

Acute renal failure

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This seminar covers the most recent information on definition, epidemiology, and clinical causes of acute renal failure. The mechanisms of acute prerenal failure and the potential interference by commonly used drugs of autoregulation of renal blood flow are discussed. We summarise some basic and recent insights into the haemodynamic and cellular pathophysiological mechanisms, mainly of postischaemic acute renal failure. Recent findings on the repair mechanisms of renal injury and the potential future therapeutic possibilities are discussed. We provide some differential diagnostic approaches for patients with acute renal failure and summarise prevention of the disorder and management of critically ill patients by dialysis and by other means. Finally, some information on the influence of gene polymorphisms on the prognosis of acute renal failure is given.

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Acute renal failure is the generic term for an abrupt and sustained decrease in renal function resulting in retention of nitrogenous (urea and creatinine) and non-nitrogenous waste products. Depending on the severity and duration of the renal dysfunction, this accumulation is accompanied by metabolic disturbances, such as metabolic acidosis and hyperkalaemia, changes in body fluid balance, and effects on many other organ systems. Definitions of acute renal failure range from severe (ie, that requiring dialysis) to slight increases in serum creatinine concentration (eg, of $44.2 \mu\text{mol/L}$). In the absence of a universal definition, a reasonable definition of acute renal failure is an acute and sustained increase in serum creatinine concentration of $44.2 \mu\text{mol/L}$ if the baseline is less than $221 \mu\text{mol/L}$, or an increase in serum creatinine concentration of more than 20% if the baseline is more than $221 \mu\text{mol/L}$.¹

The Acute Dialysis Quality Initiative group lately proposed the RIFLE system (table 1), classifying acute renal failure into three severity categories (risk, injury, and failure) and two clinical outcome categories (loss and end-stage renal disease).^{2–4}

Epidemiology

Causes of acute renal failure can be broadly divided into three categories (figure 1). In the prerenal form there is a reversible increase in serum creatinine and blood urea concentrations; it results from decreased renal perfusion, which leads to a reduction in glomerular filtration rate (GFR). Postrenal acute renal failure is due to obstruction of the urinary collection system by either intrinsic or extrinsic masses. The remaining patients have the renal form, in which structures of the nephron, such as the glomeruli, tubules, vessels, or interstitium, are affected.

The major cause of intrinsic renal azotaemia is acute tubular necrosis. This disorder is caused by ischaemic or nephrotoxic injury to the kidney and is a specific histopathological and pathophysiological entity, which can result from several distinct renal insults. Prerenal azotaemia and ischaemic acute tubular necrosis occur on a continuum of the same pathophysiological process and together account for 75% of the cases of acute renal failure.⁵ Although the terms acute renal failure and acute

	GFR criteria	Urine output criteria
Risk	Serum creatinine increased 1.5 times	<0.5 mL kg ⁻¹ h ⁻¹ for 6 h
Injury	Serum creatinine increased 2.0 times	<0.5 mL kg ⁻¹ h ⁻¹ for 12 h
Failure	Serum creatinine increased 3.0 times or creatinine=355 $\mu\text{mol/L}$ when there was an acute rise of $>44 \mu\text{mol/L}$	<0.3 mL kg ⁻¹ h ⁻¹ for 24 h or anuria for 12 h
Loss	Persistent acute renal failure; complete loss of kidney function for longer than 4 weeks	
End-stage renal disease	End-stage renal disease for longer than 3 months	

GFR=glomerular filtration rate.

Table 1: RIFLE classification⁴

tubular necrosis have quite different definitions, they are commonly used synonymously in the clinical setting and both are also used in this seminar.

Acute renal failure is common, but the incidence depends on the definition used and the population studied. In a community-based study in the UK,⁶ there were 172 cases per million adults per year of severe acute renal failure (serum creatinine concentration $>500 \mu\text{mol/L}$), with 22 per million receiving acute dialysis.

Two more recent UK population studies^{7,8} defined acute renal failure as a temporary rise in serum creatinine to at least $300 \mu\text{mol/L}$ or clinical features indicating acute deterioration of previously normal renal function. Advanced acute renal failure was defined as a first measured serum creatinine concentration of at least $500 \mu\text{mol/L}$. The annual incidence of acute renal failure ranged from 486 to 620 per million;

Search strategy and selection criteria

We searched PubMed with the search terms "acute renal failure", "renal ischaemia", and "acute dialysis". We mainly selected publications from the past 5 years, but we did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by these strategies and selected those we judged relevant. Relevant review articles and book chapters were also included. There was no restriction on language of publication.

