Continuing Medical Education

Acute Renal Failure of Nosocomial Origin

Mark Dominik Alscher, Christiane Erley, Martin K. Kuhlmann

Summary

Background: 10–20% of hospitalized patients develop acute kidney injury (AKI)/acute renal failure during their hospital stay. The mortality of nosocomial AKI is approximately 30%.

Methods: This review is based on relevant publications retrieved by a search in multiple databases (PubMed and Uptodate), archives, and pertinent medical journals.

Results: The most common causes of nosocomial AKI are volume depletion, sepsis, heart diseases, polytrauma, liver diseases, and drug toxicity. AKI can also be of postrenal (obstructive) origin, or a result of renal diseases including glomerulonephritis, vasculitis, tubulointerstitial nephritis, and cholesterol embolism. In about 13% of cases, nosocomial AKI develops on the basis of pre-existing chronic renal disease. Patients with AKI are at elevated risk of developing chronic renal disease and must be followed up appropriately after they are discharged from the hospital. Indispensable elements of the evaluation of nosocomial AKI include renal ultrasonography, the exclusion of postrenal obstruction, urine chemistry, and microbiological urinalysis. Potentially nephrotoxic drugs and those that impair renal hemodynamics must be avoided to the greatest possible extent in patients with acute renal damage. Hypotension must be avoided as well.

Conclusion: Early, specific nephrological diagnosis and treatment are important components of the management of nosocomial AKI, particularly because causally directed treatment is available for some of the conditions that underlie it.

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The average age of hospital inpatients has risen sharply in recent years, and with it the number and severity of comorbidities. Renal disease is no exception, and the increase in the incidence of acute kidney injury (AKI)/acute renal failure has been particularly prominent.

Learning goals

Our aim in writing this CME article was to provide a practically oriented synopsis of the very extensive literature on the detection and treatment of nosocomial AKI. After studying it, the reader should be:

- In a position to grasp the importance of nosocomial AKI
- Sensitive to this prognostically significant disease
- Able to recognize treatable forms of AKI and administer the appropriate treatment in cooperation with the nephrologist.

Acute kidney injury

The International Society of Nephrology (ISN) divides AKI into three stages according to functional parameters (Kidney Disease: Improving Global Outcomes [KDIGO]). The basis for diagnosis and classification of AKI is demonstration of an acute deterioration of kidney function with reference to a known or assumed baseline value. Assessment of kidney function is based on two simple parameters that can be determined inexpensively: (1) change in serum creatinine concentration and (2) the amount of urine produced in a defined period (*Table 1*) (1, 2). A 5% increase in creatinine predicts AKI with 75% sensitivity and 72% specificity (3).

The disadvantages of these parameters are (a) that only changes in excretory renal function are considered and (b) that deterioration in function is not registered until quite late, because the creatinine level does not climb above the normal range until kidney function has decreased by around 50% (2).

In contrast to AKI in the community setting, where usually no data are available for kidney function over

Diagnosis and classification

The basis for diagnosis and classification of AKI is demonstration of an acute deterioration of kidney function with reference to a known or assumed baseline value.

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TABLE 1

Definition and staging of acute kidney injury according to the AKIN criteria

Stage	Creatinine concentration	Urine output
1	1.5–1.9 × baseline or ≥ 0.3 mg/dL	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 × baseline	<0.5 mL/kg/h for >12 h
3	≥ 3.0 × baseline or ≥ 4 mg/dL or dialysis	<0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h

AKIN, Acute Kidney Injury Networks

FIGURE 1

	Risk	Stage of AKI		
		1	2	3
Discontinue nephrotoxic medications				
Stabilize volume and blood pressure				
Monitor hemodynamics				
Monitor serum creatinine level and urine output				
Avoid hyperglycemia				
Avoid contrast medium				
Noninvasive differential diagnostic procedures				
Consider invasive differential diagnostic procedures				
Adjust medication				
Consider intensive care unit/renal replacement				
No subclavian catheter				

How to proceed in acute kidney injury (AKI)

the preceding period, inpatients usually have their creatinine levels measured regularly, so nosocomial AKI is rapidly diagnosed.

Changes in the amount of urine can be detected by means of collection over a defined period, e.g., by means of temporary bladder catheterization. Body weight often increases in the course of AKI owing to edema.

A number of studies have demonstrated that severe renal damage is associated with a prolonged stay in hospital, higher costs, and greater mortality (4–6). A meta-analysis (2004–2007) included 24 studies and classified them according to the then current RIFLE criteria (6).

Definition

Any AKI that occurs or is diagnosed in a hospital inpatient is a nosocomial AKI.

The RIFLE classification distinguishes three stages of AKI:

- Risk
- Injury
- Failure.

