Acute Kidney Injury

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Contents

31.1 Introduction – 486

31.2 AKI Definitions – 487

31.3 AKI Epidemiology – 488

31.4 Risk Factors for AKI in Elderly ICU Patients – 488

31.5 Pathophysiology of AKI – 490

31.6 Diagnosis of AKI in Aged ICU Patients – 493

31.7 Treatment of AKI in the Elderly – 494

References – 495

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Learning Objectives

Aging is associated with a decline in glomerular filtration rate (GFR) resulting in diminished both renal function and renal reserve ("renal aging"). Elderly patients thus have increased chronic kidney disease (CKD) prevalence and, in cases of critical illness (e.g., sepsis/systemic inflammation, acute heart failure/cardiorenal interactions, need for surgical interventions, and/or multiple organ dysfunction), an increased likelihood of acute-on-chronic renal dysfunction. Further, significant (e.g., cardiovascular) comorbidity and polypharmacy are often present in ICU patients. The presence of age-related comorbidities (such as cardiovascular disease and/or heart failure) contributes significantly to frailty and implies a key independent risk factor for unfavorable clinical outcomes from AKI in aged ICU populations.

In the future, and with an overall aging population, this will become even more evident against the background of an increased incidence of age-associated comorbidities and an expected continuous rise in AKI incidence.

Practical Implications

AKI is characterized by a rapid loss in renal function resulting in increased systemic levels of nitrogen products as well as electrolyte, acid-base, hormonal, and fluid dysbalance. In aged patients with critical illness, the prevention of loss in renal function seems of paramount importance.

In respective elderly patients, AKI is associated with high incidence of development of end-stage renal disease (ESRD) and high in-hospital mortality rates. Prevention of AKI should be considered pivotal on intensive care units (ICUs), which imply, for example, avoidance of both nephrotoxic medication (including limiting the use of contrast media) and/or hyperglycemia as well as adequate therapy of hemodynamics. This includes the therapy for eventual right heart failure and/or avoidance of fluid overload which may result in renal venous congestion. Despite respective clinical efforts, causal therapeutic approaches, that is, interventions, for AKI are currently unavailable.

31.1 Introduction

Acute kidney injury (AKI) is a global health concern, and the prognosis of affected aged patients is poor. In respective aged ICU populations, AKI mostly presents as acute-on-chronic AKI, as aging itself is associated with a decline in glomerular filtration rates (GFR). Thus, in aged populations, renal reserve is diminished and typically impedes AKI recovery.

Increased numbers of aged ICU patients initially have AKI, later followed by accelerated chronic kidney disease (CKD) and/or end-stage renal disease (ESRD). Importantly, a number of critical illness including sepsis/ shock, acute heart failure, and/or multiple organ dysfunction prone respective patients to AKI development. However, risk profiling identifies age-related comorbidities, in particular cardiovascular disease, as a key AKI risk factor. In the light of aging populations worldwide, this will become even more evident against the background of an associated increased incidence of age-associated comorbidities. Here we summarize definitions, epidemi-

ology, risk, (patho)physiology, diagnosis, and potential therapy for AKI in this vulnerable adult patient group. Finally, available biomarkers and current and future therapeutic approaches will be discussed.

31.2 AKI Definitions

Acute kidney injury (AKI), less precise earlier referred to as "acute renal failure," is defined as an acute (within 7 days) loss in kidney function. In 2012, the Kidney Disease Improving Global Outcomes (KDIGO [1], ◘ Table 31.1 initiative) proposed specific diagnostic AKI criteria. These definitions include increased (A) serum creatinine ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h: or (B) increased serum creatinine to

