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Our paper 20 years later: from acute renal failure to acute kidney injury—the metamorphosis of a syndrome

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Abstract *Purpose:* More than 20 years ago we reported an analysis of a case series of elderly critically ill patients with acute kidney injury (AKI)—then termed acute renal failure. At that time, AKI was regarded as a "simple" complication, but has since undergone a fundamental change and actually has become one of the central syndromes in the critically ill patient. *Methods:* We have analyzed elderly patients above 65 years of age with an AKI defined as serum creatinine above 3 mg/dl corresponding to modern KDIGO stage 3, most of them requiring renal replacement therapy (RRT). Using an extremely complete data set the diagnosis differentiated the underlying disease entity, the dominant cause of AKI, acute and chronic risk factors (comorbidities). Special aspects such as severity of disease, early AKI at admission versus late AKI, early versus later start of RRT, AKI not treated by RRT in spite of indication for RRT, various measures of short-term and long-term prognosis, renal outcome, patients dying with resolved AKI, and causes of death were evaluated. *Results:* Crude mortality was 61 % which corresponds to modern studies with gross variation among the different subgroups. Age per se was not a determinant of survival either within the group of elderly patients or as compared to younger age groups. Despite an increase in mean age and disease severity during the observation period prognosis improved. A total of 17 % of patients developed a chronic kidney disease. Long-term survival as compared to the general population was low. *Conclusions:* A look back at the last two decades illustrates a remarkable evolution or rather metamorphosis of a syndrome. AKI has evolved as a central syndrome in intensive care patients, a systemic disease process associated with multiple systemic sequels and extra-renal organ injury and exerting a pronounced effect on the course of disease and short- and long-term prognosis not only of the patient but also of the kidney. Moreover, the "non-renal-naïve" elderly patient with multiple comorbidities has become the most frequent ICU patient in industrialized nations.

Keywords Acute kidney injury · Systemic consequences · Elderly · Prognosis

Introduction

More than 20 years ago we reported an analysis of a series of 243 cases of acute kidney injury (AKI)—at that time termed acute renal failure (ARF)—in elderly critically ill patients treated at one institution over a period of 15 years [1]. At the time of our study AKI was seen as a "simple" complication which was regarded as not so important because it was assumed that renal function can be supported more or less indefinitely by renal replacement modalities. An often heard statement was "no patient dies from but only with ARF".

In this investigation specifically we have differentiated the underlying disease entities, the dominant causes of AKI, acute and chronic risk factors (comorbidities). Additional aspects such as severity of disease, early AKI at admission versus late AKI, early versus later start of renal replacement therapy (RRT), AKI not treated by RRT in spite of indication for RRT, various measures of short-term and long-term prognosis, renal outcome, patients dying with resolved AKI, and causes of death were evaluated.

In the time span since this study AKI as a syndrome has undergone a fundamental evolution or rather metamorphosis which is not only illustrated by the transition of the terminology from ARF to AKI. The new term AKI and a worldwide accepted definition and staging reflect the complex continuum of renal dysfunction ranging from a risk situation to overt injury, from functional and volume-dependent stages to tubular damage.

With the central role of the kidney in maintaining the "milieu interieur" and orchestrating organ interactions, any renal dysfunction exerts a profound effect on all physiologic functions of the body and organ systems [2]. Thereby AKI fundamentally modifies the course of disease and outcome of both the patient and the kidney, not only during ICU stay but also in the long term. Actually, AKI presents the strongest denominator of outcome in the ICU patient and for long-term survival [3, 4].

Incidence of both of community- and hospital/ICU-acquired AKI is still dramatically rising and AKI has actually become an important cause of chronic kidney disease (CKD) [5].

Using a complete data set of all patients, our study has anticipated several of these developments. Such an anniversary provides the opportunity to look back at a fundamental change in the perception of an organ dysfunction which actually has become a central syndrome in the ICU patient and illustrates in many aspects the complex evolution of intensive care medicine in general and helps to define main targets for future research and advances [6].

The elderly: not "renal-naïve" patients and no longer a neglected "subgroup" of patients

Our study was focussed on "elderly" patients at an age above 65 years. The mean age of ICU patients at the time of our investigation was below 60 years and thus, we thought to analyze a specific subgroup of patients. However, the mean age of ICU patients in general has constantly increased during the last few decades and in industrialized countries is about 69 years and soon will surpass the 70-years threshold.

A further aspect presents the fact that the risk of developing AKI increases with age so a higher portion of the older patients have AKI (Fig. 1). Thus, at least two-thirds of patients with AKI are now already within this advanced age group and, in contrast to the widely held perception by many intensivists of the "geriatric patient", the elderly are no longer an earlier often neglected if not disregarded subgroup of patients but represent the majority, i.e., the "standard" patient in the ICU of the twenty-first century. This demographic aspect has fundamentally changed many facets and objectives of modern intensive care medicine in general.