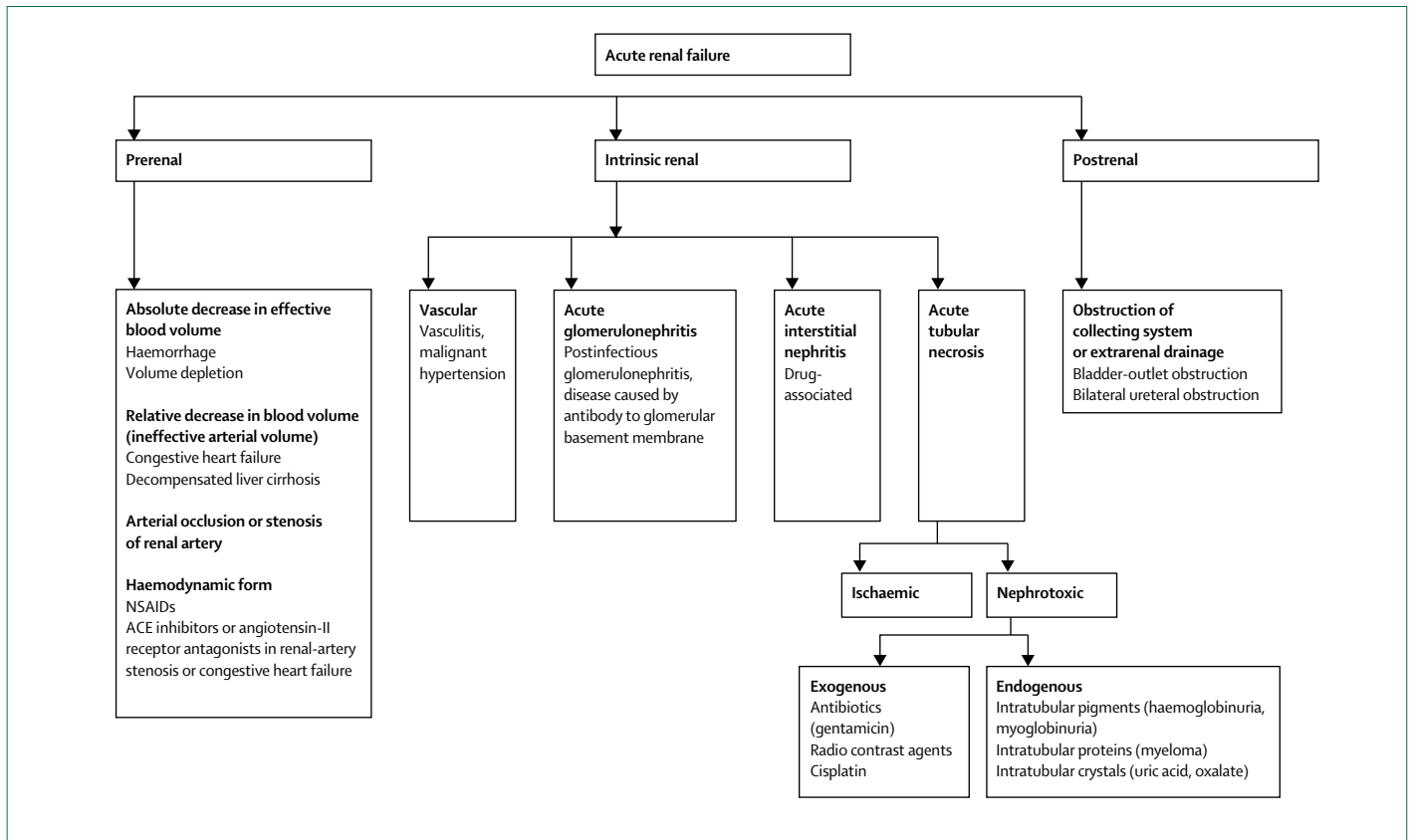


Figure 1: Classification and major causes of acute renal failure

NSAIDs=non-steroidal anti-inflammatory agents; ACE=angiotensin-converting enzyme.

advanced acute renal failure was observed in 102 per million per year.