◘ **Table 31.1** AKI categories: KDIGO, AKIN, RIFLE grading system

AKI staging criteria	KDIGO[a]	AKIN[b]	RIFLE[c]
Stage 1 (KDIGO/AKIN), risk (RIFLE)	+ SCr ≥ 0.3 mg/dl or 1.5–1.9 × baseline OR urine output <0.5 ml/kg/h for 6–12 h	+ SCr ≥ 0.3 mg/dl or 150–200% baseline OR urine output <0.5 ml/kg/h for 6–12 h	+ SCr ≥ 1.5 × baseline OR GFR decrease >25% OR urine output <0.5 ml/kg/h for 6 h
Stage 2 (KDIGO/AKIN), injury (RIFLE)	+ SCr ≥ 2.0–2.9 × baseline OR urine output <0.5 ml/kg/h for 12–24 h	+ SCr ≥ 200–300% baseline OR urine output <0.5 ml/kg/h for 12–24 h	+ SCr ≥ 2 × baseline OR GFR decrease > 50% OR urine output <0.5 ml/kg/h for 12 h
Stage 3 (KDIGO/AKIN), failure (RIFLE)	+ SCr ≥ 3.0 × baseline OR + SCr ≥ 0.3 mg/dl to ≥4.0 mg/dl OR urine output <0.3 ml/kg/h for ≥24 h OR anuria for ≥12 h OR start of RRT	+ SCr > 300% baseline OR + SCr > 0.5 mg/dl to ≥4.0 mg/dl OR urine output <0.3 ml/kg/h for >24 h OR anuria for >12 h OR start of RRT	+ SCr ≥ 3 × baseline OR GFR decrease >75% OR + SCr > 0.5 mg/dl (acute) to >4.0 mg/dl OR urine output <0.3 ml/kg/h for 24 h OR anuria for 12 h OR start of RRT
Loss (RIFLE)			Need for RRT for >4 weeks
End stage (RIFLE)			Need for RRT for >3 months

[a]KDIGO Clinical Practice Guideline for Acute Kidney Injury [1]
[b]Mehta et al. [2]
[c]Bellomo et al. [3]

≥1.5 times baseline, which has occurred within the prior 7 days: or (C) reduced urine volumes (<0.5 ml/kg/h for >6 h). Prior to classification, the KDIGO criteria allow for volume status correction and obstructive causes of AKI.

The Acute Kidney Injury Network (AKIN) [2] stated that these criteria should be applied in the context of clinical presentation and (where applicable) after adequate fluid resuscitation. Further, use of urine output (UO) criteria alone would require exclusion of obstruction AKI etiology and/or other reversible causes of reduced UO.

In addition, the RIFLE (Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease) grading system was proposed by the Acute Dialysis Quality Initiative (ADQI) [3]: (risk) 1.5-fold increase in the serum creatinine, or GFR decrease by 25%, or urine output <0.5 mL/kg/h for 6 h; (injury) twofold increase in serum creatinine, or GFR decrease by 50%, or urine output <0.5 mL/kg/h for 12 h; (failure) threefold increase in serum creatinine, or GFR decrease by 75%, or urine output of <0.3 mL/kg/h for 24 h, or anuria for 12 h; (loss) complete loss of kidney function (e.g., need for renal replacement therapy) for more than 4 weeks; and (ESRD): complete loss of kidney function (e.g., need for renal replacement therapy) for more than 3 months.

31.3 AKI Epidemiology

In light of partly differing AKI definitions and variations in populations between geographic areas, exact numbers on AKI incidence in aged ICU populations are missing. AKI incidence in hospitalized patients was described as less than 10%, whereas in the ICU population, incidences rise from 20% to 40% [4]. Among critically ill patients, those presenting with AKI seem significantly older [5]. Another report observed an incidence ranging from 28.5% to 35.5%, with 25% of ICU patients with AKI being 75 years old or above [6]. Age-related yearly AKI incidence in adults was reported to increase from 17 per million aged (<50 years) up to 949 per million in the 80–89-year-old age group [7]. The incidence of renal replacement therapy (RRT)-treated AKI in a large representative data set (decade of recording) from a nationwide US inpatient sample showed an association with age, with an absolute AKI incidence highest in elderly individuals [8].