These three stages are followed by loss of renal function, defined as complete absence of function with renal replacement treatment required for 4 weeks. A further stage is end-stage renal disease (ESRD), defined by the need for a period of renal replacement treatment exceeding 3 months. The initial letters of these five stages yield the acronym RIFLE. The original study group later became part of the Acute Kidney Injury Network (AKIN), which formulated the currently prevailing AKIN criteria (7). The diagnostic criteria for the AKIN classification comprise an abrupt (within 48 h) rise in serum creatinine level by >0.3 mg/dL (26.4 μmol/L), an increase in serum creatinine concentration by >50%, or oliguria of <0.5 mL/kg body weight (BW) for more than 6 h (stage 1).

The initial diagnosis of AKI is followed by staging. Stage 2 is defined by a two- to threefold increase in creatinine concentration or a decrease in urine excretion to <0.5 mL/kg BW for more than 12 h. The criteria for stage 3 are a more than threefold rise in serum creatinine concentration compared to baseline with an increase of at least 4 mg/dL, accompanied by reduction of urine excretion to <0.3 mL/kg BW for ≥ 24 h or anuria for ≥ 12 h. The AKIN criteria are based on evidence (Table 1).

Following the decision in 2004 to discontinue use of the term “acute renal failure” and replace it with “acute kidney injury” German-speaking internists and nephrologists are discussing whether to follow suit by also adopting terminology that refers to the damage sustained by the organ rather than its failure (8). The RIFLE, AKIN, and KDIGO definitions all describe injury, not failure, of the kidney. The logical consequence would be to use the term “akuter Nierenschaden” (ANS; = acute kidney injury) rather than the prevailing “akutes Nierenversagen” (ANV; = acute renal failure) in German. However, the German-language classification systems still refer to “ANV,” and starting to use “ANS” would hinder semantic operability until the classifications are revised to include both terms. For this reason, we took the deliberate decision to retain the usage of “ANV” in the original German version of this article.

A meta-analysis of 13 studies assessed the mortality of AKI. The relative risk (RR) increased significantly

The RIFLE criteria distinguish three stages of AKI:

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These three stages are followed by loss of renal function.

FIGURE 2

Differential diagnoses for acute kidney injury of non-prerenal origin

ACE, angiotensin-converting enzyme; GN, glomerulonephritis; HUS, hemolytic-uremic syndrome; RAS, renal artery stenosis; RPGN, rapidly progressive glomerulonephritis; SLE, systemic lupus erythematosus; TTP, thrombotic-thrombopenic purpura

from 2.40 for “risk” through 4.15 for “injury” to 6.37 for “failure” ($p < 0.0001$ for all differences) (7). With regard to hospital stay, a further study found increased costs of \$7933 per patient in the USA and prolongation of inpatient treatment by an average of 3.2 days (10).

Pathophysiology

Pathogenetically, AKI is classified as prerenal, renal, or postrenal disease. AKI of renal origin is subdivided into preglomerular, glomerular, and postglomerular (= tubulointerstitial) forms (Figure 2), although in practice mixed presentations are often observed.

Prerenal AKI (or prerenal azotemia) is caused by a sudden or prolonged reduction in renal perfusion. This can result from either of the following circumstances:

- Reduction of the effective circulating blood volume owing to circulatory factors such as volume depletion, failure of the cardiac pump function, or peripheral vasodilatation

- Mechanical impairment of renal perfusion by, for instance, unilateral or bilateral renal artery stenosis, a dissected abdominal aortic aneurysm, or renal artery embolism.

Sodium is disproportionately reabsorbed with water in the proximal tubules, and urea follows. This explains why disproportionate increases in urea levels are often detected in prerenal azotemia. Prerenal causes of AKI often lead to renal injury in the medium to long term (Figure 3). A classic example is shock due to acute volume depletion, followed later by acute tubular necrosis (ATN). At the junction of the cortex and the medulla, the kidney has a zone that is particularly prone to circulatory disorders. This is why the glomeruli are often largely spared in shock events, whereas the tubular cells and the function thereof are frequently seriously impaired.

Apart from circulatory (more precisely, septic-circulatory) factors, there are also classic renal causes of AKI (Box).

International definition

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Pathophysiological classification

Pathogenetically, AKI is classified as prerenal, renal, or postrenal disease.

Prerenal azotemia and acute tubular necrosis; AKI, acute kidney injury

FIGURE 3

The toxic causes of AKI comprise medications, radiographic contrast agents, hemolysis, rhabdomyolysis, paraproteinuria, hypercalcemia, and poisonous substances. Whether radiographic contrast agents actually cause AKI has recently been questioned (11, 12).

Postrenal AKI occurs when the outflow of urine from one or both kidneys is blocked. Typically, prostatic hyperplasia with overflow incontinence leads to AKI.

Renal function may still recover a long time after the occurrence of obstruction, so it is frequently advisable to eliminate postrenal causes (13).

Every diagnostic work-up for AKI should include sonography of the renal pelvis and urinary bladder.

Epidemiology and causes

AKI occurs occasionally in the community (two cases per 1000 inhabitants each year in Europe), but much more frequently in hospital (10 to 20% of all inpatients). The highest incidence of nosocomial AKI is found in intensive care units, where 35 to 60% of patients are affected (5, 14–17).