Textbooks usually give us the impression that any insult leading to AKI hits an otherwise healthy person or at least a person with an otherwise healthy kidney. With the mean age of AKI patients being above 65 years of age, patients are not "renal naïve" but have—besides the advanced age with its physiologic alterations of kidney structure and function—many comorbidities and underlying disease processes, like heart failure, hypertension, or type 2 diabetes mellitus with an associated chronic impairment of renal function [7]. The pattern of comorbidities is a major denominator for outcome and also for long-term sequels of AKI and also the potential transition to CKD [5, 8].

So any acute insult hits an already chronically compromised organ function. In this context—as compared to younger patient groups—a minor insult will lead to renal dysfunction. It is well recognized that the elderly is at a much higher risk for developing AKI and even moderate degrees of volume depletion can cause profound impairment of renal function [9, 10].

Age is an important cause of the dramatic worldwide increase in the incidence of AKI (Fig. 1). Moreover, acute-on-chronic renal injury has become a leading cause of AKI which exerts a major impact on short- and long-term prognosis [11, 12].

Definition and diagnosis of AKI

At the time of our investigation there was no internationally accepted definition and staging of AKI available.

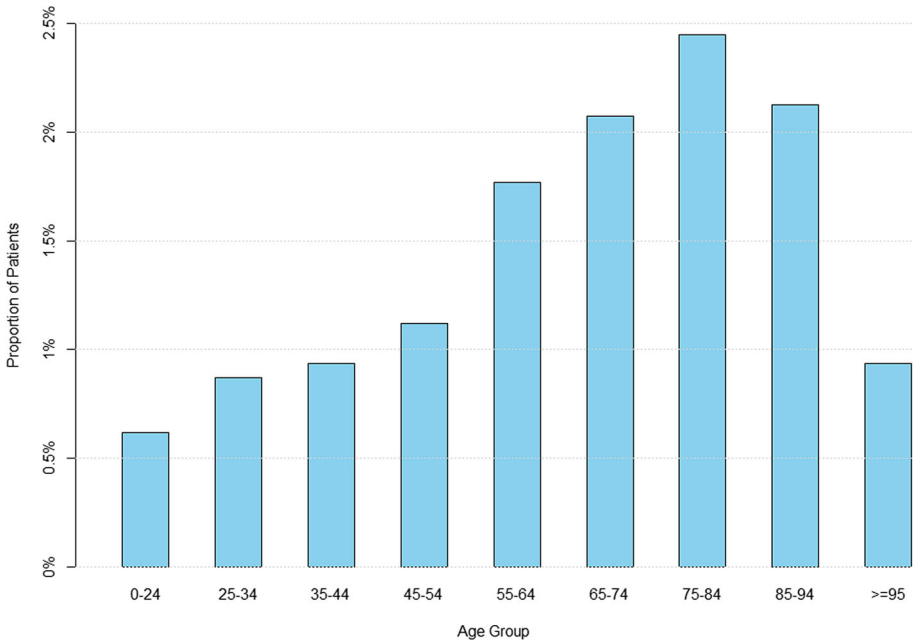

Fig. 1 Age of patients with the admission diagnosis of acute kidney injury stage 3 admitted to Austrian intensive care units during the years 2010–2014. $N = 2576$ patients. Data provided by Metnitz P. and Metnitz B., 2015; ASDI (Austrian Society for Documentation and Quality Assurance in Intensive Care)

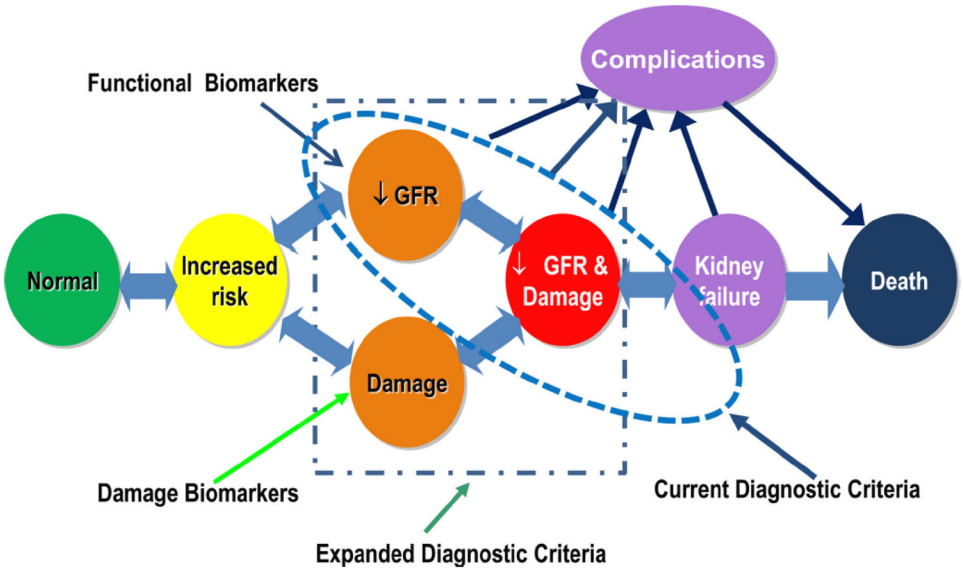

Fig. 2 Conceptual model of acute kidney injury. Kidney damage and changes in function may precede each other or occur concurrently. The availability of specific biomarkers permits recognition of kidney damage separately from changes in kidney function (from Ref. [14], with permission)