31.4 Risk Factors for AKI in Elderly ICU Patients

Factors that render elderly ICU patients more susceptible for AKI can likely be categorized into four groups:

(a) Structural and/or functional changes due to renal aging
(b) Comorbidities
(c) Acute medical conditions directly and/or or indirectly affecting the kidneys
(d) Medical diagnostic and/or therapeutic interventions

Renal aging, that is, age-related structural and functional changes, leads to a decrease in kidney weight, number of functioning nephrons, and overall kidney function. The medulla remains relatively unaltered, whereas the loss is primarily cortical [9, 10].

Interestingly, evidence demonstrates that the observed loss of kidney mass is not accompanied by a concurrent volume reduction with imaging studies showing that parenchymal kidney volume in aged kidney remains relatively unaltered [11–13]. Compensatory mechanisms in response to this loss may be an explanation, with an increase in size of the unaffected, remaining glomeruli due to hypertrophy [14, 15]. Tubulointerstitial changes, thickening of the glomerular basement membrane, and glomerulosclerosis are age-related histologic alterations, often referred to as nephrosclerosis [16, 17]. More precisely, nephrosclerosis is present whenever two or more of the following histologic features are apparent: tubular atrophy, any global glomerulosclerosis, interstitial fibrosis (>5%), and any arteriosclerosis. Despite a known correlation between nephrosclerosis, aging, mild hypertension, and healthy living donor kidneys [18], its impact on functional changes in aging is not fully explored [19, 20]. Further, morphological and anatomical changes seen in senile kidneys embrace mesangium expansion, decrease of tubules (number, size, and length), atherosclerosis, growth of the internal elastic lamina leading to fibro-intimal hyperplasia, and luminar hyalinization with an impact of lumen diameters, potentially causing stenosis [21–24].

Another functional change in the aging kidney is that active transports by the tubule can be impaired, due to reduced mitochondrial energy production leading to altered reabsorption and/or secretion [21]. With a reduction in functional nephrons, sodium retention is impaired which impacts on urine concentration ability and hence volume depletion with a consecutively increased risk of dehydration [21]. Another physiological process is impaired in the aging kidney, which is urine acidification, especially during stress, leading to systemic metabolic acidosis. A decreased production of renal 1-alpha-hydroxylase (located mainly in the proximal tubules) induces direct changes in vitamin D and calcium metabolism and possibly triggers renal osteoporosis. With an increased apoptosis rate and a concomitant reduced amount of growth factors, the senile kidney shows a slower regeneration rate in response to injury [22, 23]. This may impede the aging kidney to complete recovery. Further, animal models show an age-related decrease in podocyte density (i.e., glomerular volume per podocyte increased) which was associated with podocyte hypertrophic stress and failure leading to glomerulosclerosis [25]. Results from different models reported that glomerular enlargement alone causes glomerulosclerosis, in a podocyte-dependent manner [26]. These experimental results show that reduced podocyte density and podocyte stress can trigger age-related glomerulosclerosis [25]. More recent research analyzing human kidneys [27] (i.e., from living and deceased donors and nephrectomy samples) support a hypothesis that a gradual decline in podocyte density over the human lifespan cause hypertrophic podocyte stress in some glomeruli. Over time, this may result in glomerular tuft collapse and glomerulosclerosis (i.e., focal global glomerulosclerosis), which may present a significant etiology of ESRD in aged kidneys.

Comorbidities may lead to pre-, intra-, and/ or post-renal conditions. According to the majority of data, chronic medical conditions such as diabetes mellitus (DM), arterial hypertension (AHT), heart disease/congestive heart failure (HD/CHF), and chronic kidney disease (CKD) are considered the most common comorbidities in the elderly, proning for development of AKI [28]. Approximately 20–30% of the elderly are affected by DM and are thus at risk for diabetic nephropathy consisting in particular of glomerular and microvascular changes. Increased blood glucose levels may induce micro-

vascular injury and, secondary to its direct toxic effect, microinfarcts, which further decrease the number of functional nephrons (thus limiting renal functional reserve). In addition, changes in the production of extracellular matrix components, triggered by metabolites of nonenzymatic glycation induced by diabetic hyperglycemia, can lead to glomerular obstruction/occlusion. Furthermore, sorbitol, a metabolite of the pathway of polyols, can directly cause cellular damage via hyperosmotic stress [29, 30].

