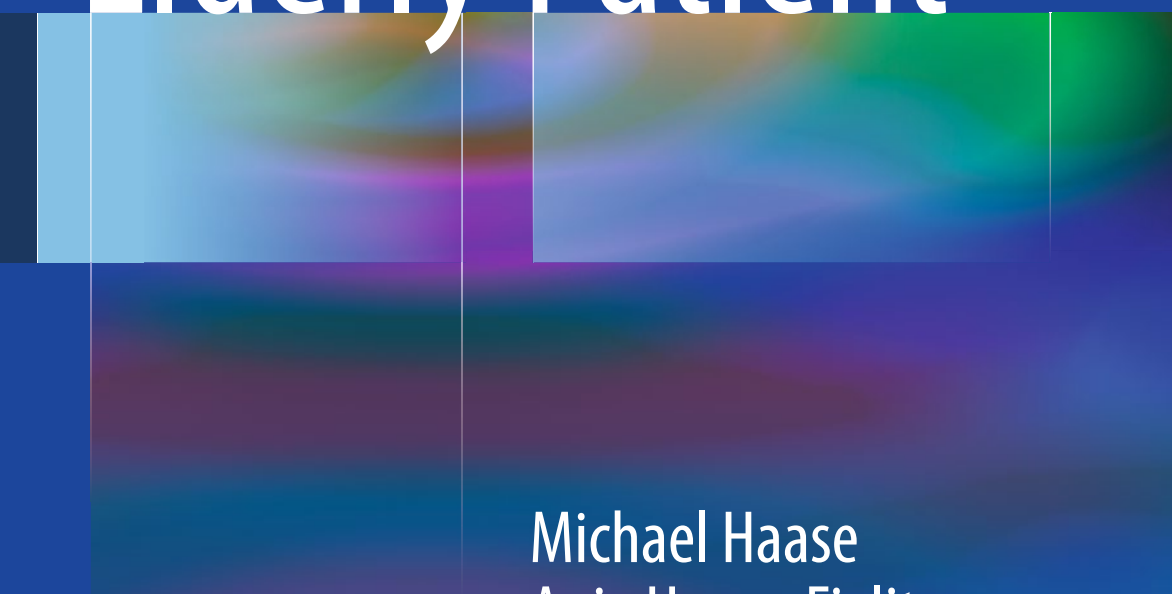
Managing Renal Injury in the Elderly Patient



Michael Haase
Anja Haase-Fielitz
Editors

Springer

Managing Renal Injury in the Elderly Patient

Michael Haase • Anja Haase-Fielitz
Editors

Managing Renal Injury in the Elderly Patient

Springer

Editors
Michael Haase, MD (MH)
Department of Nephrology and Hypertension,
Diabetology and Endocrinology
University Hospital
Otto-von-Guericke University
Magdeburg
Germany

Anja Haase-Fielitz, PharmD (AHF)
Department of Nephrology and Hypertension,
Diabetology and Endocrinology
University Hospital
Otto-von-Guericke University
Magdeburg
Germany

ISBN 978-3-642-39946-6 ISBN 978-3-642-39947-3 (eBook)
DOI 10.1007/978-3-642-39947-3
Springer Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Contents

Chapter 1
Managing Kidney Injury in Older Patients

Michael Haase and Anja Haase-Fielitz

It is a matter of fact – people grow older all over the world and increased life expectancy is associated with specific health issues. A recent meta-analysis using the data from 187 countries reported that, during the last 40 years, global male life expectancy increased from 56 years to 68 years and global female life expectancy increased from 61 years to 73 years [1].

Currently an estimated 40–50 % of all hospital and intensive care admissions are older people – aged 60 years and plus. Older patients are more susceptible to nosocomial infections, medication interactions and surgical complications. Due to cognitive and physical decline, they have a high risk of being unable to return home and requiring nursing home placement as they often have lost the ability in some basic activity of daily living during even a very short hospitalization. As the world's population is growing older, in the future years we are faced with specific and complex issues in critical care also affecting geriatric nephrology.

Acute kidney injury (AKI) represents a frequent and devastating problem in hospitalized patients and is associated with an increased risk of dying that persists after discharge from the hospital even if a (near) complete recovery of renal function occurs. An estimated 5–10 % of all hospitalized patients and up to 40 % of critically ill patients experience an episode of AKI during the course of their illness with increasing incidence observed during the last decades. Reasons for this include more aggressive medical treatment, the increasing number of comorbidities that accumulate during increasing lifespan and the ageing population in general. Patients

M. Haase, MD (MH) (✉) • A. Haase-Fielitz, PharmD (AHF)
Department of Nephrology and Hypertension,
Diabetology and Endocrinology, University Hospital,
Otto-von-Guericke University,
Leipziger Str. 44, Magdeburg,
Sachsen-Anhalt 39120, Germany
e-mail: michael.haase@med.ovgu.de, michael.haase@charite.de;
anja.haase-fielitz@med.ovgu.de

M. Haase, A. Haase-Fielitz (eds.), *Managing Renal Injury in the Elderly Patient*,
DOI 10.1007/978-3-642-39947-3_1,

with severe AKI requiring acute dialysis have a higher likelihood of developing chronic kidney disease and eventually needing chronic dialysis. Also, AKI induces injury to extrarenal organs including the lungs, heart and brain – with all of them being more susceptible to injury in older patients – leading to prolonged ventilation time, longer hospital stay but also increased rate of hospital readmission.

Internists, nephrologists, geriatricians, critical care physicians, and surgeons all treat critically ill patients with AKI or are regularly involved in the care of patients at risk of this syndrome. It is the editors' hope that this book will provide a reference for clinicians to help guide their care of older patients with AKI. We have brought together a group of international authors to cover the most recent information on epidemiology, pathogenesis and prevention of AKI in older patients. The earlier parts of this book present paragraphs on age-related changes in the kidney and the role of renal biomarkers in the diagnosis of the disease, whereas the subsequent parts are dedicated to drug kinetics and renal toxicity and paragraphs on acute dialysis in this patient population. In the final parts of the book, issues on quality of life and end of life decision-making in older patients with kidney injury will be discussed.

Leading us to the horizon of modern medicine in older patients, a recent case report on a 101-year-old patient with severe kidney injury illustrated the issues and uncertainties during the management of this patient until his death after 56 dialysis treatments [2]. While this book does not aim to give an answer to each of the reported problems, many aspects the patient and his physicians were facing while treating him are covered here.

Key messages at the beginning of each chapter and numerous figures and tables enable easy access to complex interrelationships between ageing and renal pathophysiology and function and clinical consequences and may contribute to make this book a popular reference book for clinicians, researchers, and students. Special emphasis is placed on the most recent publications important for the field carrying implication for the clinical practice. The chapters included in this book are derived from clinical experience and report the evidence for current clinical practice extracted from consensus statements if available or systematic analyses of the literature. When gaps of knowledge were identified, common sense for practical management of older patients with kidney injury was used until these gaps may be closed. We are truly indebted to the authors for their timely and expert contributions.

References

1. Wang H, Dwyer-Lindgren L, Lofgren KT et al (2012) Age-specific and sex-specific mortality in 187 countries, 1970–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2071–2094
2. Gabbay E, Hersch M, Shavit L et al (2013) Dialysis by the book? Treatment of renal failure in a 101-year-old patient. Clin Kidney J 6:90–92

Chapter 2
Incidence, Risk Factors, and Outcome

Mitchell H. Rosner, Claudio Ronco, and Dinna N. Cruz

Key Messages

1. Acute kidney injury is a disease of the elderly with the highest incidence in patients older than age 70 years.
2. Etiologies of acute kidney injury can be grouped according to the typical schema of prerenal, intrarenal, and postrenal etiologies. However, certain etiologies such volume depletion, obstruction due to prostate disease and ischemia due to sepsis are more common in older age groups.
3. Treatment of acute kidney injury is largely supportive, and in those elderly patients who require renal replacement therapy, the decision to initiate this support measure must require a careful thought process that takes into account family and patient wishes as well as the overall prognosis for functional recovery.

M.H. Rosner, MD
Department of Nephrology, University of Virginia,
1545 Running Cedar, Charlottesville,
VA 222911, USA
e-mail: mhr9r@virginia.edu

C. Ronco, MD
Department of Nephrology Dialysis and Transplantation,
St. Bortolo Hospital and International Renal Research Institute
of Vicenza (IRRIV), Viale Rodolfi 37,
Vicenza 36100, Italy
e-mail: cronco@goldnet.it

D.N. Cruz, MD, MPH (✉)
Division of Nephrology-Hypertension,
University of California, San Diego,
200 West Arbor Drive #8409, San Diego,
CA 92103-8409, USA
e-mail: dinnacruzmd@yahoo.com

M. Haase, A. Haase-Fielitz (eds.), *Managing Renal Injury in the Elderly Patient*,
DOI 10.1007/978-3-642-39947-3_2, © Springer-Verlag Berlin Heidelberg 2014

2.1 Epidemiology of AKI in Older Individuals

Throughout the world, the population is getting older [1, 2]. With medical, societal, and environmental changes, the probability of survival to older age has improved and the absolute number and proportion of older people is projected to increase in the next few decades. Of critical importance is that the fastest growing age cohort is made up of those aged ≥80 years, increasing at an estimated 3.8 % per year, and projected to represent one-fifth of all older people by 2050 [2]. There are important consequences associated with these demographic changes, namely, that we will face a population with an increased prevalence of chronic illness and functional impairment [3]. These chronic illnesses include chronic kidney disease (CKD) as well as other comorbidities that predispose to AKI [4]. Despite widely varying incidences of AKI reported in the literature (largely a reflection of differing definitions of AKI), most studies support the finding that elderly people are at higher risk for development of AKI.

For instance, there is a three- to eightfold age-dependent increase in the frequency of development of community-acquired (out of hospital) AKI in patients older than 60 years of age [5]. Not surprisingly, the past 25 years have seen the mean age of patients with AKI increase by at least 5 years and perhaps as much as 15 years [6].

Elderly patients make up the majority of hospitalized patients. By virtue of the fact that they require numerous diagnostic and therapeutic interventions as well as due to their numerous comorbid conditions, they are at risk for the development of hospital-acquired AKI. In hospitalized patients, the reported incidence of AKI varies between 5 and 7 % [7–9], and the incidence in the postoperative period ranges from 0.1 to 30 %, depending on the criteria used to define AKI and the type of surgery performed (higher rates associated with cardiovascular procedures) [10, 11]. Nearly 1 % can develop severe AKI with creatinine level above 4 mg/dl and/or need for dialysis [12, 13]. Unfortunately, postsurgical mortality rates in the setting of AKI can range from 20 to 80 %, depending on the presence of other comorbidities [10, 12, 14]. The average age of patients suffering AKI in the hospital setting is >60 years [7].

In the subset of elderly patients who develop AKI in the critical care unit, the outcomes can be devastating. It is important to realize that the elderly are becoming a greater proportion of patients in the intensive care unit (ICU). Fifty-five percent of all American intensive care unit (ICU) bed days are occupied by patients aged ≥65 years [15, 16]. Of the 17,440 patients in medical and surgical ICUs from 40 institutions in the USA, the proportion of patients who were over age 65 was 48 %. Twenty-five percent were 65–74 years old, 17.2 % were 75–84 years old, and 5.3 % were >85 years old [17]. In a multicenter study, Australian New Zealand Care Society Adult Patient (ANCIZS) database researchers determined that 13 % of 120,123 adult patients were aged ≥80 years and that the admission rate for this age group increased by 5.6 % per year during the period between 2000 and 2005 [18]. Thus, very elderly patients with numerous comorbid conditions increasingly populate the ICU. In the ICU setting, AKI is a common and important occurrence with a reported incidence of 1–25 %, depending on the population being studied and the

Table 2.1 Etiologies of acute injury in the elderly

Prerenal
(a) Intravascular volume depletion (blood loss, insensible loss, adrenal insufficiency, gastrointestinal losses (vomiting, diarrhea), urinary losses (diuretics, osmotic diuresis), third spacing of fluid)
(b) Decreased effective arterial circulating volume (decreased cardiac output (systolic heart failure, cardiac arrhythmias, pericardial disease), cirrhosis, nephrotic syndrome)
(c) Medications (nonsteroidal anti-inflammatory drugs, angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, calcineurin inhibitors)
Intrinsic renal
(a) Tubular injury: acute tubular necrosis (ischemic, nephrotoxic (medications, pigments)
(b) Interstitial: acute interstitial nephritis (allergic due to drugs)
(c) Vascular: vasculitis, thromboembolic, atheroembolic, and occlusion
(d) Glomerular: acute glomerulonephritis
Postrenal (obstructive)
(a) Upper tract obstruction (usually bilateral or with a single kidney (nephrolithiasis), papillary necrosis, pelvic neoplasms, retroperitoneal processes (neoplasms, adenopathy, fibrosis, hematoma), gastrointestinal neoplasms, radiation therapy)
(b) Lower tract obstruction (urethral strictures, nephrolithiasis, blood clots, prostatic disease (carcinoma, benign hypertrophy, calculi), neurogenic bladder)

criteria used to define its presence [19, 20]. AKI, which usually appears in the setting of acute lung injury, sepsis, and trauma in ICU patients, is associated with a mortality rate of 50–70 %, which has remained relatively constant over the last decades [21].

There is no doubt that the elderly patient in the ICU is at higher risk for AKI. The BEST Kidney collaborators, in a prospective multicenter study on 26,269 critically ill patients with a median age of 67 years, determined that 5.7 % of the patients developed severe AKI [22]. Moreover, in a recent study comparing the RIFLE and AKIN criteria, the incidence of AKI in the first 48 h of ICU stay ranged between 28.5 and 35.5 %. The mean age of the patients was 63 years, with 25 % aged >75 years, highlighting the fact that AKI is common in the elderly [23].

2.2 Etiologies of AKI in Older Individuals

Even though elderly patients often have the same spectrum of clinical conditions responsible for AKI as the general population, there are specific differences in the incidence and in the presentation of these etiologies, making this group of patients unique (Table 2.1).

Prerenal AKI and acute tubular damage (formerly referred to as acute tubular necrosis and discussed further below) account for nearly a third of cases of AKI [24]. In prerenal AKI, the mechanism responsible for kidney injury is reduced renal perfusion. Decrease in renal perfusion stimulates sympathetic nervous system activity and the release of vasoconstrictor substances (such as angiotensin II) which can lead to

a further reduction in glomerular filtration rate and, if the renal perfusion is impaired for a long period to kidney injury, ischemic acute tubular damage. Renal hypoperfusion can develop in different clinical conditions, such as reduced cardiac output (myocardial dysfunction, pericardial disease, cardiac arrhythmias), intravascular volume redistribution to interstitial spaces (cirrhosis, nephrotic syndrome, sepsis, and malnutrition), and external loss of fluids with insufficient fluid replacement (vomiting, diarrhea, bleeding, and excessive sweating due to febrile illnesses). While many of these causes can be reversed with adequate fluid replacement or vasopressor/inotropic support, others progress to ischemic acute tubular damage, especially if the insult is prolonged and severe.

Dehydration and volume depletion are commonly encountered in the elderly [25]. Being bedridden with cognitive impairment and having poor fluid oral intake are important risk factors for dehydration, which, if untreated, has a very high mortality rate [26]. This can be compounded by the impaired ability of the kidney to retain sodium in the elderly as well as by the common use of loop or thiazide diuretics in this population [25].

Numerous *intrarenal* (affecting the vasculature, glomerulus, tubules, or interstitial compartments) causes of AKI can also affect the elderly, of which ischemic or nephrotoxic acute tubular damage is the most common with an incidence ranging from 25 to 87 % [24, 27]. Sepsis is a particularly important cause of acute tubular damage, and in the setting of sepsis, the development of AKI requiring dialysis has a mortality rate greater than 80 % [28]. Vascular diseases, such as renal artery occlusion or thromboembolism, can be responsible for AKI in the elderly as well. They are usually associated with atherosclerosis, atrial fibrillation, or myocardial infarction. Older patients seem to have a higher incidence of certain rapidly progressive glomerular diseases such as antineutrophil cytoplasmic antibody and anti-glomerular basement membrane associated glomerulonephritis [29, 30]. These conditions should be suspected when the urine sediment demonstrates the presence of dysmorphic red blood cells or red blood cell casts. Older patients are also susceptible to developing rhabdomyolysis and pigment-induced acute tubular damage in the setting of acute immobilization, infectious diseases, cerebrovascular accidents, hyperosmolar state, hyponatremia, hypernatremia, hypothermia, and after falls. This should be suspected in patients who have positive urine dipstick test for blood but who have a negative urine microscopy and who have a positive urine myoglobin.

Older patients are frequently subjected to medical procedures and pharmacological treatments, which can lead to AKI. In most cases, the injury takes the form of nephrotoxic acute tubular damage, but allergic interstitial nephritis and other pathological entities may be seen. Among the drugs commonly prescribed to older patients, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEi), and angiotensin-receptor blockers (ARBs) are associated with AKI. These agents interfere with the protective autoregulatory mechanisms that maintain renal blood flow and glomerular filtration rate across a wide range of blood pressure. While NSAIDs inhibit prostaglandin production, with subsequent increased vascular resistance in the afferent arteriole, ACEi and ARBs reduce vascular resistance in the efferent arteriole, thus impairing intra-glomerular pressure [7]. In states of marginal renal perfusion, such as heart failure, volume depletion,

and renal artery stenosis, these drugs may lead to precipitous falls in renal blood flow and glomerular filtration rates, thus resulting in ischemic acute tubular damage [31, 32]. Moreover, the concomitant administration of diuretics, laxatives, and drugs that decrease appetite or the level of consciousness can worsen dehydration and volume depletion further increasing the risk for hemodynamically mediated AKI when these drugs are administered.

Acute tubular damage is the most frequent cause of AKI in the elderly and it is often associated with the use of directly nephrotoxic drugs, such as antibiotics and antifungals (particularly aminoglycosides and amphotericin B), immunosuppressive medications (cyclosporine and tacrolimus), and chemotherapeutic agents (cisplatin). Well-known risk factors for drug-induced acute tubular damage include age greater than 60 years, atherosclerotic cardiovascular disease, diabetes mellitus, preexisting chronic kidney disease, and hypoperfusion (volume depletion) states [7].

Although there are no available data on the incidence of *acute interstitial nephritis* (AIN) in the elderly, this group of patients is likely to be at increased risk due to a large number of medications that are prescribed. Antibiotics (penicillins, cephalosporins, and fluoroquinolones), diuretics, and NSAIDs are some of the more common agents responsible for this syndrome in older patients. The dose of the drug administered and the duration of the treatment and past exposure are important risk factors for the development of AIN. Recently, proton pump inhibitors, usually safe and frequently prescribed in the elderly, have been associated with AIN as well [33]. AIN should be suspected in patients with allergic symptoms (rash), presence of white blood cells (especially eosinophils) or white blood cell casts in the urine, and presence of eosinophilia on a complete blood cell count. However, none of these findings are sensitive or specific and a high degree of clinical suspicion must be present to make the diagnosis. In some cases, renal biopsy may be required. Recovery occurs after withdrawal of the drug, but it is often incomplete and some patients may require therapy with corticosteroids to improve kidney function [34].

Given the high number of diagnostic and therapeutic radiographic procedures performed in this population of patients, AKI due to iodinated radiocontrast agents is common. Contrast-induced nephropathy is often observed after cardiac and/or peripheral vascular catheterization and revascularization. Other than age, factors such as baseline renal function, diabetes, cardiac failure, emergent procedures, a high volume of contrast agent, and female sex also contribute to a higher risk for contrast-induced AKI [35].

Surgical procedures account for about one-third of acute tubular damage cases in the elderly [36]. The incidence of AKI ranges from about 0.1 % in general surgery to 31 % or more with cardiac surgery [37]. Advanced age is a risk factor for AKI development in most of these settings, but factors such as emergency surgery, presence of CKD, and baseline comorbidities are also important risk factors [37]. Hypotension during and after surgery, postoperative fluid loss, and arrhythmias are commonly encountered in the elderly and in combination with impaired renal autoregulation may induce hemodynamically mediated AKI. As stated above, concomitant use of ACEi or ARBs may exacerbate already tenuous renal perfusion. The postoperative period can often complicate by severe infections, which may also result in acute tubular damage associated with sepsis [38].

Finally, *postrenal* (obstructive) AKI accounts for 7.9–9 % of cases in patients over 65 and 70 years respectively [39, 40]. 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 due to benign prostatic hypertrophy or carcinoma. Prostate cancer is the most common neoplasm in men, affecting 50 % of males aged 50 years and increasing to 90 % by the ninth decade of life. A small percentage of these patients develop severe obstructive AKI, which if not treated can progress to irreversible renal failure. The second most common cause of obstructive AKI in males is urethral stricture disease, often secondary to trauma or past Foley catheter use. In women, important causes of ureteral obstruction, responsible for postrenal AKI, are pelvic malignancies, such as carcinoma of the cervix and ovarian neoplasms. Lymphoma and bladder and rectum carcinomas are other causes of obstructive AKI in the geriatric population.

2.3 Outcome of AKI in the Older Patients

In general, the treatment of AKI in the elderly follows the same principles as for the general population. This means careful attention to dosing medications, avoidance of further nephrotoxic insults, management of fluid, electrolyte and acid-base balance, mandatory urinary tract catheterization in case of obstructive AKI, and provision of adequate nutritional support. If iatrogenic AKI (nephrotoxic acute tubular damage) or acute interstitial nephritis is diagnosed, withdrawal of the drugs responsible for these syndromes is critical and can reverse the course of AKI especially if this is done early in the course. In case of rapidly progressive glomerulonephritis, caution must be paid in the use of immunosuppressive agents, such as corticosteroids and cytotoxic drugs, given their altered pharmacokinetics and the higher risk of opportunistic infections and complications in the elderly. Particular attention must be paid to the development of signs of sepsis, which is often occult in frail elderly patients [41].

The decision to initiate renal replacement therapy (RRT) in the elderly may be difficult. This is especially true for those individuals with significant baseline renal impairment where the likelihood of renal recovery may be low. Furthermore, patients with multiple comorbid conditions and multisystem organ failure will have a poor overall prognosis. Decisions regarding initiation of renal support therapy undoubtedly must be individualized, taking into consideration the particular clinical situation, the patient's wishes, the chances for functional renal recovery, and the probability of survival. Clinical management decisions should never be made on the basis of chronological age alone.

If a decision is made to initiate dialysis, there should be careful consideration as to the optimum mode of renal support (continuous or intermittent therapy). Owing to increased autonomic dysfunction, decreased cardiovascular reserve, and other comorbidities, older patients are more prone to hemodynamic complications during dialysis, such as intradialytic hypotension and arrhythmias [7]. Older patients are

also more vulnerable to bleeding problems and to neurologic complications resulting from rapid changes in serum electrolytes and osmolarity that occur during the dialysis session [42]. Although it has not been studied specifically in the elderly, continuous renal replacement therapy (CRRT) is associated with a more stable hemodynamic profile than intermittent dialysis in the general population and is also associated with a reduced risk of disequilibrium syndrome owing to slower osmolality shifts, which might make this modality useful in the fragile elderly population [43]. However, when choosing the type of modality, clinicians must also consider the increased risk associated with continuous anticoagulation in a population prone to bleeding as well as the higher costs associated with CRRT.

Although AKI can be fully reversible, the renal repair process also can be incomplete and result in chronically decreased kidney function. This can range from subclinical decreases in glomerular filtration rate to dialysis-dependent end-stage renal disease. Incidence rates of end-stage renal disease (ESRD) after AKI in the elderly differ widely among studies, ranging from less than 1 % to greater than 40 % [44–46]. For example, Ishani and coworkers demonstrated a 13-fold higher risk of ESRD in hospitalized elderly patients with AKI as compared to elderly patients without AKI [47]. A recent systematic review and meta-analysis has demonstrated that recovery of kidney function after AKI is approximately 28 % less likely to occur when the patient is older than 65 years [48]. 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. Little is known about mortality in elderly patients who experience AKI and do not require dialysis. In a prospective, multicenter study including hospitalized patients, no increased risk of death with advanced age was found [49]. An older study by Lameire failed to show any differences in mortality or renal recovery between patients older than 65 years and those aged 17–64 years [50]. On the contrary, a recent study by Ali et al. showed a significant and incremental increase in mortality risk with age and comorbid conditions [51]. Thus, in the absence of clear data, individualized decision making continues to be of critical importance.

Existing outcome data for elderly ICU patients requiring dialysis vary widely, with reported mortality ranging from 31 to 80 % [22]. This is due to differences between studies in terms of the definition of advanced age, treatment intensity, severity of illness, and length of follow-up. Some studies report an increased mortality risk in elderly critically ill patients with AKI [22]. Conversely, other well-conducted studies found no difference in mortality attributable to older age (although these studies are older and may not be applicable to current care patterns) [49]. One of these studies found multiple organ dysfunction syndrome (MODS) to be an independent risk factor for increased mortality [52, 53]. Interestingly, those patients with MODS often have a higher acute severity of illness and short-term mortality, but in those who survive, there is lower long-term mortality likely attributable in part to less comorbid illness. Another feature of AKI that has important implications for long-term outcomes is the duration of AKI [54]. In one study, those patients with a duration of AKI greater than 7 days had a higher mortality than those with shorter

durations of AKI [54]. Indeed, several studies on long-term outcomes of hospital survivors of MODS and AKI treated with RRT have documented a surprisingly low post-discharge mortality rate and an acceptable self-perceived quality of life [55, 56]. In a multicenter study, Australian New Zealand Care Society Adult Patient (ANCIZS) researchers demonstrated factors associated with lower survival in elderly patients admitted to the ICU [19]. Admission from a chronic care facility, comorbid illness, nonsurgical admission, greater illness severity, mechanical ventilation, and longer stay in ICU were found to be associated with lower patient survival.

2.4 Summary

AKI in the older patient is a relatively common occurrence. The etiologies of AKI in this population include prerenal, intrarenal, and postrenal causes. The elderly kidney is predisposed to AKI due to molecular, cellular, structural, and functional changes associated with aging itself as well as age-related comorbidities. Once AKI is established, older patients may have a similar prognosis to younger cohorts, but this area requires further study and an individualized approach to decision making is required.