Shock from acute volume depletion

At the junction of the cortex and the medulla, the kidney has a zone that is particularly prone to circulatory disorders. This is why the glomeruli are often largely spared in shock events, whereas the tubular cells and the function thereof are frequently seriously impaired.

The authors of a recent study analyzed 100 000 data sets from hospital inpatients diagnosed with AKI (18). AKI occurred most frequently in association with sepsis, heart disease, polytrauma, liver disease, and cardiac surgery.

A Spanish study looked even more closely at the genesis of nosocomial AKI (15): 66% of patients had prerenal azotemia or ATN, and 13% had acute-on-chronic renal failure. In 10% of cases there was a postrenal cause (obstruction), and 4% of patients had glomerulonephritis or vasculitis. In 2% the cause was tubulointerstitial nephritis, and in 1% a cholesterol crystal embolus was responsible. Notably, 20% of cases were due to drug toxicity (19).

Clinical symptoms

The clinical signs of AKI are unspecific, because the symptoms are late to manifest. This is because the specific consequences of the kidney injury and of the impaired excretory function have to be present for AKI to be detected.

Toxic causes

The toxic causes of AKI comprise medications, radiographic contrast agents, hemolysis, rhabdomyolysis, paraproteinuria, hypercalcemia, and poisonous substances. Whether radiographic contrast agents actually cause AKI has recently been questioned.

Volume expansion

Volume expansion with increased intravascular volume occurs when there is a positive fluid balance with restricted outflow. Clinically, volume expansion is manifested by systolically accentuated arterial hypertension, peripheral edema, and dyspnea with pulmonary edema. Intensive care patients with volume expansion need more prolonged ventilation, have a higher risk of infection, and are more prone to wound healing disorders. For these reasons, AKI patients with volume expansion exhibit much higher mortality (20).

Hyperkalemia

Various factors combine to produce hyperkalemia in patients with AKI. On the one hand potassium accumulates because the intake via food and fluid substitution is no longer matched by excretion, while on the other hand potassium is often displaced from the intracellular to the extracellular space, e.g., in acidosis (21).

Drugs such as ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists, and other substances that influence the renin–angiotensin–aldosterone system (e.g., nonsteroidal anti-inflammatory drugs) favor the occurrence of hyperkalemia. From 6.0 mmol/L upwards, elevated serum potassium levels are potentially life-threatening: in patients with diastolic heart failure, sudden cardiac death can occur due to electromechanical decoupling. Swift action is therefore required in the presence of a potassium concentration exceeding 6.0 mmol/L, and the urgency is particularly great at levels above 7.0 mmol/L (21).

Acidosis

Metabolic acidosis in a patient with AKI is manifested clinically by a decreased blood bicarbonate level and compensatory hyperventilation. Acidosis increases the risk of cardiac arrhythmia, hypotension, and infections and favors the development of hyperkalemia.

Other clinical consequences

The build-up of uremic toxins can cause cutaneous itching, nausea, and neurological symptoms to the point of accentuated drowsiness and concentration disorders. Uremic thrombocytopenia is expressed by an elevated risk of bleeding and an increased transfusion requirement. If AKI persists, renal anemia or myopathy may develop. In ventilated patients, this may mean prolongation of the ventilation period. Clinically relevant factors are alteration of the pharmacokinetics of renally eliminated drugs and the consequences of accumulation of active metabolites.

Volume expansion

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BOX

Classic renal causes of acute kidney injury

- Acute tubular necrosis
- Acute glomerulonephritis (e.g., IgA glomerulopathy, para- or postinfectious glomerulonephritis)
- Cardiorenal syndrome
- Toxic tubular injury
- Microbiological causes such as hantavirus, leptospires, or HIV
- Acute interstitial nephritis
- Hepatorenal syndrome
- Pregnancy-associated injury

Differential diagnosis

In the realm of internal medicine, hardly any other disease has as broad a spectrum of differential diagnoses as nosocomial AKI (*eTable*). The pathophysiology and epidemiology have to be taken into account, and in every single case a detailed diagnostic work-up is required to determine the precise cause of the acute impairment of renal function and decide on an ideally causal treatment strategy. It must be borne in mind that 20% of cases of AKI are caused by medications (16).

Diagnostic work-up

Together with sonography to exclude a postrenal obstruction (overflow incontinence), chemical and microscopic urinalysis forms an indispensable component of the diagnostic work-up for AKI. Microscopic examination of the urine is complemented by the classic dipstick testing. The primary role of urinary microscopy is to distinguish glomerular from nonglomerular hematuria (*Figure 4, Table 2*) in order to achieve early, non-invasive detection of glomerulonephritis and vasculitis, which require immediate specific treatment. Urinary microscopy is also valuable, however, in diagnosing other causes of AKI, e.g., by demonstrating epithelial cylinders or crystals (22). Renal biopsy enables confident identification of the cause of hitherto unexplained AKI, although ultrasound often enables distinction between AKI (kidney size normal or enlarged) and chronic

