosis of acute kidney injury are based on changes in creatinine, which is an inadequate marker and might identify patients when it is too late. The incidence of acute kidney injury is rising and increases with advancing age, yet clinical studies have been slow to address geriatric issues or the heterogeneity in etiologies, outcomes, or patient preferences among the elderly. Here we examine some of the current literature, identify knowledge gaps, and suggest potential research questions regarding acute kidney injury in older adults. Answering these questions will facilitate the integration of geriatric issues into future mechanistic and clinical studies that affect management and care of acute kidney injury.

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The aging kidney is marked by changes similar to those seen with chronic kidney disease (CKD; Figure 1). Structural changes such as vascular sclerosis, decreased weight, and increased percentages of sclerosing glomeruli[1–3] vary widely across individuals and within the kidney.[4] Functional changes, such as declining GFR[5] and decreased ultrafiltration coefficient with increased glomerular capillary pressure,[6] alter renal sensitivity to vasoconstrictors[7] and vasodilators,[8] reducing autoregulatory capacity and decreasing functional reserve. Thus the structural and functional changes associated with aging increase risk for acute kidney injury (AKI). The set point at which the kidney cannot autoregulate occurs at higher BP in older adults, although AKI can occur even in normotensive individuals.[9]

The incidence of AKI is increasing,[10–12] with some variation across world regions,[13] and is higher with older age (Figure 2);[12] some now even suggest that the real epidemic in nephrology is AKI, not CKD.[14] Patients with both CKD and AKI tend to be older, have ischemic heart disease, and be less likely to recover kidney function than patients with AKI alone.[13] However, the epidemiology of AKI has been difficult to determine consistently. Patients with AKI are treated by several medical specialties, and detailed information about long-term outcomes is rarely available. Moreover, estimated incidence of AKI varies by how AKI is defined,[15] the medical setting in which AKI occurs, and geographic region. Epidemiologic studies are further complicated by heterogeneity in etiology.

Comorbidities are common among older patients. Almost half of Medicare beneficiaries aged ≥65 years have three or more chronic conditions, and the number of preventable hospitalizations per 1000 beneficiaries increases with the number of chronic conditions.[16] Patients with AKI are more likely to have two or more chronic conditions, and among patients hospitalized for heart failure, 20 to 40% have CKD and 27 to 45% experience worsening of serum creatinine (SCr) by 0.3 mg/dl during their hospital stay.[17] The variable nature of comorbidities likely contributes to the heterogeneity seen in patients who are aged ≥65 years and have

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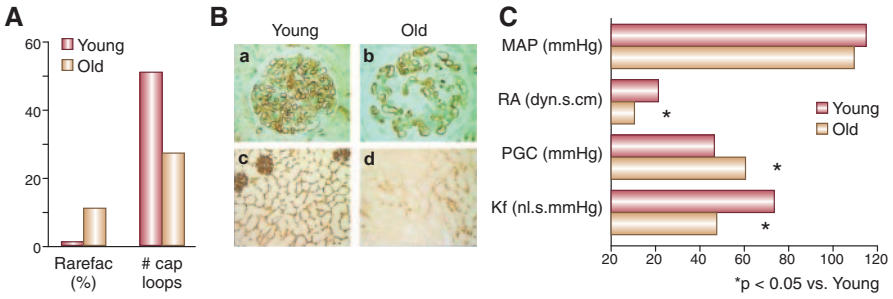

Figure 1. (A through C) The aging kidney in rats undergoes structural changes in the glomerular and peritubular capillaries (A and B)[173] and functional changes in glomerular hemodynamics (C).[6] (B) Glomerular and peritubular capillary immunostaining in young (a and c) and aging (b and d) kidneys. (a) Glomerular capillary loops stained with RECA-1 in young rats are well preserved. (b) Glomerular hypertrophy and decreased capillary loop numbers are observed in aging rats. (c and d) Photomicrographs also show normal peritubular capillary architecture by JG-12 staining in young rat (c) and focal and patchy loss in peritubular capillary staining by JG-12 in aging rats (d). MAP, mean arterial pressure; RA, preglomerular resistance; PGC, glomerular capillary pressure; Kf, glomerular capillary ultrafiltration coefficient. Magnifications: ×630 in a; ×400 in b; ×200 in c and d.