In AHT, hypertension stresses the vessel wall chronically, causing endothelial damage. Loss of elasticity of the tunica intima by hyalinization and stenosis of the lumen as well as proliferating of the internal elastic lamina, subsequently reducing renal blood flow and rising the risk for pre-renal AKI [21, 23, 30]. Atheromatous plaques may further decrease vessel lumen, therefore reducing renal blood flow even more and hence impacting on the renin-angiotensin-aldosterone system (RAAS), impairing its regulatory function. Its activity can be altered by up to 50% in elderly people when compared to a younger population [21]. Importantly, functioning feedback loops are depending on elastic afferent and efferent vessels in order to adequately respond to ischemic insults, and this may not be the case in aged kidneys.

In addition, acute and/or chronic systemic disorders can impact both on heart and on renal function. An acute and/or chronic dysfunction of one of the two organs can induce an acute and/or chronic dysfunction in the other organ [31]. Such interactions were previously referred to as cardiorenal syndromes (CRS), of which five types were classified [32] (please see below). Comorbidities proning to post-renal AKI are medical conditions associated with mass or infiltrating processes causing obstruction of the urinary tract (e.g., benign prostate hyperplasia, neoplasia, kidney stones, and/or bleeding conditions).

Acute medical conditions, for example, urinary tract infections, may lead to urinary sepsis with the risk of deterioration into septic shock with consecutive septic AKI.

Medical diagnostic and/or therapeutic interventions incl. Polypharmacy: In light of a limited drug excretion capacity, the aging kidney of polymorbid ICU patients is especially prone for "iatrogenic" AKI when contrast media and/or nephrotoxic drugs are applied [21–24, 29, 30, 33–36]. Iodinated contrast agents may cause direct tubular injury with an additional impact on intra-renal hemodynamics [28]. Commonly prescribed drugs in the elderly, such as anti-inflammatory nonsteroidals and/or antihypertensive agents such as angiotensin-converting enzyme inhibitors, may impair renal autoregulation and contribute to ATN development. Additionally, when prescribing potentially harmful nephrotoxic drugs for elderly ICU patients, one should not (over)estimate a given patients' renal function in the presence of (near to) normal serum creatinine levels. In ICU patients, this may be of particular importance in cases of presence of, for example, cachexia, sarcopenia, critical illness-induced muscular weakness (ICU-acquired weakness) [37–40], and/or other related (neuro)muscular conditions [37, 39, 41] that can typically be observed in aged ICU patients.

31.5 Pathophysiology of AKI

With advancing age, the kidneys undergo specific structural and functional changes (◘ Fig. 31.1) resulting in a decrease in kidney weight, the number of functioning nephrons, and baseline kidney function [22, 42, 43]. The loss of renal mass mainly affects the renal cortex, especially the proximal tubules [44], while the medulla does