Acidosis

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Figure 4: Urinalysis findings in acute kidney injury (AKI)

a) and b) In the event of diffuse pathology of the tubules (e.g., acute tubular necrosis), tubular epithelial and urothelial cells are often found in the urine; c) granular cylinders (e.g., pyelonephritis); d) leukocyte cylinders (e.g., interstitial nephritis); e) pigment cylinders (rhabdomyolysis, hemolysis); f) hyaline cylinders (e.g., nephrotic syndrome); g) dysmorphic erythrocytes (suspicion of glomerulonephritis)

kidney disease (CKD; small kidneys). Renal biopsy can also help to rule out important differential diagnoses in cases of nosocomial AKI in the intensive care unit. In particular, biopsy is the only way of confidently diagnosing or excluding glomerulonephritis and involvement of the kidneys in systemic disease (vasculitis, other autoimmune diseases, malignancies, etc.). A nephrologist should be consulted to determine whether renal biopsy is indicated.

The diagnostic work-up of every patient with AKI should include not only creatinine and urea (calculation of the ratio), but also serum calcium, lactate dehydrogenase (LDH), creatine kinase (CK), bilirubin, C-reactive protein (CRP), protein, albumin, glucose, and venous blood gas analysis (BGA) with determination of chloride (anion gap), and a differential blood count (Table 3). Quantification of proteinuria with determination of protein, albumin, and creatinine in a urine sample (ratio of urinary protein to urinary creatinine

correlated with 24-h proteinuria) also forms part of the basic diagnostic work-up for newly identified AKI. In the presence of the corresponding clinical presentation, investigation of other parameters is recommended, such as complement (C3, C4) and possibly autoantibodies (antinuclear factors, antineutrophilic cytoplasmic antibodies [ANCA], anti-basal membrane antibodies, and anti-double-stranded deoxyribonucleic acid antibodies [anti-ds-DNA-AB]), protein electrophoresis, and immune fixation on free light chains, among many others.

Treatment

Causal treatments are available for functional AKI due to intravascular volume depletion, acute glomerulonephritis and vasculitis, renal artery stenosis, and renal artery embolism, and for postrenal AKI. These entities should therefore not be overlooked. Drugs containing potentially nephrotoxic substances or active agents with a

Diagnostic work-up

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Urinary microscopy

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negative effect on renal thermodynamics (e.g., ACE inhibitors, angiotensin receptor antagonists, and non-steroidal antirheumatic drugs) should be discontinued if at all possible (23). Hypotension must be avoided, and any intravascular volume depletion must be swiftly compensated. In any case, the treating physician must take immediate steps to restore euolemia, bearing the broad spectrum of differential diagnoses in mind (Figure 1). Further treatment strategies are based on the occurrence of consequences and complications of AKI, such as volume expansion, electrolyte imbalance, uremia, pericardial effusion, and overdosing of medications.

The benefit of diuretic treatment is disputed (24). The practice of “flushing” the kidney with large quantities of infused fluids and administering loop diuretics (e.g., furosemide) is obsolete and nonsensical in the context of treating AKI (25). It does, however, make sense to treat volume expansion with furosemide, provided the kidneys respond (26). Prompt renal replacement therapy is often considered in cases where the treatment of volume expansion with diuretics is unsuccessful.

It remains unclear whether early renal replacement improves the prognosis. As yet there are no data that clearly show at what point renal replacement therapy becomes beneficial. Recently published studies come to differing conclusions, but tend to indicate that early replacement is not necessary (27, 28). The best way to proceed should be decided on an individual basis in discussion with the nephrology team (29). Should the patient’s life be threatened, however, immediate dialysis treatment is obligatory (30).

Nowadays, even in unstable patients, dialysis does not necessarily have to take the form of continuous hemofiltration. Trials and meta-analyses have shown that intermittent hemodialysis, sometimes in the shape of slow extended hemodialysis (SLED), has the same effect even in patients with unstable disease. A Cochrane review of 15 studies (1550 patients) found the same mortality (RR 1.01, 95% confidence interval [0.92; 1.12]) and similar hemodynamic stability (RR 0.48, [0.10; 2.28], or hypotension (RR 0.92, [0.72; 1.16]) (31). On the other hand, some causes of AKI demand urgent intermittent dialysis with high volumes of blood (up to 400 mL/min) and dialysate (up to 1.2 L/min) because that is the only way of achieving rapid and effective detoxication (intoxication with methanol, glycol, salicylate, etc.) or restoring homeostasis (life-threatening hyperkalemia, hypercalcemia, etc.) (32). Therefore the nephrologist

TABLE 2

Differentiation between glomerular and extraglomerular hematuria

	Glomerular hematuria	Extraglomerular hematuria
Coagulates	No	Sometimes
Erythrocyte cylinders	Yes	No
Dysmorphic erythrocytes/ all erythrocytes	>75%	<25%
Acanthocytes	>5%	<5%
Proteinuria >1 g/24 h	Often	Rarely

must be directly involved in deciding the form dialysis should take in each individual patient, because only she/he can offer the whole gamut of renal replacement procedures and the necessary expertise in differential diagnosis (33).