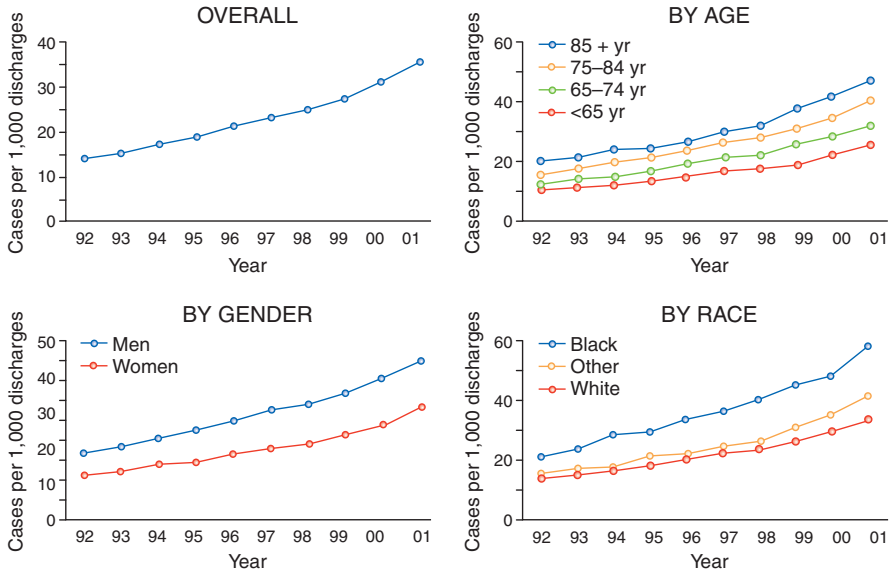

Figure 2. The overall incidence of AKI among Medicare beneficiaries has risen steadily since 1992. It is higher with older age, male gender, and black race.[12]

AKI, but treatment guidelines do not account for heterogeneity in health status or treatment effects.[18–20] Moreover, because these guidelines usually focus only on one index disease, treatment regimens are complex, expensive, and difficult to follow for older patients,[21] in whom comorbidities are common.

IMPACT OF AKI

Data from rats suggest that AKI reduces functional reserve through impairments in vessel density, regenerative capacity, and natriuretic and medullary responses.[22,23] AKI might also increase susceptibility to salt-sensitive hypertension. Older mice show more significant injury and less regenerative capacity compared with younger mice.[24] Treatment with vascular endothelial growth factor preserves microvessels and improves long-term kidney function in young mice[25] but has not been studied in older mice.

Age older than 65 is a risk factor for nonrecovery from AKI and even progression to advanced-stage CKD.[26–28] Of patients who were in the intensive care unit (ICU) and had AKI that required dialysis, only 40% recovered by day 28, approximately half died by day 60, and relatively few survived to 1 year;[29,30] where a patient is hospitalized and the day of the week the patient is admitted also matter: larger hospitals and weekdays are better.[31] AKI is associated with prolonged hospitalization and increased risk for transfer to the ICU, discharge to extended-care facilities, and in-hospital mortality.[32] Both albuminuria and low estimated GFR are independent risk factors for AKI.[33] Long-term survival of patients with AKI is poor and worsens with increasing age,[34] lower baseline GFR,[35] advanced CKD stage, and longer duration of AKI.[36] Even AKI that does not require dialysis associates with increased mortality.[37]

AKI is also a major risk factor for ESRD in patients with CKD,[35,38] particularly in the elderly.[39] Among patients with AKI and prehospitalization GFRs <45 ml/min per 1.73 m^2, almost half develop ESRD within 30 days, and even those who do not are more likely to develop ESRD within the subsequent 4 years. Thus, progression of CKD might not be a gradual process because AKI episodes associate with worsening fibrotic response and accelerated progression of disease,[40,41] particularly telomere shortening that reduces regenerative capacity[42] and increased length of primary cilia.[43]

Few studies have examined health-related quality of life (HRQOL) after AKI, and those that have varied in how HRQOL was measured.[44–48] However, the majority of patients reported satisfaction with or no change in their quality of life after AKI,[44–46] even though they functioned less well.[47,48] One large study observed that health after AKI was equivalent to or worse than death in 27% of patients.[49] Worse health associates with older age, longer hospitalization, and not living at home before hospitalization, regardless of the intensity of AKI management.