In the meanwhile the term "acute renal failure" was abandoned and replaced by the term "acute kidney injury" reflecting the fact that renal dysfunction not only represents the final stage organ dysfunction, the "failure", but includes a complex pattern of impairment of various aspects of the complex renal function, of perfusion, glomerular filtration, and tubular injury/interstitial inflammation, which may occur in a temporal sequence but also concurrently (Fig. 2) [13].

For the future this means that creatinine alone with all its shortcomings certainly cannot serve as a sufficient tool to differentiate these various patterns, the heterogeneity of renal dysfunction. Biomarkers reflecting injury in various anatomical structures of the kidney might enable an early and more differentiated diagnosis of AKI (Fig. 2) [13–16].

In the meanwhile in several international consensus conferences definitions and staging of AKI were elaborated, which recently were unified in the generally accepted KDIGO definition [17, 18].

By 2004 we had shown that even small changes in serum creatinine in the early course of disease are associated with an increased mortality, a finding confirmed in many subsequent studies [19, 20]. Small changes of serum creatinine and/or of kidney function can serve as a "Cassandra" foreseeing an ongoing but often

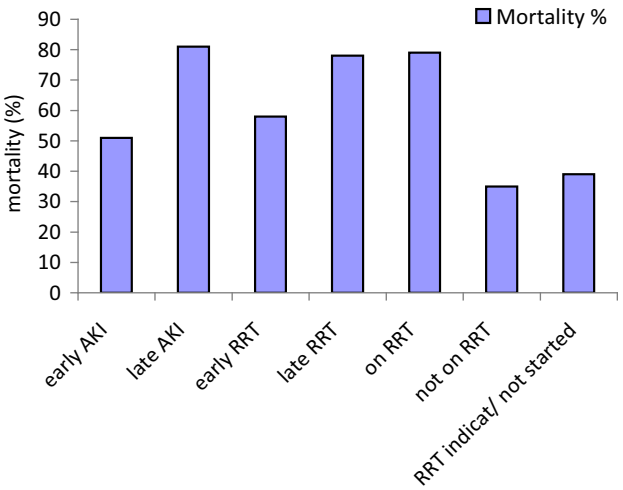

Fig. 3 Mortality of various groups of patients with AKI, early versus late, early beginning versus late beginning of RRT, patients on RRT versus patients not on RRT, and those patients fulfilling RRT criteria but not being treated. Data adapted from Ref. [1]

unrecognized pathology which negatively affects prognosis. Thus, a small rise of more than 0.3 mg/dl was included in the classification of AKI as a risk stage (stage 1 or R) [17, 19, 20].

This crucial prognostic importance of early stages of renal dysfunction has stimulated the creation of electronic alert systems and also of clinical outreach services to warn treating physicians of an impeding renal problem and to enable an early start of preventive interventions [21, 22].

Preceding these developments AKI was arbitrarily defined in our study as a rise of serum creatinine above 3.0 mg/dl, a doubling of serum creatinine in the presence of CKD and/or the need of RRT. Terminal rises in creatinine (within 48 h of death) were excluded from analysis.

The large majority of cases in our study quite accurately correspond to a stage 3 AKI in the modern KDIGO definition.

Indications for RRT were standardized and grouped into five entities, at that time mainly "renal makers", such as BUN concentration, plasma potassium, and volume overload.

The spectrum of AKI in the ICU: pathophysiology and etiology

Using an extremely complete database and analysis of every single patient by one of us, we used a sophisticated approach in the description of the patients and in the definition of subgroups of AKI.

Traditionally, pathophysiology of AKI is grouped into ischemic and nephrotoxic entities. When designing our study 25 years ago, we were already convinced that this simplistic view does not mirror the clinical situation of AKI in the critically ill patient. The evolution of AKI is much more complex and includes a broad pattern of hemodynamic alterations, cellular failure, toxic effects, coagulation activation, inflammatory mechanisms, and several other factors. This often neglected clinical complexity is also the main reason why—"lost in translation"—none of the many therapeutic interventions for the prevention/therapy of AKI which were often effective in the isolated model of animal studies were ineffective in the human situation and could not be transferred into clinical routine.

Moreover, in clinical routine it is often assumed that AKI is usually caused by a single insult. This traditional view again has to be challenged with monocausal AKI being rather an exception in the ICU patient. Despite the fact that the kidney is an extremely sensitive organ, a single insult is usually not sufficient to cause renal breakdown [23].