Recent studies have been investigating the effect of electronic warning systems (AKI alerts) on the incidence and prognosis of kidney injury. A large randomized controlled trial showed no positive effect when the database reported an AKI to the treating physician (34). A newly published before-and-after quality improvement study shows that the incidence of severe kidney injury can be reduced and the likelihood of renal recovery increased by reporting an automatically triggered alarm to the nephrologist (35). No final conclusions can yet be drawn regarding the benefits of AKI alert systems.

Hemodynamics is another important aspect of renal replacement therapy. In 30 to 70% of cases the patient experiences interdialytic falls in blood pressure that require immediate countermeasures (36–38). Mechanical renal replacement techniques always involve risks (access problems, hemodynamic instability, dysequilibrium, bleeding due to anticoagulation), and this factor should be borne in mind when deciding how to proceed.

Prognosis

The mortality of nosocomial AKI is ca. 30% overall, rising to 60.3% [58; 62,6] for intensive care patients who require dialysis (40, e1, e2). Up to a third of patients who need dialysis during their stay in an intensive care unit are still dependent on renal replacement therapy at the time of discharge from hospital (e2). This shows that a kidney injury acquired in the course of

Renal biopsy

Renal biopsy can help to rule out important differential diagnoses in cases of nosocomial AKI in the intensive care unit. Biopsy is the only way of confidently diagnosing or excluding glomerulonephritis and involvement of the kidneys in systemic disease.

“Flushing” the kidney

The practice of “flushing” the kidney with large quantities of infused fluids and administering loop diuretics (e.g., furosemide) is obsolete and nonsensical in the context of treating AKI.

TABLE 3

Differentiation between prerenal azotemia and AKI of renal origin

	Prerenal azotemia (functional renal injury)	AKI of renal origin (acute tubular necrosis)
Appearance of urine	Concentrated	Normal to diluted
Serum urea/creatinine ratio	>20–40	≈ 10
Urine output	Usually very low	Variable
Urine osmolality	>500 mosmol/L	<350 mosmol/L
Urine sodium concentration	<20 mmol/L	≥ 40 mmol/L
Urinary sediment	Bland	Dirty brown, epithelial cells, cylinders
Administration of fluids	Normalization of creatinine in 1–3 days	No effect

intensive care treatment is much more likely to be associated with long-term dependence on dialysis. Recovery of at least partial kidney function occurs, if at all, within the first 3 months. With optimal treatment, 20 to 60% of these patients eventually no longer need renal replacement therapy (e2). Even mild AKI is by no means only an interesting observation in the laboratory, as just a slight decrease in renal function may have far-reaching metabolic consequences (6). Apart from that, AKI considerably increases the risk of progressive chronic kidney disease: patients with AKI that does not necessitate dialysis at the outset have an 8 to 21% risk of becoming dependent on dialysis following an acute event in the ensuing 2 to 3 years (4, e3). This, as well as impaired renal function per se, worsens the prognosis and is thus of great significance for health care policy. Myocardial infarction, heart failure, fractures, gastrointestinal hemorrhage, and stroke are just a few of the long-term complications resulting from AKI (4). To date, only a small proportion of patients with AKI are offered nephrological follow-up visits after discharge from hospital (e4, e5). There is clear evidence that involvement of a nephrologist improves the outcome of AKI (29, e6–e9). For example, Mehta et al.'s retrospective analysis of 215 intensive care patients treated at four university medical centers in the USA showed a decrease in mortality from 53% to 22% for AKI without dialysis and from 74% to 49% for AKI with dialysis. The length of stay in intensive care went down from 17 days to 6 days when a nephrologist was involved in the treatment (e10). It is also advantageous for the patient to be seen by a nephrologist at follow-up visits (e11).

Renal replacement

It remains unclear whether early renal replacement improves the prognosis. As yet there are no data that clearly show at what point renal replacement therapy becomes necessary. Recent studies tend to indicate that early replacement is not required.

In every patient with AKI for whom renal replacement is planned, the indications and the choice and conduct of procedure must be confirmed by a nephrologist at the outset, or at the latest within 24 h of the initiation of treatment. The same nephrologist should take care of the patient at follow-up visits. The diagnostic work-up for AKI should follow a standardized scheme (eFigure).

Conflict of interest statement

The authors declare that no conflict of interest exists.

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References

1. Group KDIGOAKIW: KDIGO clinical practice guideline for acute kidney injury. *Kidney Int* 2012; (Suppl 2): 1–138.
2. Schaeffner ES, Ebert N, Delanaye P, et al.: Two novel equations to estimate kidney function in persons aged 70 years or older. *Ann Intern Med* 2012; 157: 471–81.
3. Ribichini F, Graziani M, Gambaro G, et al.: Early creatinine shifts predict contrast-induced nephropathy and persistent renal damage after angiography. *Am J Med* 2010; 123: 755–63.
4. Coca SG, Singanamala S, Parikh CR: Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int* 2012; 81: 442–8.
5. Hoste EA, Bagshaw SM, Bellomo R, et al.: Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med* 2015; 41: 1411–23.
6. Ricci Z, Cruz D, Ronco C: The RIFLE criteria and mortality in acute kidney injury: A systematic review. *Kidney Int* 2008; 73: 538–46.
7. Mehta RL, Kellum JA, Shah SV, et al.: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11: R31.
8. Alscher MD: Akutes Nierenversagen: Ein Krankheitsbild mit vielen Namen. *Dtsch Med Wochenschr* 2015; 140: 244.