References

1. Robbins LJ, Oholer SK (1990) The hospitalized elderly patient. In: Schrier RW (ed) Geriatric medicine. Saunders, Philadelphia, pp 54–67
2. Population Division. Department of Economic and Social Affairs. United Nations WHO. World Population Ageing, pp 1950–2050
3. Song X, MacKnight C, Latta R, Mitnitski AB, Rockwood K (2007) Frailty and survival of rural and urban seniors: results from the Canadian Study of Health and Aging. Aging Clin Exp Res 19:145–153
4. Hsu CY, Ordonez JD, Chertow GM, Fan D, McCulloch CE, Go AS (2008) The risk of acute renal failure in patients with chronic kidney disease. Kidney Int 74:101–107
5. Feest TG, Round A, Hamad S (1993) Incidence of severe acute renal failure in adults: results of a community based study. BMJ 306:481–483
6. Turney JH, Marshall DH, Brownjohn AM, Ellis CM, Parsons FM (1990) The evolution of acute renal failure, 1956–1988. Q J Med 74:83–104
7. Chronopoulos A, Cruz DN, Ronco C (2010) Hospital-acquired acute kidney injury in the elderly. Nat Rev Nephrol 6:141–149
8. Singri N, Ahya SN, Levin ML (2003) Acute renal failure. JAMA 289:747–751
9. Abernethy VE, Lieberthal W (2002) Acute renal failure in the critically ill patient. Crit Care Clin 18:203–222
10. Sural S, Sharma RK, Singhal M et al (2000) Etiology, prognosis, and outcome of post-operative acute renal failure. Ren Fail 22:87–97
11. Sear JW (2005) Kidney dysfunction in the postoperative period. Br J Anaesth 95:20–32
12. Mehta RL, Chertow GM (2003) Acute renal failure definitions and classification: time for change? J Am Soc Nephrol 14:2178–2187

13. Kohli HS, Bhaskaran MC, Muthukumar T et al (2000) Treatment-related acute renal failure in the elderly: a hospital-based prospective study. Nephrol Dial Transplant 15:212–217
14. Bailes BK (2000) Perioperative care of the elderly surgical patient. AORN J 72:186–207
15. Chronopoulos A, Rosner MH, Cruz DN, Ronco C (2010) Acute kidney injury in elderly intensive care patients: a review. Intensive Care Med 36:1454–1464
16. Angus DC, Barnato AE, Linde-Zwirble WT et al (2004) Use of intensive care at the end of life in the United States: an epidemiologic study. Crit Care Med 32:638–643
17. Knaus WA, Wagner DP, Draper EA et al (1991) The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 100:1619–1636
18. Bagshaw SM, Webb SA, Delaney A et al (2009) Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. Crit Care 13:R45
19. de Mendonca A, Vincent JL, Suter PM et al (2000) Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med 26:915–921
20. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J (1998) Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 104: 343–348
21. Silvester W, Bellomo R, Cole L (2001) Epidemiology, management, and outcome of severe acute renal failure of critical illness in Australia. Crit Care Med 29:1910–1915
22. Uchino S, Kellum JA, Bellomo R et al; Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294:813–818
23. Joannidis M, Metnitz B, Bauer P et al (2009) Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med 35:1692–1702
24. Cheung CM, Ponnusamy A, Anderton JG (2008) Management of acute renal failure in the elderly patient: a clinician's guide. Drugs Aging 25:455–476
25. Lavizzo-Mourey R, Johnson J, Stolley P (1988) Risk factors for dehydration among elderly nursing home residents. J Am Geriatr Soc 36:213–218
26. Weinberg AD, Pals JK, Levesque PG, Beal LF, Cunningham TJ, Minaker KL (1994) Dehydration and death during febrile episodes in the nursing home. J Am Geriatr Soc 42:968–971
27. Lameire NVJ, Vanholder R, Ringoir S (1991) A review of the pathophysiology, causes and prognosis of acute renal failure in the elderly. Geriatric Nephrol Urol 1:77–87
28. Wardle EN (1994) Acute renal failure and multiorgan failure. Nephrol Dial Transplant 9(Suppl 4):104–107
29. Preston RA, Stemmer CL, Materson BJ, Perez-Stable E, Pardo V (1990) Renal biopsy in patients 65 years of age or older. An analysis of the results of 334 biopsies. J Am Geriatr Soc 38:669–674
30. Keller FMC, Buttner P (1994) Risk factors for long-term survival and renal function in 64 patients with rapidly progressive glomerulonephritis (RPGN). Geriatric Nephrol Urol 4:5–12
31. Kleinknecht D, Landais P, Goldfarb B (1987) Pathophysiology and clinical aspects of drug-induced tubular necrosis in man. Contrib Nephrol 55:145–158
32. Hollenberg N (1983) Medical therapy of renovascular hypertension: efficacy and safety of captopril in 269 patients. Cardiovasc Rev Rep 4:852–858
33. Ni N, Moeckel GW, Kumar C (2010) Late-onset omeprazole-associated acute interstitial nephritis. J Am Geriatr Soc 58:2443–2444
34. Simpson IJ, Marshall MR, Pilmore H et al (2006) Proton pump inhibitors and acute interstitial nephritis: report and analysis of 15 cases. Nephrology (Carlton) 11:381–385
35. McCullough PA, Adam A, Becker CR et al; CIN Consensus Working Panel (2006) Epidemiology and prognostic implications of contrast-induced nephropathy. Am J Cardiol 98:5K–13K
36. Pascual J, Orofino L, Liaño F et al (1990) Incidence and prognosis of acute renal failure in older patients. J Am Geriatr Soc 38:25–30
37. Rosenfeld JB, Shohat J, Grosskopf I, Boner G (1987) Acute renal failure: a disease of the elderly? Adv Nephrol Necker Hosp 16:159–167

38. Noor S, Usmani A (2008) Postoperative renal failure. Clin Geriatr Med 24:721–729
39. Macias-Nunez JF, Lopez-Novoa JM, Martinez-Maldonado M (1996) Acute renal failure in the aged. Semin Nephrol 16:330–338
40. World Health Organization (1998) The World Health Report. 50 facts: Global health situation and trends. WHO, Washington DC, pp 1995–2025
41. Fontanarosa PB, Kaeberlein FJ, Gerson LW, Thomson RB (1992) Difficulty in predicting bacteremia in elderly emergency patients. Ann Emerg Med 21:842–848
42. Bonello MPD, Ricci Z, Zamperetti N, Ronco C (2009) Acute renal failure in the elderly critically ill patient. In: Ronco CBR, Kellum JA (eds) Critical care nephrology. Saunders/Elsevier, Philadelphia, pp 1675–1680
43. Hsieh CW, Chen HH (2007) Continuous renal replacement therapy for acute renal failure in the elderly. Int J Gerontol 1:46–51
44. Bhandari S, Turney JH (1996) Survivors of acute renal failure who do not recover renal function. QJM 89:415–421
45. Schiffl H (2006) Renal recovery from acute tubular necrosis requiring renal replacement therapy: a prospective study in critically ill patients. Nephrol Dial Transplant 21:1248–1252
46. Liano F, Felipe C, Tenorio MT et al (2007) Long-term outcome of acute tubular necrosis: a contribution to its natural history. Kidney Int 71:679–686
47. Ishani A, Xue JL, Himmelfarb J et al (2009) Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol 20:223–238
48. Schmitt R, Coca S, Kanbay M, Tinetti ME, Cantley LG, Parikh CR (2008) Recovery of kidney function after acute kidney injury in the elderly: a systematic review and meta-analysis. Am J Kidney Dis 52:262–271
49. Pascual J, Liano F (1998) Causes and prognosis of acute renal failure in the very old. Madrid Acute Renal Failure Study Group. J Am Geriatr Soc 46:721–725
50. Lameire N, Matthys E, Vanholder R et al (1987) Causes and prognosis of acute renal failure in elderly patients. Nephrol Dial Transplant 2:316–322
51. Ali T, Khan I, Simpson W et al (2007) Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol 18:1292–1298
52. Van Den Noortgate N, Mouton V, Lamot C et al (2003) Outcome in a post-cardiac surgery population with acute renal failure requiring dialysis: does age make a difference? Nephrol Dial Transplant 18:732–736
53. Gong Y, Zhang F, Ding F, Gu Y (2012) Elderly patients with acute kidney injury (AKI): clinical features and risk factors for mortality. Arch Gerontol Geriatr 54:e47–e51
54. Coca SG, King JT Jr, Rosenthal RA, Perkal MF, Parikh CR (2010) The duration of postoperative acute kidney injury is an additional parameter predicting long-term survival in diabetic veterans. Kidney Int 78:926–933
55. Gopal I, Bhonagiri S, Ronco C, Bellomo R (1997) Out of hospital outcome and quality of life in survivors of combined acute multiple organ and renal failure treated with continuous venovenous hemofiltration/hemodiafiltration. Intensive Care Med 23:766–772
56. Morgera S, Kraft AK, Siebert G, Luft FC, Neumayer HH (2002) Long-term outcomes in acute renal failure patients treated with continuous renal replacement therapies. Am J Kidney Dis 40:275–279

Chapter 3
Assessing Glomerular Filtration Rate in Older Adults

Elke Schaeffner

Key Messages

1. Currently available methods of glomerular filtration rate (GFR) estimation have limitations in older adults.
2. Although not specifically validated in this patient population, the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) are the most widely used equations to estimate renal function in older adults.
3. The recently published Berlin Initiative Study [BIS]1 and BIS2 equations are the only equations specifically developed for estimating GFR in older adults. Confirmation by external validation is needed.

3.1 Introduction

Glomerular filtration rate (GFR) is still worldwide considered the best indicator of kidney function. In clinical daily routine, GFR is often estimated (eGFR) by mathematical equations in order to avoid a time-consuming clearance measurement requiring an exogenous contrast agent. Accurate assessment of kidney function is important as the chronic kidney disease (CKD)-staging system is significantly determined by the GFR value. It also has clinical implications such as adequate adjustment of drug dosing, improved decision making in imaging testing, help in the timing of initiation of renal replacement therapy, and evaluation for kidney donation. In older adults where prevalence rates of CKD are considerably higher than in younger populations, all clinical scenarios named above are of great importance.

E. Schaeffner, MD, MSc (Epi), PD
Department of Nephrology and Intensive Care Medicine,
Charité University Medicine, Augustenburger Platz 1,
Berlin, 13353, Germany
e-mail: elke.schaeffner@charite.de

M. Haase, A. Haase-Fielitz (eds.), *Managing Renal Injury in the Elderly Patient*,
DOI 10.1007/978-3-642-39947-3_3,

3.2 Endogenous Filtration Markers

Serum creatinine as an endogenous filtration marker has determined GFR estimating equations for the last decades. Whereas creatinine is an imprecise marker as it is influenced by muscle mass, serum cystatin C seems to be less vulnerable to extrarenal factors and has been included as additional test in recent clinical practice guidelines of Kidney Disease: Improving Global Outcomes (KDIGO) to estimate baseline renal function when eGFR estimation based on serum creatinine is less accurate [1]. Clinical laboratories that determine serum cystatin C should measure cystatin C using an assay with calibration traceable to the international standard reference material [1]. Advantages of serum cystatin C compared to creatinine are its independence of muscle mass as well as age- and gender-specific illnesses. Especially in older age where loss of muscle mass is a common condition, cystatin C is suggested to be a more adequate marker [2]. The wide use of serum cystatin C is limited by thyroid dysfunction, use of moderate- to high-dose corticosteroids, and the fact that not all laboratories offer cystatin C analysis. Besides, serum cystatin C measurement is more expensive than creatinine.

3.3 Current GFR-Estimating Equations

Several of the most common equations to estimate GFR are listed in Box 3.1.

The worldwide most often used creatinine-based formula is the abbreviated (four variables: serum creatinine, age, race, and gender) Modification of Diet in Renal Disease (MDRD) Study equation [3] which derived from the original six-variable MDRD equation which additionally included blood urea nitrogen and albumin [4].

The MDRD Study equation [3] was developed and validated in CKD populations not including individuals older than 70 years [5]. Although the four-variable MDRD equation is more practical in daily routine for older people compared with the formerly used Cockcroft Gault formula [6] or creatinine clearance measurement, as it does not require weight or any urine collections, the MDRD equation [3] still overestimates GFR in older, often malnourished adults with reduced muscle mass and is therefore not a precise equation to be recommended in subjects aged 70 and older.

The chronic kidney disease epidemiology collaboration (CKD-EPI) study equation, which was published 10 years later [7], is also creatinine based, did include few older adults only, and was also predominantly created in CKD populations. The CKD-EPI is somewhat more precise and accurate than the MDRD Study equation, especially at higher GFR values, but is not explicitly validated in elderly persons either. A very recently published consecutive CKD-EPI $_{\text{creatinine-cystatin C}}$ equation contains both creatinine and cystatin C and performs better than equations based on either of these markers alone and thus may be useful as a confirmatory test for CKD [8].

Box 3.1 Common equations to estimate glomerular filtration rate (eGFR)

Cockcroft-Gault equations [6]	$\text{eGFR [mL/min]} = \frac{(140 - \text{age [years]}) \times \text{BW [kg]}}{72 \times \text{Serum creatinine [mg/dL]}} \times 0.85 \text{ (if female)}$
(6-variable) MDRD-Study equation [4]	$\text{eGFR [mL/min/1.73m}^2\text{]} = 170 \times \text{Serum creatinine [mg/dL]}^{-0.999} \times \text{Age [years]}^{-0.176} \times \text{(BUN) [mg/dL]}^{-0.17} \times \text{Albumin [g/dL]}^{0.318} \times 0.762 \text{ (if female)} \times 1.18 \text{ (if African American)}$
(4-variable) MDRD-Study equation [3]	$\text{eGFR [mL/min/1.73m}^2\text{]} = 186 \times \text{Serum creatinine [mgl/dL]}^{-1.154} \times \text{Age [years]}^{-0.203} \times 0.742 \text{ (if female)} \times 1.21 \text{ (if African American)}$
CKD-EPI equation [7] (expressed as single equation)	$\text{eGFR [mL/min/1.73m}^2\text{]} = 141 \times \min(\text{Serum creatinine [mg/dL]}/\kappa, 1)^{\alpha} \times \max(\text{Serum creatinine}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if African American)}$ κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Serum creatinine/κ or 1, and max indicates the maximum of Serum creatinine/κ or 1
CKD-EPI equation from serum creatinine and cystatin C [8] (expressed as single equation)	$\text{eGFR [mL/min/1.73 m}^2\text{]} = 135 \times \min(\text{Serum creatinine [mg/dL]}/\kappa, 1)^{\alpha} \times \max(\text{Serum creatinine}/\kappa, 1)^{-0.601} \times \min(\text{Serum cystatin C [mg/L]}/0.8, 1)^{-0.375} \times \max(\text{Serum cystatin C [mg/L]}/0.8, 1)^{-0.711} \times 0.995^{\text{Age}} \times 0.969 \text{ (if female)} \times 1.08 \text{ (if African American)}$ κ is 0.7 for females and 0.9 for males, α is –0.248 for females and –0.207 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1
BIS1 [9]	$\text{eGFR [mL/min/1.73m}^2\text{]} = 3736 \times \text{Serum creatinine [mg/dL]}^{-0.87} \times \text{Age [years]}^{-0.95} \times 0.82 \text{ (if female)}$
BIS2 [9]	$\text{eGFR [mL/min/1.73m}^2\text{]} = 767 \times \text{Serum cystatin C [mg/L]}^{-0.61} \times \text{Serum creatinine [mg/dL]}^{-0.40} \times \text{Age [years]}^{-0.57} \times 0.87 \text{ (if female)}$
Jelliffe formula [10, 11]	$\text{eGFR [mL/min/1.73m}^2\text{]} = \frac{98 - 0.8 \times (\text{Age [years]} - 20)}{\text{Serum creatinine [mg/dL]}} \times 0.9 \text{ (if female)}$

Note that the Cockcroft-Gault equation is estimating the creatinine *clearance* whereas all other equations are estimating *GFR*

The goal of the Berlin Initiative Study (BIS) was to assess kidney function exclusively in adults aged 70 years and older by comparing existing equations to a gold standard measurement (iohexol plasma clearance) and to derive a novel estimating equation that would estimate GFR more correctly in this patient group [9]. The new Berlin Initiative Study [BIS]1 (creatinine based) and BIS2 (creatinine and cystatin C based) equations showed better precision and sufficient agreement with measured GFR, especially in patients with CKD stages 1–3 [9]. Both equations were developed and internally validated in a population with a mean age of 78 years in order to fill the gap of nonexisting eGFR equations for older adults. The BIS1 equation was recently externally validated and showed excellent results [12].

A 24-h collection of urine (creatinine clearance) may for certain individuals be a more useful method to assess kidney function instead of any eGFR equation. However, especially in older age, correct urine sampling can be difficult due to mental or physical problems such as incontinence or prostate hyperplasia or other.

3.4 Acute Kidney Injury

Estimating GFR in patients with non-stable renal function as it occurs during acute kidney injury is challenging due to fluctuations in creatinine production and fluid balance. GFR prediction equations overestimate kidney function in patients with acute kidney injury but are however still useful to estimate preoperative or prehospital baseline renal function. The Jelliffe equation [10, 11] was developed to estimate GFR in the setting of non-steady-state kidney function. However, validation in older patients is lacking.

In summary, accurate assessment of eGFR is difficult especially in older adults. Only the two recent BIS equations [9] were exclusively created for older adults. Confirmation of these findings by external validation is needed.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO). Acute Kidney Injury Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2:1–138
2. Shlipak MG, Katz R, Sarnak MJ et al (2006) Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. Ann Intern Med 145:237–246
3. National Kidney Foundation (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39:S1–S266
4. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130:461–470
5. Stevens LA, Coresh J, Feldman HI et al (2007) Evaluation of the modification of diet in renal disease study equation in a large diverse population. J Am Soc Nephrol 18:2749–2757

6. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
7. Levey AS, Stevens LA, Schmid CH et al (2009) CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604–612
8. Inker LA, Schmid CH, Tighiouart H et al (2012) CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 367:20–29
9. Schaeffner ES, Ebert N, Delanaye P et al (2012) Two novel equations to estimate kidney function in persons aged 70 years or older. Ann Intern Med 157:471–481
10. Jelliffe R (1973) Creatinine clearance: Bedside estimate. Ann Intern Med 79:604
11. Jelliffe R (2002) Estimation of creatinine clearance in patients with unstable renal function, without a urine specimen. Am J Nephrol 22:320–324
12. Koppe L, Klich A, Dubourg L et al (2013) Performance of creatinine-based equations compared in older patients. J Nephrol 26:716–723

Chapter 4
Risk Assessment and Diagnostic Criteria of Acute Kidney Injury: The Role of Tubular Damage Markers

Michael Haase and Anja Haase-Fielitz

Key Messages

1. Incidence rates of developing chronic kidney disease or end-stage renal disease after an episode of acute kidney injury are reported to be up to 20–40 %.
2. Clinicians are encouraged to perform frequent clinical risk assessment (incl. routine laboratory renal parameters) for development of acute kidney injury because patient management depends on it.
3. Serum creatinine and urine output are not ideal for early diagnosis of acute kidney injury.
4. Acute tubular damage markers are recommended to be used as additional parameters for AKI diagnosis or risk assessment. Their use may contribute to earlier diagnosis (which already is the first intervention) and likely to improved patient outcomes.
5. Medical or nephrological follow-up of renal function in older patients who had developed AKI is required.

4.1 Introduction

Over the next 30 years, the number of over-65s is predicted to more than double, from 506 million in 2008 to 1.3 billion [1]. Older hospitalized patients are at increased risk of developing acute kidney injury (AKI) and progression to end-stage renal disease (ESRD) which can be explained by age-related changes in the kidney and systemic vasculature, higher susceptibility to sepsis, in addition to frequent comorbidities, and

M. Haase, MD (MH) (✉) • A. Haase-Fielitz, PharmD (AHF)
Department of Nephrology and Hypertension,
Diabetology and Endocrinology, University Hospital, Otto-von-Guericke University,
Leipziger Str. 44, Magdeburg, Sachsen-Anhalt 39120, Germany
e-mail: michael.haase@med.ovgu.de, michael.haase@charite.de;
anja.haase-fielitz@med.ovgu.de

M. Haase, A. Haase-Fielitz (eds.), *Managing Renal Injury in the Elderly Patient*,
DOI 10.1007/978-3-642-39947-3_4, © Springer-Verlag Berlin Heidelberg 2014

high exposure to iatrogenic insults such as surgery, radiocontrast agents, and medications [2–4]. An almost linear increase in mortality with increasing degree of acute renal filtration function loss has been described [5]. Experimental and strong clinical data implicate AKI as one of the most important factors for the transition of acute tubular damage to CKD [3, 6–8]. Additionally, during critical illness, AKI has been implicated as an instigator and multiplier of pulmonary, cardiac, hepatic, and neurologic dysfunction [9–12]. Identified pathways include inflammatory cascades, apoptosis, the induction of remote oxidative stress, and differential molecular expression. For example, isolated AKI can cause interstitial erythrocytes and intra-alveolar bleeding in the lungs within hours to a day as shown in animal experiments applying ischemia reperfusion to the kidneys [9]. Macrophage inhibition reversed the effect. Following AKI, the number of pulmonary aquaporin channels decreased [10], which may, in part, explain the early increased susceptibility of patients with AKI to develop pulmonary edema.

4.2 Chronic Kidney Disease and Risk of Acute Kidney Injury or Vice Versa

Preexisting chronic kidney disease (CKD) has been demonstrated to be a risk factor for AKI [3, 13, 14]. Ishani and colleagues demonstrated that older patients with CKD (mean age 79.2 years) who had an episode of AKI were 41 times more likely to develop ESRD than patients without CKD [3]. Also, in AKI survivors, risk factors associated with progression to CKD after hospital discharge have been identified and include advanced age, diabetes mellitus, decreased baseline glomerular filtration rate (GFR), and severity of AKI [15, 16]. In a cohort of 353 critically ill patients (mean age 60 years) with AKI requiring renal replacement therapy (RRT), 64.0 % of all patients left the hospital with an eGFR $\leq$60 mL/min/1.73 m^2, and 8.2 % of all cases and 21.1 % of patients with preexisting CKD required dialysis after hospital discharge [16].

Older patients constitute the fastest growing segment of the ESRD population in the USA with an increasing incidence from 28.6 % in 1980 to 49.5 % in 2000 [17]. A meta-analysis including data from 17 studies compared renal recovery – defined as independence of dialysis requirement – in patients aged 65 years or older with that of patients being younger than 65 years [18]. Recovery of renal function after AKI is about 28 % less likely to occur in older patients, a finding which was consistent in various subgroup and sensitivity analyses. Even AKI with apparently full recovery confers an increased risk for subsequent development of CKD [6]. However, only a minority of patients after an episode of AKI are referred to nephrology care after hospital discharge [19], diminishing the chance for improved long-term patient care.

4.3 Renal Function Markers for Diagnosis of AKI

Serum creatinine has been the basis by which renal function has been estimated for several decades; however, its value – especially in older and sicker individuals – has been frequently debated. By consensus, AKI is defined by a time-dependent and

magnitude-graded increase in serum creatinine or decline in urine output, a concept first suggested in 2004 by the Acute Dialysis Quality Initiative (ADQI) as the RIFLE criteria [20]. Such renal filtration function-based AKI definition was early adapted by the AKI Network [21], and 8 years after initial publication, the KDIGO Initiative embraced the concept and classification [22].

Just recently, the ADQI proposed – *in addition* to such renal filtration function-based AKI definitions – to use acute tubular damage markers [23]. Under this new diagnostic approach, in the appropriate clinical setting, AKI can be defined by abnormal levels of tubular damage biomarkers even in the absence of oliguria or elevated serum creatinine.

4.3.1 Serum Creatinine

The concentration of serum creatinine is affected by factors that influence its generation (e.g., age, gender, muscle mass, diet), glomerular filtration rate (e.g., hypertension), and tubular secretion (e.g., CKD or acute events such as AKI). The clinical usefulness of serum creatinine to timely diagnose and assess the severity of AKI is limited, as serum creatinine only rises 24–48 h after the renal injurious event. This relates to the fact that the GFR must decline to approximately half the normal level before the serum creatinine concentration begins to rise above the upper limit of normal. Also, fluid resuscitation in critically ill patients often results in a positive fluid balance, diluting serum creatinine and delaying timely diagnosis of AKI [24].

These limitations of serum creatinine are even much more pronounced in older and sicker patients especially due to changes in body composition, comorbid conditions that cause malnutrition, and the frequent use of medications that can interfere with the measurement of serum creatinine. Interpretation of renal function based on serum creatinine or urea concentration alone should be avoided in older individuals.

In the light of high probability for renal (tissue) salvage early after injury, the Kidney Disease: Improving Global Outcomes (KDIGO) Initiative suggests that delay in the diagnosis of AKI, at least in part, results from currently used diagnosis parameters basing on renal function such as serum creatinine and urine output. To protect as much salvageable kidney tissue as possible, in their recently published clinical practice guidelines for AKI [22], the KDIGO Initiative highlights the importance of risk assessment for individual patient management and concludes that acute tubular damage markers may feature AKI diagnosis if proven to be of better diagnostic performance than the classical clinical and routine biological parameters [22] (see Sects. 4.4 and 4.5).

4.3.2 Fluid Balance and Urine Output

Fluid overload especially in the setting of oligo-anuric AKI is an important modifiable prognostic factor. Fluid overload participates in the pathogenesis of hypoxemia and myocardial and lung edema, leading to a delay in recovery. Evidence

suggests that even a relatively small positive fluid balance contributes to increased morbidity and mortality in various patient cohorts [25–28], although specific data in older patients are missing.

Positive fluid balance early after admission to the intensive care unit was associated with increased mortality in patients with AKI [25]. The mean age in this study was 61 years [25]. In 601 critically ill patients (mean age 63 years), fluid balance and urine volume were independent risk factors for 28-day mortality after adjusting for age and other modifiers [26]. A combined volume and creatinine kinetic model demonstrated that fluid resuscitation leads to significant underestimation of serum creatinine and AKI severity [24]. This factor alone further delayed diagnosis of AKI by up to 9 h. Fluid dilution alone, however, could not explain the rapid reduction of creatinine observed in the majority of patients, suggesting a reduction of serum creatinine production to be a potential further cause for the disability of creatinine to function as early marker for AKI. In contrast, tubular damage biomarkers increased within a few hours after cardiac arrest, indicating AKI even in the absence of an increase in serum creatinine [24].

By consensus, oliguria is an important part of detecting acute renal function loss. Hourly urine output measurements are part of the RIFLE [20] and AKIN [21] classification as changes in urine output might precede changes in serum creatinine. However, most episodes of oliguria (urine output <0.5 mL/kg/h for more than 6 h) are not followed by AKI [28]. The sensitivity of urine output is limited when diuretics are administered, a frequent confounder in critically ill older adults, and its specificity is reduced in the presence of (undetected) dehydration. Further, the urine output criterion for AKI diagnosis lacks practicability when an indwelling urinary catheter is not present.

Therefore, reduced urine output is not easily interpretable and may occur in differently severe affected patient groups. Mild to moderate oliguria according to RIFLE class R or I (or AKIN 1 or 2) may indicate (i) physiological downregulation of urine output however still associated with increased risk of a subsequent loss of renal filtration function or (ii) an already existing mild to moderate acute loss of renal function. More severe oliguria (RIFLE class F or AKIN 3) may identify patients with severe loss of GFR.

4.3.3 Serum Cystatin C

Serum cystatin C may have advantages as renal function marker compared to serum creatinine especially for older, malnourished patients with long periods of hospitalization. Thus, serum cystatin C has been proposed as better filtration marker than serum creatinine not being affected by factors such as age, gender and weight, muscle mass, diet, and physical activity. A large body of evidence over the past several years supports the use of serum cystatin C as an alternative and more sensitive endogenous renal function marker for detecting even minor GFR reduction compared to serum creatinine [29–31]. Cystatin C is an endogenous protease inhibitor

produced at a constant rate by nucleated cells. It is freely filtered by the glomerulus, reabsorbed and catabolized, but it is not secreted by the tubules.

In older cardiac surgery patients, a significant increase in cystatin C was observed 1 day earlier than plasma creatinine [32]. Also, in the setting of older critically ill patients (mean age 70 years), serum cystatin C detected AKI (defined as serum creatinine increase >50 %) 1–2 days earlier than serum creatinine and was a moderate predictor of the need for acute renal replacement therapy [33].

Prevalence estimates of reduced renal function vary considerably depending on prediction formula used, making an accurate assessment of GFR – especially in older individuals – difficult. In the light of variation in creatinine metabolism especially amongst older comorbid patients, new equations based on standardized serum cystatin C measurements have been proposed by the CKD-EPI consortium [34–36]. A better performance of the equations combining creatinine and cystatin C compared to the CKD-EPI equation was demonstrated [34], a finding which is supported by studies showing a better estimate of mortality risk when using cystatin C compared to creatinine-based equations particularly in older population [29, 37, 38]. Differences between the observed underestimation of GFR obtained with MDRD compared to CKD-EPI equations seem to decrease with age, especially in subjects older than 70 years [36]. Two recent equations (BIS1 and BIS2) using serum creatinine and serum cystatin C were exclusively created for older adults and might prove favorable in estimating GFR in persons aged 70 years or older with normal or mild to moderately reduced renal function [39].

Finally, cystatin C has prognostic relevance particularly in older population [37, 38].

4.3.4 Proteinuria

Evidence exists that proteinuria is toxic to the tubules due to multiple pathways such as induction of tubular chemokine expression and complement activation leading to inflammatory cell infiltration in the interstitium and sustained fibrogenesis [40, 41]. Proteinuria is a well-described marker of CKD. Also, the risk of mortality and progression to AKI are independently increased in patients with higher levels of proteinuria [42].

It is well described that proteinuria adds prognostic value to GFR for understanding risks of AKI, cardiovascular disease, and mortality [43]. In the setting of cardiac surgery (patients mean age 71 years), preoperative proteinuria (urine albumin-to-creatinine ratio and urine dipstick) was an independent predictor for the risk of developing mild AKI, acute dialysis, and prolonged intensive care unit and hospital stay [43].

Information on proteinuria in addition to eGFR might be used in identifying patients at risk of developing AKI [14].

In sum, despite the acknowledged limitations of serum creatinine and urine output as markers of glomerular filtration rate and lacking a practicable alternative parameter for assessing renal function in real time, the use of renal function markers is essential for (i) diagnosis of acute function loss, (ii) determination of severity of acute function loss (stages 1, 2, 3), (iii) renal prognosis of affected patients, and (iv) renal function estimation for drug dosing.

Characteristics of renal marker	Acute tubular damage (e.g., NGAL)	Filtration function ↓ (e.g., serum creatinine)
Information about filtration function	–	✓
Information about tubular stress/damage	✓	–
Generation from injured cells	✓	–
Production exclusively in injured organ	–	–
Dose of injury-effect response	✓	✓
Information on etiology	?	–
Rapid kinetics (within hours)	✓	–
Component in pathophysiology	✓	–
Non-invasive	✓	✓
Clinical consequence (actionability)	(✓)	✓
Endpoint in clinical studies	(✓)	✓
Easy, rapid and robust measurement	✓	✓
Costs	14–20 Euros/20–25 USD	2 Euros /2 USD (enzym.)

Fig. 4.1 Characteristics of renal function markers compared to markers of acute tubular damage

4.4 Classical Clinical and Routine Biological Parameters of AKI Risk Assessment or Diagnosis

Just recently, the KDIGO Initiative completed the first ever, international, multidisciplinary clinical practice guidelines for AKI [22]. In its first part, the value of a standardized AKI definition has been emphasized; however, the limitations of current routine biological renal markers (creatinine, urea, urine output) have also been explicitly acknowledged (Fig. 4.1). Additionally, clinicians have been encouraged to perform best possible clinical renal risk assessment (although often imprecise). Correct risk assessment has since long been considered to be of enormous value as patient management depends on it.

Classical clinical renal risk assessment aims to predict (i) a developing and soon clinically detectable acute renal function loss or (ii) progression of established AKI or (iii) recovery from it. Such risk assessment typically considers comorbidities especially previous history of chronic heart as well as renal insufficiency and involves judgment on magnitude and slope of serum creatinine and urea increase and urine output decline and assessment of acid-base status and electrolytes during the last few hours to days. Urine microscopy and renal ultrasound may also be performed, however are relatively elaborate tools, provide experienced staff, and will in most cases only detect established AKI or CKD. Such complex risk assessment procedure may be further improved by providing clinicians with the test result of acute tubular damage marker measurement [44, 45]. Measurement of biochemically detectable proteins of acute tubular damage may add an additional dimension of renal risk assessment.

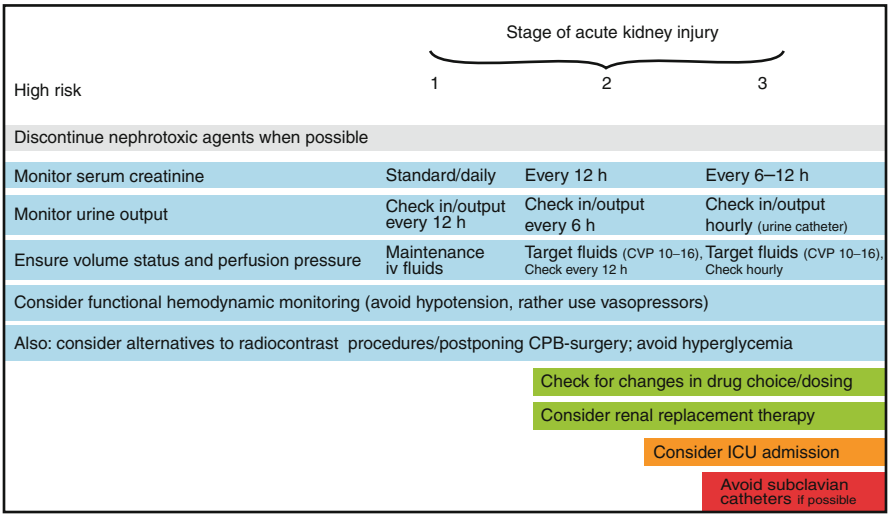


Fig. 4.2 Management according to risk for or grade of established acute kidney injury (AKI) [22]

4.5 Acutely Injured Renal Tissue Is Salvageable

The concept of improved risk assessment enabling earlier intervention raises the question whether acutely injured renal tissue is salvageable. There is accumulating evidence supporting common sense, that – in analogy to the situation in acute cardiologic or neurologic care where it is already generally accepted that "time is heart and time is brain" – timely renal care with the avoidance of a second injury may save kidney function and improve short- and long-term outcomes. Accordingly, indirect and direct evidence for the rationale of early nephroprotection will be briefly presented.