This is illustrated by the example of cardiopulmonary resuscitation. Despite the often extended no-flow periods, more severe stages of AKI (AKI 3 and requirement for RRT) affected less than 5 % of patients at our institution [24]. Higher rates of use of RRT such as reported in recent papers are mainly due to differences in case mixes (mean age of patients, comorbidities) and an expansion of "non-renal" indications for RRT [25, 26].

So usually it is a combination, a pattern of insults leading to renal dysfunction. Hemodynamic alterations, coagulation activation, mechanical ventilation using higher PEEP levels, nephrotoxic mediations and contrast media, an inflammatory state, or heart failure all may contribute concertedly to renal dysfunction.

In our study we have tried to address these various factors and in our analysis we have separately differentiated the underlying disease process (15 entities), the main causes of AKI (16 items) (Table 1), acute risk factors (10 items), and chronic risk factors/comorbidities (6 items, Table 2). This sophisticated analysis is still unique in 25 years and we are convinced that such an approach is appropriate in describing such a multifaceted syndrome as AKI in the critically ill patient.

The five leading main causes of AKI according to this analysis were cardiac causes (congestive heart failure), perioperative AKI, exsiccosis/hyperosmolar states (as often seen in the elderly), sepsis, and hypovolemic shock (Table 1). Interstitial nephritis, an often underdiagnosed and neglected cause of AKI in the ICU, was present in 8 % of cases.

Subgroups of AKI patients: definition and outcome

In the analysis of prognosis we evaluated various aspects which gained interest or even became standard later on. Some of those actually have not been investigated since (Fig. 3).

Table 1 Acute renal failure in the elderly: Main causes of ARF (data from Ref. [1])

Cause	*N*	Mortality (%)
Cardiac failure/cardiogenic shock	40	70
Post surgery (excl. hypovolemia)	31	61
Exsiccosis/hyperosmolar syndrome	29	28
Septicemia/septic shock	27	70
Hypovolemic shock (hemorrhage etc.)	26	65
Peritonitis/pancreatitis	21	67
Acute interstitial nephritis	16	50
Cardiopulmonary resuscitation	13	69
Shock (other causes)	9	100
Renoparenchymal and renovasclar	8	86
Medicaments/contrast media	6	0
Hemolysis/myolysis	4	75
Parainfectious (pneumonia etc.)	4	75
Postrenal	4	25
Hepatic failure	2	100
Hypercalcemia	2	0
Total	242	61

Table 2 Acute and chronic risk factors for the development of acute renal failure in the elderly (data from Ref. [1])

	N	%
Chronic risk factors		
Chronic renal impairment	79	33
Hypertension	69	29
Diabetes type I + II	37	15
Chronic cardiac failure	33	14
Chronic hepatic disease	19	8
Chronic pyelonephritis	9	4
Acute risk factors		
Hypovolemia	91	37
Septicemia	42	17
Artificial ventilation	38	16
Hypotension (non-hypovolemic)	26	11
Peritonitis	25	10
Diffuse intravascular coagulation	14	6
Electrolyte derangements	9	4
Acute interstitial nephritis	9	4
Medicaments/contrast media	8	3
Hemolysis/myolysis	5	2

Total mortality was 61 % which parallels findings from later investigations [27, 28]. Mortality of elderly patient aged over 65 years (61 %) was not higher than in younger age groups at our institution at this time, being 57 % in patients below 18 years and 59 % in patients aged 18–65 years. Nor could we see an effect of age on mortality within this group of patients itself of over 64 to over 80 years of age.

In the general ICU population age correlates with mortality. We hypothesize that in the elderly, because of age-associated alterations in renal function and the many comorbidities, a comparably minor insult will lead to AKI and this less severe disease constellation may mask any negative impact of age on outcome [10].

Severity of AKI (stages according to plasma creatinine, BUN, diuresis, and need for RRT) was associated with outcome. Of patients on RRT only 29 % survived.

At this time we have already separated AKI at admission ("early AKI") and AKI developing in the ICU ("unit acquired AKI") with a large difference in prognosis (49 vs. 19 % survival). Even in the presence of conflicting studies we are convinced that if AKI is developing within the ICU setting and an optimal therapeutic environment is available, prognosis is worse than if AKI is present on admission [29].

Patients in whom RRT was initiated early, i.e., at a BUN level below 90 mg/dl, had a better prognosis than those in whom RRT was started late (BUN above 120 mg/dl), a finding which was confirmed in many subsequent cohort studies [30]. The timing of the optimal start of RRT in AKI at present is actually one of the most controversial subjects in the care of patients with AKI and several ongoing RCTs hopefully will help to clarify this problem.

But we also assessed the evolution of renal function during the ICU stay. Actually, several of the patients died in spite of the fact that AKI was resolved. This important fraction of patients (in our investigations 19 % of non-survivors) is missed in most investigations.