Patients who die from AKI often die from complications associated with distant organ injury. In animal studies, AKI associates with pulmonary changes such

as increased vascular permeability, alveolar hemorrhage, and vascular congestion.[50–53] Expression of sodium channels and aquaporin 5 decreases,[53] apoptosis increases,[50,54] and the actin cytoskeleton and junctions in pulmonary endothelial cells are altered.[55] In mouse models, AKI associates with inflammation in brain astrocytes, upregulation of glial fibrillary acidic protein in the corpus callosum and cerebral cortex, and increased numbers of microglia in the hippocampus, as well as altered cellular junctions and electrical conductivity of endothelial cells from the blood-brain barrier.[56] AKI also leads to dysfunction of the liver, gastrointestinal tract, bone marrow, and heart.[57] However, the mechanisms underlying the distant effects of AKI remain poorly understood, and the effects of age have not been studied on AKI-induced distant organ dysfunction.

CAUSES OF AKI

Sepsis, which is more common among persons older than 60 years, frequently associates with AKI. Although traditional wisdom suggests that sepsis-associated AKI involves acute tubular necrosis, little to no evidence of necrosis or apoptosis of tubular cells has been found on autopsy of patients who died of septic shock.[58] Instead, increasing evidence suggests that sepsis-associated AKI is an inflammatory event. Serum IL-6 levels predict incidence of AKI, severity, and mortality among patients admitted to the ICU[59] with acute respiratory distress syndrome[60] or community-acquired pneumonia,[61] and nonpharmacologic interventions that blunt systemic inflammation can reduce kidney injury.[62]

The effects of polypharmacy and drug toxicity exacerbate increased susceptibility of the elderly to AKI. Drugs commonly associated with AKI (Table 1) are often co-prescribed or multiprescribed for older adults,[63–70] and age-related changes in renal function and pharmacokinetics increase exposure to small molecules and the risk for toxicities. Moreover, long-term use of drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), which attenuate prostaglandin function, might act synergistically with processes that reduce arterial volume and perfusion pressure, increasing drug uptake by and ischemia along the proximal tubules. Not surprising, then, drug-related AKI is common among older adults, and AKI is a common adverse drug reaction that results in or prolongs hospitalization in seniors.[70,71] New NSAID use doubles the risk for AKI in adults aged ≥65 years,[70] and the average age is 78 years among patients hospitalized within the first 45 days of starting an NSAID prescription.[72] Many cases of drug-related AKI result from inappropriate prescribing practices.[73]

Table 1. Drug classes commonly used in older adults and linked to AKI[63–70]

NSAIDs
Diuretics
ACE inhibitors
ARBs
Antibiotics
Contrast agents

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAID, Nonsteroidal anti-inflammatory drug.

Contrast-induced nephropathy (CIN) may develop after contrast-enhanced computed tomography or angiographic procedures and represents one of the most common forms of iatrogenic AKI. An estimated 100,000 to 125,000 cases of postangiography CIN occur in the United States each year.[74] Major risk factors for CIN include decreased kidney function, diabetes, heart failure, volume depletion, and concomitant nephrotoxin exposure.[69,71] The risk for CIN increases with age,[65] but this association attenuates after adjustment for comorbidities.[69,71] Low or iso-osmolal contrast agents, intravenous isotonic fluids, and avoidance of concomitant nephrotoxins such as NSAIDs can be effective in reducing risk for CIN.[75] However, because of increased risk for CIN, many older patients, particularly patients with CKD, do not receive necessary diagnostic tests.[76] In addition, although scoring systems have been developed to identify patients who are at increased risk for CIN,[77,78] diagnostic criteria and population characteristics have differed across studies, resulting in varied risk estimates.[77,79–83]