Firstly, late intervention in acute renal care appears to be harmful [46]. Secondly, beneficial effect was shown for early intervention saving heart and brain tissue and improving outcome in sepsis and acute respiratory distress syndrome [47, 48]. Also, renal recovery after ischemia-related injury is more rapid and can be expected complete the shorter the hypoxic period after cadaveric renal transplantation or renal revascularization is. Two recent studies directly compared early acute renal care with classical clinical routine in conjunction with KDIGO-proposed measures directed at nephroprotection (Fig. 4.2). Both reported significantly reduced AKI incidence [49, 50]. The first of both achieved improved renal outcomes performing earlier adjusted fluid management and pausing of ACE inhibitors associated with less AKI compared with late nephrology consultation [49]. The second study implemented an automated AKI alert system and focused again on early adjusted fluid but also on vasopressor management and withdrawal of nephrotoxins which was related with a reduced AKI rate compared with the observation period during which usual renal awareness was applied [50].

At this stage, there is not and probably there won't be a single preventive or therapeutic measure to cure AKI. It is becoming increasingly clear that multiple simultaneous early actions may be required to ameliorate the severity of the syndrome or accelerate recovery from AKI.

4.6 Acute Tubular Damage Biomarkers for Risk Assessment and Diagnosis of AKI and Potential Implications for Patient Management

In their recently published clinical practice guidelines for AKI [22], the KDIGO Initiative highlights the importance of risk assessment for individual patient management and concludes that acute tubular damage markers may feature AKI diagnosis once proving better diagnostic performance than the classical clinical and routine biological parameters. Along these lines the next paragraph will address issues related to the interpretation of an acute tubular damage marker signal and potential actions in response to it.

Currently, risk assessment performance of several acute tubular damage markers has been compared with that of serum creatinine, including neutrophil gelatinase-associated lipocalin (NGAL), cell cycle arrest-inducing markers (such as insulin-like growth factor-binding protein 7 [IGFBP7] and tissue inhibitor of metalloproteinases-2 [TIMP-2]), interleukin-18, liver-type fatty acid-binding protein (L-FABP), and kidney injury molecule-1 (KIM-1) [44, 51–57] (see Fig. 4.1).

Exemplary for other acute tubular damage markers, the chapter will focus on NGAL with most comprehensive experimental and clinical data available in the literature. NGAL is a protease-resistant polypeptide with a molecular weight of 25 kDa, which is released from the distal nephron in response to ischemic, toxic, or inflammatory insult to the kidney or from other organs. Overall, the predictive value of NGAL for an acute loss of renal function developing and becoming clinically detectable during the next few days after biomarker measurement is at AUC-ROC of approximately 0.8 including data from all available studies in this context enrolling more than 6,500 critically ill patients (ICU and Emergency Department) and more than 6,000 patients who underwent all types of cardiac surgical procedures. However, the confidence intervals of this finding were relatively wide and the result does not imply "perfect accuracy" of acute tubular damage markers for determination of AKI risk. Mathematical models [58] demonstrated that even a perfect biomarker will not be able to perfectly predict an imperfect gold standard or endpoint, respectively (i.e., serum creatinine or urine output-based AKI). Also, it is common sense that a signal reflecting tubular damage may not perfectly match that of filtration function. Therefore, alternative criteria evaluating whether the signal of acute tubular damage markers is "true" or not should be considered.

Accordingly, in an animal experiment of nephrotoxin exposure using histopathological readouts as endpoint of renal injury, KIM-1 has been shown to nearly perfectly detect minor acute tubular damage whereas serum creatinine and urea were insufficient in this regard [59].

Direct comparison of the predictive value of NGAL in more than 1,500 patients [51–54] with that of early and simultaneously measured serum creatinine showed higher discriminatory value of NGAL for AKI prediction. Also, in more than 4,500 patients admitted to an emergency room or an intensive care unit, NGAL (or KIM) positivity indicated worse renal and overall outcomes even in the absence of classical AKI (creatinine increase or urine output decline) [44, 55, 56]. These findings led to the concept of "subclinical AKI" [23], i.e., acute tubular damage without clinically detectable renal function loss.

Another aspect in favor of acute tubular damage markers in this regard is that hypothesis-free approaches (genome-wide analysis or comparison of protein expression of samples from subjects with vs. without renal injury) uncovered several markers of tubular damage with NGAL, KIM-1, and cell cycle arrest-inducing markers (TIMP-2/IGFBP7) being among them.

In addition, for NGAL, there is comprehensive data from animal experiments and clinical studies (>5,000 patients) that a relatively strong dose-effect response exists, i.e., the more severe or prolonged the renal injurious insult was, the higher was the detected NGAL concentration in urine or plasma [51, 52, 60–65]. For KIM-1 [66] and NGAL [67], there is experimental data that these markers arise from acutely injured cells but no from intact renal tubular cells with the latter being found during volume depletion [67].

For initiation of earlier treatments, a bundle of considerations or interventions was recommended by the KDIGO practice guidelines for AKI (Fig. 4.2). Basing on the above data, the recent Acute Dialysis Quality Initiative's Consensus Conference 2012 has now recommended the use of tubular damage markers for AKI diagnosis complementary to renal function markers [68, 69] (Fig. 4.3). Their suggestions also include the notion that especially patients with an imminent renal stressor such as sepsis, shock, or nephrotoxin use may be considered for biomarker measurement. Given the list of measures to do in the setting of high risk for AKI or established AKI, measurement of a reliable acute tubular damage biomarker may already be considered as first intervention. In the absence of any RCT proving such statement, routine measures of acute renal care, including searching drugs for nephrotoxins, searching for sepsis, initiation of hemodynamic monitoring, optimization of hemodynamics, and postponing or specifically modifying interventions with contrast use, may then be performed earlier, potentially associating with improved renal outcome.

4.7 Summary

Acute kidney injury (AKI) is a frequent complication in hospitalized patients, especially in older patients, and associated with substantially increased morbidity and mortality. International consensus clinical practice guidelines have identified currently used renal function parameters such as serum creatinine and urine output contributing to a delay in the diagnosis of AKI. At the time of diagnosis of established AKI, irreversible organ damage may already have occurred. The guidelines have further recommended clinicians to carry out individual renal risk assessment.

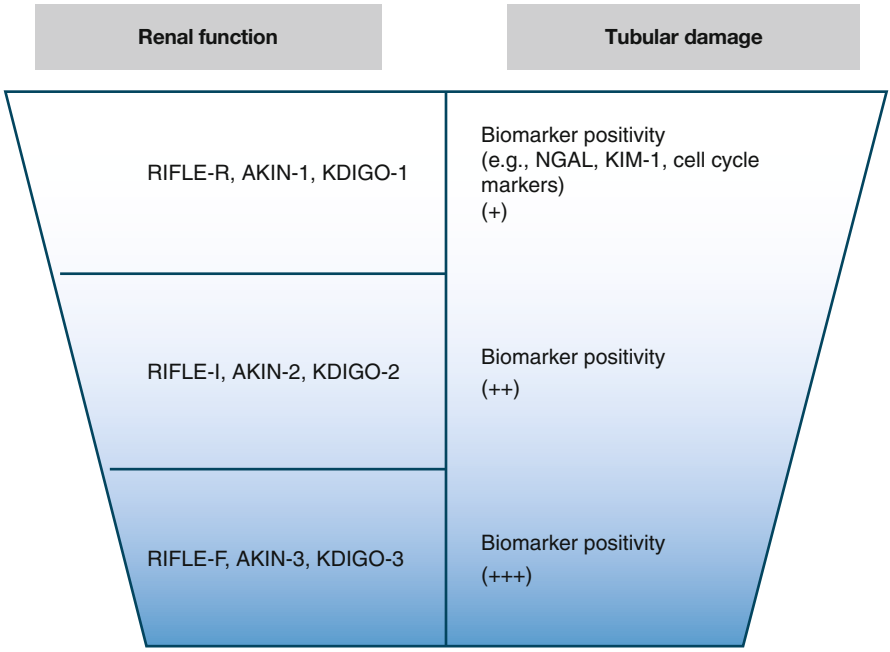


Fig. 4.3 New criteria for the diagnosis of acute kidney injury (AKI) (Adapted from [68]). In order to diagnose AKI, selecting the worst criterion (renal function criteria according to RIFLE, AKIN, or KDIGO classification or damage criteria) is recommended. In the appropriate clinical setting, this new damage biomarker criterion will enhance the ability of RIFLE/AKIN/KDIGO classification to define AKI. There are currently insufficient injury biomarker data to support staging of AKI; however, AKI stages basing on renal function changes are suggested to remain. The semiquantitative trend for increasing biomarker severity associated with increasing kidney damage is suggested by the literature and is displayed by darkening background color as well as the symbols: +/++/+++. *AKIN* acute kidney injury network, *RIFLE* risk, injury, failure, loss of renal function, end-stage renal disease classification, *KDIGO* Kidney Disease: Improving Global Outcome

Clinical and experimental data suggest using acute tubular damage markers for improved renal risk assessment. Acute tubular damage biomarkers may guide earlier initiation of nephroprotection, improved fluid management, or withdrawal of nephrotoxins directed at improvement of outcomes in patients developing AKI. Therefore, the "Acute Dialysis Quality Initiative" has now recommended the use of tubular damage markers for AKI diagnosis complementary to renal function markers.

References

1. Kinsella K, Wan H (2009) U.S. Census Bureau, International Population Reports, P95/09-1. An aging world: 2008. U.S. Government Printing Office, Washington, DC
2. Chronopoulos A, Cruz DN, Ronco C (2010) Hospital-acquired acute kidney injury in the elderly. Nat Rev Nephrol 6:141–149

3. Ishani A, Xue JL, Himmelfarb J et al (2009) Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol 20:223–228
4. Haase M, Story DA, Haase-Fielitz A (2011) Renal injury in the elderly: diagnosis, biomarkers and prevention. Best Pract Res Clin Anaesthesiol 25:401–412
5. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C (2006) An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med 34:1913–1917
6. Bucaloiu ID, Kirchner HL, Norfolk ER et al (2012) Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. Kidney Int 81:477–485
7. Ko GJ, Grigoryev DN, Linfert D et al (2010) Transcriptional analysis of kidneys during repair from AKI reveals possible roles for NGAL and KIM-1 as biomarkers of AKI-to-CKD transition. Am J Physiol Renal Physiol 298:F1472–F1483
8. Yang L, Besschetnova TY, Brooks CR, Shah JV, Bonventre JV (2010) Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. Nat Med 16:535–543
9. Kramer AA, Postler G, Salhab KF, Mendez C, Carey LC, Rabb H (1999) Renal ischemia/reperfusion leads to macrophage-mediated increase in pulmonary vascular permeability. Kidney Int 55:2362–2367
10. Feltes CM, Van Eyk J, Rabb H (2008) Distant-organ changes after acute kidney injury. Nephron Physiol 109:80–84
11. Liu M, Liang Y, Chigurupati S et al (2008) Acute kidney injury leads to inflammation and functional changes in the brain. J Am Soc Nephrol 19:1360–1370
12. Grams ME, Rabb H (2012) The distant organ effects of acute kidney injury. Kidney Int 81:942–948
13. Thakar CV, Arrigain S, Worley S et al (2005) A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol 16:162–168
14. James MT, Hemmelgarn BR, Wiebe N et al (2010) Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. Lancet 376: 2096–2103
15. Chawla LS (2011) Acute kidney injury leading to chronic kidney disease and long-term outcomes of acute kidney injury: the best opportunity to mitigate acute kidney injury? Contrib Nephrol 174:182–190
16. Fortrie G, Stads S, de Geus HR, Groeneveld AB, Zietse R, Betjes MG (2013) Determinants of renal function at hospital discharge of patients treated with renal replacement therapy in the intensive care unit. J Crit Care 28:126–132
17. US Renal Data System (2006) USRDS 2006 annual data report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda
18. Schmitt R, Coca S, Kanbay M et al (2008) Recovery of kidney function after acute kidney injury in the elderly: a systematic review and meta-analysis. Am J Kidney Dis 52:262–271
19. Siew ED, Peterson JF, Eden SK et al (2012) Outpatient nephrology referral rates after acute kidney injury. J Am Soc Nephrol 23:305–312
20. Bellomo R, Ronco C, Kellum JA et al (2004) Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 8:R204–R212
21. Mehta RL, Kellum JA, Shah SV et al (2007) Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 11(2):R31
22. Kidney Disease: Improving Global Outcomes (KDIGO). Acute Kidney Injury Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2:1–138
23. Haase M, Kellum JA, Ronco C (2012) Subclinical AKI-an emerging syndrome with important consequences. Nat Rev Nephrol 8:735–739
24. Pickering JW, Ralib AM, Endre ZH (2013) Combining creatinine and volume kinetics identifies missed cases of acute kidney injury following cardiac arrest. Crit Care 17:R7
25. Payen D, de Pont AC, Sakr Y et al; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators (2008) A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 12:R74

26. Teixeira C, Garzotto F, Piccinni P et al; for the NEFROlogia e Cura INTensiva (NEFROINT) Investigators (2013) Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. Crit Care 17:R14
27. Pradeep A, Rajagopalam S, Kolli HK et al (2010) High volumes of intravenous fluid during cardiac surgery are associated with increased mortality. HSR Proc Intensive Care Cardiovasc Anesth 2:287–296
28. Prowle JR, Liu YL, Licari E et al (2011) Oliguria as predictive biomarker of acute kidney injury in critically ill patients. Crit Care 15:R172
29. Hojs R, Bevc S, Ekart R, Gorenjak M, Puklavec L (2006) Serum cystatin C as an endogenous marker of renal function in patients with mild to moderate impairment of kidney function. Nephrol Dial Transplant 21:1855–1862
30. Stevens LA, Coresh J, Schmid CH et al (2008) Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis 51:395–406
31. Dharnidharka VR, Kwon C, Stevens G (2002) Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis 40:221–226
32. Ristikankare A, Pöyhiä R, Kuitunen A et al (2010) Serum cystatin C in elderly cardiac surgery patients. Ann Thorac Surg 89:689–694
33. Herget-Rosenthal S, Marggraf G, Hüsing J et al (2004) Early detection of acute renal failure by serum cystatin C. Kidney Int 66:1115–1122
34. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T (2012) Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 14:20–29
35. Peralta CA, Shlipak MG, Judd S, Cushman M, McClellan W, Zakai NA (2011) Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. JAMA 14:1545–1552
36. Delanaye P, Cavalier E, Moranne O, Lutteri L, Krzesinski JM, Bruyère O (2013) Creatinine-or cystatin C-based equations to estimate glomerular filtration in the general population: impact on the epidemiology of chronic kidney disease. BMC Nephrol 14:57
37. Sarnak MJ, Katz R, Stehman-Breen CO et al (2005) Cystatin C concentration as a risk factor for heart failure in older adults. Ann Intern Med 142:497–505
38. Shlipak MG, Sarnak MJ, Katz R et al (2005) Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med 352:2049–2060
39. Schaeffner ES, Ebert N, Delanaye P et al (2012) Two novel equations to estimate kidney function in persons aged 70 years or older. Ann Intern Med 157:471–481
40. Mohamed R, Jayakumar C, Ranganathan PV, Ganapathy V, Ramesh G (2012) Kidney proximal tubular epithelial-specific overexpression of netrin-1 suppresses inflammation and albuminuria through suppression of COX-2-mediated PGE2 production in streptozotocin-induced diabetic mice. Am J Pathol 181:1991–2002
41. Yang X, Kume S, Tanaka Y et al (2011) GW501516, a PPARδ agonist, ameliorates tubulointerstitial inflammation in proteinuric kidney disease via inhibition of TAK1- NFκB pathway in mice. PLoS One 6:e25271
42. Hemmelgarn BR, Manns BJ, Lloyd A et al (2010) Relation between kidney function, proteinuria, and adverse outcomes. JAMA 303:423–429
43. Coca SG, Jammalamadaka D, Sint K et al; Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury Consortium (2012) Preoperative proteinuria predicts acute kidney injury in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg 143: 495–502
44. Di Somma S, Magrini L, De Berardinis B et al (2013) Additive value of blood neutrophil gelatinase-associated lipocalin to clinical judgement in acute kidney injury diagnosis and mortality prediction in patients hospitalized from the emergency department. Crit Care 17:R29
45. Haase-Fielitz A, Westphal S, Bellomo R et al (2012) Tubular damage biomarkers linked to inflammation or iron metabolism predict acute kidney injury. TH-PO133, Kidney Week (Congress of the American Society of Nephrology)
46. Mehta RL, McDonald B, Gabbai F et al (2002) Nephrology consultation in acute renal failure: does timing matter? Am J Med 113:456–461

47. Rivers E, Nguyen B, Havstad S et al; Early Goal-Directed Therapy Collaborative Group (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
48. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR et al (2006) Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 354:2564–2575
49. Balasubramanian G, Al-Aly Z, Moiz A et al (2011) Early nephrologist involvement in hospital-acquired acute kidney injury: a pilot study. Am J Kidney Dis 57:228–234
50. Colpaert K, Hoste EA, Steurbaut K et al (2012) Impact of real-time electronic alerting of acute kidney injury on therapeutic intervention and progression of RIFLE class. Crit Care Med 40:1164–1170
51. Haase-Fielitz A, Bellomo R, Devarajan P et al (2009) Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery-a prospective cohort study. Crit Care Med 37:553–560
52. de Geus HR, Bakker J, Lesaffre EM, le Noble JL (2011) Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. Am J Respir Crit Care Med 183:907–914
53. Shapiro NI, Trzeciak S, Hollander JE et al (2010) The diagnostic accuracy of plasma neutrophil gelatinase-associated lipocalin in the prediction of acute kidney injury in emergency department patients with suspected sepsis. Ann Emerg Med 56:52–59
54. Makris K, Markou N, Evodia E et al (2009) Urinary neutrophil gelatinase-associated lipocalin (NGAL) as an early marker of acute kidney injury in critically ill multiple trauma patients. Clin Chem Lab Med 47:79–82
55. Haase M, Devarajan P, Haase-Fielitz A et al (2011) The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol 57:1752–1761
56. Nickolas TL, Schmidt-Ott KM, Canetta P et al (2012) Diagnostic and prognostic stratification in the emergency department using urinary biomarkers of nephron damage: a multicenter prospective cohort study. J Am Coll Cardiol 59:246–255
57. Kashani K, Al-Khafaji A, Ardiles T et al (2013) Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 17:R25
58. Waikar SS, Betensky RA, Emerson SC, Bonventre JV (2012) Imperfect gold standards for kidney injury biomarker evaluation. J Am Soc Nephrol 23:13–21
59. Vaidya VS, Ozer JS, Dieterle F et al (2010) Kidney injury molecule-1 outperforms traditional biomarkers of kidney injury in preclinical biomarker qualification studies. Nat Biotechnol 28:478–485
60. Bennett M, Dent CL, Ma Q et al (2008) Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. Clin J Am Soc Nephrol 3:665–673
61. Koyner JL, Bennett MR, Worcester EM et al (2008) Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. Kidney Int 74:1059–1069
62. Krawczeski CD, Goldstein SL, Woo JG et al (2011) Temporal relationship and predictive value of urinary acute kidney injury biomarkers after pediatric cardiopulmonary bypass. J Am Coll Cardiol 58:2301–2309
63. Nickolas TL, O'Rourke MJ, Yang J et al (2008) Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann Intern Med 148:810–819
64. Cruz DN, de Cal M, Garzotto F et al (2010) Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. Intensive Care Med 36:444–451
65. Krawczeski CD, Woo JG, Wang Y, Bennett MR, Ma Q, Devarajan P (2011) Neutrophil gelatinase-associated lipocalin concentrations predict development of acute kidney injury in neonates and children after cardiopulmonary bypass. J Pediatr 158:1009–1015
66. Ichimura T, Asseldonk EJ, Humphreys BD, Gunaratnam L, Duffield JS, Bonventre JV (2008) Kidney injury molecule-1 is a phosphatidylserine receptor that confers a phagocytic phenotype on epithelial cells. J Clin Invest 118:1657–1668

67. Paragas N, Qiu A, Zhang Q et al (2011) The Ngal reporter mouse detects the response of the kidney to injury in real time. Nat Med 17:216–222
68. Haase M, McCullough PA, Shaw AD et al (2013) Diagnosis of acute kidney injury using functional and injury biomarkers: workgroup statements from the tenth acute dialysis quality initiative consensus conference. Contrib Nephrol 182:13–29
69. McCullough PA, Bouchard J, Waikar SS et al (2013) Implementation of novel biomarkers in the diagnosis, prognosis, and management of acute kidney injury: executive summary from the tenth consensus conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol 182:5–12

Chapter 5
Pathogenesis and Susceptibility to Injury

Mitchell H. Rosner, Dinna N. Cruz, and Claudio Ronco

Key Messages

1. The aging kidney undergoes specific structural and functional changes that lead to increased susceptibility to injury when exposed to toxic insults.
2. Cellular and molecular changes also account for increased susceptibility to injury and include reduced regenerative capacity, changes in antioxidant defenses, alterations in growth factors, telomere shortening, mitochondrial changes, and increases in apoptosis.
3. These structural, functional, cellular, and molecular changes also impair repair processes, meaning that the injured kidney may not recover completely and older patients suffering from acute kidney injury may have a greater likelihood of developing chronic kidney disease or end-stage renal disease.

M.H. Rosner, MD (✉)
Department of Nephrology, University of Virginia Health System,
800133, 1545 Running Cedar, Charlottesville,
VA 22908, USA
e-mail: mhr9r@virginia.edu

D.N. Cruz, MD, MPH
Division of Nephrology-Hypertension,
University of California, San Diego,
200 West Arbor Drive #8409, San Diego,
CA 92103-8409, USA
e-mail: dinnacruzmd@yahoo.com

C. Ronco, MD
Department of Nephrology Dialysis and Transplantation,
St. Bortolo Hospital and International Renal Research
Institute of Vicenza (IRRIV), Viale Rodolfi 37,
Vicenza 36100, Italy
e-mail: cronco@goldnet.it

M. Haase, A. Haase-Fielitz (eds.), *Managing Renal Injury in the Elderly Patient*,
DOI 10.1007/978-3-642-39947-3_5, © Springer-Verlag Berlin Heidelberg 2014

5.1 Introduction

Acute kidney injury (AKI) is frequently encountered in the older patients [1–7]. While some of the increased susceptibility to the development of AKI in older patients can be attributed to clinical variables such as underlying comorbid conditions and exposure to multiple potentially nephrotoxic medications and procedures (many of which can be addressed with careful attention to risk factors and avoidance of toxic insults), specific structural, functional, hemodynamic, and cellular changes occur with aging that predispose the kidney to injury when subjected to stress (summarized in Fig. 5.1). An understanding of these changes in the kidney with aging is critical in allowing for rational design of novel preventative and therapeutic strategies in AKI.

5.2 Structural Alterations in the Pathogenesis of AKI (Box 5.1)

In the absence of a specific disease such as hypertension or diabetes mellitus, the kidney undergoes age-dependent structural changes that ultimately lead to a significant decrease in renal mass and functioning nephron numbers [8, 9]. Wald demonstrated that there is a 19 % decline in male and 9 % decline in female kidney weight in individuals aged 70–79 years as compared with those 20–29 years of age [10]. Importantly, the loss of renal mass is primarily cortical, with relative sparing of the medulla, and the number of functioning glomeruli declines roughly in parallel with the changes in renal weight [11–13]. Thus, the incidence of sclerotic glomeruli rises with advancing age, increasing from less than 5 % of the total at the age of 40, to 10–30 % of the total glomeruli by the eighth decade [14, 15]. On renal histology, glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis often occur together (termed nephrosclerosis when two or more such changes are present) and become more common with aging [16]. The prevalence of nephrosclerosis was 2.7 % for patients aged 18–29 years, 16 % for patients aged 30–39 years, 28 % for patients aged 40–49 years, 44 for patients aged 50–59 years, 58 % for patients aged 60–69 years, and 73 % for patients aged 70–77 years [16]. These microanatomical changes of tubular atrophy and glomerulosclerosis with aging may account for the macroanatomical reduction in kidney size by 10 % per decade of age seen on the computed tomographic scans of adults [17].

There are also important renal vascular changes that occur with aging: intimal thickening, capillary dropout, dysfunctional responses to the autonomic nervous system, and atherosclerosis. These vascular changes may contribute to the process of nephrosclerosis through relative ischemia of the renal parenchyma [18, 19]. One could hypothesize that in the setting of hypoxic and hemodynamic stress such as with sepsis or cardiac failure that these vascular changes may render the renal tubules more susceptible to injury than would be expected in a "younger" kidney with more vascular reserve.

Apoptosis, or programmed cell death, is important in the depletion in the number of cells that occur with aging [20–23]. Not only is there an age-related increase in apoptosis, but under stress conditions (e.g., ischemia/reperfusion injury) the number of apoptotic cells is greater in aged rats as compared to younger animals [22]. This

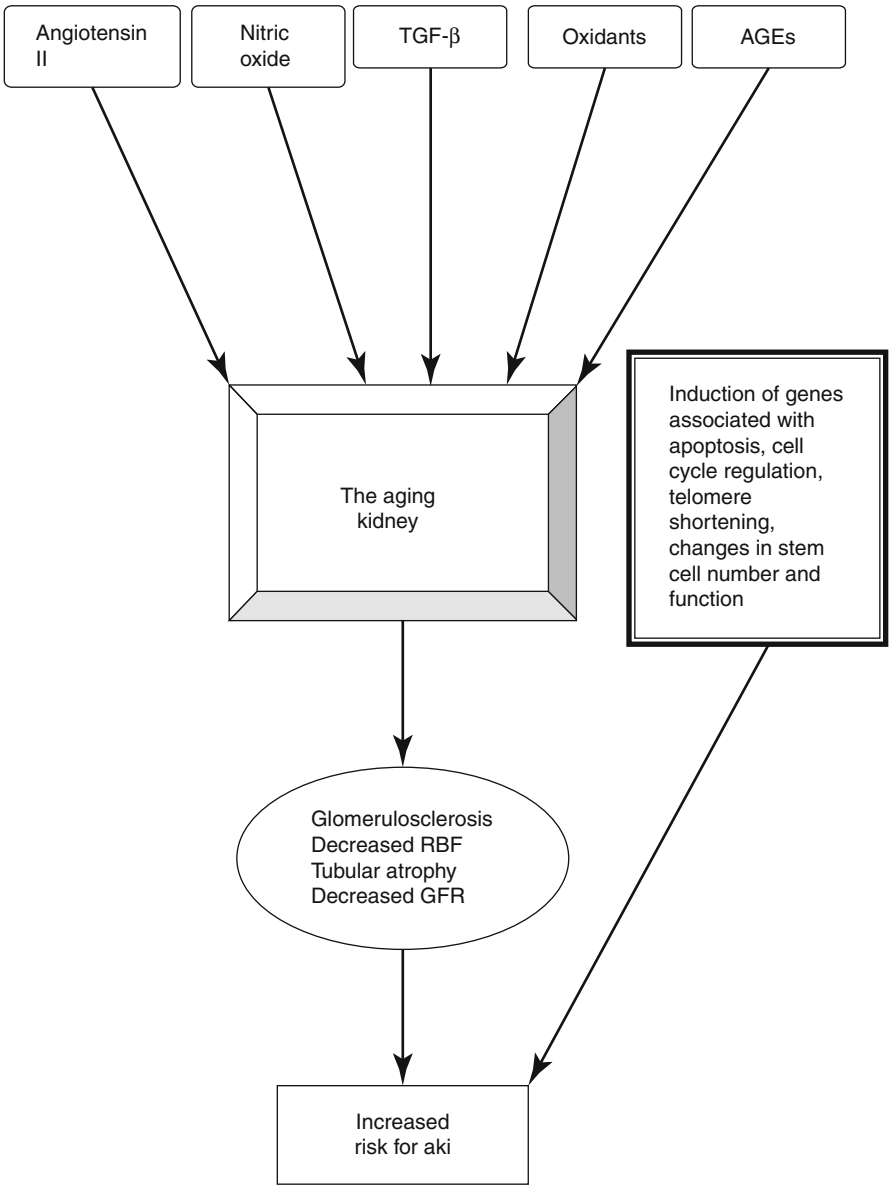


Fig. 5.1 Factors associated with age-related changes in renal function and structure that may increase susceptibility to the development of acute kidney injury (AKI). *TGF-β* transforming growth factor-**β**, *AGE* advanced glycation end products, *RBF* renal blood flow, *GFR* glomerular filtration rate

increased basal rate of apoptosis may, in part, also increase the risk for any nephrotoxic insult to result in irreversible cell death.

Loss of glomerular and peritubular capillary in the aging kidney correlated with alterations in vascular endothelial growth factor and with the development of glomerulosclerosis and tubulointerstitial fibrosis [24]. Impaired angiogenesis associated with progressive loss in renal microvasculature and may thus also have a pivotal role in age-related nephropathy. Also, serum levels of epidermal growth factor (EGF) as well as responsiveness of EGF receptors are decreased with aging in various cell types [25, 26]. As functional EGF receptor activity is an essential component of the kidney's ability to recover from acute injury, there is first evidence of impaired repair and cell survival in the aging kidney linked to renal growth factors.

The link between parenchymal loss and structural nephron changes in the aging kidney and a higher susceptibility to acute damage is somewhat tenuous and not clearly delineated. For example, a substantial reduction in renal mass surprisingly protected against ischemia/reperfusion injury in a 5/6 nephrectomy model [27]. Thus, it may be that other alterations that occur with aging may be more important than simply a loss in nephron numbers. Furthermore, there is little correlation between the amount of nephrosclerosis and actual glomerular filtration rate, suggesting that other factors may be operative [16].