Prognosis

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9. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P: Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the 2nd International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; 8: R204–12.
10. Silver SA, Long J, Zheng Y, Chertow GM: Cost of acute kidney injury in hospitalized patients. *J Hosp Med* 2017; 12: 70–6.
11. Wilhelm-Leen E, Montez-Rath ME, Chertow G: Estimating the risk of radiocontrast-associated nephropathy. *J Am Soc Nephrol* 2017; 28: 653–9.
12. Weisbord SD, Gallagher M, Jneid H, et al.: Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med* 2018; 378: 603–14.
13. Hamdi A, Hajage D, van Glabeke E, et al.: Severe post-renal acute kidney injury, post-obstructive diuresis and renal recovery. *BJU Int* 2012; 110: E1027–34.
14. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT: Hospital-acquired renal insufficiency: a prospective study. *Am J Med* 1983; 74: 243–8.
15. Liano F, Pascual J: Epidemiology of acute renal failure: a prospective, multicenter, community-based study. Madrid Acute Renal Failure Study Group. *Kidney Int* 1996; 50: 811–8.
16. Uchino S, Kellum JA, Bellomo R, et al.: Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005; 294: 813–8.
17. Susantitaphong P, Cruz DN, Cerda J, et al.: World incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol* 2013; 8: 1482–93.
18. Jannot AS, Burgun A, Thervet E, Pallet N: The diagnosis-wide landscape of hospital-acquired AKI. *Clin J Am Soc Nephrol* 2017; 12: 874–84.
19. Mehta RL, Awdishu L, Davenport A, et al.: Phenotype standardization for drug-induced kidney disease. *Kidney Int* 2015; 88: 226–34.
20. Teixeira C, Garzotto F, Piccinni P, et al.: Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. *Crit Care* 2013; 17: R14.
21. Alscher MD: [“The silent killer: hyper- and hypokalaemia”]. *Dtsch Med Wochenschr* 2016; 141: 1531–6.
22. Kimmel M, Shi J, Wasser C, Bieggler D, Alscher MD, Schanz MB: Urinary [TIMP-2], [IGFBP7] – novel biomarkers to predict acute kidney injury. *Am J Nephrol* 2016; 43: 375–82.
23. Meersch M, Schmidt C, Hoffmeier A, et al.: Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med* 2017; 43: 1551–61.
24. Ejaz AA, Mohandas R: Are diuretics harmful in the management of acute kidney injury? *Opin Nephrol Hypertension* 2014; 23: 155–60.
25. Cantarovich F, Rangoonwala B, Lorenz H, Verho M, Esnault VL: High-dose furosemide in acute renal failure study G: High-dose furosemide for established ARF: a prospective, randomized, double-blind, placebo-controlled, multicenter trial. *Am J Kidney Dis* 2004; 44: 402–9.
26. Pacifici GM, Viani A, Schulz HU, Frercks HJ: Plasma protein binding of furosemide in the elderly. *Eur J Clin Pharmacol* 1987; 32: 199–202.
27. Meersch M, Kullmar M, Schmidt C, et al.: Long-term clinical outcomes after early initiation of RRT in critically ill patients with AKI. *J Am Soc Nephrol* 2018; 29: 1011–9.
28. Barbar SD, Clere-Jehl R, Bourredjem A, et al.: Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. *N Engl J Med* 2018; 379: 1431–42.
29. Askenazi DJ, Heung M, Connor MJ, et al.: Optimal role of the nephrologist in the intensive care unit. *Blood Purif* 2017; 43: 68–77.
30. Brown JR, Rezaee ME, Hisey WM, Cox KC, Matheny ME, Sarnak MJ: Reduced mortality associated with acute kidney injury requiring dialysis in the United States. *Am J Nephrol* 2016; 43: 261–70.
31. Rabinathan K, Adams J, Macleod AM, Muirhead N: Intermittent versus continuous renal replacement therapy for acute renal failure in adults. *Cochrane Database Syst Rev* 2007: CD003773.
32. Ghannoum M, Lavergne V, Gosselin S, et al.: Practice trends in the use of extracorporeal treatments for poisoning in four countries. *Semin Dial* 2016; 29: 71–80.
33. Erley C: Nephrologische Betreuung bei Nierenversagen auf der Intensivstation. *Der Nephrologe* 2018; 13: 195–201.
34. Wilson FP, Shashaty M, Testani J, et al.: Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. *Lancet* 2015; 385: 1966–74.
35. Park S, Baek SH, Ahn S, et al.: Impact of electronic acute kidney injury (AKI) alerts with automated nephrologist consultation on detection and severity of AKI: a quality improvement study. *Am J Kidney Dis* 2018; 71: 9–19.
36. Capuano A, Sepe V, Cianfrone P, Castellano T, Andreucci VE: Cardiovascular impairment, dialysis strategy and tolerance in elderly and young patients on maintenance haemodialysis. *Nephrol Dial Transplant* 1990; 5: 1023–30.
37. Raja RM: Sodium profiling in elderly haemodialysis patients. *Nephrol Dial Transplant* 1996; 11 (Suppl 8): 42–5.
38. Douvris A, Malhi G, Hiremath S, et al.: Interventions to prevent hemodynamic instability during renal replacement therapy in critically ill patients: a systematic review. *Crit Care* 2018; 22: 41.
39. Lafrance JP, Miller DR: Acute kidney injury associates with increased long-term mortality. *J Am Soc Nephrol* 2010; 21: 345–52.
40. Uchino S, Bellomo R, Morimatsu H, et al.: Continuous renal replacement therapy: a worldwide practice survey. The beginning and ending supportive therapy for the kidney (B.E.S.T. kidney) investigators. *Intensive Care Med* 2007; 33: 1563–70.