A prospective hospital-based study, again in the UK,⁹ found that the incidence of renal replacement therapy for acute renal failure was 131 per million per year, with a further 72 per million per year receiving this treatment for acute on chronic renal failure.⁹

An estimated 5–20% of critically ill patients experience an episode of acute renal failure during the course of their illness, in many cases accompanied by multiorgan dysfunction syndrome.^{10–12} Metnitz and colleagues¹³ found that acute renal failure requiring renal replacement therapy complicated 4.9% of admissions to intensive-care units. Acute renal failure occurs in about 19% of patients with moderate sepsis, 23% of those with severe sepsis, and 51% of those with septic shock when blood cultures are positive.¹⁴

A recent analysis from the PICARD Study Group observed a changing range of acute renal failure in critically ill patients, characterised by a large burden of comorbidity, such as pre-existing chronic kidney disease, and extensive extrarenal complications, necessitating dialysis in most of the patients.¹⁵ There was also a wide variation across US institutions in characteristics of patients and practice patterns.

Acute prerenal failure

Prerenal azotaemia, in which the integrity of the renal tissue is preserved, is an appropriate physiological response to renal hypoperfusion¹⁶ and can complicate any disease characterised by either true hypovolaemia or a reduction in the effective circulating volume, such as low cardiac output, systemic vasodilatation, or intrarenal vasoconstriction. Hypovolaemia leading to a fall in systemic blood pressure activates several neurohumoral vasoconstrictive systems which act in concert to maintain the blood pressure and preserve cardiac output and cerebral perfusion.¹⁷

The kidney responds to changes in renal perfusion pressure by autoregulating renal blood flow and GFR within fairly narrow limits. When the blood pressure falls, gradual dilation of preglomerular arterioles is mediated by the generation within the kidney by angiotensin of vasodilating products of arachidonic acid (prostaglandin I₂)^{18,19} and of nitric oxide.²⁰ In the lower zone of autoregulation, concomitant vasoconstriction of the postglomerular arterioles, mainly under the influence of angiotensin II, maintains a constant glomerular capillary hydrostatic pressure.

The tubuloglomerular feedback mechanism stabilises both GFR and fluid delivery to the distal nephron and is

mediated by a complex communication between the macula densa and the glomerular microvasculature. In settings of acute volume depletion associated with increased proximal reabsorption, tubuloglomerular feedback mitigates the prerenal reduction in GFR.^{16,17}

Drugs that interfere with the autoregulation of renal blood flow and GFR can provoke acute prerenal failure. Acute inhibition of cyclo-oxygenase (type I or II) by non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the GFR and renal blood flow in particular clinical situations, such as atherosclerotic cardiovascular disease in a patient older than 60 years, pre-existing chronic renal insufficiency (serum creatinine >180 $\mu\text{mol/L}$), and states of renal hypoperfusion such as in sodium depletion, diuretic use, hypotension, and sodium-avid states such as cirrhosis, nephrotic syndrome, and congestive heart failure.^{21,22} Hyperkalaemia, sometimes out of proportion to the degree of renal impairment, can occur when these patients are concomitantly treated with potassium-sparing diuretics, inhibitors of angiotensin-converting enzyme (ACE), or angiotensin-II-receptor blockers.^{23,24} There is little evidence that NSAIDs impair renal function in otherwise healthy individuals.

Haemodynamic acute renal failure caused by ACE inhibitors or by angiotensin-II-receptor blockers develops in patients with stenosis of the renal artery in a solitary kidney or with bilateral renal-artery stenosis. Renovascular disease has been found in 34% of elderly people with heart failure,²⁵ but patients with hypovolaemia, severe chronic heart failure, polycystic kidney disease, or intrarenal nephrosclerosis without renal-artery stenosis are also at risk. The frequency of acute renal failure induced by ACE inhibitors varies between 6% and 23% in patients with bilateral renal-artery stenosis and increases to 38% in patients with unilateral stenosis in a single kidney.²⁶

Prerenal azotaemia can be corrected if the extrarenal factors causing the renal hypoperfusion are reversed. When not corrected, persistent renal hypoperfusion will ultimately lead to ischaemic acute tubular necrosis.

Acute postrenal acute renal failure

In any patient presenting with acute renal failure, an obstructive cause must be excluded because prompt intervention can result in improvement or complete recovery of renal function. Obstructive uropathy is more common in selected populations such as older men with prostatic disease and patients with a single kidney or intra-abdominal cancer, particularly pelvic cancer.^{27,28} Severe ureteral obstruction is also seen with small inflammatory aortic aneurysms; this type of obstruction can be successfully treated with corticosteroids when surgery is not an option.²⁹ Most causes of obstructive uropathy are amenable to therapy and the prognosis is generally good, depending on the underlying disease.