Box 5.1 Anatomical and Functional Changes of the Aging Kidney

1. Structural changes
   - 1.1. Glomerular changes
     - Glomerulosclerosis
     - Tubular atrophy/interstitial fibrosis
     - Increase in glomerular basement membrane (GBM) permeability
     - Progressive folding and thickening of the GBM
   - 1.2. Vascular changes
     - Arteriosclerosis/vascular sclerosis (fibrointimal hyperplasia)
     - Intimal thickening
     - Medial hypertrophy
     - Arteriolar hyalinosis
     - Microvasculopathy
   - 1.3. Tubulointerstitial changes
     - Tubular atrophy
     - Decreased volume and length of proximal tubules
     - Increased number of diverculi of the distal convoluted tubule
2. Functional changes
   - Decreased GFR (not clearly explained by changes in glomerular size, density, or glomerulosclerosis)
   - Decrease in afferent arteriolar resistance > rise in glomerular capillary pressure
   - Decreasing ultrafiltration coefficient associates with increased glomerular capillary pressure
   - Decreased autoregulatory capacity and decreased functional reserve

5.3 Renal Functional Changes Associated with Aging (see Box 5.1)

With renal senescence, there is a variable decrease in glomerular filtration rate (GFR) [28–31]. Rowe and others demonstrated a reduction in creatinine clearance with age, beginning at age 34 and accelerating after age 65 (an approximate 1 ml/min per 1.73 m^2 per year decline in GFR occurring after age 50). Another study from the Mayo Clinic on living donors demonstrated a linear GFR decline of 6.3 ml/min/1.73 m^2 per decade of age [16]. Of critical importance is that this age-related decline in GFR is not predictable nor an inevitable consequence of aging. For example, 35 % of elderly subjects had a stable creatinine clearance over 20 years [31]. Why are some elderly individuals able to maintain GFR, while others have variable but inexorable declines in kidney function [32]? Some factors that may account for this variable decline in GFR associated with aging include: (1) racial differences (African-Americans have a faster decline in creatinine clearance as compared to Caucasians) [33]; (2) ill-defined genetic factors that may impact on cellular and molecular pathways involved in aging; (3) underlying comorbid conditions (and their treatment) such as hypertension, heart failure, diabetes mellitus, and vascular disease; and (4) environmental factors such as exposure to nephrotoxins (lead, heavy metals).

It is important to realize that a rise in serum creatinine may not be evident with increasing age despite a decrease in GFR. This is, in part, due to decreases in muscle mass and protein intake with age which directly lower the serum creatinine independently of changes in kidney function [32]. The use of serum creatinine as a surrogate to estimate GFR in the older individuals often overestimates the true creatinine clearance. This is critically important when determining the proper dosing of medications and in the assessment of risk to the aged kidneys from toxic, metabolic, and ischemic events. To some extent this issue is addressed with the use of regression formulas that aim to correct confounding variables on the relationship of serum creatinine to GFR or creatinine clearance. Two of the most common equations in clinical use are the Modification of Diet in Renal Disease (MDRD) equation and Cockcroft-Gault equation [34]. A study investigated the ability of these GFR-estimating equations to predict survival in community-dwelling elderly subjects and demonstrated superiority of the Cockcroft-Gault equation as compared to the MDRD equation [35]. Recently, Schaeffner and colleagues have proposed a new GFR-estimating equation to be specifically utilized in patients aged >70 years [36]. This equation was derived from 610 subjects who were greater than 70 years old and used iohexol clearance as the gold standard. The Berlin Initiative Study (BIS) equation worked particularly well in classifying patients with mild to modest kidney function [36]. More data is needed in determining which estimated GFR equation performs the best in the older patient.

One of the most critical issues in determining estimated GFR is that it allows risk stratification of patients that may be exposed to nephrotoxic medications or procedures. In all cases, the worse the baseline GFR, the higher the risk of acute kidney injury [37]. The estimated GFR allows for the identification of high-risk individuals

and designing strategies to protect older patients from the development of AKI. Reliance simply on serum creatinine may not uncover these high-risk patients.

5.4 Renal Hemodynamics and Decreases in Functional Reserve in Aging

As described, there are decreases in renal mass with aging and under normal conditions; these changes may be functionally compensated for by adaptations in renal hemodynamics that maintain a sufficient GFR. These compensatory changes may be lacking in the aging kidney [38]. A common test of renal hemodynamic reserve is the ability of the kidney vasculature to vasodilate in response to intravenous amino acids or a high-protein meal. Fliser et al. compared renal hemodynamics before and after an amino acid infusion in healthy normotensive young (median age 26 years) and older subjects (median age 70 years) and demonstrated that the increase in renal blood flow in the elderly was markedly impaired with a much higher renal vascular resistance in the elderly group [39]. This finding has been confirmed by others using various other techniques in healthy elderly individuals and has demonstrated that advancing age is associated with a decrease in baseline renal blood flow (RBF) [39–41]. More previous work has demonstrated that RBF is maintained through approximately the fourth decade; thereafter, there is a 10 % decline per decade [40–42]. This decrease in RBF is greater than can be accounted for by simply loss of renal mass [43]. A partial explanation for the increases in renal vascular resistance and fall in RBF with age may be the increased irregularity and tortuosity of the preglomerular vessels that occurs with aging [44]. Functionally, the increase in renal vascular resistance associated with the fall in RBF may indicate that the aged kidney is compensating for underlying glomerulosclerosis to maintain GFR through efferent arteriolar vasoconstriction.

Changes in vascular response to vasoconstrictor and vasodilating substances may be critical in accounting for the fall in renal function with aging [39]. Renal sympathetic-mediated vasoconstriction appears to be exaggerated in the aging kidney, and there is poor response to vasodilatory mediators such as atrial natriuretic peptide (ANP) and prostacyclin (PGI2) [45–47]. Furthermore, most studies support that the aging renal vasculature appears to exhibit exaggerated angiotensin II-mediated vasoconstriction [48, 49]. This sensitivity to angiotensin II can lead to exaggerated vasodilation in response to angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) and perhaps a higher risk for fall in GFR when these drugs are used, especially in the setting of volume depletion when angiotensin II levels may be high.

It is likely that changes in renal hemodynamics, which maintain GFR in the basal state, may lead to an increased risk for AKI during stress [38]. As an example, during a forced water diuresis, magnetic resonance imaging demonstrated the inability to improve medullary oxygenation in the older subjects as compared to the younger ones [50].

Impairment in nitric oxide (NO) production in the elderly kidney may also lead to an increased risk for AKI [51–54]. Normally, NO has an important role in renal protection from ischemic insults and this protective role may be blunted in the aged kidney [55]. Interestingly, older rats fed L-arginine for 7 days prior to renal artery occlusion have a marked improvement in GFR and renal plasma flow with a decrease in renal vascular resistance as compared to rats receiving placebo when exposed to ischemic insult [56]. A strategy for renal protection of the elderly kidney is suggested by recent experimental evidence suggesting that statin use may increase NO production and mitigate the pronounced decrease in GFR and renal blood flow seen in a model of renal artery occlusion in older experimental animals [57]. Two retrospective studies analyzed the effect of preoperative statin use in more than 100,000 patients undergoing cardiac surgery [58, 59]. Huffmyer and colleagues found an age-dependent decrease in the risk of renal replacement therapy, however with no decreases in the risk of AKI [58]. Across various AKI definitions, statin use was consistently associated with a decreased risk with adjusted odds ratios varying from 0.74 to 0.80 [59].

These findings are not in line with a pilot double-blind randomized controlled trial in 100 cardiac surgical patients (with more than 50 % being older than 70 years) at increased risk of postoperative AKI demonstrating that short-term perioperative statin use was not associated with a reduced incidence of postoperative AKI [60]. Selecting all randomized controlled trials comparing any statin treatment before cardiac surgery to no preoperative statin therapy or placebo, a recent Cochrane review concluded that preoperative statin therapy reduces the risk of postoperative atrial fibrillation and shortens the stay on the intensive care unit and in the hospital; however, statin pretreatment had no influence on perioperative mortality, stroke, myocardial infarction, or AKI [61].

The mechanism for decreased NO production in aged kidneys is, in part, due to an age-associated increase in the levels of N(G)-asymmetric dimethylarginine (ADMA), an endogenous NO synthetase inhibitor [62]. There was a direct and independent correlation with age-related increases in ADMA levels and falls in effective renal plasma flow that occur with aging [62].

5.5 Cellular and Molecular Changes Associated with Aging

Aging renal cells may be more vulnerable to damaging insults due to changes in cellular function that decrease their ability to withstand stress.

For instance, telomere length decreases in the aging renal cortex and may be a marker of a limited survival capability for this cell population and impair the ability to regenerate injured cells [63–65]. In an animal experiment using renal ischemia/reperfusion injury as AKI-triggering event, critical telomere shortening in the kidney led to increased senescence and apoptosis, limiting regenerative capacity in response to injury [65].

In addition, there is increased expression of messenger RNA (mRNA) and proteins associated with senescence including the cell-cycle inhibitor p16INK4a, p53, cyclooxygenases 1 and 2, transforming growth factor β-1, and heat shock protein A5 [66].

Microarray analysis from renal tissue harvested from aged animals has been analyzed to assess the response to ischemic injury and investigate the differences in gene expression between young and older animals [67, 68]. The expression of 92 genes was changed by aging (either increased or decreased) including claudin-7, kidney injury molecule-1, zinc-α(2)-glycoprotein (Zag), and matrix metalloproteinase-7. [67, 68]. Zag had been previously implicated in epithelial cell proliferation inhibition. Thus, the increased expression of Zag in the aged kidneys may mechanistically explain some of the increased susceptibility of aged kidneys to nephrotoxic insults [68]. This approach of identifying key injury-response genes that are altered during the aging process yields potential mechanistic targets for therapeutic approaches in the future.

Another change that occurs with aging is increased vulnerability to ischemic damage secondary to decreases in cellular antioxidant defenses [69]. Studies have demonstrated both an increase in free radical generation and a deficiency of antioxidant enzymes in aging renal tissue in response to increased oxidative stress and a concomitant higher propensity for more severe damage [70, 71]. An example of this is a study in aged rats, where there were increased markers of oxidative and lipid peroxidation, isoprostanes, advanced glycosylation end products, and heme oxygenase induction [72]. Interestingly, these markers of oxidative stress decreased with antioxidant treatment (high-dose vitamin E) [72]. Vitamin E has also been shown to be protective in an ischemia/reperfusion model of renal injury [73].

Peroxisome proliferator-activated receptor (PPAR)-γ agonist may ameliorate aging-related progressive renal injury in an animal experiment [74]. The use of PPAR-γ agonist reduced systemic and renal oxidative stress, attenuated mitochondrial injury, reduced proteinuria, and improved GFR. Pioglitazone, a synthetic PPAR-γ agonist, reduced markers of oxidative stress in a renal IR injury model in rats [75] and in an animal model of drug-induced nephrotoxicity [76].

Another interesting observation is that caloric restriction suppresses age-related oxidative stress as well as the susceptibility to ischemic injury [77, 78]. Restriction of calories is more powerful than any other specific dietary manipulation (protein or lipid restriction) in preserving renal function in senescent rodents [79, 80]. Not only does this retard the onset of chronic progressive nephrosclerosis, but it completely prevents the development of renal failure in very old animals [81–83]. Mechanistically, caloric restriction may act through increasing the levels of a group of proteins termed sirtuins [84]. Sirtuins are members of the silent information regulator 2 (Sir2) family, a family of Class III histone/protein deacetylases that are increased in expression after caloric restriction [85, 86]. SIRT1 deacetylates a large number of transcriptional factors and cofactors involved in cell growth, differentiation, stress resistance, reducing oxidative damage, and metabolism [86]. SIRT1 levels decrease in the aged kidneys which is associated with increased mitochondrial oxidative stress and morphological changes in mitochondria [87]. Resveratrol,

a plant polyphenol, is a potent activator of SIRT1 activity and has been shown to have renal protective effects in several nephrotoxic and ischemic model systems [88, 89].

Further, both local and systemic and direct and indirect pathways are involved in processes of age-related fibrosis and are impacted by bone marrow-derived cells. Young bone marrow alleviates renal aging, including decreasing deposition of collagen IV in the mesangium and less β-galactosidase staining, an indicator of cell senescence [90].

Angiopoietin 2, an autocrine activator of endothelial cells, seems to be increased in older mice priming the endothelial cells for an exaggerated response to a second hit, e.g., an inflammatory stimulus [91].

5.6 Is Renal Repair Impaired in Older Individuals?

In general, one of the hallmarks of aging is impairment in the ability to repair and regenerate injured cells. In the aging kidney, a decline of renal progenitor cells, a reduction of the peritubular capillary – the area that supplies renal tubules with oxygen – and a decrease in the degree of DNA synthesis in renal tubules after injury were observed.

This impairment in repair processes can be reflected in several ways: (1) minor insults may lead to cumulative damage that normally would have been repaired, (2) AKI may be more prolonged due to impaired healing, and (3) AKI may never recover and lead to end-stage renal disease.

Several clinical observations support the importance of defects in renal repair in clinical important outcomes, for example, (1) kidneys that are harvested from donors above age 65 years suffer from a rate of delayed graft function (essentially ischemic acute tubular necrosis) that is twice as high as that seen in younger donors [92], (2) older patients suffering an episode of AKI have a 13-fold higher relative risk of developing end-stage renal disease (this number rises to 41.2-fold if patients have baseline chronic kidney disease) [93], and (3) a recent meta-analysis of recovery rates of kidney function after AKI in the older patients has demonstrated that recovery after AKI is approximately 28 % less likely to occur when the patient is older than 65 years [94].

This loss of proliferative potential will likely lead to significant impairment in the repair processes and increased susceptibility to cumulative stresses.

5.7 Summary and Implications for Therapy

Older patients are at higher risk for the development of AKI and the likelihood of complete renal recovery is impaired. This is due to age-related changes in kidney structure, cellular and molecular function, and hemodynamic reserve. Recent

studies have identified key pathways that could offer potential therapeutic targets to reduce susceptibility to injury as well as to increase the potential for restorative repair. For instance, therapeutic activation of the sirtuin pathways or antioxidant defenses may hold promise but require much experimental work. Currently, therapy rests on prevention of ischemic and nephrotoxic insults, and where these insults are unavoidable or unanticipated, we must focus on limiting exposure and restoring normal hemodynamics. Given the anticipated growth in the elderly population, devising strategies for nephroprotection and therapy for AKI will be critical in improving outcomes.

References

1. Feest TJ, Round A, Hamad S (1993) Incidence of severe acute renal failure in adults: results of a community-based study. BMJ 306:481–489
2. Turney JH, Marshall DH, Brownjohn AM, Ellis CM, Parsons FM (1990) The evolution of acute renal failure. QJM 74:83–89
3. Groeneveld ABJ, Tran DD, Van der Meulen J, Nauta JJ, Thijs LG (1991) Acute renal failure in the intensive care unit: predisposing, complicating factors affecting outcome. Nephron 59: 602–607
4. Pascual J, Orofino L, Liano F, Marcén R, Orte L, Ortuño J (1990) Incidence and prognosis of acute renal failure in older patients. J Am Geriatr Soc 38:25–32
5. Ali T, Khan I, Simpson W et al (2007) Incidence and outcome in acute kidney injury: a comprehensive population-based study. J Am Soc Nephol 18:1292–1298
6. Macias-Nunez JF, Lopez-Novoa JM, Martinez-Maldonado M (1996) Acute renal failure in the aged. Semin Nephrol 16:330–342
7. Jerkic M, Vojvodic S, Lopez-Novoa JM (2001) The mechanism of increased renal susceptibility to toxic substances in the elderly. Int Urol Nephrol 32:539–547
8. Choudhury DRD, Levi M (2004) Effect of aging on renal function ad disease. In: Brenner B (ed) Brenner and Rector's the kidney, 7th edn. Saunders, Philadelphia, p 2305
9. Esposito C, Plati A, Mazzullo T et al (2007) Renal function and functional reserve in healthy elderly individuals. J Nephrol 20:617–623
10. Wald H (1937) The weight of normal adult human kidneys and its variability. Arch Pathol Lab Med 23:493–500
11. Tauchi H, Tsuboi K, Okutomi J (1971) Age changes in the human kidney of the different races. Gerontologia (Basel) 17:87–97
12. McLachlan MSF (1978) The aging kidney. Lancet 2:143–145
13. Goyal VK (1982) Changes with age in the human kidney. Exp Gerontol 17:321–331
14. Kaplan C, Pasternack B, Shah H, Gallo G (1975) Age-related incidence of sclerotic glomeruli in human kidneys. Am J Pathol 80:227–234
15. Kappel B, Olsen S (1980) Cortical interstitial tissue and sclerosed glomeruli in the normal human kidney related to age and sex. Virchows Arch 387:271–277
16. Rule AD, Amer H, Cornell LD et al (2010) The association between age and nephrosclerosis on renal biopsy among healthy adults. Ann Intern Med 152:561–567
17. Gourtsoyiannis N, Prassopoulos P, Cavouras D, Pantelidis N (1990) The thickness of the renal parenchyma decreases with age: a CT study of 360 patients. AJR Am J Roentgenol 155: 541–544
18. Musso CG, Oreopoulos DG (2011) Aging and physiological changes of the kidneys including changes in glomerular filtration rate. Nephron Physiol 119(suppl 1):1–5

19. Thomas SE, Anderson S, Gordon KI, Oyama TT, Shankland SJ, Johnson RJ (1998) Tubulointerstitial disease in aging: evidence for underlying peritubular capillary damage, a potential role for renal ischemia. J Am Soc Nephrol 9:231–242
20. Ma LJ, Nakamura S, Whitsitt JS et al (2000) Regression of sclerosis in aging by an angiotensin inhibition-induced decrease in PAI-1. Kidney Int 58:2425–2436
21. Qiao X, Chen X, Wu D et al (2005) Mitochondrial pathway is responsible for aging-related increase of tubular cell apoptosis in renal ischemia/perfusion injury. J Gerontol A Biol Sci Med Sci 60:830–839
22. Lee JH, Jung KJ, Kim JW et al (2004) Suppression of apoptosis by calorie restriction in aged kidney. Exp Gerontol 39:1361–1368
23. Zhang JH, Zhang Y, Herman B (2003) Caspases, apoptosis and aging. Ageing Res Rev 1:357–366
24. Kang DH, Anderson S, Kim YG et al (2001) Impaired angiogenesis in the aging kidney: vascular endothelial growth factor and thrombospondin-1 in renal disease. Am J Kidney Dis 37:601–611
25. Shurin GV, Yurkovetsky ZR, Chatta GS, Tourkova IL, Shurin MR, Lokshin AE (2007) Dynamic alteration of soluble serum biomarkers in healthy aging. Cytokine 39:123–129
26. Tran KT, Rusu SD, Satish L, Wells A (2003) Aging-related attenuation of EGF receptor signaling is mediated in part by increased protein tyrosine phosphatase activity. Exp Cell Res 289:359–367
27. Vercauteren SR, Ysebaert DK, De Greef KE, Eyskens EJ, De Broe ME (1999) Chronic reduction in renal mass in the rat attenuates ischemia/reperfusion injury and does not impair tubular regeneration. J Am Soc Nephrol 10:2551–2559
28. Epstein M (1996) Aging and the kidney. J Am Soc Nephrol 7:1106–1122
29. Andres R (1969) Physiological factors of aging significant to the clinician. J Am Geriatr Soc 17:274–277
30. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW (1976) The effect of age on creatinine clearance in man: a cross-sectional and longitudinal study. J Gerontol 31:155–163
31. Lindeman RD, Tobin JD, Shock NW (1985) Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc 33:278–285
32. Lew SQ, Bosch JP (1991) Effect of diet on creatinine clearance and excretion in young and elderly healthy subjects and in patients with renal disease. J Am Soc Nephrol 2:856–865
33. Luft FC, Fineberg NS, Miller JZ, Rankin LI, Grim CE, Weinberger MH (1980) The effects of age, race and heredity on glomerular filtration rate following volume expansion and contraction in normal man. Am J Med Sci 279:15–25
34. Levey AS, Coresh J, Balk E et al (2003) National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification and stratification. Ann Intern Med 139:137–146
35. Pizzarelli F, Lauretani F, Bandinelli S et al (2009) Predictivity of survival according to different equations for estimating renal function in community-dwelling elderly subjects. Nephrol Dial Transplant 24:1197–1205
36. Schaeffner ES, Ebert N, Delanaye P et al (2012) Two novel equations to estimate kidney function in persons aged 70 years or older. Ann Intern Med 157:471–481
37. Thakar CV, Arrigain S, Whorley S, Yared YP, Paganini EP (2005) A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol 16:162–168
38. Lameire N, Hoste E, Van Loo A, Dhondt A, Bernaert P, Vanholder R (1996) Pathophysiology, causes and prognosis of acute renal failure in the elderly. Ren Fail 18:333–340
39. Fliser D, Zeler M, Nowack R, Ritz E (1993) Renal functional reserve in healthy elderly subjects. J Am Soc Nephrol 3:1371–1377
40. Davies DF, Shock NW (1950) Age changes in glomerular filtration rate, effective renal plasma flow and tubular excretory capacity in adult males. J Clin Invest 29:496–506
41. Miller JH, McDonald RK, Shock NW (1951) The renal extraction of p-aminohippurate in the aged individual. J Gerontol 6:213–216

42. Faulstick D, Yiengst MJ, Oussler DA, Schock NW (1962) Glomerular permeability in young and old subjects. J Gerontol 17:40–44
43. Hollenberg NK, Adams DF, Solomon HS, Rashid A, Abrams HL, Merrill JP (1974) Senescence and the renal vasculature in normal man. Circ Res 34:309–316
44. Davidson AJ, Talner LB, Downs WM (1969) A study of the angiographic appearance of the kidney in an aging normotensive population. Radiology 92:975–983
45. Lakatta EG (1993) Cardiovascular regulatory mechanisms in advanced age. Physiol Rev 73: 413–420
46. Moritoki H, Yoshikawa T, Hisayama T, Takeuchi S (1992) Possible mechanisms of age-associated reduction of vascular relaxation caused by atrial natriuretic peptide. Eur J Pharmacol 210:61–67
47. Sato I, Kaji K, Morita I, Nagao M, Murota S (1993) Augmentation of endothelin-1, prostacyclin and thromboxane A2 secretion associated with in vitro ageing in cultured human umbilical vein endothelial cells. Mech Ageing Dev 71:73–80
48. Zhang XZ, Qui C, Baylis C (1997) Sensitivity of the segmental renal arterioles to angiotensin II in the aging rat. Mech Ageing Dev 97:183–188
49. Baylis C (1993) Renal responses to acute angiotensin II inhibition and administered angiotensin II in the ageing, conscious, chronically catheterized rat. Am J Kidney Dis 22:842–849
50. Prasad PV, Epstein FH (1999) Changes in renal medullary pO2 during water diuresis as evaluated by blood oxygenation level-dependent magnetic resonance imaging: effects of aging and cyclooxygenase inhibition. Kidney Int 55:294–303
51. Reckelhoff JF, Manning RD (1993) Role of endothelium-derived nitric oxide in control of renal microvasculature in aging male rats. Am J Physiol 265(suppl):R1123–R1128
52. Moncada S, Palmer RM, Higgs EA (1991) Nitric oxide: physiology, pathophysiology and pharmacology. Pharmacol Rev 43:109–114
53. Reckelhoff JF, Kellum JA, Blanchard EJ, Bacon EE, Wesley AJ, Kruckeberg WC (1994) Changes in nitric oxide precursor, L-arginine and metabolites, nitrate and nitrite with aging. Life Sci 55:1895–1901
54. Tan D, Cernadas MR, Aragoncillo P et al (1998) Role of nitric oxide-related mechanisms in renal function in ageing rats. Nephrol Dial Transplant 13:594–600
55. Rivas-Cabanero L, Rodriguez-Barbero A, Arevalo M, López-Novoa JM (1995) Effect of Ng-nitro-L-arginine methyl ester on gentamicin-induced nephrotoxicity in rats. Nephron 71:203–208
56. Sabbatini M, Sansone G, Uccello F et al (1994) Functional versus structural changes in the pathophysiology of acute ischemic renal failure in aging rats. Kidney Int 45:1355–1362
57. Sabbatini M, Pisani A, Uccello F et al (2004) Atorvastatin improves the course of ischemic acute renal failure in aging rats. J Am Soc Nephrol 15:901–909
58. Huffmyer JL, Mauermann WJ, Thiele RH, Ma JZ, Nemergut EC (2009) Preoperative statin administration is associated with lower mortality and decreased need for postoperative hemodialysis in patients undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 23:468–473
59. Brunelli SM, Waikar SS, Bateman BT et al (2012) Preoperative statin use and postoperative acute kidney injury. Am J Med 125:1195–1204
60. Prowle JR, Calzavacca P, Licardi E et al (2012) Pilot double-blind, randomized controlled trial of short-term atorvastatin for prevention of acute kidney injury after cardiac surgery. Nephrology 17:215–224
61. Liakopoulos OJ, Kuhn EW, Slottosch I, Wassmer G, Wahlers T (2012) Preoperative stain therapy for patients undergoing cardiac surgery. Cochrane Database Syst Rev (4):CD008493. doi:10.1002/14651858.CD008493.pub2
62. Kielstein JT, Bode-Boger SM, Frolich JC, Ritz E, Haller H, Fliser D (2003) Asymmetric dimethylarginine, blood pressure, and renal perfusion in elderly subjects. Circulation 107: 1891–1899
63. Melk A, Ramassar V, Helms LM et al (2000) Telomere shortening in kidneys with age. J Am Soc Nephol 11:44–51

64. Melk A, Kittikowit W, Sandhu I et al (2003) Cell senescence in rat kidneys in vivo increases with growth and age despite lack of telomere shortening. Kidney Int 63:2134–2141
65. Westhoff JH, Schildhorn C, Jacobi C et al (2010) Telomere shortening reduces regenerative capacity after acute kidney injury. J Am Soc Nephrol 21:327–336
66. Melk A, Schmidt BM, Takeuchi O, Sawitzki B, Rayner DC, Halloran PF (2004) Expression of p16INK4a and other cell cycle regulator and senescence associated genes in aging human kidney. Kidney Int 65:510–519
67. Chen G, Bridenbaugh EA, Akintola AD (2007) Increased susceptibility of aging kidney to ischemic injury: identification of candidate genes changed during aging, but corrected by caloric restriction. Am J Physiol Renal Physiol 293:F1272–F1281
68. Schmitt R, Marlier A, Cantley LG (2008) Zag expression during aging suppresses proliferation after kidney injury. J Am Soc Nephrol 19:2375–2383
69. Miura K, Goldstein RS, Morgan DG, Pasino DA, Hewitt WR, Hook JB (1987) Age-related differences in susceptibility to renal ischemia in rats. Toxicol Appl Pharmacol 87:284–292
70. Papa S, Skulachev VP (1997) Reactive oxygen species, mitochondria, apoptosis and aging. Mol Cell Biochem 174:305–311
71. Beckman KB, Ames BN (1998) The free radical theory of aging matures. Physiol Rev 78: 547–581
72. Reckelhoff JF, Kanji V, Racusen LC et al (1998) Vitamin E ameliorates enhanced renal lipid peroxidation and accumulation of F2-isoprostanes in aging kidneys. Am J Physiol 274: R767–R774
73. Özkaya D, Naziroğlu M, Armağan A et al (2011) Dietary vitamin C and E modulates oxidative stress induced-kidney and lens injury in diabetic aged male rats through modulating glucose homeostasis and antioxidant systems. Cell Biochem Funct 29:287–293
74. Yang HC, Deleuze S, Zuo Y, Potthoff SA, Ma LJ, Fogo AB (2009) The PPARgamma agonist pioglitazone ameliorates aging-related progressive renal injury. J Am Soc Nephrol 20:2380–2388
75. Reel B, Guzeloglu M, Bagriyanik A et al (2013) The effects of PPAR-γ agonist pioglitazone on renal ischemia/reperfusion injury in rats. J Surg Res 182(1):176–184. doi:10.1016/j.jss.2012.08.020, pii: S0022-4804(12)00745-7
76. Jesse CR, Bortolatto CF, Wilhelm EA, Roman SS, Prigol M, Nogueira CW (2012) The peroxisome proliferator-activated receptor-γ agonist pioglitazone protects against cisplatin-induced renal damage in mice. J Appl Toxicol. doi:10.1002/jat.2818 [Epub ahead of print]
77. Yu BP (1996) Aging and oxidative stress: modulation by dietary restriction. Free Radic Biol Med 21:651–668
78. Baylis C, Corman B (1998) The aging kidney: insights from experimental studies. J Am Soc Nephrol 9:699–709
79. Masoro E (1988) Food restriction in rodents, an evaluation in its role in the study of aging. J Gerontol 43:59–64
80. Kennedy G (1957) Effect of old age and over-nutrition on the kidney. Br Med Bull 13: 67–81
81. Wyndham J, Everitt A, Everitt S (1983) Effect of isolation and food restriction begun at 50 days on the development of age-associated renal disease in the male Wistar rat. Arch Gerontol Geriatr 2:317–332
82. Tucker S, Mason R, Beauchene R (1976) Influence of diet and feed restriction on kidney function of aging male rats. J Gerontol 31:264–270
83. Bras G, Ross H (1964) Kidney disease and nutrition in the rat. Toxicol Appl Pharmacol 6:247–252
84. Allard JS, Perez E, Zou S, de Cabo R (2009) Dietary activators of Sirt1. Mol Cell Endocrinol 299:58–63
85. Cohen HY, Miller C, Bitterman KJ et al (2004) Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. Science 305:390–392
86. Dali-Youcef N, Lagouge M, Froelich S, Koehl C, Schoonjans K, Auwerx J (2007) Sirtuins: the "magnificent seven", function, metabolism and longevity. Ann Med 39:335–345

87. Kitada M, Kume S, Takeda-Watanabe A, Kanasaki K, Koya D (2013) Sirtuins and renal diseases: relationship with aging and diabetic nephropathy. Clin Sci (Lond) 124:153–164
88. Do Amaral CL, Francescato HD, Coimbra TM et al (2008) Resveratrol attenuated cisplatin-induced nephrotoxicity in rats. Arch Toxicol 82:363–370
89. Sebai H, Ben-Attia M, Sani M, Aouani E, Ghanem-Boughanmi N (2008) Protective effect of resveratrol on acute endotoxemia-induced nephrotoxicity in rat through nitric oxide independent mechanism. Free Radic Res 42:913–920
90. Yang HC, Rossini M, Ma L-J, Zuo Y, Ma J, Fogo AB (2011) Cells derived from young bone marrow alleviate renal aging. J Am Soc Nephrol 21:2028–2036
91. Wulfert FM, van Meurs M, Kurniati NF et al (2012) Age-dependent role of microvascular endothelial and polymorphonuclear cells in lipopolysaccharide-induced acute kidney injury. Anesthesiology 117:126–136
92. United States Renal Data System (USRDS) (2007) The 2007 USRDS Annual Data Report (ADR) reference tables. http://www.usrds.org/reference.htm
93. Ishani A, Xue JL, Himmelfarb J et al (2009) Acute kidney injury increases risk of ESRD among the elderly. J Am Soc Nephrol 20:223–228
94. Schmitt R, Coca S, Kanbay M, Tinetti ME, Cantley LG, Parikh CR (2008) Recovery of kidney function after acute kidney injury in the elderly: a systematic review and meta-analysis. Am J Kidney Dis 52:262–271

Chapter 6
Drug Kinetics, Dosing, and Renal Toxicity in Older Adults

Frieder Keller and Ulla Ludwig

Key Messages

1. Age alone is no reason to change the normal drug dose.
2. The prevalence of impaired kidney function increases with age and with it the need for a drug dose adjustment.
3. If the glomerular filtration rate (GFR) is less than 60 mL/min, dose adjustment is needed.
4. Since the risk of serious adverse effects is growing, glibenclamide, metformin, methotrexate, lithium, and low-molecular-weight heparins should be avoided in older adults.
5. As an injurious event, even a single dose of nonsteroidal anti-inflammatory drug (NSAID) may contribute to acute (on chronic) kidney injury especially in older patients who frequently present with reduced renal filtration reserve.