In addition, we specifically assessed a group of patients who fulfilled the criteria for initiating RRT but who had not been dialyzed. This included a fraction of patients in whom therapy was withheld because of the terminal state of the patients (15 % of AKI patients, all of whom died), but also a group of patients in whom the treating physicians did not initiate RRT because they assumed that the patient could be better supported by conservative measures (12 % of patients). This group of subjects—which has received much interest in recent years—had a much better prognosis (61 % survival rate) [31, 32]. With the current recommendations of "early RRT" the identification of such patients who actually will not profit from an early initiation presents an important aspect for the management of AKI in the future [32]. Overall mortality of the patients with AKI decreased from above 80 % at the beginning to about 50% at the end of the observation period of 15 years. This was seen in spite of the fact that severity of disease (as assessed by APACHE score, the rate of septicemia and of mechanical ventilation) and the mean age of patients have increased. Whether prognosis of AKI in fact has improved during the last decades remains to be a subject of controversy.

In our investigation we also assessed "renal prognosis". At this time it was a dogma that when a patient survives the disease leading to AKI the kidney will completely recover. In our investigation 35 % of surviving patient showed a transition of AKI into a chronic kidney problem. On the other hand only 4 % of patients remained RRT dependent.

In the meanwhile it is generally accepted that AKI increases the risk of CKD [5, 33]. With the dramatic increase in the incidence of AKI, AKI has actually

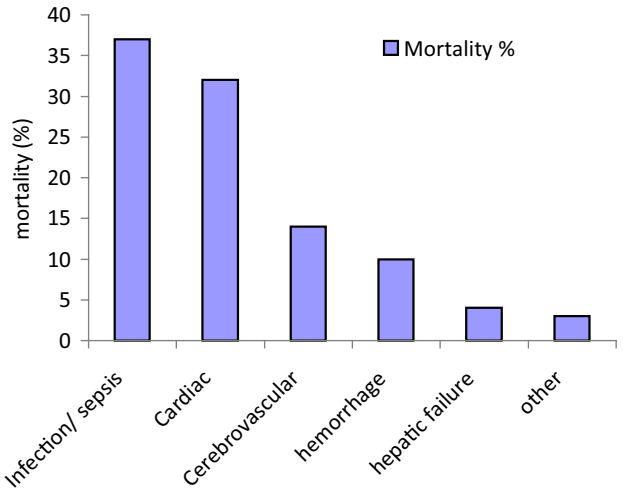

Fig. 4 Causes of death in elderly patients with acute kidney injury. Data adapted from Ref. [1]

become an important cause of CKD and the "epidemic" of end-stage renal disease [34].

Causes of death were differentiated into seven groups (severe infection/sepsis, cardiac causes, cerebral/cerebrovascular causes, hemolysis/haemorrhage, hepatic failure and other causes (Fig. 4)). Sepsis and septic shock were the leading causes of death, which points to the profound impact of AKI on immuncompetence. Not a single death could be attributed to conventional complications of AKI (such as hyperkalemia, volume overload etc.) (which actually are associated with a much better prognosis [35]). Severe infections as the leading causes of death in patients with AKI have been confirmed in various studies [36, 37].

We also analyzed long-term prognosis of the patients after being discharged from the hospital in comparison to the general Austrian population of the same age. We did not dare to publish these somewhat distressing results. This profound effect of AKI on long-term prognosis has been confirmed in many subsequent studies for several age groups [38–40]. This negative impact of AKI certainly is more prominent in the elderly with an already high "background" mortality rate.

AKI: the recognition as a systemic disease process

Even when at the time of our study "ARF" mostly was seen just as a "simple" complication, it was our conviction that acute kidney dysfunction causes a broad pattern of specific systemic consequences and complications.

Originally, our main interest was focused on the metabolic consequences of AKI where we described a series of specific and distinct alterations [41–44]. Even in our case series we evaluated metabolic aspects, such as insulin resistance and hyperglycemia and also hypertriglyceridemia but this information was—along with several other aspects—not included into the final publication.

In the meanwhile, it has become generally accepted that AKI "is more than a kidney disease", that AKI actually is a "pan-metabolic, pan-endocrine and pan-organ" problem, that AKI presents a systemic syndrome modulating any critical illness and course of disease, and exerting a pronounced effect on short- and long-term prognosis not only of the patient but also of the kidney [2, 45, 46]. This specific and independent effect of AKI on prognosis—the "attributable" mortality—we have later detailed and this finding again was confirmed in many subsequent investigations [28, 47].

Specifically, AKI plays a fundamental role in modulating and augmenting any inflammatory process and in addition is associated with a profound depression of immunocompetence. This includes the release of cytokines and inflammatory mediators, increase in oxidative stress, activation of various immune cells, neutrophil extravasation, generalized endothelial injury, increased vascular permeability, and tissue edema formation [2].