CIN associates with prolonged hospitalization and increased in-hospital and short-term risk for mortality.[77,83] In patients who undergo percutaneous interventions, postprocedure CIN associates with coronary vessel reocclusion, myocardial infarction (MI), and stroke.[77,83] Only a few studies have rigorously examined longer term outcomes after CIN, and they demonstrated increased long-term risk for mortality, persistent decline in kidney function, and accelerated progression to ESRD.[84–88]

MECHANISMS UNDERLYING AKI

The mechanisms of AKI are too vast to review completely here[89]; however, there some interesting new observations have been made in the past few years. Age-related mechanisms such as stress-induced cellular senescence associate with AKI,[90] and use of peroxisome proliferator–activated preceptor γ agonists are protective in experimental models[91] but in humans have adverse effects (fluid retention among others) that could be problematic for the elderly.[92] Overall expression of the senescence marker p16(INK4A) and the percentage of cells expressing p16(INK4A), particularly in the glomerulus, tubules, and interstitial space, are higher in older kidneys than in younger ones.[93,94] Telomere shortening,[42] Dicer-associated microRNAs,[95] and heme oxygenase–regulated autophagy[96] are important new modulators for risk for AKI. Chordin 1–regulated expression of bone morphogenic protein 7 also plays a role in restoring tubular epithelia after AKI.[97] More study is needed to determine whether senescent cells in the aging kidney undergo accelerated cell death or impair injury response.[90] It is possible that fewer tubular epithelial cells are available to de-differentiate and proliferate in response to injury,[41,98] hindering repair and decreasing the likelihood of recovery from AKI.

Inflammation, which is a chronic state in many older adults and associated with mortality, disability, declines in muscle strength,[99–102] and frailty,[100,103–111] might

also contribute to increased susceptibility to AKI. In animal models, activation of the chemokine system after ischemia/reperfusion promotes production of CCR2, ultimately leading to AKI and its downstream effects.[112,113] Response to injury involves upregulation of TLR4 in the proximal tubular cells and infiltrating leukocytes[114,115] and communication among proximal tubular cells, endothelial cells, and white blood cells.[116] Although data in humans are limited, levels of proinflammatory factors are higher in patients with advanced CKD[117,118] as well as mice,[119] and a cascade of chemokine production and activation of proinflammatory factors likely lead to interstitial fibrosis, CKD, and distant-organ injury.[112,113,120]

Reactive oxygen species (ROS) and advanced glycation end products (AGEs) increase with age, and levels of the anti-inflammatory AGE receptor AGER1, which binds and quenches excess AGEs and ROS and inactivates the proinflammatory receptor RAGE,[121,122] are reduced under chronic oxidative conditions such as aging, CKD, or type 2 diabetes.[122] In mouse studies, RAGE induces ROS and superoxide in diabetic mitochondria,[123] and the severity of AKI depends on a functioning endoplasmic reticulum stress pathway and preexisting levels of ROS.[124] In humans, AGE serum levels rise with falling GFR.[122] AGER1, AGEs, and ROS may be influenced by simple and economical dietary changes in both normal adults and patients with diabetes. Therefore, all three are effective targets for preventing or managing AKI.[125]