6.1 Importance of Kidney Function for Appropriate Choice of Drug and Drug Dosage

Drug-induced nephrotoxicity may cause up to 20 % of community- and hospital-acquired episodes of acute kidney injury (AKI) [1] among them approximately 30–40 % are older adults. Chronic kidney disease (CKD) is highly prevalent

F. Keller (✉)
Internal Medicien 1, Department of Nephrology, University Hospital Ulm,
Albert Einstein Allee 23, Ulm D-89070, Germany
e-mail: frieder.keller@uni-ulm.de

U. Ludwig
Internal Medicine 1, Nephrology, University Hospital,
Albert Einstein Allee 23, Ulm D-89070, Germany
e-mail: ulla.ludwig@uniklinik-ulm.de

M. Haase, A. Haase-Fielitz (eds.), *Managing Renal Injury in the Elderly Patient*,
DOI 10.1007/978-3-642-39947-3_6, © Springer-Verlag Berlin Heidelberg 2014

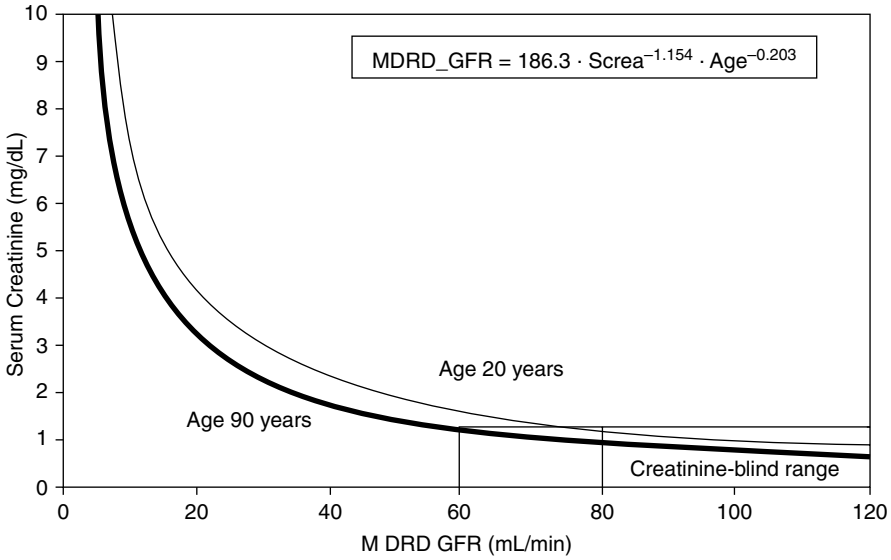


Fig. 6.1 Age and creatinine-blind range – serum creatinine depends on glomerular filtration rate (GFR) according to a hyperbolic function [2]

in older adults and is a risk factor for nephrotoxin-induced acute renal function loss and adverse events related to a lack of dose adjustment. This is further complicated by acute (on chronic) loss of renal function.

As the glomerular filtration rate (GFR) cannot yet be measured directly, filtration markers such as serum creatinine or serum cystatin C are used as surrogate parameters for estimation of renal function. Renal function can become reduced in the "creatinine-blind" range, without a perceptible increase in creatinine concentration. Creatinine-based equations have been developed to overcome the numerous limitations of serum creatinine and to estimate GFR. Although these equations carry limitations as outlined elsewhere in this book (Chap. 3) and still are not able to reflect GFR in real time, they should be considered in older adults.

Of note, in older adults, alterations in body composition, especially reduced muscle mass, extend the "creatinine-blind" range and delay recognition of significant losses of renal filtration function even more than in younger patients (Fig. 6.1) resulting in the need for timely and appropriate drug choice and dosage.

6.2 Drug Kinetics and Age

About half of all medications (or active metabolites thereof) are eliminated by the kidneys. Since half of older patients have reduced renal function, this is important for drug dosage, as in these patients drugs will be slower eliminated and have the potential to accumulate.

Pharmacokinetics for patients with renal impairment is based on the *Dettli equation* [3] calculating the individual elimination capacity (Q). According to this

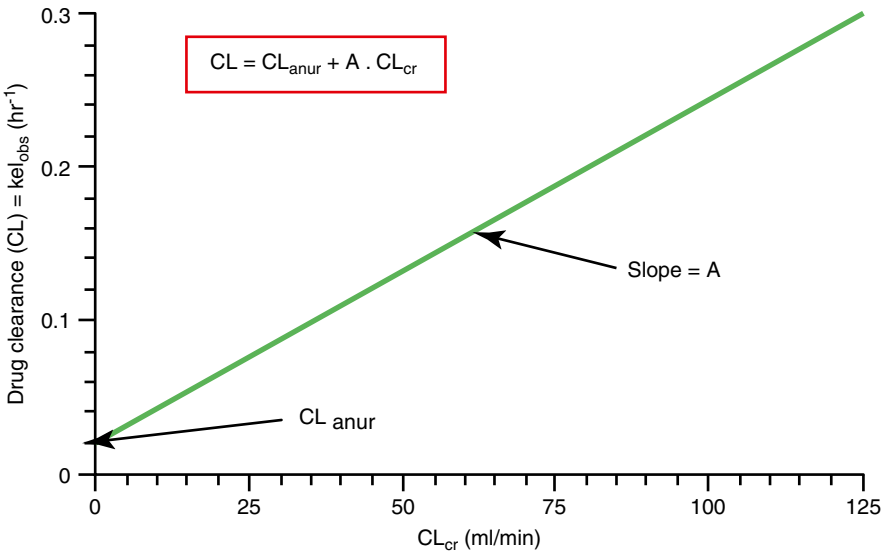


Fig. 6.2 Dettli plot [3]

equation, the drug clearance (CL) or its observed elimination rate constant (k_{el}) is a linear function of the creatinine clearance (CL_{cr}) and is determined by the axis intercept and slope (A) of the line, both being different for each medication. The axis intercept indicates the nonrenal elimination fraction (Q_0) also called anuria clearance (CL_{anur}) (Fig. 6.2).

$$CL = CL_{anur} + A \cdot CL_{crea}$$

For instance, if 80 % of a drug is eliminated via the kidney, the nonrenal fraction amounts to 20 %. The axis intercept Q_0 is 0.20, and a medication clearance of 20 % is to be expected when kidney function is absent.

Dettli established two dose adjustment rules: The dose of a drug must be reduced in inverse proportion to the half-life $T_{1/2}$ (the Dettli-1 rule), or the interval between doses must be prolonged proportionally to the half-life $T_{1/2}$ (the Dettli-2 rule). The half-life ($T_{1/2}$) changes in a manner inversely proportional to the drug clearance (CL) as long as the volume of distribution (V_D) remains constant:

$$T_{1/2} = 0.693 \cdot \frac{V_D}{C_L}$$

If the half-life with normal ($T_{1/2norm}$) and absent renal function ($T_{1/2fail}$) is known, the dose adjustment can be calculated for each patient depending on his or her GFR. Alternatively, the renally eliminated fraction (fren) of a medication can be used:

$$\frac{\text{Dose}}{\text{Interval}} = \left(\frac{\text{Dose}}{\text{Interval}}\right)_{norm} \cdot \left[1 - \left(1 - \frac{T_{1/2norm}}{T_{1/2fail}}\right) \cdot \left(1 - \frac{eGFR_{patient}}{eGFR_{norm}}\right)\right]$$

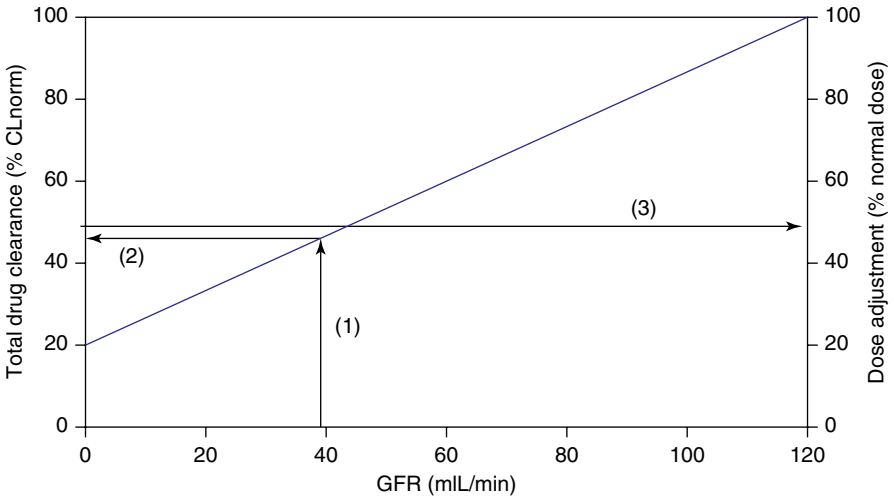


Fig. 6.3 Drug clearance and dose adjustment according to glomerular filtration rate (GFR) – exemplary dose adjustment for a GFR of 40 mL/min

$$\frac{\text{Dose}}{\text{Interval}} = \left(\frac{\text{Dose}}{\text{Interval}}\right)_{\text{norm}} \cdot \left[1 - \text{fren} \cdot \left(1 - \frac{\text{eGFR}}{\text{eGFR}_{\text{norm}}}\right)\right]$$

Figure 6.3 shows an exemplary dose calculation for a GFR of 40 mL/min (1) in which the drug clearance of roughly 45 % would to be expected (2). In this example, one can generally either reduce the individual dose to 45 % (3) or extend the dosage interval to 2.2 times its original value (1/0.45 = 2.2). The decision depends on which is more important: the peak level or the time over the minimal effective concentration. One can also calculate a suggested dose for each medication and each patient on the internet [www.dosing.de].

However, Dettli's rule provides a strong proportional relationship between renal function and drug dose and thereby implies the administration of too low doses or much too wide intervals between doses in patients with severe renal function loss. Still, the use of Dettli's rule is recommended in outpatient care and for central nervous system drugs.

In contrast to the proportionality rule of Dettli, adjusting drugs to a targeted peak can be achieved by the *half-dosage rule of Kunin* [4]. This rule results in peak drug levels that are the same as those in patients with normal renal function but markedly higher trough levels; the area under the curve is greater than with the Dettli rule and thus can be associated with more frequent adverse effects. The rule by Kunin generally yields higher doses than Dettli's rules and thus seems to provide severely ill patients with a higher chance of effective treatment. The rule says that one should start with a normal starting dose ($D_{\text{start}} = D_{\text{norm}}$) and that half of the starting dose has to be given after one half-life ($T_{1/2}$) in each case [4]. In sum, the half-dosage rule of Kunin should be preferred to achieve effective peak levels especially for critically

ill patients, for anti-infective therapy, or those being on continuous renal replacement therapy. Corresponding dosing recommendations are published (www.uni-ulm.de/nephrologie/dosantibio.pdf).

The general dosage rule as proposed by *David Czock* is a combination of Dettli-2 rule and the Kunin rule:

$$C_{\text{peak}} = \text{const.}$$

$$D = D_{start} \cdot \left[1 - \exp\left(-0.693 \cdot \frac{Tau}{T_{1/2}} \right) \right]$$

$$Tau = \frac{T_{1/2}}{0.693} \cdot \ln\left(\frac{C_{peak}}{C_{trough}} \right)$$

$$Tau \geq T_{1/2} \quad for \quad C_{trough} = const. = Dettli \;\; 2 \;\; rule$$

$$\text{Tau} \geq T_{1/2} \quad \text{for} \quad C_{\text{trough}} = \frac{1}{2} \cdot C_{\text{peak}} = \text{Kunin rule}$$

The general dosing rule should be used mainly in the intensive care patients and for anti-infective drugs (C_{peak}=const.). Dettli's proportionality rule and Kunin's halving rule may be deemed to be special cases of the general dosage rule.

6.3 Drug Dosage in Older Patient with Impaired Renal Function

A GFR of 30–60 mL/min, suggestive of stage 3 CKD, is observed in 15–30 % of people who are aged>65 years [6]. Impaired renal function can have pronounced effects on the pharmacokinetics of many drugs as a result of alterations in disposition, reductions in glomerular filtration, altered tubular secretion, reabsorption, or metabolism [7, 8]. Studies have determined that up to 67 % of prescriptions dispensed to older patients with impaired renal function contain errors [9, 10] with dosing errors (approx. 50 %) and the prescription of contraindicated drugs (approx. 25 %) being the most frequent medication errors [11].

Due to its hyperbolic dependence, the half-life indicates more clearly than the drug clearance that medication dosage needs only to be adjusted if the GFR is below 60 mL/min (Fig. 6.4).

Pharmacokinetic studies have shown that half-life changes most drastically in older patients [2]. It has been demonstrated for 127 drugs that, while the half-life in older patients was prolonged by 40 % on average, the clearance remains practically unchanged [2]. The half-life and clearance would actually have to relate to one another in an inversely proportional manner ($T_{1/2}$=0.693 × V_D/ CL), but the volume

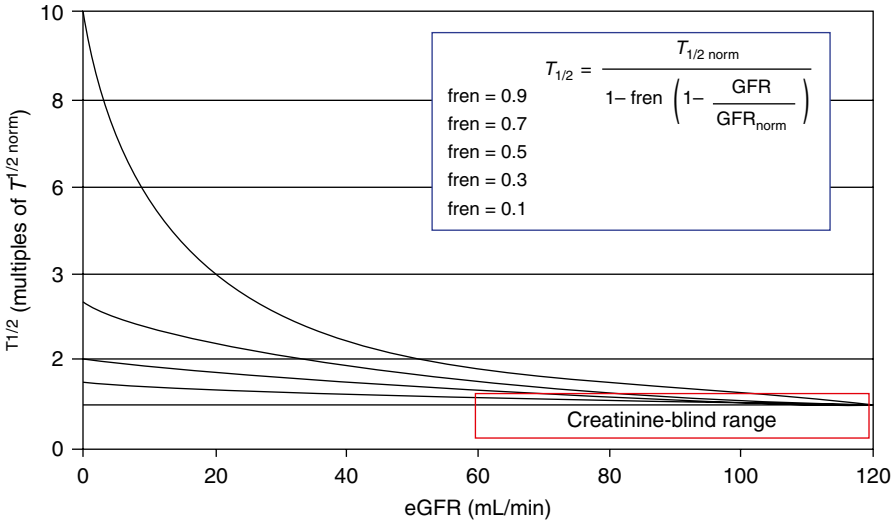


Fig. 6.4 Half-life and renal function – similar to the creatinine-blind range, renal function loss significantly impacts half-life only at a glomerular filtration rate (GFR) < 60 mL/min

of distribution was 20 % higher on average in older patients [2]. The findings have the following consequences:

A drug dose does not need to be adjusted due to age alone – this is demonstrated by the unchanged drug clearance. Whereas the starting dose should be increased in older patients, since the distribution volume tends to be higher, the maintenance dose has to be reduced due to the longer half-life.

6.4 Extracorporeal Renal Replacement Therapy and Intensive Care

The risk of AKI increases with age and critical illness. Several issues need to be considered if extracorporeal renal replacement therapy (RRT) becomes necessary, especially when drugs with predominant renal clearance are administered. Drug removal during extracorporeal RRT depends on many factors; among them are physicochemical characteristics of the drug and treatment characteristics, including mode of RRT, membrane (material, pore-size, surface), and blood/dialysate/substitution fluid flow used. Extent of drug removal is directly proportional to membrane surface area, the mode of replacement fluid administration, ultrafiltration, and/or dialysate flow rates. Alterations in protein binding (i.e., hypoalbuminemia), volume of distribution, and nonrenal clearance are also of importance; however they pose the problem of being less quantifiable.

The application of continuous renal replacement therapy (CRRT) significantly alters the pharmacokinetic behavior of many drugs which may be of

immense interest, since the risk of underdosing anti-infective drugs may lead to therapeutic failure and/or the spread of breakthrough resistance, whereas overdosing drugs increases the risk of adverse events. Thus, clinicians should consider therapeutic drug monitoring as a helpful tool for optimizing drug exposure during extracorporeal RRT.

During RRT, diffusion [dialysis], convection [filtration], and a combination of both [diafiltration] are the physicochemical processes responsible for the removal of solutes from the blood through semipermeable membranes. Drugs with low molecular weight and limited distribution volume and those that are water soluble are most likely to be removed by extracorporeal RRT and will require extra dosing. If possible drugs (especially anti-infective drugs and erythropoietin) are administered after intermittent RRT to compensate for blood purification effect; however at the start of critical illness, the first dose of anti-infective drugs should be given immediately, that is, before commencement of RRT. There are also certain drugs such as insulin, calcium, analgetics, or those which are required due to acute worsening of condition during RRT (cardiac arrhythmias, hypotensive periods) which need to be administered during intermittent RRT.

After hemodialysis, D_{suppl} (supplementary dose) can be estimated by multiplication of eliminated fraction (F_{R}) by starting dose (D_{start}):

$$D_{\text{suppl}} = F_{\text{R}} \cdot \text{D}_{\text{start}}$$

$$D_{\text{HD}} = D_{\text{anur}} + D_{\text{suppl}}$$

$$D_{\text{HD}} \sim D_{\text{Start}}$$

To estimate drug elimination during continuous hemofiltration (D_{HF}), total creatinine clearance [CL_{crea}TOT], combining residual renal clearance [CL_{crea}Ren] and the extracorporeal clearance determined by blood and substitution fluid flow [CL_{crea}HF], is necessary:

$$\text{CL}_{\text{crea}}\text{TOT} = \text{CL}_{\text{crea}}\text{Ren} + \text{CL}_{\text{crea}}\text{HF}$$

The general pharmacokinetic concept of drug clearance [CL_{HF}] as a linear function of creatinine clearance can also be applied for drug elimination via hemofiltration:

$$\text{CL}_{\text{HF}} = \text{CL}_{\text{anur}} + A \cdot \text{CL}_{\text{crea}}\text{TOT}$$

For instance, if a patient has a serum creatinine of 2.5 mg/dL under hemofiltration, this roughly corresponds to a GFR of 30 mL/min, and one will be able to conduct dosing according to Dettli or Kunin or generally according to Czock [5]:

$$\left(\frac{\text{Dose}}{\text{Interval}}\right)_{\text{hf}} = \left(\frac{\text{Dose}}{\text{Interval}}\right)_{\text{norm}} \cdot \left[1 - \text{fren} \cdot \left(1 - \frac{\text{eGFR}}{\text{eGFR}_{\text{norm}}}\right)\right]$$

Tank dialysis (slow low-efficiency dialysis) is a hybrid of intermittent hemodialysis and continuous hemofiltration. In this case, dosing should also be conducted once the procedure has been completed, analogously to the dose after hemodialysis (D_{HD}) – however this only applies to days when dialysis is performed.

6.5 Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) refers to the individualization of drug dosage by maintaining blood concentrations of this drug within therapeutic range. This involves the measurement of drug concentration especially in those drugs known for their narrow therapeutic range (e.g., antiarrhythmic drugs or anticonvulsants). Also, cyclosporin, tacrolimus, sirolimus, everolimus, and mycophenolic acid would also not be administered with much success in transplantation medicine without TDM. In the setting of intensive care medicine, TDM has been established for several antibiotics among them aminoglycosides such as gentamicin and amikacin, as well as for vancomycin.

But drug monitoring only makes sense if a target level has been defined and if the response to the result of the measured level is adequate. High levels are not necessarily toxic – blood sampling may erroneously have been taken in the distribution phase. Low levels not always need a dose increase – it often makes more sense to investigate adherence and motivate patients to comply.

Interpreting the target level is complex.

Low levels will already be effective if plasma binding is reduced. A classic example is phenytoin, with a target level of 5 mg/L (not 10 mg/L) in renal insufficiency or hypoproteinemia.

In contrast, higher trough levels will be required in order to achieve adequate peak levels in the case of reduced kidney function with slower elimination.

If, for example, the half-life of a drug is five times longer because of renal impairment, its dose should be reduced to 20 % of the normal dose (1/5 = 0.20). If the dose is thus reciprocally lowered and the interval between doses is unchanged, then the area under the curve will be the same as in the normal case but with higher trough values, which are what is usually measured in drug monitoring. This can easily lead clinicians unfamiliar with the relevant pharmacokinetics to draw false conclusions and then reduce the dose of the drug still further, e.g., in the case of vancomycin or gentamicin. In order to achieve effective levels in patients with renal failure, the trough values of vancomycin should lie between 10 and 20 mg/L and those of gentamicin between 2 and 4 mg/L.

6.6 Drug Toxicity in Older Adults

The issue of pharmaceutical drugs causing harm to older patients is a subject of debate. The estimated annual rate of adverse drug reactions or events for people aged 65 years or older has been found to be twice as high compared to those being

Table 6.1 Drugs that do and do not depend on renal function [16]

Class	Dependent on renal function	Independent of renal function
Analgesics	Morphine (M6-glucuronide), pethidine (norpethidine)	Fentanyl, levomethadone
Antiarrhythmic drugs	Sotalol	Amiodarone
Antibiotics	Ciprofloxacin, levofloxacin	Moxifloxacin
Antidiabetic drugs	Glibenclamide, glimepride (hydroxy metabolite)	Gliquidone, gliclacide
	Nateglinide	Pioglitazone
	Sitagliptine	
Anticonvulsants	Gabapentin, pregabalin, lamotrigine, levetiracetam	Carbamazepine, phenytoin, valproate
Antihypertensive drugs	Atenolol	Bisoprolol, carvedilol, metoprolol, propranolol
Cholesterol-lowering drugs	Bezafibrate, fenofibrate	Simvastatin, niacin
Drugs for gout and other rheumatological conditions	Methotrexate	Colchicine, hydroxychloroquine, leflunomide
Cardiovascular drugs	Digoxin	Digitoxin
Psychoactive drugs	Lithium, mirtazapine	Amitriptyline, citalopram (metabolites?), haloperidol, risperidone
Antiviral drugs	Acyclovir	Brivudine
Cytostatic drugs (20)	Actinomycin D, bleomycin, capecitabine, carboplatin, cisplatin, cyclophosphamide, doxorubicin, epirubicin, etoposide, gemcitabine (dFdU), ifosfamide, irinotecan, melphalan, methotrexate, oxaliplatin, topotecan	Anastrozole, docetaxel, doxorubicin-peg-liposomal, erlotinib, fluorouracil, gefitinib, leuprorelin, megestrol, paclitaxel, tamoxifen, terozol, vincristine, trastuzumab

younger than 65 [12]. About 10 drugs account for 85 % of overdoses in patients with renal function loss including ß-lactam antibiotics, cephalosporins, fluoroquinolones, azoles, and histamine blockers [13].

Recently some consensus for recommendations regarding drug avoidance and replacement in older patients was achieved and published in several "lists." Although none of these lists consider renal function, they may be valuable for clinical consideration. Firstly, the Beers criteria [14], developed from a North American working group, identify medications that pose potential risks outweighing potential benefits for people 65 years and older. Secondly, the PRISCUS list summarizes potentially inappropriate medications in older patients and, importantly, suggests alternative drugs, with specific reference to drugs used in the German language area [15].

Of note, as soon as renal function declines, drugs should either be stopped, replaced, or dose adjusted. In most of the cases, alternative (renal function independent) non-nephrotoxic drugs are available, which can be used even if renal function is impaired [16] (Table 6.1). Before initiation of therapy, assessment of baseline renal function in older patients is of importance. During therapy, TDM, monitoring of renal function and vital signs, as well as avoidance of nephrotoxic drug combinations are advised. Medications which are absolutely or relatively contraindicated in

Table 6.2 The most important drugs whose use in patients with renal function loss is absolutely or relatively contraindicated or problematic from a clinical nephrological standpoint [16]

Class	Drug	Contraindicated or to be avoided if possible when:	Reason
Analgesics	Pethidine	GFR <60	Convulsions
Antibiotics	Cefepime	GFR <30	CNS toxicity
Phase-prophylactic psychotropic drugs	Lithium	GFR <60	Nephro- and neurotoxicity
Antidiabetic drugs	Glibenclamide, glimepiride	GFR <60	Hypoglycemia
	Metformin	GFR <60	Lactic acidosis
Diuretics	Spironolactone, eplerenone	GFR <30	Hyperkalemia
Immune suppressants	Methotrexate	GFR <60	Myelotoxicity
Radiological contrast media	Gadolinium	GFR <30	Nephrogenic systemic fibrosis
LMW-heparin	Enoxaparin	GFR <60	Risk of hemorrhage

patients with CKD are listed in Table 6.2 and include cefepime, spironolactone, eplerenone, contrast media, and nonsteroidal anti-inflammatory drugs [16]. Nephrology consultation may be advisable in these cases. However, for example, nonsteroidal anti-inflammatory drugs may be replaced by tilidine or hydromorphone with frequent monitoring of side effects.

Low-molecular-weight heparins, among them enoxaparin, are one of the medication groups which should be avoided in older patients [17]. The reason for this is the accumulation kinetics of enoxaparin in a deep compartment, similar to that of methotrexate. Instead, unfractionated heparins should be given.

The issue as to whether metformin may be administered at a GFR of under 60 mL/min has been the subject of discussion in recent years, and some propose that metformin may even be administered at a GFR of 30 mL/min. This may constitute an unnecessary risk given the potential for lactic acidosis although extremely rare. In critically ill patients, continuous administration of insulin and, in patients with severe CKD, dipeptidyl peptidase-4 (DPP-4) inhibitors such as sitagliptin and vildagliptin may be preferred.

6.7 The 3 Dosing Rules in Gerontopharmacology

Polypharmacy is one problem with gerontopharmacology. The older the patients get, the more medications they have to take (5 and more is common). The first but obsolete rule of gerontological pharmacology states: All medications should be reduced to one half of common dose in older patients as a general rule. This rule is incorrect, since the average medication clearance in older patients often does not change at all, and half a dose may be ineffective – for example, considering chemotherapeutics. With a reduced dose, the concentrations can fall below the pharmacodynamic threshold [2].

The second rule was formulated for psychotropic medications: "start low and go slow" [18]. This rule certainly applies to psychotropic and antihypertensive medications for pharmacodynamic reasons, but it is incorrect when it comes to chemotherapeutics and antibiotics.

The third rule comes from infectiology: In contrast to the Gurwitz rule [18], the following applies for the success of antibiotic treatment or chemotherapy: Commencing treatment at an early state is of decisive importance – Paul Ehrlich already called for "frapper vite et frapper forte." One could translate this as "hit hard and hit fast." However, antibiotics with a concentration-dependent effect must be handled differently from those with a time-dependent effect. The peak level is important for antibiotics with a concentration-dependent effect, while the trough level is important for antibiotics with a time-dependent effect [19]. In the case of concentration-dependent effects, one would adjust the dose using Dettli-2 rule or just combine the Dettli and Kunin rules using the generalized rule formulated by Czock (see above). In the case of time-dependent effects, one would only reduce the dose but would not prolong the interval – i.e., one would use Dettli-1 rule. But one should not go below the threshold concentration with the time-dependent effect – i.e., a short dosing interval must be chosen. For concentration-dependent effects, increasing the dosage still produces a greater effect.

6.8 Summary

Contrary to the popular dosing rule "Use only one half of normal dose in older patients," changes in pharmacodynamics justify the common medication rule in older patients – "start low + go slow" – especially for drugs that act on the central nervous system and cardiovascular drugs; however, in the case of anti-infective and anticancer therapy, the rule should be "hit hard + go fast" to produce the target effect immediately also in older patients. For specific recommendations relating to drug dosage or drug choice for patients with reduced renal function, several website are recommended:

- www.americangeriatrics.org/files/documents/beers/2012BeersCriteria_JAGS.pdf
- priscus.net/download/PRISCUS-Liste_PRISCUS-TP3_2011.pdf
- http://www.uni-ulm.de/nephrologie/dosantibio.pdf
- www.dosing.de

References

1. Bellomo R (2006) The epidemiology of acute renal failure: 1975 versus 2005. Curr Opin Crit Care 12:557–560
2. Aymanns C, Keller F, Maus S, Hartmann B, Czock D (2010) Review on pharmacokinetics and pharmacodynamics and the aging kidney. Clin J Am Soc Nephrol 5:314–327
3. Dettli L (1976) Drug dosage in renal disease. Clin Pharmacokinet 1:126–134

4. Kunin CM (1967) A guide to use of antibiotics in patients with renal disease. A table of recommended doses and factors governing serum levels. Ann Intern Med 67:151–158
5. Czock D, Keller F (2007) Mechanism-based pharmacokinetic-pharmacodynamic modeling of antimicrobial drug effects. J Pharmacokinet Pharmacodyn 34:727–751
6. Robinson BE (2006) Epidemiology of chronic kidney disease and anemia. J Am Med Dir Assoc 7(9 Suppl):S3–S6
7. Lam Y, Banerji S, Hatfield C, Talbert RL (1997) Principles of drug administration in renal insufficiency. Clin Pharmacokinet 32:30–57
8. Bhardwaja B, Carroll NM, Raebel MA et al (2011) Improving prescribing safety in patients with renal insufficiency in the ambulatory setting: the Drug Renal Alert Pharmacy (DRAP) program. Pharmacotherapy 31:346–356
9. Wong NA, Jones HW (1998) An analysis of discharge drug prescribing amongst elderly patients with renal impairment. Postgrad Med J 74:420–422
10. Hu KT, Matayoshi A, Stevenson FT (2001) Calculation of the estimated creatinine clearance in avoiding drug dosing errors in the older patient. Am J Med Sci 322:133–136
11. Joosten H, Drion I, Boogerd KJ et al (2013) Optimising drug prescribing and dispensing in subjects at risk for drug errors due to renal impairment: improving drug safety in primary healthcare by low eGFR alerts. BMJ Open 24:3(1)
12. Budnita DS, Pollock DA, Weidenbach KN et al (2006) National surveillance of emergency department visits for outpatient adverse drug events. JAMA 296:1858–1866
13. Sheen SS, Choi JE, Park RW et al (2007) Overdose rate of drugs requiring renal dose adjustment: data analysis of 4 years prescriptions at a tertiary teaching hospital. J Gen Intern Med 23:423–428
14. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012;60:616–631.
15. Holt S, Schmiedl S, Thürmann PA (2010) Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Arztebl Int 107(31–32):543–551
16. Hartmann B, Czock D, Keller F (2010) Drug therapy in patients with chronic renal failure. Dtsch Arztebl Int 107:647–655
17. Hoffmann P, Keller F (2012) Increased major bleeding risk in patients with kidney dysfunction receiving enoxaparin: a meta-analysis. Eur J Clin Pharmacol 68:757–765
18. Gurwitz JH (1995) Start low and go slow: dosing of antipsychotic medications in elderly patients with dementia. Arch Intern Med 155:2017–2018
19. Eyler RF, Mueller BA (2010) Antibiotic pharmacokinetic and pharmacodynamic considerations in patients with kidney disease. Adv Chronic Kidney Dis 17:392–403

Chapter 7
Acute Dialysis in Older Patients

Celine Foote and Meg J. Jardine

Key Messages

1. There is a high incidence of acute kidney injury (AKI) in older patients which is associated with poorer outcomes compared to younger patients.
2. There is a lack of evidence about treatment of AKI in older patients, and therefore recommendations are generalized from data in patients of all ages.
3. Initiation of extracorporeal renal replacement therapy can be based on clinical parameters (fluid, electrolyte, and metabolic status) rather than single laboratory findings such as serum urea or creatinine levels.
4. Potential complications of renal replacement therapy for AKI include those associated with vascular access (infection and inflammation) and myocardial ischemia.
5. Continuous renal replacement therapies are suggested for those with cardiovascular compromise and multiorgan failure.
6. The optimal dose for intermittent hemodialysis is a Kt/V of 3.9 per week when using intermittent and an effluent volume of 20–25 mL/kg/h for continuous renal replacement therapy.