Within this context AKI also exerts profound effect on other organ systems, such as the lungs, the heart, liver, and brain. With this broad pattern of "distant organ injury" AKI nowadays is seen as a modifier, a "motor" of multiple organ dysfunction syndrome [2, 48].

The main causes of death in our series were infections, a situation which has not changed for 50 years (Fig. 4) [36]. These systemic effects and especially the impact of renal dysfunction on manifold immunologic functions of the kidney certainly present a main area of research for the future [49].

Ethical implications

In these years of intensive care medicine three decades ago it was questioned whether invasive and expensive therapies such as RRT are justified in such old critically ill patients. However, the last three decades have witnessed a fundamental change in the demography. The age group of 65 years and more are no longer a marginalized sector of the society. This group is not only a rapidly growing but also an increasingly important part of society, contributing essentially to the social life and culture of modern communities. This seminal demographic development also has fundamentally changed the practice of intensive care medicine. The elderly have become our main patient population with prognosis not being fundamentally different from other age groups.

Nobody would question nowadays that age per se should not be the justification to withhold any kind of therapy, reflecting the basic ethical principles of

beneficence and justice [40]. Relevant certainly, much more than age, are the physical and cognitive condition of the patient before ICU admission, such as frailty, the pattern of comorbidities, the potential reversibility of an acute intermittent complication leading to ICU admission, and the perspective to regain autonomy, functionality, and the pre-ICU-state. Decisions have to be based on a careful assessment of the individual situation of every single patient and care has also to be taken to avoid "overtreatment", therapeutic futility. These considerations are especially relevant for the decision to initiate RRT.

AKI: where is the future?

The fundamental importance of kidney function for maintaining fluid compartments of the body, electrolyte balance, blood pressure regulation, oxygen sensing, the complex metabolic and endocrine functions, and—more recently in focus—the essential immunologic functions render renal dysfunction a multifaceted systemic disease process [2]. Actually, AKI is not a "cute" kidney injury, but a systemic syndrome modulating any critical illness and the course of disease, exerting a pronounced effect on short- and long-term prognosis not only of the patient but also of the kidney.

Interestingly, epidemiological and clinical studies on AKI have been mainly generated by intensivists/ICU nephrologists and AKI was often neglected by the traditional nephrology community. With a sharp rise in incidence of both out-of-hospital (community-acquired) AKI [50] and AKI developing within the hospital (hospital-acquired) of about 10 % year [51] awareness of AKI among nephrologists has also caught up and nowadays AKI is perceived as one of the central syndromes of nephrology; and World Kidney Day 2013 has been dedicated to AKI [34, 52].

With the dramatic increase in incidence and the disproportionate resource utilization AKI has a significant impact on the heath care system in general with its intrinsic limitations of resources.

Despite the fact that patients are getting older and more severely ill, prognosis of AKI has somewhat improved during recent decades—as also illustrated by our study. Nevertheless, mortality remains distressingly and unacceptably high [53].

Thus, the leading topics for the future on one side are strategies for prevention of renal injury, and on the other side—when AKI has become manifest—therapeutic interventions, both pharmacological and extracorporeal, to mitigate or avoid the multiple systemic consequences and long-term sequels of renal dysfunction.

To this end early diagnosis of AKI including the discrimination of functional alterations and of impeding or manifest cellular injury by biomarkers, the identification of mechanisms of long-term consequences and mediators of chronic renal injury, and potential targets to stimulate renal regeneration are critical areas of research [54]. We have to learn more about non-renal consequences and distant organ injury and impact on immunologic functions and impairment of immunocompentence [49].

Moreover, mediators of "uremic memory"—the fact that even when AKI has fully reversed and renal function normalized, a resolved AKI affects the further course of life and long-term survival in a patient—should be identified [55].

Finally, it has become distressingly clear that the currently available RRT modalities, which are admittedly rather simple, actually at best can support isolated aspects of excretory renal dysfunction but not replace the multiple and sophisticated renal functions. Moreover, it is increasingly recognized that currently available RRT modalities are also associated with many and in part serious side effects. Among these much debated recently is the potential of intermittent hemodialysis to promote chronic renal injury [56].

Thus, for future developments it will be mandatory that extracorporeal treatment modalities are also improved so that these more appropriately can assist a broader spectrum of renal functions and more effectively deserve the term "replacement therapy".

Compliance with ethical standards

Conflicts of interest None of the authors has any conflict of interest concerning the content of this text.