DEFINING AND DIAGNOSING AKI

Diagnostic criteria for AKI are based on changes in SCr or GFR, which is typically estimated on the basis of creatinine clearance,[126] yet SCr levels are influenced not only by GFR[127] but also by creatinine generation rate, tubular secretion, and volume of distribution.[128] SCr also depends on nonrenal factors such as muscle mass, nutrition, infection, and medications, all of which can be affected by age; for example, experimental sepsis reduces creatinine production and blunts the rise in serum creatinine, making it more difficult to recognize early AKI.[129] Many patients admitted to the hospital have abnormal baseline levels of SCr,[130] and among ICU patients,[131] SCr-based diagnoses have a false-positive rate of 19%. This baseline variability in SCr makes it difficult to maintain sensitivity using percentage change in diagnosing AKI; some recommend that the definition of AKI use an absolute change over a short interval.[132] Moreover, creatinine- and GFR-based AKI diagnoses occur late, potentially blunting the effect of early interventions (Figure 3). Estimation of renal function using cystatin C[133] or oliguria[134] might be more specific or sensitive than creatinine, but they are also influenced by age-associated factors. Nevertheless, in cross-sectional studies, equations using cystatin C are a better predictor of mortality in the elderly than those using creatinine.[135]

Diagnosis of AKI is further complicated by the lack of definition of the prerenal state; by differences in how diagnostic criteria are applied across settings; and, in older adults, by an already-reduced renal reserve and the higher likelihood of preexisting CKD. Diagnosis thus might benefit from molecular markers that could allow clinicians to detect AKI before SCr changes occur (Figure 3). For example, elevations in neutrophil gelatinase-associated lipocalin in the urine are moderately predictive of risk for AKI in the critically ill[136] and show a robust signal for AKI in the emergency department, even when confounded by underlying CKD.[137]

Molecular biomarkers (Table 2) could further aid in stratifying diagnoses, ascertaining the site and cause of AKI, predict-

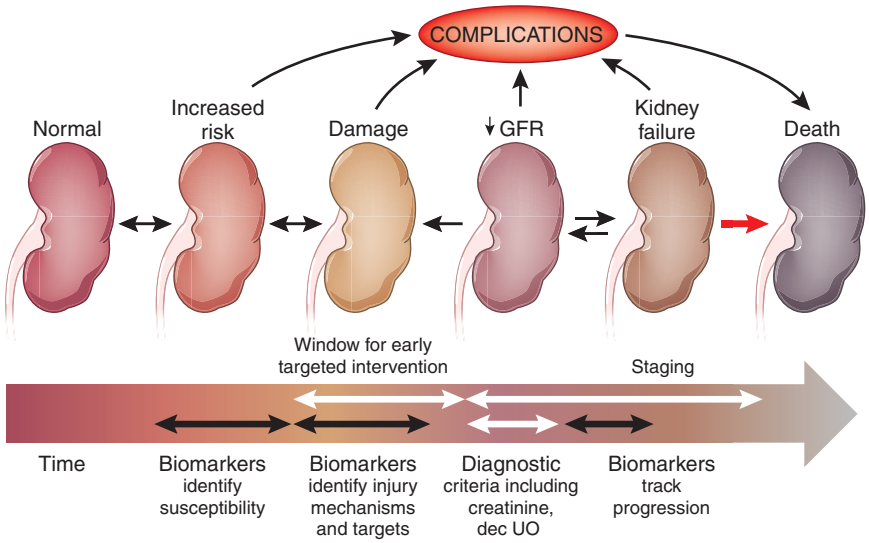

Figure 3. Diagnostic criteria rely on SCr, which is a delayed marker and might identify AKI too late for effective intervention. Biomarkers might prove useful not only in diagnosis but also in risk assessment, identifying targets for intervention, and monitoring progression or response to intervention. Reprinted from reference 174, with permission.

Table 2. Candidate biomarkers for AKI[172]

Biomarker	Settings Studied	Measured from	Used for	Diagnostic Accuracy (ROC)
NGAL	Cardiac surgery	Serum	Early diagnosis	0.53 to 0.96
	Emergency department	Plasma	Detection of established AKI	
	Hospitalized patients	Urine	Prognosis	
	Kidney transplant			
	Sepsis			
IL-18	Cardiac surgery	Urine	Detection of established AKI	0.70 to 0.95
	ICU		Early diagnosis	
	Hospitalized patients		Prognosis	
	Transplant			
KIM-1	Hospitalization	Urine	Established AKI	0.61 to 0.78
	Cardiac surgery		Prognosis	
L-FABP	Cardiac surgery	Urine	Early diagnosis	0.81
	Contrast			

NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule 1; L-FABP, liver-type fatty acid–binding protein; ROC, receiver operating characteristic.

ing outcomes, and monitoring responses to interventions.[138] However, most candidate biomarkers have a short half-life and would have to be measured at the time injury occurs. In addition, these markers have been studied primarily in animal models. Although not all,[136] most human studies to date are single-center studies with small sample sizes and few events. Biomarker assays are not standardized, and older people have not been evaluated systematically. Moreover, the performance of injury biomarkers is likely underestimated because they are validated relative to the gold standard, creatinine, which is a marker of function. Analyses of the effects of aging and comorbidities on candidate biomarkers are just now starting to appear.[136]

MANAGING AKI

Individuals aged ≥65 years are hospitalized more often than younger individuals,[139,140] and hospitalization increases their risk for new functional disabilities,[139,141] dementia,[142] and mortality.[143] However, standard AKI care does not address these risks. Nor does it account for patient preferences, which can vary across diseases and individuals, on the basis of the risk and burdens associated with intervention.[144] Comprehensive management strategies such as Geriatric Evaluation and Management and Acute Care for Elders improve care and daily function, but their effects have not been determined for patients with AKI.

Risk assessment and early detection might increase the potential for preventing or reversing AKI, but current scoring systems to assess risk[78,145] do not include comorbidities or nephrotoxic drugs or procedures. Likewise, studies of secondary prevention strategies such as the administration of atrial natriuretic peptide[146] and erythropoietin[147] have yielded mixed results, and the success of these strategies might depend on dosage, population, timing, and method of delivery.

Initial fluid resuscitation is a common and often necessary step in treating AKI. However, salt and water overload is an inevitable complication that predisposes patients to fluid accumulation, which can occur rapidly and take weeks to resolve.[148] Fluid accumulation is associated with increased mortality risk,[149,150] edema of the kidney and other organs, and further AKI.[151] Daily management of critical illness does not address subclinical fluid accumulation, and the nature of the relationship between fluid accumulation and AKI is poorly understood. In addition, the severity of AKI is often underestimated because GFR estimates do not account for fluid accumulation.

The degree of volume expansion varies among body compartments and with age, and optimal fluid volume requirements, as well as the ability of the patient to tolerate deviations from those requirements, often depend on clinical context.[152,153] The relationship between the adequacy of initial fluid resuscitation and the intensity of postresuscitation fluid management can influence in-hospital mortality. Early transition to fluid removal or restriction might thus be warranted in patients with AKI.

Poor nutritional status at the time of ICU admission is also associated with higher mortality risk,[154] and among ICU patients with AKI, fewer than half have normal nutritional status[155] or receive nutritional support. The lack of appropriate nutritional support for these patients might arise partly from difficulties in assessing nutritional status. Common markers such as serum albumin and body composition might be suboptimal in patients with AKI[156] because they are influenced by extracellular volume, inflammatory status, and catabolic illness and do not measure metabolic responses to nutritional interventions.[157]

How to provide nutrition to patients with AKI, particularly older individuals, has not been studied in clinical trials. Traditional support for critically ill patients with AKI includes a low-protein diet to control uremia, but these patients can show a net negative protein balance of 1.0 g/kg per day,[158] and during dialysis they can lose as much as 1.4 g of amino acids and 5 g/d protein.[159–163] Continuous hemofiltration, with or without dialysis, allows patients to receive much higher quan-

tities of nutrients,[164] but there are no significant differences in nitrogen balance, blood urea nitrogen, urine flow, or survival between patients with normal protein uptake and those with high protein uptake.[165]

Acute cardiorenal syndrome, in which AKI follows acute heart disease, is common and has several causes, including medications and procedures used to manage MI.[166] It affects prognosis,[166–168] particularly among older patients with reduced left ventricular systolic function, yet management decisions for patients with acute heart disease do not always address the presence of AKI. In addition, because most studies have focused on acute cardiorenal syndrome, less is known about acute renocardiac syndrome, in which AKI after an MI increases the risk for a second MI.[138,169] Nothing is known about the incidence of acute renocardiac syndrome or its relationship with aging.