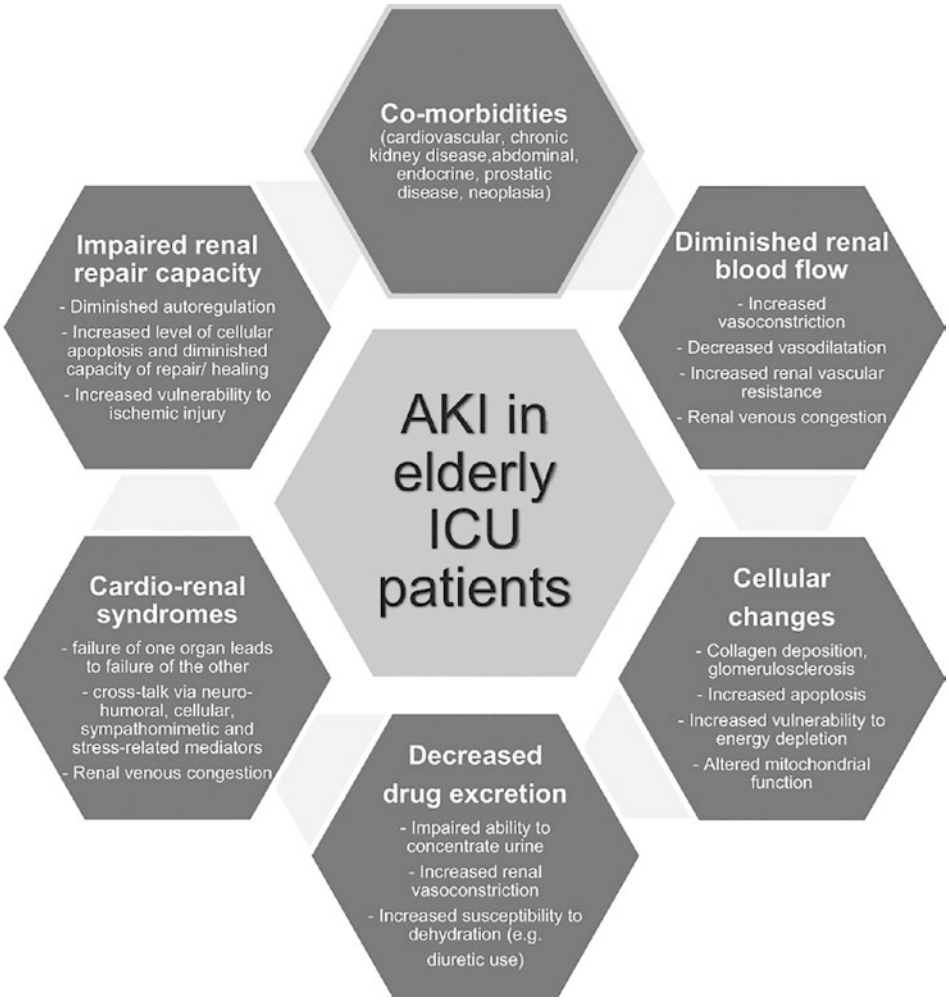

Fig. 31.1 Risk factors and pathophysiology of AKI in the elderly

change relatively little in aged individuals [10]. Aging however affects not only the number of nephrons but also proper glomerular function [22]. Data show that the number of sclerotic glomeruli reaches 10–30% by the age of 80 [45]. All of these factors result in a significant decline in renal function (eGFR) and renal autoregulatory capacity in aged individuals [22, 43]. While the extent of age-related reduction of renal function is individual and depends on several factors (e.g., gender, race, or genetic predisposition) [46], age-related renal functional decline together with important comorbidities (such as chronic heart failure, abdominal, or chronic inflammatory disease) makes, as discussed above, the kidney of elderly ICU patients particular susceptible to AKI [47, 48]. In addition, as mentioned, the repair capacity of the aging kidney is also impaired [49–51], leading to a transition to chronic kidney disease in 20–30% of elderly patients suffering from AKI [42, 52].

Pre-renal AKI is considered the most common cause of AKI in the elderly, accounting for about 40–60% of cases [42, 53, 54]. Several age-related factors that

make elderly ICU patients more vulnerable to pre-renal AKI were identified. One of the key underlying changes is a relatively steady decline in renal blood flow (RBF) with advancing age [54], amounting to a loss of about 10% per decade of life [55]. As touched above, another important factor is the age-related reduction in functional renal reserve [54, 56, 57]. The decrease in RBF might be attributed to the rise in renal vascular resistance due to decrease NO production [55, 56]. In addition, renal vasoconstriction (sympathetic or angiotensin-II mediated) increases with advancing age [54, 58, 59], while vasodilatory mechanisms decline [60], resulting in an increased renal vascular resistance [59]. These age-related adaptations are enhanced by concomitant comorbidities commonly associated with age and make elderly ICU patients particular vulnerable to suffer from AKI [42, 43, 58]. In addition, the relatively high prevalence of CKD in the elderly (approx. 38% of patients >65 years of age are considered to be affected [61]) per se constitutes a risk factor for development of AKI [62]. When the elderly patient becomes critically ill with associated circulatory insufficiency/ ischemia [42, 63], surgery [64], systemic infection [65], dehydration [66], or drug toxicity [67], the already decreased autoregulatory defense mechanism of the aging kidney is soon overwhelmed leading to a severe decline in RBF and renal ischemic injury [22, 63, 67]. In addition, a declined capacity to concentrate urine increases the risk for severe dehydration in the elderly [22, 68, 69] and might contribute to a vicious cycle of renal damage [54].