References

1. Druml W, Lax F, Grimm G, Schneeweiss B, Lenz K, Laggner AN (1994) Acute renal failure in the elderly 1975–1990. Clin Nephrol 41:342–349
2. Druml W (2014) Systemic consequences of acute kidney injury. Curr Opin Crit Care 20:613–619
3. 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
4. Hobson CE, Yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ, Bihorac A (2009) Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. Circulation 119:2444–2453

5. Chawla LS, Eggers PW, Star RA, Kimmel PL (2014) Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 371:58–66
6. Citerio G, Bakker J, Bassetti M, Benoit D, Cecconi M, Curtis JR, Hernandez G, Herridge M, Jaber S, Joannidis M, Papazian L, Peters M, Singer P, Smith M, Soares M, Torres A, Vieillard-Baron A, Timsit JF, Azoulay E (2014) Year in review in Intensive Care Medicine 2013: I. Acute kidney injury, ultrasound, hemodynamics, cardiac arrest, transfusion, neurocritical care, and nutrition. Intensive Care Med 40:147–159
7. 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
8. Fortrie G, Stads S, Aarnoudse AJ, Zietse R, Betjes MG (2015) Long-term sequelae of severe acute kidney injury in the critically ill patient without comorbidity: a retrospective cohort study. PLoS One 10:e0121482
9. Coca SG (2010) Acute kidney injury in elderly persons. Am J Kidney Dis 56:122–131
10. Kane-Gill SL, Sileanu FE, Murugan R, Trietley GS, Handler SM, Kellum JA (2015) Risk factors for acute kidney injury in older adults with critical illness: a retrospective cohort study. Am J Kidney Dis 65:860–869
11. Hsu CY, Chertow GM, McCulloch CE, Fan D, Ordonez JD, Go AS (2009) Nonrecovery of kidney function and death after acute on chronic renal failure. Clin J Am Soc Nephrol 4:891–898
12. Wu VC, Huang TM, Lai CF, Shiao CC, Lin YF, Chu TS, Wu PC, Chao CT, Wang JY, Kao TW, Young GH, Tsai PR, Tsai HB, Wang CL, Wu MS, Chiang WC, Tsai IJ, Hu FC, Lin SL, Chen YM, Tsai TJ, Ko WJ, Wu KD (2011) Acute-on-chronic kidney injury at hospital discharge is associated with long-term dialysis and mortality. Kidney Int 80:1222–1230
13. Thomas ME, Blaine C, Dawnay A, Devonald MA, Ftouh S, Laing C, Latchem S, Lewington A, Milford DV, Ostermann M (2015) The definition of acute kidney injury and its use in practice. Kidney Int 87:62–73
14. Murray PT, Mehta RL, Shaw A, Ronco C, Endre Z, Kellum JA, Chawla LS, Cruz D, Ince C, Okusa MD (2014) Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th acute dialysis quality initiative consensus conference. Kidney Int 85:513–521
15. Schetz M, Gunst J, Van den Berghe G (2014) The impact of using estimated GFR versus creatinine clearance on the evaluation of recovery from acute kidney injury in the ICU. Intensive Care Med 40:1709–1717
16. Glassford NJ, Schneider AG, Xu S, Eastwood GM, Young H, Peck L, Venge P, Bellomo R (2013) The nature and discriminatory value of urinary neutrophil gelatinase-associated lipocalin in critically ill patients at risk of acute kidney injury. Intensive Care Med 39:1714–1724
17. 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
18. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, Metnitz PG (2009) Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med 35:1692–1702
19. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, Hiesmayr M (2004) Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol 15:1597–1605
20. Linder A, Fjell C, Levin A, Walley KR, Russell JA, Boyd JH (2014) Small acute increases in serum creatinine are associated with decreased long-term survival in the critically ill. Am J Respir Crit Care Med 189:1075–1081
21. Colpaert K, Hoste EA, Steurbaut K, Benoit D, Van Hoecke S, De Turck F, Decruyenaere J (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
22. Thomas ME, Sitch A, Baharani J, Dowswell G (2015) Earlier intervention for acute kidney injury: evaluation of an outreach service and a long-term follow-up. Nephrol Dial Transplant 30:239–244
23. Parekh DJ, Weinberg JM, Ercole B, Torkko KC, Hilton W, Bennett M, Devarajan P, Venkatachalam MA (2013) Tolerance of the human kidney to isolated controlled ischemia. J Am Soc Nephrol 24:506–517
24. Domanovits H, Schillinger M, Mullner M, Thoennissen J, Sterz F, Zeiner A, Druml W (2001) Acute renal failure after successful cardiopulmonary resuscitation. Intensive Care Med 27:1194–1199
25. Geri G, Guillemet L, Dumas F, Charpentier J, Antona M, Lemiale V, Bougouin W, Lamhaut L, Mira JP, Vinsonneau C, Cariou A (2015) Acute kidney injury after out-of-hospital cardiac arrest: risk factors and prognosis in a large cohort. Intensive Care Med 41:1273–1280
26. Tujjar O, Mineo G, Dell'Anna A, Poyatos-Robles B, Donadello K, Scolletta S, Vincent JL, Taccone FS (2015) Acute kidney injury after cardiac arrest. Crit Care 19:169
27. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294:813–818
28. Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, Le Gall JR, Druml W (2002) Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med 30:2051–2058
29. Guerin C, Girard R, Selli JM, Perdrix JP, Ayzac L (2000) Initial versus delayed acute renal failure in the intensive care unit. A multicenter prospective epidemiological study. Rhone-Alpes Area Study Group on acute renal failure. Am J Respir Crit Care Med 161:872–879
30. Karvellas CJ, Farhat MR, Sajjad I, Mogensen SS, Leung AA, Wald R, Bagshaw SM (2011) A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. Crit Care 15:R72
31. Bagshaw SM, Uchino S, Kellum JA, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten HM, Ronco C, Bellomo R (2013) Association between renal replacement therapy in critically ill patients with severe acute kidney injury and mortality. J Crit Care 28:1011–1018
32. Gaudry S, Ricard JD, Leclaire C, Rafat C, Messika J, Bedet A, Regard L, Hajage D, Dreyfuss D (2014) Acute kidney injury in critical care: experience of a conservative strategy. J Crit Care 29:1022–1027
33. Coca SG, Singanamala S, Parikh CR (2010) Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 81:442–448
34. Lewington AJ, Cerda J, Mehta RL (2013) Raising awareness of acute kidney injury: a global perspective of a silent killer. Kidney Int 84:457–467