C. Foote, MBBS, FRACP (✉)
Renal and Metabolic Division, The George Institute for Global Health,
University of Sydney, Level 10, KGV Missenden Road, Camperdown,
Sydney, NSW 2050, Australia
e-mail: cfoote@georgeinstitute.org.au

M.J. Jardine, MBBS, PhD
Department of Renal, Royal Prince Alfred Hospital Sydney,
Renal and Metabolic Division, Nephrology Department,
The George Institute for Global Health,
Concord Repatriation General Hospital, Missenden Road,
Camperdown, Sydney, NSW 2050, Australia
e-mail: mjardine@georgeinstitute.org.au

M. Haase, A. Haase-Fielitz (eds.), *Managing Renal Injury in the Elderly Patient*,
DOI 10.1007/978-3-642-39947-3_7, © Springer-Verlag Berlin Heidelberg 2014

7.1 Introduction

Increases in life expectancy in the developed world have resulted in the growth of the elderly population. It is predicted that by the year 2030, the number of people aged over 65 will have nearly doubled and will constitute more than one-fifth of the US population [1]. Although many pathological entities are more common in older individuals, this seems to be particularly true for acute kidney injury (AKI) [1]. AKI is common, affecting 2–7 % of all hospital admissions [2], occurs at even higher rates in older patients [1] and appears to be growing in frequency at rates of around 3–11 % annually [3, 4]. The imminent demographic increase in the elderly population means AKI in the older patients will remain a prominent issue in the delivery of hospital services.

Acute kidney injury has consistently been associated with worse outcomes [5–7] for older patients including an increased risk of end-stage renal disease (ESRD) [6] confirmed by a recent meta-analysis [7]. The high incidence of AKI in the aging can be attributed to at least two factors: (1) the normal kidney undergoes age-dependent structural and functional alterations leading to a significant decrease in renal mass, functioning nephron numbers, and baseline kidney function [8], and (2) the incidence and duration of comorbidities affecting kidney function such as high blood pressure and diabetes accumulate with age, again reducing kidney reserve and making kidney function more susceptible to insults.

There is unfortunately limited data specific to older patients in AKI which means that treatment recommendations are generally derived from general studies. Numerous randomized controlled trials (RCTs) have been conducted in the treatment of AKI [9–21, 46–48] (Table 7.1), but to date, none have reported on outcomes for elderly subgroups.

Several organizations have published guidelines [22, 23] for management of AKI and similarly have not addressed older patients as a specific subgroup. However, the comparative higher rates of AKI in older patients mean that they are generally well represented in trials. More than 5,000 people with AKI have participated in randomized trials since 2000 focussing on mode and timing of initiation of renal replacement therapy (RRT) and outcomes. In half of these studies, patients were aged 65 or older (see Table 7.1).

In considering treatment of AKI with RRT, there are several aspects which need to be assessed:

- When to commence RRT
- Potential complications of RRT
- Which RRT modality to use
- How intensively to provide RRT
- When RRT is no longer required
- Continuous RRT and nutrition
- The prognosis of patients with AKI

Table 7.1 Randomized trials since 2000 focussing on acute renal replacement therapy

Authors	Publication year	Number of patients	Mean age [years]
Schwenger et al. [9]	2012	232	66
Wu et al. [10]	2012	73	61
RENAL Study [11]	2009	1,508	65
Hannover Dialysis Outcome study [12]	2009	156	51
Lins et al. [13]	2009	316	66
The VA/NIH Trial Network [14]	2008	1,124	60
Tolwani et al. [15]	2008	200	60
Saudan et al. [16]	2006	206	64
Vinsonneau et al. [17]	2006	360	65
Uehlinger et al. [18]	2005	125	67
Augustine et al. [48]	2004	80	61
Bouman et al. [20]	2002	106	68
John et al. [46]	2001	30	62
Mehta et al. [47]	2001	166	55
Ronco et al. [21]	2000	425	61
Overall		*5,107*	*62*

Based on table from Schmitt et al. [7] and updated from 2007 to present

7.1.1 When to Commence Renal Replacement Therapy

Whether and when to provide RRT are two of the fundamental questions facing nephrologists and intensive care practitioners in most cases of severe AKI. Unfortunately, none of the large RCTs in this area have included initiation parameters as a study factor, and the optimal time and thresholds for RRT start remain undefined. Factors that may influence decision making on RRT initiation include thresholds and progression rate of parameters such as volume status, uremia, hyperkalemia and acidosis, concurrent medical conditions, and perceptions of AKI prognosis and overall prognosis. Concerns about risks associated with the RRT procedure may delay RRT initiation, including hypotension, cardiac effects, and complications of vascular access such as infection and anticoagulant administration. Specific concerns that RRT may compromise recovery of renal function and increase the progression of CKD may also delay or prevent RRT initiation [24].

Only a few, small RCTs have attempted to evaluate the effect of early versus late initiation of RRT on outcome in AKI [10, 19, 20]. In two studies enrolling critically ill surgical patients with postoperative AKI (mean age 61), early initiation of RRT was associated with a higher survival rate [10, 19]. However, in a more general cohort of critically ill patients with oliguric AKI (mean age 68), survival at 28 days and recovery of renal function were not improved using high ultrafiltrate volumes or early initiation of hemofiltration [20]. No study specifically focussed on older patients or provided a comparison in outcome differences between younger and older patients.

Completion of the above trials demonstrates studies of these questions are feasible, and as dialysis therapy is associated with both potential benefits and harms, further trials would clearly inform practice.

In addition, several observational studies have analyzed the association of timing for RRT initiation with outcomes [25–28, 30, 31, 33]. Overall, they suggest that early initiation of RRT may be associated with survival benefit but is limited by their susceptibility to bias. Very early reports compared early start patients (defined by lower serum urea concentration) and found an association with better survival but also treated the early starters more intensely [25, 26]. A more recent study used serum creatinine- and urine output-based AKI Network criteria [29] as starting criterion for RRT included critically ill patients with a mean age of 56 years and found reduced morbidity and mortality for early starters [30]. A prospective multicenter observational cohort study by the Program to Improve Care in Acute Renal Disease (PICARD) [31] analyzed RRT initiation—as inferred by blood urea nitrogen (BUN) concentration—in 243 patients with a mean age of 56 years and found an increased risk of death associated with initiation at higher BUN after adjusting for age, hepatic failure, sepsis, thrombocytopenia, and serum creatinine and stratifying for site and initial RRT modality [31]. Also, in 98 AKI patients after major abdominal surgery (mean age 67), late initiation of RRT (defined as Injury or Failure class of the RIFLE definition [32]) was an independent predictor of increased mortality [33]. There were no significant baseline differences between the two groups other than a higher eGFR and lower serum creatinine in the late start group.

Thus, the consensus from several observational studies and some RCTs suggests that "early" initiation of RRT in AKI are associated with improved patient survival, although none of these studies specifically focussed on older patients.

The KDIGO international clinical practice guidelines for management of AKI [22] acknowledge the lack of evidence in this regard but suggest initiation of RRT should occur emergently when life-threatening changes in fluid, electrolyte, and acid–base balance exist. They also state that considerations should include the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single BUN and serum creatinine thresholds alone—when making decisions to start RRT. Similarly, the UK Renal Association [23] recommends basing decision to commence RRT on clinical parameters (fluid, electrolyte, and metabolic status of individual patients) and proposes that the threshold for initiating RRT should be lowered when AKI occurs as part of multiorgan failure.

7.1.2 Potential Complications of Renal Replacement Therapy

Potential complications of dialysis therapy to consider include those associated with the need for vascular access and those of the dialysis procedure itself.

Providing RRT for AKI generally necessitates the placement of a central venous catheter (CVC) with the attendant risks of exit site infections and catheter-related bacteremia, estimated at 2.5–5.5 cases/1,000 patient-days in maintenance dialysis [34]. Recent studies have also postulated a chronic inflammatory mechanism independent of overt bacteremic episodes, demonstrating a relationship between CVC

use, elevated CRP, lower serum albumin, and lower hemoglobin values [34–36]. A causal link is supported by the finding that CRP levels decrease after CVC removal [34]. Elevated CRP is also independently linked with increased mortality [36].

The infection risk of CVC use for AKI may be less with intermittent dialysis therapies. A cohort study (mean age 65) which examined differences in the risk of catheter-related colonization in patients undergoing intermittent hemodialysis (IHD) as compared with continuous RRT (CRRT) found an increased risk of catheter-tip colonization for CRRT when baseline differences and time on each modality were taken into account [37]. However, no specific subgroup analysis was performed in older patients [37]. A measure which is sometimes employed to decrease infection risk is the placement of a jugular compared to a femoral CVC. A large RCT which examined this question demonstrated no reduction in the risk of infection except for those with a high BMI, but again no older subgroup analysis was conducted [38]. One large study which specifically examined the impact of CVC use in older patients found that in patients aged ≥75 years at chronic dialysis initiation, the use of CVC at dialysis initiation was associated with an independent mortality risk after controlling for factors such as patient age, comorbidities, and late referral and commencing dialysis without prepared access [39].

There is also an emerging body of evidence suggesting that subclinical myocardial ischemia is precipitated by hemodialysis. The presence of reductions in myocardial blood flow was confirmed at peak dialytic stress even in the absence of angiographically significant coronary disease [40]. It is understood that in the long term, these recurrent ischemic insults lead to myocardial functional and structural changes which result in fixed systolic dysfunction, arrhythmias, and heart failure. No studies have thus far been conducted in patients with AKI. It is plausible although unknown whether hemodialysis prescribed for AKI, particularly IHD, is associated with similar phenomena given that patients with AKI are likely to suffer from similar comorbidities to CKD patients.

There are some suggestions from pathological studies that hemodialysis itself for AKI, while being life sustaining, may contribute to the prolongation of kidney failure. The presence of fresh ischemic lesions on kidney biopsies in patients with prolonged AKI being treated with dialysis was first noted in combat casualties in Vietnam in whom AKI was predominantly a result of hypoperfusion secondary to trauma or surgery [41]. The consistent pathological finding of focal areas of fresh tubular necrosis estimated to be 48–72 h old was found in those treated with dialysis which was unlikely to be the result of the initial ischemic insult 3–4 weeks earlier. This was true in the absence of hemodynamic events in the 4–5 days preceding the biopsies [41].

7.1.3 Which Renal Replacement Therapy Modality to Use

7.1.3.1 Hemodialysis Versus Peritoneal Dialysis (PD)

In general the experience with acute PD in AKI is limited and generally reserved for pediatric settings and used in regions with limited resources [42]. However, acute PD remains a feasible option for the treatment of selected patients with AKI.

One study has reported an advantage for CRRT compared to PD but was hampered by the fact that the dose of dialysis delivered by PD was low [43]. More recently, a randomized trial of 120 participants with acute tubular damage (mean age 63) has suggested broadly equivalent patient outcomes and metabolic control when PD was conducted at high volume (36–44 L/day) compared to daily IHD for the treatment of AKI [44]. An observational study of outcomes for a cohort of older patients (mean age 73.5) with an unplanned start to maintenance dialysis found significantly less bacteremia in patients receiving acute PD than those receiving hemodialysis (RR 0.16) [45]. None of the assessed covariables including patient age at time of dialysis had a significant impact on the risk of bacteremia [45].

7.1.3.2 Intermittent Versus Continuous Hemodialysis

Although it is widely perceived that CRRT is superior to IHD in hemodynamically unstable patients, prospective RCTs have failed to confirm this supposition.

Six RCTs comparing CRRT and IHD from Europe and the USA have been published so far [13, 17, 18, 46–48] which consistently demonstrate no difference in outcomes between CRRT and IHD after adjusting for patient variables. A number of meta-analyses reached the same conclusion [49–51]. A Cochrane Collaboration analysis concluded that outcomes (hospital and ICU mortality, length of hospitalization, and renal recovery) were similar in critically ill patients with AKI treated with CRRT and IHD [49]. One meta-analysis of observational studies reporting outcomes from AKI [7] examined the interaction of choice of hemodialysis therapy (intermittent versus continuous) with age and found that older patients undergoing intermittent therapies were at a significantly greater risk of renal non-recovery than young patients (RR 1.52). The relative risk for renal non-recovery after continuous RRT was only slightly increased compared to younger patients (RR 1.19), and this increase did not reach statistical significance.

This data may support the notion that the choice of RRT modality may be of particular importance in the elderly with patients older than 65 years appearing to have better chances of renal recovery when treated with continuous RRT. However, this needs to be examined more closely through a well-conducted RCT.

In summary, analysis of the currently published studies does not allow evidence-based guidelines for the selection of RRT modality for the treatment of AKI especially in older patients. In clinical practice however, many clinicians chose intermittent hemodialysis/hemofiltration for cardiovascularly stable patients, and continuous therapies for those with cardiovascular compromise and multiorgan failure, and this is supported by suggestions made in AKI guidelines [22].

7.1.4 How Intensively to Provide Renal Replacement Therapy

Multiple observational studies suggest that increasing weekly hours of hemodialysis delivered to patients with ESKD are associated with better clinical outcomes.

Recent research has focussed on the optimal dose of IHD or CRRT determining survival in patients with AKI [11, 12, 14–16, 20, 21].

Controversy remains about the best way to measure and what constitutes optimal dose of RRT for patients with AKI. The methods used for RRT dose quantification in AKI have not been fully validated and have several limitations. RRT dose, by itself, may also have less impact on mortality both in patients with very high or very low chance of surviving but may be most important in patients with intermediate scores of disease severity. Compliance with threshold dialysis doses in AKI is often not achieved and the factors predicting poor compliance include older age (>65 years), male gender, and intradialytic hypotension [52]. In addition, it is possible that dose and timing are closely linked factors, i.e., a high RRT dose may not work adequately if provided late. Currently, only one small RCT (mean age 68) considered both variables and found no difference in those randomized to early start high-dose, early start low-dose, and late start low-dose CVVH, although the study was clearly underpowered [20].

Traditionally in AKI studies, the dose (or intensity) of treatment has been assessed by urea clearance in dialysis-based modalities and by ultrafiltration volume (a surrogate of urea clearance), in the convective therapies. The urea clearance achieved during CRRT is approximately equal to the effluent flow rate (dialysis and ultrafiltration flow rate combined). Although widely used for evaluation of RRT in maintenance dialysis for CKD, measures which include assessment of serum urea have important limitations as tools for RRT dosing in AKI. AKI patients are metabolically unstable and have variations in urea generation. Selection of target serum urea levels as indicators of dialysis dose is therefore arbitrary notwithstanding the fact that urea is influenced by extrarenal factors such as ethnicity, age, and gender.

7.1.4.1 Intensity of Intermittent Hemodialysis (IHD)

There is a paucity of data regarding optimal treatment doses for IHD in AKI. Analysis of a prospectively collected database has shown that higher doses of IHD, defined as a urea reduction ratio (URR) > 58 %, improved survival [53]. However, it should be noted that this cutoff dose, equivalent to a Kt/V of around 1, is lower than that recommended for IHD for established ESRD.

Only one study has evaluated the effect of daily and alternate day IHD on the outcome among patients with AKI [54]. This quasi-RCT reported both lower mortality and shorter duration of AKI in the daily IHD group. However the dose of hemodialysis delivered to the alternate day group was low (mean delivered Kt/V of 0.94). This probably accounted for the markedly increased time-averaged urea concentration and the high incidence of complications including gastrointestinal bleeding, mental status alteration, and infection reported in this group [54].

Due to the lack of RCTs addressing the minimum dose of RRT required in AKI, a consensus panel convened by the multinational Acute Dialysis Quality Initiative (ADQI) recommended that patients with AKI receive at least the minimum dose that is considered appropriate for patients with established ESRD [55].

7.1.4.2 Intensity of Continuous Renal Replacement Therapy (CRRT)

Two large multicentre randomized controlled studies have been published recently to provide much needed guidance on the optimal dose of CRRT in critically ill patients [11, 14].

The Veteran Affairs/National Institute of Health Acute Renal Failure Trial Network (ATN) study was performed in 1,124 critically ill patients across the USA [14], while the Randomized Evaluation of Normal Versus Augmented Level of Renal Replacement Therapy (RENAL) was conducted in 1,508 critically ill patients in Australia and New Zealand [11]. The ATN study (mean age 59.6) showed no additional beneficial patient outcome with a delivered CVVHDF dose (pre-dilution) of 35 mL/kg/h compared to 20 mL/kg/h [14]. The RENAL trial (mean age 64.5) failed to demonstrate any survival benefit from receiving post-dilution CVVHDF at a dose of 40 mL/kg/h versus 25 mL/kg/h [11].

These studies have now provided evidence that there is no survival benefit in critically ill patients receiving ultrafiltration doses >25 mL/kg/h. The prescription of a higher dose is prudent to allow for circuit clotting in order to ensure delivery of the required dose. The recently published KDIGO guidelines recommend delivering a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI and delivering an effluent volume of 20–25 mL/kg/h for CRRT in AKI [22].

In summary, there is no evidence that high-dose CRRT for patients with AKI reduce mortality.

7.1.4.3 Intensity of Peritoneal Dialysis (PD)

Only limited data are available investigating the effects of PD dose on outcomes in AKI. A small RCT found that in critically ill patients with AKI, intensive PD dose did not lower the mortality or improve the recovery of kidney function or metabolic control [56]. High-volume PD (consisting of 16–22 exchanges/day) has been used effectively for selected AKI patients and is reported to deliver adequate metabolic and fluid control; although age was identified as major risk factor for death in a recent prospective study [57].

7.1.5 When Renal Replacement Therapy Is No Longer Required

Assessment of potentially improving kidney function during RRT and the possibility of ceasing treatment are not straightforward. In intermittent hemodialysis, for example, fluctuations of solute levels prevent achieving a steady state and thus exclude the use of clearance measurements. Native kidney function can only be assessed during the interdialytic period through evaluations of urine volume, urinary excretion of creatinine, and changes in serum creatinine and urea. However, intermittent

treatment results in posttreatment rebound in solute levels and nonrenal factors, such as volume status and catabolic rate, can also affect creatinine and urea levels.

The evidence base for discontinuation of RRT with recovering renal function is even less clear than that for its initiation. A post hoc analysis from an international, multicenter study found that urine output at the time of first stopping continuous RRT was the most important predictor of sustained discontinuation, especially if not enhanced by diuretics. Those who returned to RRT within 7 days had a higher mortality than those who did not, although this could have been due to deterioration in overall condition rather than early cessation of renal support [58]. Sometimes, transition from continuous to intermittent therapy is necessary, but no specific guidance can be provided as to how to manage this. Large observational studies demonstrate that considerable variation in practice exists [58].

7.1.6 Continuous Renal Replacement Therapy and Nutrition

Several water-soluble substances including vitamins, amino acids, trace elements, and carnitine are lost during extracorporeal RRT especially during continuous RRT [59–61]. In particular, there are significant losses of vitamin C, phosphate, folate, thiamine, and vitamin B6 during CRRT exists [59, 62, 63]. It is therefore recommended that additional amounts of these vitamins and phosphate should be administered to patients treated with CRRT.

Although trace elements are not lost in significant amounts in the ultrafiltrate during CRRT (because only nonprotein-bound trace elements can be filtered), serum concentration of antioxidant trace elements such as selenium, zinc, and copper is generally low in these patients, and supplementation should be considered [59, 64]. The administration of essential amino acids is not superior to a mixture of essential and nonessential amino acids [65]. Further, there are no clinically important differences in amino acid losses during IHD or CRRT [65].

Adequate supplementation is recommended to counterbalance the decrease in phosphate and the loss of some vitamins during CRRT. Although there are studies evaluating nutritional support during CRRT in patients with AKI, patient-related prognostic outcome data are lacking.

7.1.7 Prognosis of AKI

Another important consideration is the prognosis of AKI. One meta-analysis has examined recovery of kidney function following AKI in older patients versus younger patients [7]. Recovery of kidney function after AKI is approximately 28 % less likely to occur when the patient is older than 65 years (Fig. 7.1) [7]. This finding is similar to subgroup analyses and single-center reports which also demonstrate slower or less complete renal recovery after AKI in an age-dependent manner [66, 67].

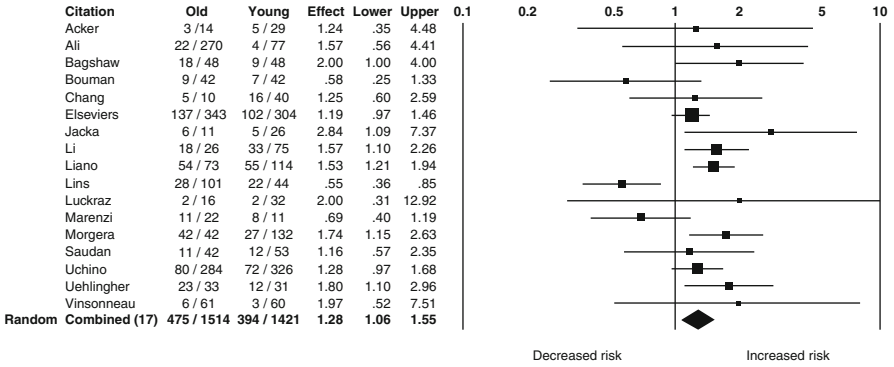


Fig. 7.1 Relative risk of non-recovery of renal function after acute kidney injury in older patients compared with younger patients. Pooled relative risk for non-recovery of renal function from acute kidney injury stratified by elderly status. Test for heterogeneity: $\chi^2 = 35.81$; df = 16; $P = 0.003$; I2 = 55 % (From Ref. [7])

7.2 Summary

Older patients are at high risk of AKI due to their age and comorbidities, and when AKI occurs in this group, it is associated with considerable morbidity and mortality. Lack of age-specific data exists around the management of AKI, and therefore recommendations come from studies in the general population and in elderly CKD patients.

Extracorporeal renal replacement therapy for AKI should be initiated based on clinical parameters and should provide a Kt/V of 3.9 per week for intermittent therapies and an effluent volume of 20–25 mL/kg/h for continuous therapies. Consideration should also be given to the potential complications of renal replacement therapy including infection, inflammation, and myocardial ischemia.

References

1. Pascual J, Orofino L, Liano F et al (1990) Incidence and prognosis of acute renal failure in older patients. J Am Geriatr Soc 38:25–30
2. Liangos O, Wald R, O'Bell JW, Price L, Pereira BJ, Jaber BL (2006) Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey. Clin J Am Soc Nephrol 1:43–51
3. Bagshaw SM, George C, Bellomo R, Committee ADM (2007) Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. Crit Care 11:R68
4. Xue JL, Daniels F, Star RA et al (2006) Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. J Am Soc Nephrol 17:1135–1142
5. Liano F, Pascual J (1996) Epidemiology of acute renal failure: a prospective, multicenter, community-based study. Madrid Acute Renal Failure Study Group. Kidney Int 50:811–818

6. Ishani A, Xue JL, Himmelfarb J et al (2009) Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol 20:223–228
7. Schmitt R, Coca S, Kanbay M, Tinetti ME, Cantley LG, Parikh CR (2008) Recovery of kidney function after acute kidney injury in the elderly: a systematic review and meta-analysis. Am J Kidney Dis 52:262–271
8. Gourtsoyiannis N, Prassopoulos P, Cavouras D, Pantelidis N (1990) The thickness of the renal parenchyma decreases with age: a CT study of 360 patients. Am J Roentgenol 155:541–544
9. Schwenger V, Weigand MA, Hoffmann O et al (2012) Sustained low efficiency dialysis using a single-pass batch system in acute kidney injury – a randomized interventional trial: the REnal Replacement Therapy Study in Intensive Care Unit PatiEnts. Crit Care 16:R140
10. Wu SC, Fu CY, Lin HH et al (2012) Late initiation of continuous veno-venous hemofiltration therapy is associated with a lower survival rate in surgical critically ill patients with postoperative acute kidney injury. Am Surg 78:235–242
11. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L et al (2009) Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 361:1627–1638
12. Faulhaber-Walter R, Hafer C, Jahr N et al (2009) The Hannover Dialysis Outcome study: comparison of standard versus intensified extended dialysis for treatment of patients with acute kidney injury in the intensive care unit. Nephrol Dial Transplant 24:2179–2186
13. Lins RL, Elseviers MM, Van der Niepen P, SHARF Investigators (2009) Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial. Nephrol Dial Transplant 24:512–518
14. VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, O'Connor TZ et al (2008) Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 359:7–20
15. Tolwani AJ, Campbell RC, Stofan BS, Lai KR, Oster RA, Wille KM (2008) Standard versus high-dose CVVHDF for ICU-related acute renal failure. J Am Soc Nephrol 19:1233–1238
16. Saudan P, Niederberger M, De Seigneux S et al (2006) Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int 70:1312–1317
17. Vinsonneau C, Camus C, Combes A et al (2006) Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. Lancet 368:379–385
18. Uehlinger DE, Jakob SM, Ferrari P et al (2005) Comparison of continuous and intermittent renal replacement therapy for acute renal failure. Nephrol Dial Transplant 20:1630–1637
19. Sugahara S, Suzuki H (2004) Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. Hemodial Int 8:320–325
20. Bouman CSC, Oudemans-Van Straaten HM, Tijssen JGP, Zandstra DF, Kesecioglu J (2002) Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Crit Care Med 30:2205–2211
21. Ronco C, Bellomo R, Homel P et al (2000) Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 356:26–30
22. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2: 1–138
23. Lewington A, Kanagasundaram S (2011) Renal Association Clinical Practice Guidelines on acute kidney injury. Nephron Clin Pract 118(Suppl 1):c349–c390
24. Palevsky PM, Baldwin I, Davenport A, Goldstein S, Paganini E (2005) Renal replacement therapy and the kidney: minimizing the impact of renal replacement therapy on recovery of acute renal failure. Curr Opin Crit Care 11:548–554

25. Conger JD (1975) A controlled evaluation of prophylactic dialysis in post-traumatic acute renal failure. J Trauma 15:1056–1063
26. Parsons FM, Hobson SM, Blagg CR, McCracken BH (1961) Optimum time for dialysis in acute reversible renal failure. Description and value of an improved dialyser with large surface area. Lancet 1:129–134
27. Gettings LG, Reynolds HN, Scalea T (1999) Outcome in post-traumatic acute renal failure when continuous renal replacement therapy is applied early vs. late. Intensive Care Med 25:805–813
28. Demirkilic U, Kuralay E, Yenicesu M et al (2004) Timing of replacement therapy for acute renal failure after cardiac surgery. J Card Surg 19:17–20
29. Mehta RL, Kellum JA, Shah SV et al (2007) Acute Kidney Injury Network Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 11:R31
30. Leite TT, Macedo E, Pereira SM et al (2013) Timing of renal replacement therapy initiation by AKIN classification system. Crit Care 17:R62
31. Liu KD, Himmelfarb J, Paganini E et al (2006) Timing of initiation of dialysis in critically ill patients with acute kidney injury. Clin J Am Soc Nephrol 1:915–919
32. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P (2004) Acute Dialysis Quality Initiative workgroup Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 8:R204–R212
33. Shiao C-C, Wu V-C, Li W-Y et al (2009) Late initiation of renal replacement therapy is associated with worse outcomes in acute kidney injury after major abdominal surgery. Crit Care 13:R171
34. Hung AM, Ikizler TA (2008) Hemodialysis central venous catheters as a source of inflammation and its implications. Semin Dial 21:401–404
35. Hung A, Pupim L, Yu C et al (2008) Determinants of C-reactive protein in chronic hemodialysis patients: relevance of dialysis catheter utilization. Hemodial Int 12:236–243
36. Snaedal S, Heimburger O, Qureshi AR et al (2009) Comorbidity and acute clinical events as determinants of C-reactive protein variation in hemodialysis patients: implications for patient survival. Am J Kidney Dis 53:1024–1033
37. Foote C, Ninomiya T, Gallagher M et al (2012) Survival of elderly dialysis patients is predicted by both patient and practice characteristics. Nephrol Dial Transplant 27:3581–3587
38. Parienti JJ, Thirion M, Mégarbane B et al; Members of the Cathedia Study Group (2008) Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. JAMA 299:2413–2422
39. Parienti JJ, Dugué AE, Daurel C et al; Members of the Cathedia Study Group (2010) Continuous renal replacement therapy may increase the risk of catheter infection. Clin J Am Soc Nephrol 5:1489–1496
40. McIntyre CW, Burton JO, Selby NM et al (2008) Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. Clin J Am Soc Nephrol 3:19–26
41. Teschan PE, Baxter CR, O'Brien TF, Freyhof JN, Hall WH (1960) Prophylactic hemodialysis in the treatment of acute renal failure. Ann Intern Med 53:992–1016 and republished in J Am Soc Nephrol 1998;9:2384–2397
42. Mishra OP, Gupta AK, Pooniya V, Prasad R, Tiwary NK, Schaefer F (2012) Peritoneal dialysis in children with acute kidney injury: a developing country experience. Perit Dial Int 32:431–436
43. Phu N, Hien T, Mai N (2002) Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. N Engl J Med 347:895–902
44. Gabriel DP, Caramori JT, Martim LC, Barretti P, Balbi AL (2008) High volume peritoneal dialysis vs daily hemodialysis: a randomized, controlled trial in patients with acute kidney injury. Kidney Int Suppl (108):S87–93
45. Koch M, Kohnle M, Trapp R, Haastert B, Rump LC, Aker S (2012) Comparable outcome of acute unplanned peritoneal dialysis and haemodialysis. Nephrol Dial Transplant 27:375–380