Advancing age also results in intrarenal changes. Morphological changes include increased interstitial collagen degradation and hyperplasia of fibrotic tissues [67, 70, 71]. Respective changes are again accelerated by diabetes mellitus and/or other metabolic disorders [22, 42]. In addition, increased cellular apoptosis, changes in immune cell functions, disintegration of cellular basal membranes, and the high dependency on appropriate energy supply due to an accelerated depletion of ATP related to mitochondrial alterations, especially in proximal tubular system [44], make the aging kidney additionally vulnerable for AKI progression [52, 71].

Acute tubular necrosis is a typical underlying pathology for AKI in the elderly [47, 72]. The aforementioned morphological and structural changes lead to a markedly decreased ability of, for example, drug and contrast media excretion in aged kidneys, which in turn increases the risk for additional kidney injury [47, 67]. The use of diuretics, which are commonly prescribed in elderly patients (e.g., for treatment of systemic arterial hypertension), may accelerate drug toxicity by impairing the kidneys ability to concentrate urine and thus facilitate dehydration [52]. Further, advancing age is associated with increased levels of neurohumoral mediators that result in renal vasoconstriction, which make the kidney susceptible to nephrotoxic agents [52]. This may be especially problematic in cases of nonsteroidal anti-inflammatory drug use which not only leads to dehydration but also inhibits prostaglandin-mediated renal vasodilatation [73].

While post-renal causes account for only about 2–4% of AKI cases in the critically ill [54], the prevalence increases with age [22, 74, 75]. For example, high prevalence of prostatic disease increases the risk of the elderly male patient to suffer from post-renal AKI by up to 35% [76]. Further, other post-renal diseases such as kidney stones, malignancies, and/or dysfunctional bladder diseases increase the vulnerability of elderly patients to develop post-renal AKI [42].

A further important mechanism associated with AKI is cardiorenal syndromes [77, 78]. The cardiorenal syndrome is pathophysiological disorder of the heart and

kidney in which the organs "cross talk" with dysfunction of one organ resulting in acute or chronic dysfunction of the other organ [31, 77]. Pathophysiologically, there are several underlying mechanisms involved. First, altered hemodynamics such as low cardiac output and diminished venous return may affect both organs [31]. Second, neurohumoral dysregulation (especially of the RAAS system), inflammatory, cellular immune-mediated, and stress-related mechanisms may play a key role [31]. Third, cardiovascular disease-related factors such as cachexia/malnutrition-associated clinical problems, mineral bone disease, and/ or anemia may play a role [31]. Given the rather high incidence of cardiovascular disease in the elderly, the cardiorenal syndromes are an entity for AKI that warrants recognition in the elderly [22].

Another potential contributor to increased rates of AKI in the critically ill, especially in the elderly ICU population, is the occurrence of renal venous hypertension resulting in renal venous congestion [31]. It is thought to mainly occur in cases of acute or chronic heart failure with increased backward pressure to venous return, diminished efferent renal blood flow, and resulting increased intra-glomerular hydrostatic pressure [31]. Neurohumoral, inflammatory, hyperhydration, and sympathomimetically mediated factors are considered to be important also [31]. Renal venous hypertension may induce decreased arterial RBF, increase plasma renin activity, and increase aldosterone levels, which may ultimately result in diminished glomerular filtration rates [79, 80]. Morphologically, tubular hypertrophy, tubulointerstitial renal fibrosis, and intra-glomerular sclerosis were observed [81]. It thus seems that renal venous congestion could accelerate the natural aging process of the kidney and thus progression to chronic kidney disease.