RESEARCH DIRECTIONS

The relationship between aging and AKI remains poorly understood and requires further mechanistic and clinical studies. Future work should address the many factors that increase susceptibility of older adults to AKI (Figure 4). Suggested research questions are listed in Supplemental Table 1.

AKI research can benefit from studies that evaluate existing cohorts and databases (Supplemental Table 3). However, most of these cohorts are interrogated only retrospectively and may confound AKI with CKD. In addition, retrospective and observational studies in ICU settings are difficult to interpret because of high mortality rates and the multiplicity of factors underlying patients' illnesses. Therefore, a prospective cohort should be established on the basis of gaps in and lessons learned from existing cohorts.

Heterogeneity among older patients with AKI also remains poorly understood. Future studies should pay close attention to baseline or predisease measures, as well as responses to acute stress, to determine whether they predict clinical outcomes. Other studies are needed to explore how the mechanistic cycles underlying chronic disease differ across types and severity of AKI. Both animal and human studies are needed, but animal studies should incorporate age and comorbidity, if possible, to be clinically relevant.

Biomarkers are usually evaluated on the basis of their performance at all steps of clinical care, when it might be better to determine the stage for which a biomarker is best suited, for example prediction *versus* monitoring treatment response. In addition, biomarkers may prove more useful if they are linked to outcomes or measures of value to clinicians and patients. Biomarker panels, which should not be restricted to markers of AKI and CKD alone, might enhance future studies and improve clinical care. Such panels should include markers validated in studies of cardiovascular disease and aging.

Clinical trials of AKI are hampered by suboptimal randomization, long recruitment periods, and small and nonrepresentative patient populations,[170] and they often rely on acute SCr changes as an outcome or diagnostic criterion,[147] despite the low specificity of SCr and its inability to indicate mild injury.[171,172] Intervention trials are especially limited because SCr is a delayed marker, there are no consistent criteria for initiating an intervention, and most trials do not account for heterogeneity in baseline function or pathophysiology.[170] Some of these challenges could be addressed by using a combination of traditional risk factors and biomarkers to enroll patients at an earlier stage and enrich study populations for AKI events.

It is not clear who should see AKI patients during follow-up, how best to inform patients and their families about the risks and benefits of interventions, and how to tailor interventions to their preferences. Many AKI studies have focused on mortality, but the effect of AKI on functional status and HRQOL might be equally important to older adults. Clinical care can benefit from models of care and computerized decision-support systems and from clinical studies that collect more information on patient preferences.

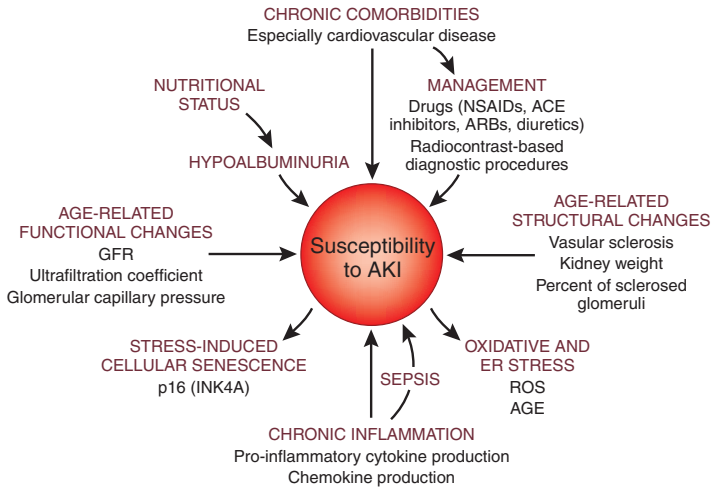

Figure 4. Factors contributing to increased susceptibility of older individuals to AKI. Future research and clinical care should address these factors. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

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DISCLOSURES

None.

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