46. John S, Griesbach D, Baumgartel M, Weihprecht H, Schmieder RE, Geiger H (2001) Effects of continuous haemofiltration vs intermittent haemodialysis on systemic haemodynamics and splanchnic regional perfusion in septic shock patients: a prospective, randomized clinical trial. Nephrol Dial Transplant 16:320–327
47. Mehta RL, McDonald B, Gabbai FB et al (2001) A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. Kidney Int 60:1154–1163
48. Augustine JJ, Sandy D, Seifert TH, Paganini EP (2004) A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. Am J Kidney Dis 44:1000–1007
49. Rabindranath K, Adams J, Macleod AM, Muirhead N (2007) Intermittent versus continuous renal replacement therapy for acute renal failure in adults. Cochrane Database Syst Rev (3):CD003773
50. Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R (2008) Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. Crit Care Med 36:610–617
51. Pannu N, Klarenbach S, Wiebe N, Manns B, Tonelli M, Alberta Kidney Disease Network (2008) Renal replacement therapy in patients with acute renal failure: a systematic review. JAMA 299:793–805
52. Rosa-Diez G, Greloni G, Crucelegui M et al (2012) Factors determining a low dose of haemodialysis as measured by ionic dialysance in critical patients with acute kidney injury. Nefrologia 32:359–566
53. Kanagasundaram NS, Greene T, Larive AB et al (2003) Prescribing an equilibrated intermittent hemodialysis dose in intensive care unit acute renal failure. Kidney Int 64:2298–2310
54. Schiffl H, Lang SM, Fischer R (2002) Daily hemodialysis and the outcome of acute renal failure. N Engl J Med 346:305–310
55. Kellum JA, Mehta RL, Angus DC, Palevsky P, Ronco C, Workgroup A (2002) The first international consensus conference on continuous renal replacement therapy. Kidney Int 62:1855–1863
56. Ponce D, Brito GA, Abrão JG, Balb AL (2011) Different prescribed doses of high-volume peritoneal dialysis and outcome of patients with acute kidney injury. Adv Perit Dial 27:118–124
57. Ponce D, Berbel MN, Regina de Goes C, Almeida CT, Balbi AL (2012) High-volume peritoneal dialysis in acute kidney injury: indications and limitations. Clin J Am Soc Nephrol 7:887–894
58. Uchino S, Bellomo R, Morimatsu H et al (2009) Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. Crit Care Med 37:2576–2582
59. Berger MM, Shenkin A, Revelly JP (2004) Copper, selenium, zinc, and thiamine balances during continuous venovenous hemodiafiltration in critically ill patients. Am J Clin Nutr 80:410–416
60. Story DA, Ronco C, Bellomo R (1999) Trace element and vitamin concentrations and losses in critically ill patients treated with continuous venovenous hemofiltration. Crit Care Med 27:220–223
61. Bellomo R, Martin H, Parkin G, Love J, Kearley Y, Boyce N (1991) Continuous arteriovenous haemodiafiltration in the critically ill: influence on major nutrient balances. Intensive Care Med 17:399–402
62. Fortin MC, Amyot SL, Geadah D, Leblanc M (1999) Serum concentrations and clearances of folic acid and pyridoxal-5-phosphate during venovenous continuous renal replacement therapy. Intensive Care Med 25:594–598
63. Wiesen P, Van Overmeire L, Delanaye P, Dubois B, Preiser JC (2011) Nutrition disorders during acute renal failure and renal replacement therapy. JPEN J Parenter Enteral Nutr 35:217–222
64. Nakamura AT, Btaiche IF, Pasko DA, Jain JC, Mueller BA (2004) In vitro clearance of trace elements via continuous renal replacement therapy. J Ren Nutr 14:214–219
65. Bellomo R (2002) How to feed patients with renal dysfunction. Blood Purif 20:296–303
66. Rodgers H, Staniland JR, Lipkin GW, Turney JH (1990) Acute renal failure: a study of elderly patients. Age Ageing 19:36–42
67. Arora P, Kher V, Kohli HS, Sharma RK, Gupta A, Jha R (1993) Acute renal failure in the elderly: experience from a single centre in India. Nephrol Dial Transplant 8:827–830

Chapter 8
Quality of Life, Functional Status, and Specific Medical Problems in Older Patients

Gargi Banerjee, Anja Haase-Fielitz, and Edwina A. Brown

Key Messages

1. Geriatric assessment tools and management for older patients improve care and daily function, but their effects have not yet been determined for older adults at risk for or with established acute kidney injury.
2. Multidisciplinary strategies to reduce long-term morbidity and mortality in older patients with acute kidney injury after hospital discharge are required.
3. Systematic cognitive testing before initiation of extracorporeal renal replacement therapy and periodically thereafter may be warranted.
4. Nutritional requirements should be frequently assessed in older patients with acute kidney injury, individualised, and carefully adapted to renal replacement therapy.

8.1 Introduction

Compared to younger patients developing acute kidney injury (AKI), older patients with AKI have higher rates of short- and long-term mortality, experience longer stay in hospital, a more frequent rate of transfer to subacute care facilities and a rapid cognitive and functional decline [1, 2]. Age is a risk factor for non-recovery from AKI or progression to (advanced) chronic kidney disease (CKD)

G. Banerjee, MA, BMBCh • E.A. Brown, DM (Oxon), FRCP (✉)
Imperial College Renal and Transplant Centre, Hammersmith Hospital,
Du Cane Road, London W12 0HS, UK
e-mail: e.a.brown@imperial.ac.uk; gargibanerjeeg@gmail.com

A. Haase-Fielitz, PharmD (AHF)
Department of Nephrology and Hypertension,
Diabetology and Endocrinology, University Hospital,
Otto-von-Guericke University, Leipziger Str. 44,
Magdeburg 39120, Germany
e-mail: anja.haase-fielitz@med.ovgu.de

M. Haase, A. Haase-Fielitz (eds.), *Managing Renal Injury in the Elderly Patient*,
DOI 10.1007/978-3-642-39947-3_8, © Springer-Verlag Berlin Heidelberg 2014

including end-stage renal disease (ESRD) [3]. If CKD is a result of AKI, patients will live with renal function loss in its various stages until their death as CKD is not curable.

Specific aspects of age-related management of patients with AKI include the avoidance of polypharmacy and potential nephrotoxic medication as well as discontinuation of predominantly renally excreted medication. Further aspects are the establishment of strategies to prevent or slow functional decline, cognitive changes and the development of additional morbidities during AKI. Assessment of fluid balance and nutritional status in older patients with AKI and appropriate replacement and monitoring are also of importance, taking into account renal function and alteration in volume distribution. Older patients with AKI have an increased incidence of extrarenal organ complication. Fluid overload is a particular risk factor for older patients with limited cardiac reserve and was identified as prognostic factor for mortality in patients with AKI [4].

Geriatric assessment tools and management for older patients improve care and daily function, but their effects have not been determined for older adults at risk for AKI. There are unfortunately only limited data on short-term and long-term impact of AKI on outcomes meaningful to older patients, their families and medical staff including health-related quality of life, physical and cognitive function and independence. However, the development of patient-centred decision-making tools to assist older AKI patients and their representatives in care options is urgently needed. Quality of life can be improved by recognising and optimising management of the problems associated with old age, particularly when making treatment decisions about modality of extracorporeal renal replacement therapy (RRT) or even no RRT.

8.2 General Quality of Life

Several studies have examined health-related quality of life (HRQOL) in patients with AKI especially in those requiring extracorporeal RRT [5–12]. In most of the studies, the short form 36 (SF-36), a widely used generic standardised health status questionnaire for measuring physical and mental health status, was used [13].

In a recent observational cohort study, including 749 critically ill patients (mean age 70), survivors with AKI and those without AKI showed no significant differences between the HRQOL 6 months after discharge from the intensive care unit [5]. However, both groups showed a significantly lower HRQOL at 6 months compared with an age-matched general population. Age was a significant predictor of changes in the physical than in the mental health [5]. Almost all patients enrolled in a small pilot study, even those with the worst self-reported quality of life and greatest physical disability, considered RRT as the right decision [6]. In a Finnish study investigating 703 medical and surgical patients receiving RRT for AKI, survivors had a low health-related quality of life; however, they were satisfied with their health as the general population [7]. Similar findings arise from a

prospective observational study conducted in seven ICUs in France including 204 patients (mean age 66) with RRT-dependent AKI [8]. At 6 months, 77 out of 204 patients were alive. Quality of life (SF-36 and Index of Activities of Daily Living) significantly increased from day 28 to 6 months. Survivors had an impaired quality of life compared to a reference age- and sex-matched French population but sustained autonomy in their daily lives [64 % of patients were fully autonomous, 69 % were living in their homes, 12 % were still undergoing RRT and 94 % would agree to undergo the same management again] [8]. Measuring changes in health status in postoperative critically ill patients, Abelha and colleagues found an improved subjective perception of quality of life 6 months after discharge from intensive care in patients that met AKI criteria (mean age 68), although they were more dependent in activities of daily living [9]. A better HRQOL was reported for younger AKI patients requiring RRT and for those without previous CKD [10].

The Veterans Affairs/NIH Acute Renal Failure Trial Network assessed predictors of health utility among 60-day survivors of AKI requiring RRT [11]. In addition to the overall HRQOL score, this study focussed on four prespecified attributes that were hypothesised and would be most likely to be affected by AKI, namely, ambulation, cognition, emotion, and pain. Intensity of RRT did not have a substantial effect on any of these factors among survivors [11]. Although no long-term data were reported, a significant proportion of survivors reported an extremely low HRQOL within the 60-day assessment period [11]. In a multicenter study including 595 AKI patients (mean age 64), the authors found that SF-36 scores (and with it quality of life) after 1–2 years were negatively correlated with age; Charlson comorbidity index and body mass index, however, did not show any significant relationship with renal function, treatment modalities, and length of stay in the hospital [12].

For older patients burdened by AKI- or CKD-related comorbidities and with the general features of ageing, quality of life is frequently of more importance than length of life. The impact of RRT in general – regardless if in the setting of acute or chronic – the effect of different RRT modalities on patients' quality of life, is often not discussed prior to starting treatment. This requires a realistic consideration of the impact of RRT on factors such as physical function, cognitive function and mental health. Indeed, the assumption is made that the patient will feel better. The following patient quote comes from recent patient interviews done as part of the BOLDE study enrolling chronic dialysis patients aged 65 years or older [14].

> *HD patient*: 'Just a walk in the park he said for you, having dialysis… it's nothing to worry about … I thought it bloody well is …more than a walk in the park!' *Wife*: 'Because they were saying once he starts on the dialysis, he would be a lot better after 3 months but… I haven't found any change at all.' *Patient*: 'Well again to me I have to be honest….the people who telling these things, they has an idea …, they never gone on dialysis for themselves…. So, what they telling you is only to give you a bit of courage….you have to be in it to know it.'

All of the above findings should be taken into consideration when counselling patients facing the prospect of RRT in the ICU.

8.3 Physical Function

'Functional status' is a broad term that encompasses both physical mobility and the ability to perform tasks necessary for independent living [15]. Thus functional status is a key point of quality of life, a strong predictor of survival, the need for nursing, health care costs and an important factor in decisions about medical procedures including the use of feeding tubes or cardiopulmonary resuscitation [15–19].

There are several factors in patients with AKI or in those with CKD secondary to an episode of AKI influencing physical function. This includes the decision to initiate extracorporeal RRT and the mode of RRT, the degree of oedema, the grade of uraemia or anaemia and the occurrence of electrolyte disturbances. Burdens of RRT in relation to daily function also include surgery for vascular or peritoneal access placement and their potential surgical complications such as infection or bleeding. In addition very high rates of primary maturation failure of the arteriovenous fistula are observed in older patients leading to high rates of rehospitalisation [20].

Older patients are at a high risk for modest to severely impaired renal function at hospital discharge after AKI [21]. Besides advanced age, further risk factors associated with AKI survivors progressing to CKD include decreased baseline GFR, severity of AKI, diabetes mellitus and a low concentration of serum albumin. In this regard, a study in elderly patients with CKD requiring haemodialysis focussing on nondisease-specific outcomes such as mobility and self-care found that only 5 % had no functional impairment of any type and at least half the subjects were dependent for at least one of the 'core' activities of daily living (walking, transferring, bathing, dressing) [17]. Of interest, a marked decrease in functional status has been noted in the period surrounding RRT initiation [14]. On one hand, this suggests that the deficits observed are not simply due to uraemia or other electrolyte disturbances but that it is worth considering the impact of RRT-associated factors, such as fatigue, dizziness, and decreased time for physical activity [14]. In both the RRT and non-RRT populations, other important factors such as polypharmacy and poor baseline mobility due to other comorbidities are likely to also play a role [17, 22].

Critically ill patients with impaired renal function, in particular those being on continuous RRT (CRRT), frequently experience fluid and electrolyte disturbances due to a loss of minerals, vitamins, amino acids and trace elements leading to serious consequences. The development of hypophosphatemia due to an enormous removal by CRRT is associated with muscular weakness, confusion, respiratory failure and arrhythmias [23]. Thus plasma phosphorus concentrations in critically ill patients should be monitored and maintained within normal range [23]. In addition hypomagnesemia is a vital but underdiagnosed electrolyte abnormality in critically ill patients and is associated with increased rate of mortality [24]. Symptoms include hyperexcitability, dizziness, muscle cramps, and weakness as well as fatigue. Independent of the development of acute renal function loss or the need for CRRT, the presence of hypomagnesemia is common among older subjects and mainly associated with malnutrition, diabetes mellitus or the use of diuretics or proton pump inhibitors. Normal serum magnesium level should be targeted.

In addition, 75 % of dialysis patients aged 60 years or above met criteria for frailty [25]. Falls are one of the markers of frailty and are likely to contribute to functional decline and the need for hospitalisation [26]. The reasons why patients with impaired renal function are more likely to fall are multifactorial and include those relating to the predisposing cause of a patient's kidney disease, those relating to loss of kidney function itself (e.g. anaemia, uraemia, electrolyte disturbances) and those relating to the treatment (e.g. polypharmacy, RRT-associated hypotension or arrhythmias).

8.4 Cognitive Function

'Cognition' is conventionally defined as 'the act or process of knowing' [27]; this broad term comprises a number of higher mental processes, including those involved in information retention and recall, organisation, problem solving, focussing and shifting of attention, and language use and comprehension [28].

The only study addressing cognitive function in patients with AKI investigated the potential association between cognition and subsequent mortality [29]. This study found in 439 patients surviving AKI who were treated with RRT (age, 36 % 60–74 years; 13 % ≥ 75 years) that lower cognition at 60 days after start of RRT was associated with higher 1-year mortality.

The Assessment, Serial Evaluation and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) study plans to prospectively enrol a cohort of 1,100 adult AKI patients as well as a cohort of matched hospitalised patients without AKI [30]. Participants will be followed for up to 4 years and will undergo serial evaluation, including collection of data on lifestyle behaviours, quality of life and functional status, cognitive function, receipt of therapies, and renal and cardiovascular events [30].

Given the lack of data assessing cognition during and after AKI, the next paragraph uses analogies to CKD patients, a high-risk population for the development of AKI.

Between 16 and 38 % of patients with ESRD and between 30 and 55 % of those aged 75 years or above meet criteria for cognitive impairment [31]. Cognitive impairment is associated with an increased risk of mortality, prolonged hospitalisation, withdrawal from RRT, a greater utilisation of health care resources and decreased quality of life [31, 32]. It is also likely to have major impact on adherence with instructions relating to medication or dietary modifications and on decision-making for both immediate care (e.g. pre-emptive vascular access, choice of dialysis modality) and those regarding future management, including end-of-life decisions [31]. A recent meta-analysis concluded that CKD was a significant and independent risk factor for the development of cognitive decline [33]. Independent of age, there appears to be a graded relationship between eGFR and the prevalence of cognitive impairment [33]. In more than 850 community-dwelling older adults without dementia (mean age 81), it has been demonstrated that a lower eGFR at baseline is associated with a greater rate of cognitive decline after 3 years, with the same effect as being 3 years older at baseline [34].

Vascular risk factors such as hypertension and diabetes as well as nonvascular 'nephrogenic' risk factors and treatment-related factors are likely to contribute substantially towards the cognitive dysfunction seen in this patient group.

Managing cognitive impairment in older patients with AKI or chronic renal function loss requires early recognition and appropriate investigation, before management of the condition itself. Early recognition can be achieved by cognitive impairment screening using brief assessments such as the clock-drawing task or the Mini-Cog test. Once identified, patients should have a full history (including a collateral history from a relative or caregiver), examination and investigations to exclude potentially reversible causes of their cognitive impairment, namely, structural head imaging (usually CT or MRI) and a serum dementia screen (B12, folate, TFT) [28, 32]. Delirium, depression and RRT-dependent causes also need to be excluded.

Systematic cognitive testing before RRT initiation and periodically thereafter may be warranted.

8.5 Nutrition

Nutritional status is a major prognostic factor in patients with AKI affecting length of stay in hospital, complication rates and mortality [35]. However, how to provide nutrition to patients with AKI, particularly older individuals, has not yet been studied in clinical trials.

In the general population, ageing is associated with weight loss and changes in body composition, in particular a decline in muscle mass and strength (sarcopenia) and an (initial) increase in fat mass [36, 37].

Evaluation of nutritional status in (older) patients with AKI is difficult, due to the presence of acute illness, pre-existing poor nutritional status, loss of muscle mass, acceleration in muscle protein catabolism (e.g. due to sepsis, trauma, surgery or chemotherapy), alterations in body water distribution (with the presence of oedema and fluid overload), electrolyte disturbances and the increased urea generation [38–40].

Nutrient requirements for patients with AKI are highly heterogeneous, depending on underlying acute and chronic comorbidities, catabolic rate, metabolic derangements and the presence of RRT (mode, filter surface area, blood/dialysate/substitute flow). However, the main goals of nutritional support in patients with AKI are the same as those for critically ill patients having normal renal function: (1) to ensure the delivery of adequate amounts of nutrients, (2) to prevent protein-energy wasting, (3) to promote wound healing and tissue reparation and (4) to support immune system function and reduce mortality [38].

8.5.1 Glucose

Acute kidney injury is characterised by an insulin-resistant state leading to hyperglycaemia.

In more than 6,000 critically ill patients (mean age 60), intensive glucose control was associated with moderate and severe hypoglycaemia, both of which were

associated with an increased risk of death (RR1.41–2.1) [41]. The association exhibits a dose–response relationship; however, data cannot prove a causal relationship [41].

8.5.2 Lipid Metabolism

Lipid abnormalities and related clinical consequences are well described in patients with CKD.

There is also evidence that in patients with AKI, derangements of lipid metabolism including an increase in plasma triglycerides, very low-density lipoproteins and low-density lipoprotein as well as a reduction in serum cholesterol and high-density lipoprotein occur, most likely related to impaired lipolysis [38, 42].

8.5.3 Proteins

Metabolic disturbances specific to AKI can exacerbate the catabolism of critical illness. Catabolic factors in AKI include insulin resistance, reduced glucogenesis, metabolic acidosis, release of inflammatory mediators, depletion of antioxidative substances, secretion of catabolic hormones and several more leading to protein breakdown. Data available indicate that there is no metabolic advantage for a protein restriction in AKI and that moderate increases in protein intake improve nitrogen balance without increasing urea generation [43].

8.5.4 Micronutrients (Trace Elements, Vitamins, Amino Acids)

The dose of micronutrients which should be administered to patients with AKI is unknown. However, serum levels of water-soluble vitamins, amino acids and trace elements are generally low in patients with AKI especially in those on extracorporeal continuous RRT. The effect of RRT on nutritional status will be described in Chap. 7.

Acute kidney injury is characterised by an inflammatory response in the kidney and oxidative stress. Recent experimental data point towards a possible role for some pharmaco-nutrients with anti-inflammatory effects (glutamine and omega-3 fatty acids), in the prevention of renal function deterioration and in enhancing renal function recovery after an episode of AKI [38, 44–46]. However, randomised controlled trials investigating patient-related outcomes after supplementation are missing.

In the absence of controlled evidence, it would seem reasonable to provide at least the recommended daily allowance (RDA) of vitamins, trace elements and minerals adjusted for estimated losses during RRT.

For CKD, several studies have confirmed that malnutrition is common in affected patients and worsens with age, in particular in haemodialysis patients [47, 48]. This is partly due to metabolic factors, but the impact of social factors should not be overlooked. This is demonstrated by nutritional data from the BOLDE study which has shown that that lower nutritional intake in older patients on dialysis was influenced by fewer social networks, lower subjective physical quality of life, increased postcode deprivation score and the presence of possible depression [14]. Counteracting the conditions that promote malnutrition is challenging for older people with ESRD especially in view of their limited intakes. The haemodialysis study (HEMO) showed that the standardised calorie and protein intakes in patients aged 65 years and over are lower than in those younger than 50 years, and are substantially lower than recommended [49]. In addition nutritional intakes, meal frequency and appetite were compromised on dialysis compared to non-dialysis days [50].

8.6 The 'AKI Card'

A suggestion for improving management of (older) patients with acute-on-chronic and chronic-through-acute kidney injury may be equipping patients with an 'AKI card' – similar to the 'hypertension pass' – and, although the evidence in this regard may be sparse, such 'AKI card' could probably help to facilitate improved patient management.

For patients after an episode of AKI, the card could include information on possible cause of AKI, grade (RIFLE/AKIN class) and duration of AKI as well as the grade of recovery (eGFR before and after AKI). In addition, in patients with CKD, who are at higher risk to develop AKI, the card could include information on the last serum creatinine concentration/eGFR value, CKD risk factors and procedures performed (e.g. cardiac surgery, contrast-media administration). Also, information on permitted and not advisable medications (e.g. NSAID) and an indication of drug dosing according to renal function may be included. A written recommendation to the patient for a timely appointment with the nephrology outpatient department for regular checkups might also be part of the card.

8.7 Summary

The principal determinants of quality of life, as rated by the older person, are the value of being independent and being in control of one's own life [51]. This can be challenging when managing older patients with or after an episode of acute kidney injury (AKI), particularly in those requiring acute renal replacement therapy or developing end-stage renal disease secondary to AKI. Not only are features of ageing, such as physical and cognitive impairment, more common because of the

associated comorbidities, but also the rate of deterioration can be exacerbated by renal replacement therapy. Managing cognitive impairment in older patients with AKI or chronic renal function loss requires early recognition and appropriate investigation, before management of the condition itself.

Multidisciplinary strategies and the development of an 'AKI card' could help to reduce long-term morbidity and mortality in older patients with AKI after hospital discharge.

References

1. Chao CT, Wu VC, Lai CF, NSARF Group (2012) Advanced age affects the outcome-predictive power of RIFLE classification in geriatric patients with acute kidney injury. Kidney Int 82:920–927
2. Coca SG (2010) Acute kidney injury in elderly persons. Am J Kidney Dis 56:122–131
3. Schmitt R, Coca S, Kanbay M, Tinetti ME, Cantley LG, Parikh CR (2008) Recovery of kidney function after acute kidney injury in the elderly: a systematic review and meta-analysis. Am J Kidney Dis 52:262–271
4. Grams ME, Estrella MM, Coresh J, Brower RG, Liu KD (2011) National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. Fluid balance, diuretic use, and mortality in acute kidney injury. Clin J Am Soc Nephrol 6:966–973
5. Hofhuis JG, van Stel HF, Schrijvers AJ, Rommes JH, Spronk PE (2013) The effect of acute kidney injury on long-term health-related quality of life: a prospective follow-up study. Crit Care 17:R17
6. Maynard SE, Whittle J, Chelluri L, Arnold R (2003) Quality of life and dialysis decisions in critically ill patients with acute renal failure. Intensive Care Med 29:1589–1593
7. Ahlstrom A, Tallgren M, Peltonen S, Rasanen P, Pettila V (2005) Survival and quality of life of patients requiring acute renal replacement therapy. Intensive Care Med 31:1222–1228
8. Delannoy B, Floccard B, Thiolliere F et al (2009) Six-month outcome in acute kidney injury requiring renal replacement therapy in the ICU: a multicentre prospective study. Intensive Care Med 35:1907–1915
9. Abelha FJ, Botelho M, Fernandes V, Barros H (2009) Outcome and quality of life of patients with acute kidney injury after major surgery. Nefrologia 29:404–414
10. Morsch C, Thomé FS, Balbinotto A, Guimarães JF, Barros EG (2011) Health-related quality of life and dialysis dependence in critically ill patient survivors of acute kidney injury. Ren Fail 33:949–956
11. Johansen KL, Smith MW, Unruh ML et al; VA/NIH Acute Renal Failure Trial Network (2010) Predictors of health utility among 60-day survivors of acute kidney injury in the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network Study. Clin J Am Soc Nephrol 5:1366–1372
12. Van Berendoncks AM, Elseviers MM, Lins RL, SHARF Study Group (2010) Outcome of acute kidney injury with different treatment options: long-term follow-up. Clin J Am Soc Nephrol 5:1755–1762
13. Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473–483
14. Brown EA, Johansson L, Farrington K et al (2010) Broadening Options for Long-term Dialysis for the Elderly (BOLDE): differences in quality of life on peritoneal dialysis compared to haemodialysis for older patients. Nephrol Dial Transplant 25:3755–3763
15. Kurella Tamura M, Covinsky KE, Chertow GM, Yaffe K, Landefeld CS, McCulloch CE (2009) Functional status of elderly adults before and after initiation of dialysis. N Engl J Med 361:1539–1547

16. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J (1998) Importance of functional measures in predicting mortality among older hospitalized patients. JAMA 279: 1187–1193
17. Cook WL, Jassal SV (2008) Functional dependencies among the elderly on hemodialysis. Kidney Int 73:1289–1295
18. Carey EC, Walter LC, Lindquist K, Covinsky KE (2004) Development and validation of a functional morbidity index to predict mortality in community-dwelling elders. J Gen Intern Med 19:1027–1033
19. Bowling CB, Muntner P (2012) Epidemiology of chronic kidney disease among older adults: a focus on the oldest old. J Gerontol A Biol Sci Med Sci 67:1379–1386
20. Monroy-Cuadros M, Yilmaz S, Salazar-Bañuelos A, Doig C (2012) Independent prediction factors for primary patency loss in arteriovenous grafts within six months. J Vasc Access 13: 29–35
21. Fortrie G, Stads S, de Geus HR, Groeneveld AB, Zietse R, Betjes MG (2013) Determinants of renal function at hospital discharge of patients treated with renal replacement therapy in the intensive care unit. J Crit Care 28:126–132
22. Schneider V, Lévesque LE, Zhang B, Hutchinson T, Brophy JM (2006) Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: a population-based, nested case–control analysis. Am J Epidemiol 164:881–889
23. Lee JW (2010) Fluid and electrolyte disturbances in critically ill patients. Electrolyte Blood Press 8:72–81
24. Limaye CS, Londhey VA, Nadkart MY, Borges NE (2011) Hypomagnesemia in critically ill medical patients. J Assoc Physicians India 59:19–22
25. Brown EA, Johansson L (2011) Epidemiology and management of end-stage renal disease in the elderly. Nat Rev Nephrol 7:591–598
26. Cook WL, Tomlinson G, Donaldson M et al (2006) Falls and fall-related injuries in older dialysis patients. Clin J Am Soc Nephrol 1:1197–1204
27. http://www.merriam-webster.com/dictionary/cognition. Accessed 30 Dec 2012
28. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/symptoms/cognitive-dysfunction/index.aspx. Accessed 30 Dec 2012
29. Joyce VR, Smith MW, Johansen KL et al; Veteran Affairs/National Institutes of Health Acute Renal Failure Trial Network (2012) Health-related quality of life as a predictor of mortality among survivors of AKI. Clin J Am Soc Nephrol 7:1063–1070
30. Go AS, Parikh CR, Ikizler TA; Assessment Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury Study Investigators (2010) The assessment, serial evaluation, and subsequent sequelae of acute kidney injury (ASSESS-AKI) study: design and methods. BMC Nephrol 11:22
31. Kurella Tamura M, Yaffe K (2011) Dementia and cognitive impairment in ESRD: diagnostic and therapeutic strategies. Kidney Int 79:14–22
32. Madero M, Gul A, Sarnak MJ (2008) Cognitive function in chronic kidney disease. Semin Dial 21:29–37
33. Etgen T, Chonchol M, Förstl H, Sander D (2012) Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis. Am J Nephrol 35:474–482
34. Buchman AS, Tanne D, Boyle PA, Shah RC, Leurgans SE, Bennett DA (2009) Kidney function is associated with the rate of cognitive decline in the elderly. Neurology 73:920–927
35. Fiaccadori E, Lombardi M, Leonardi S, Rotelli CF, Tortorella G, Borghetti A (1999) Prevalence and clinical outcome associated with preexisting malnutrition in acute renal failure: a prospective cohort study. J Am Soc Nephrol 10:581–593
36. Goodpaster BH, Park SW, Harris TB et al (2006) The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci 61:1059–1064
37. Cornoni-Huntley JC, Harris TB, Everett DF et al (1991) An overview of body-weight of older persons, including the impact on mortality – the National-Health and Nutrition Examination Survey. 1. Epidemiologic follow-up-study. J Clin Epidemiol 44:743–753

38. Fiaccadori E, Parenti E, Maggiore U (2008) Nutritional support in acute kidney injury. J Nephrol 21:645–656
39. Fouque D, Kalantar-Zadeh K, Kopple J et al (2008) A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int 73:391–398
40. Workeneh BT, Rondon-Berrios H, Zhang L et al (2006) Development of a diagnostic method for detecting increased muscle protein degradation in patients with catabolic conditions. J Am Soc Nephrol 17:3233–3239
41. NICE-SUGAR Study Investigators, Finfer S, Liu B et al (2012) Hypoglycemia and risk of death in critically ill patients. N Engl J Med 367:1108–1118
42. Druml W, Laggner A, Widhalm K, Kleinberger G, Lenz K (1983) Lipid metabolism in acute renal failure. Kidney Int Suppl 16:S139–S142
43. Krenitsky K, Rosner MH (2011) Nutritional support for patients with acute kidney injury: how much protein is enough or too much? In: Parrish CR (ed) Practical gastroenterology. Nutrition issues in gastroenterology, vol 96. Vivian Mahl (Publ.), NY, USA. pp 28–42
44. Peng ZY, Zhou F, Wang HZ et al (2013) The anti-oxidant effects are not the main mechanism for glutamine's protective effects on acute kidney injury in mice. Eur J Pharmacol 705:11–19
45. Hu YM, Pai MH, Yeh CL, Hou YC, Yeh SL (2012) Glutamine administration ameliorates sepsis-induced kidney injury by downregulating the high-mobility group box protein-1-mediated pathway in mice. Am J Physiol Renal Physiol 302:F150–F158
46. Hong S, Lu Y (2013) Omega-3 fatty acid-derived resolvins and protectins in inflammation resolution and leukocyte functions: targeting novel lipid mediator pathways in mitigation of acute kidney injury. Front Immunol 4:13
47. Aparicio M, Cano N, Chauveau P et al (1999) Nutritional status of haemodialysis patients: a French national cooperative study. French Study Group for Nutrition in Dialysis. Nephrol Dial Transplant 14:1679–1686
48. Cianciaruso B, Brunori G, Traverso G et al (1995) Nutritional status in the elderly patient with uraemia. Nephrol Dial Transplant 10(Suppl 6):65–68
49. Burrowes JD, Cockram DB, Dwyer JT et al (2002) Cross-sectional relationship between dietary protein and energy intake, nutritional status, functional status, and comorbidity in older versus younger hemodialysis patients. J Ren Nutr 12:87–95
50. Burrowes JD, Larive B, Cockram DB et al (2003) Hemodialysis (HEMO) Study Group. Effects of dietary intake, appetite, and eating habits on dialysis and non-dialysis treatment days in hemodialysis patients: cross-sectional results from the HEMO study. J Ren Nutr 13: 191–198
51. Ahmed S, Addicott C, Qureshi M, Pendleton N, Clague JE, Horan MA (1999) Opinions of elderly people on treatment for end-stage renal disease. Gerontology 45:156–159

Chapter 9
End-of-Life Decision Making in Older Patients with Acute Kidney Injury and End-Stage Renal Disease: Ethical Perspectives

Sana R. Akbar and Rebecca J. Schmidt

Key Messages

1. End-of-life discussions with elderly patients facing the prospect of dialysis are challenging and require acknowledgement of and respect for ethical principles.
2. This chapter explores the ethical aspects of end-of-life decision making in the elderly patient facing major life transitions and decisions related to (1) the pursuit of dialysis because of AKI, (2) the consideration of dialysis when there is progression of CKD to ESRD, and (3) the continuation or withdrawal of dialysis in patients whose clinical status has changed since the initiation of dialysis.