31.6 Diagnosis of AKI in Aged ICU Patients

Serum creatinine (SCr) likely is the most commonly used biomarker to assess renal function despite obvious limitations of the marker. When renal filtration capacity declines, SCr levels typically rise not immediately, but in a delayed fashion. Therefore, SCr levels may not adequately reflect "real-time" renal function. When a SCr increase is documented, however, loss of renal function has occurred.

Further, SCr levels depend on production, removal rates, and volumes of distribution, all of which are typically impaired in the elderly population [55]. Among the many variables influencing SCr levels, age may be somewhat neglected. With loss of muscle mass due to aging, baseline SCr levels in the elderly may be lower than expected and should likely be adjusted. Kidney injury with an expected rise in SCr levels may be masked and a diagnosis of AKI therefore missed or delayed. In addition, low protein intake and/or altered protein metabolism is another factor for a low baseline SCr levels [21, 22, 24]. Thus, SCr does not constitute an ideal marker for AKI diagnosis in the elderly [82]. Novel AKI markers that are currently under investigation include cystatin C, neutrophil gelatin-associated lipocalin (NGAL), kidney injury molecule-1, kidney injury molecule 1 (KIM-1), L-type fatty acid-binding protein (L-FABP), netrin 1, N-acetyl-beta-D-glucosaminidase (NAG), alfa1-macroglobulin, or interleukin-18 [23, 24, 29, 35]. Some were investigated and validated in multiple studies as predictors of AKI in specific patient cohorts, both in adults and children, but none of these studies specifically analyzed elderly ICU pop-

ulations [22, 29, 33, 35, 36]. Of the respective markers, it appears that only cystatin C was thoroughly validated and could be considered a reliable alternative biomarker for AKI, especially when used in combination with SCr [83–88]. Among the additional markers, NGAL was tested extensively. An increase in urinary NGAL may indicate unfavorable outcome in septic patients with AKI or in ICU patients [89, 90]. In elderly patients with CKD, serum NGAL reflects renal impairment and was found associated with cystatin C, urea, SCr, and eGFR. In a recent study among elderly CKD patients (mean age 75.3 +/− 12.1 years), increasing NGAL levels correlate with an increased 2- and 5-year risk of ESRD [91].

31.7 Treatment of AKI in the Elderly

No targeted, that is, specific, treatment for AKI in the elderly population is currently available. In association with a considerably increased mortality rate in this patient population, the focus of clinical management lies on preventive measures. Elderly ICU patients have to be monitored closely with regard to clinical course: fluid balance, electrolytes, hemodynamics, addressing hypovolemia, and hypotension, together aiming for an optimal volume status with preserved macro- and microcirculation (and organ perfusion). Respective clinical parameters should especially be remembered when operations and/or invasive interventions are performed.

Drug-induced AKI, iatrogenic, either via direct (dose-independent) or indirect (dose-dependent) nephrotoxicity, poses another key element, necessitating vigilant patient monitoring. Drugs that should be used with caution include drugs that impact on renal/intrarenal hemodynamics (e.g., anti-inflammatory substances), diuretics, and angiotensin-converting enzyme inhibitors. Medication should ideally be individualized and tailored based on GFR [23]. Whenever imaging studies become necessary, it is recommended to prefer studies that would not require contrast media. However, when indicated and unavoidable, iso-osmotic nonionic low osmolar contrast media should be applied in the lowest volumes possible. Protocols to prevent contrast media-induced AKI should be adhered to and be present on all ICUs.

Globally, rising attention of health-care professionals for the particular renal vulnerability will be important in the future. Key in management of respective patients at risk may be careful monitoring of the elderly ICU patient, with the overall aim to prevent AKI or limit respective complications.

Take-Home Messages

- Elderly ICU patients are at risk for AKI due to a number of reasons including (a) renal aging, (b) presence of age-related comorbidities, and (c) polypharmacy and/or application of potentially nephrotoxic agents.
- Assessment of urinary output and repeat assessment of, for example, 6-h SCr-clearance may best allow to monitor individual renal (dys)function.
- No causative therapy for AKI is currently available which places the clinical management focus on effective AKI prevention.
- With an overall aging society, the incidence of AKI on intensive care units will likely increase, rendering AKI a major concern of global health-care systems.

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