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► Supplementary material

For eReferences please refer to:
www.aerzteblatt-international.de/ref0919

eFigure, eTable:
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Renal replacement procedures

In every patient with AKI for whom renal replacement is planned, the indications and the choice and conduct of procedure must be confirmed by a nephrologist at the outset, or at the latest within 24 h of the initiation of treatment.

CME credit for this unit can be obtained via cme.aerzteblatt.de until 26 May 2019.

Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

In the context of intensive care, with what is severe kidney injury associated?

- a) With an increased risk of urinary incontinence after discharge from hospital
- b) With an elevated likelihood of prostate cancer
- c) With an increased risk of sepsis
- d) With a greatly elevated likelihood of long-term dependence on dialysis
- e) With a 100% probability of decubitus

Question 2

What does the acronym RIFLE stand for?

- a) Reinjection, injury, farouche, lection, emergency
- b) Reanimation, injection, fraction, lung, excretion
- c) Risk, injury, failure, loss, endstage
- d) Risk, involved, frame, luxation, exodus
- e) Right heart syndrome, invasively, foramen, left ventricle, endothelial tissue

Question 3

Which of the following approximates the mortality of nosocomial acute kidney injury?

- a) 0%
- b) 15%
- c) 30%
- d) 45%
- e) 60%

Question 4

What urea/creatinine ratio is a sign of kidney injury of renal origin?

- a) ≈ 10
- b) ≈ 20
- c) ≈ 30
- d) ≈ 40
- e) ≈ 50

Question 5

Which of the following is frequently found in intensive care patients with volume expansion?

- a) Urticaria
- b) Dementia
- c) Upper extremity neuropathy
- d) Wound healing disorder
- e) Venous thromboses

Question 6

What is frequently a cause of prerenal acute kidney injury?

- a) Cholesterol embolism
- b) Sarcoidosis
- c) Acute tubular necrosis
- d) Postinfectious immune complex
- e) Abrupt reduction in renal perfusion

Question 7

From what concentration is elevated serum potassium potentially life-threatening?

- a) From 2.0 mmol/L
- b) From 3.0 mmol/L
- c) From 4.0 mmol/L
- d) From 5.0 mmol/L
- e) From 6.0 mmol/L

Question 8

What is the principal diagnostic contribution of urinary microscopy?

- a) Demonstration of leukocytes
- b) Identification of dysmorphic erythrocytes
- c) Differentiation of glomerular from nonglomerular hematuria
- d) Identification of lipids
- e) Demonstration of squamous cell carcinoma

Question 9

Which of the following drugs is appropriate for the treatment of renal volume expansion?

- a) Spironolactone
- b) Furosemide
- c) Hydrochlorothiazide
- d) Bumetanide
- e) Piretanide

Question 10

Which class of drugs favors the development of hyperkalemia?

- a) Antiarrhythmics
- b) ACE inhibitors
- c) Serotonin reuptake inhibitors
- d) Betalactam antibiotics
- e) Paracetamol

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„Determinants of Perioperative Outcome in Frail Older Patients“ (issue 5/2019) until 28 April 2019, The Management of Pilonidal Sinus“ (issue 1–2/2019) until 31 March 2019
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Supplementary material to:

Acute Renal Failure of Nosocomial Origin

by Mark Dominik Alscher, Christiane Erley, and Martin K. Kuhlmann

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eReferences

- e1. Network VNARFT, Palevsky PM, Zhang JH, et al.: Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008; 359: 7–20.
- e2. Cerda J, Liu KD, Cruz DN, et al.: Promoting kidney function recovery in patients with AKI requiring RRT. *Clin J Am Soc Nephrol* 2015; 10: 1859–67.
- e3. Gammelager H, Christiansen CF, Johansen MB, Tonnesen E, Jespersen B, Sorensen HT: Five-year risk of end-stage renal disease among intensive care patients surviving dialysis-requiring acute kidney injury: a nationwide cohort study. *Crit Care* 2013; 17: R145.
- e4. Harel Z, Wald R, Bargman JM, et al.: Nephrologist follow-up improves all-cause mortality of severe acute kidney injury survivors. *Kidney Int* 2013; 83: 901–8.
- e5. Kirwan CJ, Blunden MJ, Dobbie H, James A, Nedungadi A, Prowle JR: Critically ill patients requiring acute renal replacement therapy are at an increased risk of long-term renal dysfunction, but rarely receive specialist nephrology follow-up. *Nephron* 2015; 129: 164–70.
- e6. Balasubramanian G, Al-Aly Z, Moiz A, et al.: Early nephrologist involvement in hospital-acquired acute kidney injury: a pilot study. *Am J Kidney Dis* 2011; 57: 228–34.
- e7. Ponce D, Zorzenon Cde P, dos Santos NY, Balbi AL: Early nephrology consultation can have an impact on outcome of acute kidney injury patients. *Nephrol Dial Transplant* 2011; 26: 3202–6.
- e8. Costa e Silva VT, Liano F, Muriel A, Diez R, de Castro I, Yu L: Nephrology referral and outcomes in critically ill acute kidney injury patients. *PloS one* 2013; 8: e70482.
- e9. Soares DM, Pessanha JF, Sharma A, Brocca A, Ronco C: Delayed nephrology consultation and high mortality on acute kidney injury: a meta-analysis. *Blood Purif* 2017; 43: 57–67.
- e10. Mehta RL, McDonald B, Gabbai F, et al.: Nephrology consultation in acute renal failure: does timing matter? *Am J Med* 2002; 113: 456–61.
- e11. Silver SA, Siew ED: Follow-up care in acute kidney injury: lost in transition. *Adv Chronic Kidney Dis* 2017; 24: 246–52.

eTABLE

Classification of acute kidney injury by pathophysiology

Differential diagnosis	Nephrological work-up
AKI of prerenal origin	
Shock	Intraoperative BP decrease, tachycardia, mean arterial pressure, signs of sepsis, medical history, BCM, ECHO, urine osmolality
Hypotension	Systolic heart failure, orthostatic hypotension, tachycardia, cutaneous turgor, jugular vein pressure, short bowel syndrome
Sepsis	Signs of sepsis, CRP, procalcitonin, IL-6
Renal artery stenosis	Abdominal flow sound, duplex sonography of renal arteries, RI, magnetic resonance angiography
Renal embolism	AF, ECG, duplex sonography, magnetic resonance angiography, computed tomography with contrast medium
Abdominal aortic aneurysm	Abdominal flow sound, abdominal sonography, peripheral pulses, thoracic radiography, magnetic resonance angiography or computed tomography
Cholesterol crystal embolism	Blue toe syndrome, livedo reticularis, status post invasive procedure
Intravasal hypovolemia	Edema, ascites, anasarca, urinary electrolytes, diuretic dose, serum calcium
AKI of renal origin	
Parainfectious glomerulonephritis	Nephritic urinary sediment, complement factors, renal biopsy
Interstitial nephritis	Medication history, skin changes, tubular marker proteins, eosinophiluria, renal biopsy
HELLP syndrome	Pregnancy, proteinuria, BP
HUS/TTP	Complement factors, BC, parameters of hemolysis
Renal vein thrombosis (?)	DVT?, nephrotic syndrome?, anticoagulation
Drug-related/toxic	Medication history, drug levels (antibiotics, immunosuppressants)
Acute tubular necrosis	Epithelial cylinders, isosthenuria
Functional AKI	Nonsteroidal antirheumatic drugs, ACE inhibitors, ARB, HFpEF
Vasculitis	Skin changes, ANCA, parameters of LE, renal biopsy
Rejection	Intrarenal RI, renal biopsy
AKI of postrenal origin	
Incorrectly inserted bladder catheter	Urine production, bladder sonography
Obstruction of bladder catheter	Bladder sonography
Drug-induced urinary retention	Medication history
Hydronephrosis	Crystalluria, sonography

ACE, Angiotensin-converting enzyme; AF, atrial fibrillation; AKI, acute kidney injury; ANCA, anti-neutrophilic cytoplasmic antibodies; ARB, Angiotensin receptor blockers; BC, blood count; BCM, body composition monitor; BP, blood pressure; CRP, C-reactive protein; DVT, deep vein thrombosis; ECG, electrocardiogram; ECHO, echocardiography (of the heart); HFpEF, heart failure with preserved ejection fraction; HUS, hemolytic-uremic syndrome; IL-6; interleukin-6; LE, lupus erythematosus; RI, resistance index; TTP, thrombotic-thrombopenic purpura

eFIGURE

How to proceed
after diagnosis of
acute kidney failure
(AKI) by a nephrol-
ogist; BW, body
weight