9.1 Introduction

End-of-life care requires the comprehensive assessment and management of a broad array of clinical, emotional, social, and spiritual issues. Establishing whether a patient has decision-making capacity, identifying their individual goals of care, and determining the availability of advance directives are all integral to the decision-making process through which the clinician must guide patients and their families. Once the ethically appropriate options have been identified, discussion of the burdens and benefits of treatments, their impact on quality of life, presentation of survival statistics, and information specific to each patient's prognosis can be addressed. Meanwhile, for some patients the option to withhold or withdraw treatment may be an appropriate consideration depending on their overall clinical condition.

S.R. Akbar, MD (✉) • R.J. Schmidt, DO, FACP, FASN
WVU Section of Nephrology, Department of Medicine/Nephrology,
West Virginia University School of Medicine, 1 Medical Center Drive,
Morgantown, WV 26506, USA
e-mail: sakbar@hsc.wvu.edu; rschmidt@hsc.wvu.edu

M. Haase, A. Haase-Fielitz (eds.), *Managing Renal Injury in the Elderly Patient*,
DOI 10.1007/978-3-642-39947-3_9,

Acute kidney injury occurs in as many as 36–67 % of intensive care unit (ICU) patients [1, 2] and is frequently caused by acute tubular necrosis from septic shock. Approximately 5 % of ICU patients with AKI require renal replacement therapy. For patients with AKI requiring dialysis, observational studies have indicated that the hospital mortality rate for AKI in the ICU exceeds 50 % [1–6]. Nephrologists commonly see patients at the brink of requiring dialysis to sustain life for whom a decision about pursuing dialysis is urgently needed. This decision cannot be made in haste. The nephrologist needs to carefully assess the whole situation including the medical necessity for dialysis and the ethical issues that may arise pertaining to the patients care prior to making the decision. Longer life spans consequent to medical and technological advancements have led to an increased prevalence of chronic illnesses and an ever growing elderly population. The proportion of patients older than 65 years of age starting dialysis has increased by nearly 10 % annually, representing an overall increase of 57 % between 1996 and 2003 [4, 7, 8]. Older CKD patients have unique needs by virtue of advanced age, high prevalence of comorbid conditions, slower progression of renal disease, and reduced survival [9]. Nephrologists will continue to see an increasing number of elderly patients with renal disease progression facing the decision to undergo or forgo dialysis. Discussions dealing with end-of-life issues require knowledge of a patient's prognosis, a patient's values, and an understanding of related ethical principles considered in the context of known medical facts. The decision to start dialysis is a personal one that is directed by one's medical condition and motivated by the desire to prolong life and by the willingness to accept the inherent risks and burdens.

Acceleration of comorbid illnesses in patients on dialysis may be subtle and not immediately life threatening but emotionally and physically debilitating for patients and their families, in addition to being ethically challenging for their nephrology caregiver. Continuing dialysis in patients with clinical deterioration poses an additional ethical dilemma for nephrology caregivers especially when patients lose mental acuity and depend on family members or in some cases, state-appointed guardians for decision making. Such a change in clinical status warrants review of the benefits dialysis is providing to a given patient and should trigger conversation about the option of withdrawal.

Three clinical scenarios are presented (Boxes 9.1, 9.2, and 9.3), which illustrate common challenges facing elderly patients with acute and chronic kidney failure:

1. A patient with AKI and the medical indication for dialysis
2. A patient with progressive CKD who is contemplating dialysis
3. A patient with ESRD on chronic dialysis for whom continuation of dialysis may not be warranted due to changes in their clinical presentation

Ethical questions common to end-of-life discussions for older patients are listed in Table 9.1.

Box 9.1 Acute Kidney Injury in Older Patients
A 78-year-old female with medical history of dementia, congestive heart failure, chronic kidney disease stage III, and severe peripheral vascular disease presented with complaints of nausea, decreased oral intake, vomiting, chest pain radiating to the back, and decreased urine output. Upon arrival, she was found to have a BUN/Cr of 98/8.65, potassium of 6.3 mg/dL, phosphorus of 7.5 mg/dL, pH of 7.20, and BP of 210/111 mmHg. She was unable to provide history due to alteration of her mental status. Her baseline creatinine is 1.2 mg/dL (eGFR of 45 mL/min 2 months ago). She underwent an emergent CT with intravenous contrast to rule out aortic dissection. Upon further history gathering, it was learned that the patient had been prescribed ibuprofen which she had been taking on a routine basis for arthritic pains. Prior to admission, the patient was residing in an assisted living facility and was unable to perform all her activities of daily living.

Box 9.2. Advanced Chronic Kidney Disease in Older Patients
A 76-year-old male with a history of diabetes, hypertension, new onset dementia, coronary artery disease, and history of two percutaneous angioplasties with stents, congestive heart failure (ejection fraction of 25 %), and CKD stage IV presents for his routine nephrology follow-up appointment and is found to have progressive worsening of his renal parameters. The patient currently resides in an assisted care living facility and is unable to perform his activities of daily living.

Box 9.3 Older Patient with End-Stage Renal Disease
A 86-year-old female with a history of hypertension, diabetes, coronary artery disease, congestive heart failure, and ESRD (on hemodialysis for 5 years) has been admitted to the hospital multiple times in the last 3 months for various reasons such as volume overload, hypertensive emergency, gastrointestinal bleed, and the management of a nonhealing ulcer on the foot. The patient is now admitted with anemia (Hb of 7.0 g/dL) and septic shock. During the prolonged hospital stay, she is treated with multiple antibiotics and undergoes an amputation of the tarsal metatarsal joint initially followed by a below-the- knee amputation. She also develops a stage 3 sacral decubitus ulcer. Workup of her anemia led to the findings of a colonic mass which on biopsy was found to be adenocarcinoma. On imaging, she was also noted to have significant lymphadenopathy and hepatic metastases. Patient at baseline is totally dependent on others for all activities of daily living.

Table 9.1 Ethical questions

1. What are the patient's wishes?
2. Does the patient have decision-making capacity?
3. What are the options for the patient?
4. Is the nephrologist obligated to dialyze every patient?
5. Should a patient's age be a factor in whether or not to offer dialysis?
6. How will dialysis or continued dialysis impact the patient's quality of life?
7. What impact will forgoing, undergoing, or continuing dialysis have on the patient?
8. Will proceeding or continuing with dialysis cause harm to the patient?

9.2 Acute Kidney Injury in Older Patients

The case of an older patient developing AKI is presented in Box 9.1. Relevant ethical questions are listed in Table 9.1. Presuming the presence of decision-making capacity, the patient's wishes must be determined. When patients have decision-making capacity, their wishes are of paramount importance ethically and legally. In this case, the patient's mentation is altered and she is not capable of making decisions; hence her wishes are unknown. In these situations, an advance directive or discussion with the medical power of attorney (MPOA) or health proxy is important.

The nephrologist must assess the overall clinical scenario and determine the medically appropriate options. At this time there is no specific age that limits nephrologists from offering dialysis to patients; however, the individual patient context must be considered when determining the options and plans for care. Dialysis is associated with risks and burdens, and the patient should be informed of these in full, particularly in the context of her clinical comorbidities and presentation. Options for this patient include (1) to forgo dialysis, (2) to begin dialysis, and (3) to undergo a time-limited trial of dialysis. The latter option may be particularly helpful to patients whose desire for long-term dialysis is minimal and for whom the prognosis of recovery from AKI is unclear. The ethical principles of patient autonomy, beneficence, and non-maleficence play a fundamental role in the decision-making process of cases such as this one.

The decision to begin dialysis in the setting of AKI must be tempered by evolving literature that suggests that renal replacement therapy may not improve survival or quality of life for many elderly patients. Calculators that use patient age, comorbidities, and serum albumin level to evaluate prognosis and predict outcomes are available for patients with advanced renal disease; similar methods for estimating renal prognosis in patients with AKI have not been verified. A lifetime commitment to dialysis at this time may not provide a survival benefit for this patient by virtue of her significant comorbid conditions, nor does it guarantee improvement in her quality of life. Hence, offering a time-limited trial of dialysis may provide the patient time to possibly regain sufficient mentation and alertness to make a decision about long-term dialysis. Uncertainty as to the permanency of her need for dialysis makes the decision-making process difficult.

The consequences of initiating dialysis on the patients' quality of life and the medical, emotional, and spiritual implications of forgoing dialysis must be considered. In this elderly patient, the presence of multiple comorbidities and moderately severe CKD at baseline suggests long-term dialysis might be confounded by the need for hospitalizations and complications of chronic illnesses. It is difficult to predict the likelihood for renal recovery such that dialysis is no longer needed in cases such as this with AKI.

The impact of forgoing dialysis on quality and quantity of life must also be considered. Although dialysis is a means to sustain life, it may also be viewed as a forestalling of death. Dialysis may be taxing on the patient due to her frailty and comorbidities. Forgoing dialysis would require continued medical management of the complications of AKI as well as preparing both the patient and the family for the dying process and its management. Thus, clarification that quantity of survival may not be accompanied by quality of life is an important part of this conversation.

Should the patient choose to forgo dialysis and if medical management for AKI is not successful and renal function does not recover, comfort measures should become the focus of care. Review of literature suggests that 8–22 % of critically ill patients suffering an episode of severe AKI fail to recover kidney function during hospitalization and need to be discharged on chronic dialysis [10–12]. Data also suggests that renal recovery after AKI is approximately 28 % less likely to occur when the patient is older than 65 years of age [10]. In a systematic review and meta-analysis performed by Schmitt et al., it was reported that elderly patients tend to do better in terms of renal recovery when treated with continuous renal replacement therapy rather than intermittent renal replacement therapy [12]. Patients who choose a time-limited trial of dialysis have the opportunity to overcome the acute illness and watch for renal recovery. Should a time-limited trial be pursued, a specific time frame and parameters to assess for propriety of continued dialysis should be determined at onset.

9.3 Advanced Chronic Kidney Disease in Older Patients

The case of an older patient with advanced CKD is presented in Box 9.2. The relevant ethical questions that need to be addressed are listed in Table 9.1. Careful assessment of the patient's overall condition including comorbidities, functional status, decision-making capacity, nutritional status, and support system is important when deciding whether to offer dialysis or not. In the midst of this decision-making process, the ethical principles of patient autonomy, beneficence, non-maleficence, and professional integrity are key. In a patient with near end-stage congestive heart failure, performing frequent renal replacement therapy may pose more risks of hemodynamic collapse associated with cardiac stress than benefits from uremic toxin removal. In addition, the presence of dementia limits the patient's understanding of their surroundings as well as their ability to cooperate with staff performing the dialysis procedure. Thus, in this case, the presence of significant cardiac disease,

dementia, and inability to perform activities of daily living suggests that the patient will do poorly on dialysis. Moreover, CKD patients in this age group often succumb to cardiac disease and do not live long enough to progress to ESRD. Review of literature suggests that congestive heart failure is associated with poor outcomes in patients who are on maintenance hemodialysis. Numerous small cohorts demonstrate high death rates in patients who have heart failure and are on hemodialysis [13, 14].

Given the presence of severe congestive heart failure, new onset dementia, and ongoing dependence on others to take care of him, dialysis may prolong but not improve this patients' quality of life, though the latter will be a function of each patient's own set of personal values. As in the previous illustration, the nephrologist is obligated to clearly inform the patient and his legal medical decision makers about risks and benefits of dialysis so that the patient can make an informed decision about the potential impact of dialysis. Many nephrologists would not consider it professionally ethical to offer dialysis to a patient with these clinical conditions who is unable to understand the magnitude of the decision at hand and for whom dialysis is not likely to provide physical or emotional comfort.

Appropriate options for the patient may be to withhold dialysis and pursue medical management for his ESRD in this case scenario. An additional option might be a time-limited trial of dialysis to see if the patient can tolerate the burdens of dialysis. In the Renal Physicians Association guidelines titled "Clinical Practice Guideline for Shared Decision Making in the Appropriate Initiation and Withdrawal from Dialysis," shared decision making is emphasized as the preferred model for medical decision making, and it addresses the ethical need to fully inform patients about the risks and benefits of treatments, as well as the need to ensure that patients' values and preferences play a prominent role. In this patient, the act of withholding dialysis values the ethical principles of beneficence and non-maleficence while proceeding with dialysis may subject the patient to adverse effects such as hemodynamic compromise and potentially be more harmful.

Once a patient is determined to have decision-making capacity, the risks, benefits, and various options along with survival data should be presented to the patient, from which the patient can make an informed decision. In patients with early onset dementia and thus limited or no decision-making capacity, an advance directive will be instructive and the medical power of attorney or proxy, if known, is needed for contextual perspective. In this case, because the patient has early onset dementia and is dependent on others to help perform his activities of daily living, the addition of dialysis could become burdensome and detract from the patient's quality of life; the need to be transported multiple times a week to and from the dialysis unit and the potential for frequent hospitalizations are just some of the potential burdens this patient will face. The patient's inability to comprehend the basis for these burdens is an additional consideration.

In this case, the potential for doing harm with the pursuit of dialysis may outweigh its potential benefits. Initiating dialysis may prolong his life, but it is not

likely to decrease the degree of his dependence on others for assistance with mobility and transport. Progression of his dementia may preclude him from understanding the need to sit quietly during the dialysis treatment, subjecting him to the risk of bleeding should the needles be displaced. The loss of dignity associated with complete dependency is also a consideration when the impact of dialysis on both the quality and quantity of life is balanced.

9.4 Older Patients with End-Stage Renal Disease

Patients with ESRD, such as the patient described in Box 9.3, especially those of older age, often face deterioration in their health status, and changing circumstances may impact their clinical tolerance for the dialysis procedure as well as their emotional desire to continue. The relevant ethical questions that need to be addressed while continuing care for such a patient are listed in Table 9.1.

In this case, it would be appropriate and ethically responsible to talk to the family and patient about withdrawing dialysis. The patient's current status, the frequency of recent multiple hospital readmissions, multiple surgeries, and ongoing poor clinical prognosis are important factors to consider when reviewing a patient's plan of care and may prompt the nephrologist to suggest that this patient withdraw from treatment. While considering the various options available to the patient, the ethical principles of beneficence, non-maleficence, and professional integrity are revealed.

The recent diagnosis of a life-limiting condition such as an advanced malignancy worsens the overall poor prognosis and, if present at the outset of dialysis, may have prompted a different decision. Data suggests that there is a high incidence of malignancy in ESRD patients, and most patients are able to tolerate chemotherapy with ongoing dialysis; there are limited reports on the prognosis of ESRD patients diagnosed with non-treatable cancers or those with significant metastatic disease. In cases such as this where the patient has multiple comorbidities and a diagnosis of a life-limiting condition, the continuation of dialysis is not likely to improve survival or quality of life. This patient may benefit from a palliative comfort-focused care approach without dialysis while in the comfort of their home with family at the bedside. There is no mention of incompetency or dementia in this patient; thus, presentation of the available clinical data pertinent to their medical condition, treatment options, and prognosis along with a discussion to clarify the patient's wishes for end-of-life care is in order.

Even if amenable to treatment, the presence of an advanced malignancy is likely to reduce not only survival but also the patient's functional capacity. The nephrologist is ethically obligated to discuss the impact of continued dialysis in the context of the patient's changing medical status. The patient may decide that the burdens associated with dialysis are no longer acceptable and that withdrawal and supportive care are desired.

9.5 Specific Attention

The term "technical imperative" implies an obligation on the part of the nephrologist to dialyze a patient solely based on medical indications without consideration of the risks and benefits specific to the individual patient. Such an approach not only negates the principle of professional integrity but also jeopardizes the principles of beneficence and non-maleficence. Health economists report that this type of behavior increases cost without necessarily improving patient quality of life. In the United States, dialysis patients live approximately one-third as long as non-dialysis patients of the same age and gender. The 5-year probability of survival for all ESRD patients on dialysis is 39 %, and for those over the age of 65, it is only 18 % [15]. These poor survival statistics highlight the need for comprehensive and repeated assessment of patient clinical, emotional, and social status.

Patient autonomy, along with the principles of beneficence and non-maleficence, are of utmost importance. First and foremost is determination of decision-making capacity. This will help to determine if the patient or an assigned MPOA will be making the decisions of medical care. It is the ethical and professional obligation of the nephrologist to explain in detail the patient's condition pertaining to the renal function and the impact of the current ongoing medical issues so that an informed decision can be made. If the patient is deemed to have decision-making capacity, the nephrologist may discuss the available options with the patient; however, if the patient lacks decision-making capacity, then it is essential to seek out the MPOA and review the patients' advance directives, if available.

The next major issue to determine is the nature of the patients' wishes. Did the patient have advance directives? There may be circumstances when the wishes of the family are counter to those expressed by the patients' advance directives. In these situations the nephrologist must consider the views of the assigned MPOA and provide data to clarify potential misunderstandings, and do what is best for the patient while respecting the patients' wishes. If conflict in decision making persists, a palliative or ethics consultation should be obtained.

As older patients approach stage IV vs V CKD, discussions clarifying the progression of CKD are important so that expectations can be clarified, values determined, and goals for care set. Shared decision-making involves discussions pertaining to (1) the various dialysis modalities available, (2) withholding dialysis while continuing medical management, (3) time-limited trials of dialysis, and (4) the possibility that if dialysis is begun, withdrawal may become appropriate. The pros and cons related to each option must be explained to the patient and/or MPOA with supporting data in a clear, empathetic, and concise manner so that an informed decision can be made.

Prior to the initiation of dialysis, elderly patients must be informed about its modest benefit in their age group and the possibility of conservative therapy that does not involve dialysis. Patients must be informed that they may undergo functional decline during the first year of dialysis and it is likely that they may not experience any functional improvement with dialysis. Optimal care requires clear, informed conversations about the patient's goals, given his or her disease and the

ability of the various treatments to achieve these goals. Numerous studies comparing dialysis with active medical management without dialysis do not uniformly show a survival benefit with dialysis [9, 16–21], and the survival advantage, when present, may come with substantial burdens that negatively affect quality of life in elderly patients. In addition to the occurrence of adverse physical symptoms while on dialysis, many patients experience multiple interdialytic symptoms, the aggregate of which can cause difficulty with activities of daily living [9, 20].

Although dialysis can be seen as a means to sustain life, for patients suffering from the associated personal indignities, dialysis may be viewed as merely a forestalling of death. Such a "clinically sustained existence," as characterized by Kaufman et al. [22], fosters a sense of prolongation without progress. This dilemma highlights the need to emphasize to the patient and the MPOA that quality of life does not always equate with quantity of survival. Research studies have clearly identified a population of CKD patients for whom the prognosis is particularly poor. This population has been found to include patients with two or more of the following characteristics: (1) elderly (defined as patients who are age 75 years and older), (2) patients with high comorbidity scores (e.g., modified Charlson Comorbidity Index score of 8 or greater), (3) marked functional impairment (e.g., Karnofsky Performance Status Scale score of less than 40), and (4) severe chronic malnutrition (e.g., serum albumin level less than 2.5 g/dL). Patients in this population should be clearly informed that dialysis may not confer a survival advantage or improve functional status over medical management without dialysis and that dialysis entails significant burdens that may detract from their quality of life [16]. Prognostic calculators and other tools are available to estimate survival in CKD patients facing dialysis [23]. For patients meeting two or more of the criteria mentioned above, dialysis may entail an unnecessary medicalization of death.

Professional integrity allows the nephrologist to refrain from offering dialysis to patients for whom the risks of dialysis are likely to outweigh the benefits. Many older CKD patients have a lower likelihood of living long enough to require dialysis [9] and are more likely to die of cardiovascular disease than develop ESRD [9, 24]. Further, patients choosing dialysis over maximum conservative management survived three times as long but had higher hospitalization rates, spent more time in the hospital, and were less likely to die at home [9, 12, 18]. For patients deciding to forgo dialysis, goals of medical management and those measures available to assure that the patient is comfortable and pain- free are important factors to present to the patient and their families.

Changes in clinical status warrant evaluation of the continued propriety of dialysis and consideration for withdrawal. Comorbidities such as congestive heart failure, peripheral vascular disease, coronary artery disease, chronic obstructive pulmonary disease, and cancer confer increased risk of death on dialysis and predict poorer survival. A high prevalence of frailty has been noted among older patients on dialysis and is associated with a threefold higher risk of death [9]. Marked functional impairment, a history of falls, and the inability to transfer are indicators of poor prognosis along with hypo-albuminemia in patients on dialysis [9, 20]. The

surprise question, "Would I be surprised if this patient died in the next 12 months?" has been recognized as a simple and reliable method of identifying sicker incident dialysis patients at high risk for early death [9, 25]. Cohen et al. found five variables to be independently associated with early mortality: older age, dementia, hypoalbuminemia, diagnosis of peripheral vascular occlusive disease, and a negative response to the surprise question. An integrated 6-month prognostic tool using these variables has been validated for prevalent hemodialysis population [9, 26]. These tools must be used in order to give the patient and their family information about prognosis and survival so they can make an informed decision.

9.6 Summary

End-of-life discussions and decision making in the elderly patients with acute kidney injury, progressive CKD, or those patients with ESRD require an age-attuned approach, and as with all such conversations, the clinician must be clear and empathetic in their communication. Discussions and decisions with regard to dialysis in the elderly patients with advanced CKD should ideally begin long before symptoms occur and dialysis is needed. Determination of decision-making capacity and determining a health care surrogate are of utmost importance. Shared decision making is the preferred model for medical decision making because it addresses the ethical need to fully inform patients about the risks and benefits of the various treatment options, as well as the need to ensure that the patients' values and preferences play a prominent role [16]. Informed consent for older patients should include presentation of risks, benefits, and burdens associated with dialysis, age-specific estimates of prognosis with and without dialysis, and potential for loss of independence and decline in functional status with initiation of dialysis [9].

End-of-life discussions require acknowledgement and respect for the ethical principles of beneficence, non-maleficence, and professional integrity. Decisions must be based on the preferences of the patient as expressed by an advance directive or assigned decision maker. In situations where the patient lacks decision-making capacity, review of the patients' wishes as documented in the advance directives or known to the medical power of attorney (MPOA) is required. When faced with situations where the wishes of the MPOA are not the wishes of the patient or are in conflict with the advance directives, the nephrologist and the MPOA must come to a consensus that supports the patients' wishes.

Dialysis may not be the best option for some patients, and the decision to pursue dialysis will be influenced by clinical, psychosocial, and emotional factors contributing to current status as well as prognosis. Contextual issues facing patients with AKI, progressive CKD, or those on dialysis with deteriorating clinical status constitute important ethical considerations when making decisions to start or stop dialysis. The care of our elderly patients requires an age-attuned approach, and nephrologists are uniquely poised to ensure that whatever decisions are made, comfort is provided and the dying process is peaceful and dignified.

References

1. Moss AH (2012) To dialyze or not: the patient with metastatic cancer and AKI in the Intensive Care Unit. Clin J Am Soc Nephrol 10:1–6
2. Dennen P, Douglas IS, Anderson R (2010) Acute kidney injury in the intensive care unit: an update and primer for the intensivist. Crit Care Med 38:261–275
3. Ostermann M, Chang RWS (2007) Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med 35:1837–1843
4. Uchino S, Kellum JA, Bellomo R et al (2005) Beginning and ending supportive therapy for the kidney (BEST Kidney) Investigators: acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294:813–818
5. Mehta RL, Pascual MT, Soroko S et al (2004) Program to improve care in acute renal disease: spectrum of acute renal failure in the intensive care unit: the PICARD experience. Kidney Int 66:613–1621
6. Liaño F, Felipe C, Tenorio MT et al (2007) Long-term outcome of acute tubular necrosis: a contribution to its natural history. Kidney Int 71:679–686
7. Kurella M, Covinsky KE, Collins AJ, Chertow GM (2007) Octogenarians and nonagenarians starting dialysis in the United States. Ann Intern Med 146:177–183
8. Renal Data System US (2009) USRDS 2009 Annual Data Report: atlas of end-stage renal disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda
9. Schmidt R (2012) Informing our elders about dialysis: is an age-attuned approach warranted? Clin J Am Soc Nephrol 7:1–7
10. Bagshaw SM (2008) Short- and long-term survival after acute kidney injury. Nephrol Dial Transplant 23:2126–2128
11. Bagshaw SM, Laupland KB, Doig CJ et al (2005) Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care 9:R700–R709
12. Schmitt R, Coca S, Kanbay M, Tinetti ME, Cantley LG, Parikh CR (2008) Recovery of kidney function after acute kidney injury in the elderly: a systemic review and meta-analysis. Am J Kidney Dis 52:262–271
13. Banerjee D, Ma JZ, Collins AJ, Herzog CA (2007) Long-term survival of incident hemodialysis patients who are hospitalized for congestive heart failure, pulmonary edema, or fluid overload. Clin J Am Soc Nephrol 2:1186–1190
14. Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Parfrey PS (1995) Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. Kidney Int 47:884–890
15. Issen AC (2011) Difficult decisions about care and treatment in end-stage renal disease. www.hospiceofthecomforter.org. pp 4–9.
16. Renal Physicians Association (2010) Clinical practice guideline for shared decision making in the appropriate initiation and withdrawal from dialysis, 2nd edn. Renal Physicians Association, Rockville
17. Smith C, Da-Silva-Gane M, Chandna S, Warwicker P, Greenwood R, Farrington K (2003) Choosing not to dialyse: evaluation of planned non-dialytic management in a cohort of patients with end-stage renal failure. Nephron Clin Pract 95:c40–c46
18. Carson RC, Juszczak M, Davenport A, Burns A (2009) Is maximum conservative management an equivalent treatment option to dialysis for elderly patients with significant comorbid disease? Clin J Am Soc Nephrol 4:1611–1619
19. Wong CF, McCarthy M, Howse ML, Williams PS (2007) Factors affecting survival in advanced chronic kidney disease patients who choose not to receive dialysis. Ren Fail 29:653–659
20. Ellam T, El-Kossi M, Prasanth KC, El-Nahas M, Khwaja A (2009) Conservatively managed patients with stage 5 chronic kidney disease-outcomes from a single center experience. QIM 102:547–554

21. Murtagh FE, Marsh JE, Donohoe P, Ekbal NJ, Sheerin NS, Harris FE (2007) Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. Nephrol Dial Transplant 22:1955–1962
22. Kaufman SR, Shim JK, Russ AJ (2004) Revisiting the biomedicalization of aging: clinical trends and ethical challenges. Gerontologist 44:731–738
23. Touchcalc. www.touchcalc.com. Accessed 8 Feb 2013
24. Dalrymple LS, Katz R, Kestenbaum B et al (2011) Chronic kidney disease and the risk of end-stage renal disease versus death. J Gen Intern Med 26:379–385
25. Moss AH, Ganjoo J, Sharma S et al (2008) Utility of the "surprise" question to identify dialysis patients with high mortality. Clin J Am Soc Nephrol 3:1379–1384
26. Cohen LM, Ruthazer R, Moss AH, Germain MJ (2010) Predicting six-month mortality for patients who are on maintenance hemodialysis. Clin J Am Soc Nephrol 5:72–79

Index

M. Haase, A. Haase-Fielitz (eds.), *Managing Renal Injury in the Elderly Patient*,
DOI 10.1007/978-3-642-39947-3, © Springer-Verlag Berlin Heidelberg 2014