35. Liborio A, Leite T, Neves F, Bezerra C (2015) AKI complications in critically ill patients: association with mortality rates and RRT. Clin J Am Soc Nephrol 10:21–28
36. Woodrow G, Turney JH (1992) Cause of death in acute renal failure. Nephrol Dial Transplant 7:230–234
37. Selby NM, Kolhe NV, McIntyre CW, Monaghan J, Lawson N, Elliott D, Packington R, Fluck RJ (2012) Defining the cause of death in hospitalised patients with acute kidney injury. PLoS One 7:e48580
38. Singbartl K, Kellum JA (2012) AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int 81:819–825
39. Horkan CM, Purtle SW, Mendu ML, Moromizato T, Gibbons FK, Christopher KB (2015) The association of acute kidney injury in the critically ill and postdischarge outcomes: a cohort study. Crit Care Med 43:354–364
40. Druml W (2005) Long term prognosis of patients with acute renal failure: is intensive care worth it? Intensive Care Med 31:1145–1147
41. Druml W, Fischer M, Sertl S, Schneeweiss B, Lenz K, Widhalm K (1992) Fat elimination in acute renal failure: long-chain vs medium-chain triglycerides. Am J Clin Nutr 55:468–472
42. Druml W, Burger U, Kleinberger G, Lenz K, Laggner A (1986) Elimination of amino acids in acute renal failure. Nephron 42:62–67
43. Metnitz GH, Fischer M, Bartens C, Steltzer H, Lang T, Druml W (2000) Impact of acute renal failure on antioxidant status in multiple organ failure. Acta Anaesthesiol Scand 44:236–240
44. Druml W, Schwarzenhofer M, Apsner R, Horl WH (1998) Fat-soluble vitamins in patients with acute renal failure. Miner Electrolyte Metab 24:220–226
45. Kelly KJ (2006) Acute renal failure: much more than a kidney disease. Semin Nephrol 26:105–113
46. Druml W (2004) Acute renal failure is not a "cute" renal failure! Intensive Care Med 30:1886–1890
47. Vaara ST, Pettila V, Kaukonen KM, Bendel S, Korhonen AM, Bellomo R, Reinikainen M (2014) The attributable mortality of acute kidney injury: a sequentially matched analysis*. Crit Care Med 42:878–885
48. Scheel PJ, Liu M, Rabb H (2008) Uremic lung: new insights into a forgotten condition. Kidney Int 74:849–851
49. Rogers NM, Ferenbach DA, Isenberg JS, Thomson AW, Hughes J (2014) Dendritic cells and macrophages in the kidney: a spectrum of good and evil. Nat Rev Nephrol 10:625–643
50. Hsu CY, McCulloch CE, Fan D, Ordonez JD, Chertow GM, Go AS (2007) Community-based incidence of acute renal failure. Kidney Int 72:208–212
51. Hsu RK, McCulloch CE, Dudley RA, Lo LJ, Hsu CY (2013) Temporal changes in incidence of dialysis-requiring AKI. J Am Soc Nephrol 24:37–42
52. Li PK, Burdmann EA, Mehta RL (2013) Acute kidney injury: global health alert. Kidney Int 83:372–376
53. Waikar SS, Curhan GC, Wald R, McCarthy EP, Chertow GM (2006) Declining mortality in patients with acute renal failure, 1988 to 2002. J Am Soc Nephrol 17:1143–1150
54. Ferenbach DA, Bonventre JV (2015) Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. Nat Rev Nephrol 11:264–276
55. Venkatachalam MA, Weinberg JM, Kriz W, Bidani AK (2015) Failed tubule recovery, AKI-CKD transition, and kidney disease progression. J Am Soc Nephrol. doi: 10.1681/ASN.2015010006
56. Schneider AG, Bellomo R, Bagshaw SM, Glassford NJ, Lo S, Jun M, Cass A, Gallagher M (2013) Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med 39:987–997