Important clinical sequelae of postrenal acute renal

failure are the postobstructive diuresis and the presence of hyperkalaemic renal tubular acidosis.²⁹ Profuse diuresis (>4 L/day) can occur after the release of the obstruction; it does not occur unless both kidneys, or a single functioning kidney, are completely obstructed. The period of total obstruction is short in most cases, a few days to a maximum of a week. Once the obstruction is relieved, the urine output generally ranges from 4 L to 20 L per day; some patients become volume depleted, necessitating careful monitoring and adjustment of the volume and electrolyte status during the diuretic phase.

The development of hyperkalaemic hyperchloraemic tubular acidosis is indolent in most cases, and the abnormality tends to persist after correction of the obstruction. Patients in whom the hyperkalaemia is not corrected as their acute renal failure is reversed, by treatment of the obstructive lesion, should be investigated for the presence of tubular acidosis.^{29,30}

Acute tubular necrosis

The worldwide range of factors that cause acute tubular necrosis shows great variability among populations: tropical diseases and snake-bites in Africa, India, southeast Asia, and Latin America;³¹ crushing injuries in earthquake-prone regions;^{32,33} trauma in civilian and military settings; and exposure to an increasing number of environmental and therapeutic nephrotoxic agents.

In intensive-care units, 35–50% of cases of acute tubular necrosis can be attributed to sepsis.^{10,12,34,35} The disorder is increasingly recognised in the context of multiple organ failure, especially in critically ill patients; only a minority of cases in intensive-care units occur without failure of another organ.^{12,34,36}

Acute tubular necrosis after surgery accounts for 20–25% of all cases of hospital-acquired acute renal failure; many of them have prerenal causes.^{37,38} Groups at risk include patients with pre-existing renal impairment, hypertension, cardiac disease, peripheral vascular disease, diabetes mellitus, jaundice, and advanced age. New forms of postsurgery acute tubular necrosis, such as those following liver and cardiac transplantation, reflect changes in types of surgical interventions.⁵

Acute radiocontrast nephropathy is the third commonest cause of acute tubular necrosis in patients admitted to hospital,⁵ and up to 7% need temporary dialysis or progress to end-stage renal disease. The occurrence of radiocontrast nephropathy is associated with increased risk of death³⁹ and leads to an extended hospital stay and increased health-care costs.⁴⁰

Several classes of antibacterial, antifungal, antiviral,⁴¹ and antineoplastic^{42–44} agents are nephrotoxic. Also some environmental agents⁴⁵ and recreational drugs⁴⁶ can cause acute renal failure.

Pathogenesis of acute tubular necrosis

Two components are important in the acute decrease of GFR: a vascular component, including intrarenal

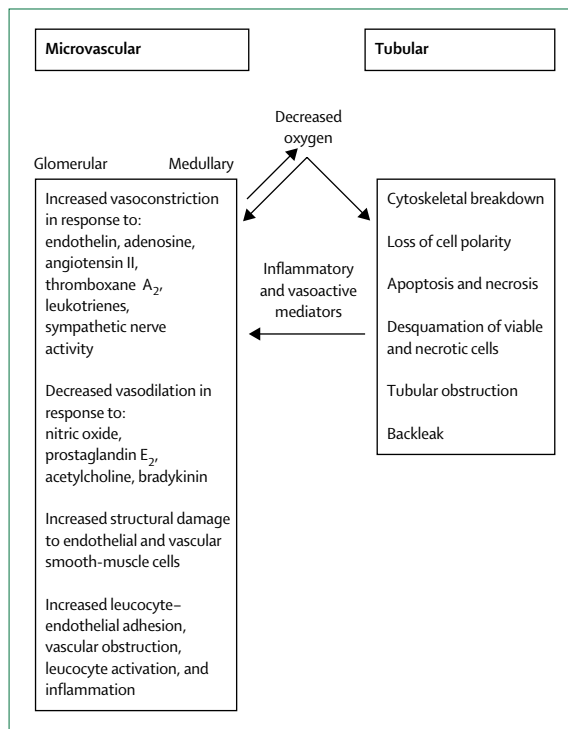


Figure 2: Pathophysiology of ischaemic acute renal failure
 Reproduced with permission from Bonventre and Weinberg.⁵⁴

vasoconstriction with a fall in glomerular filtration pressure, vascular congestion in the outer medulla, and activation of tubuloglomerular feedback; and a tubular component, including tubular obstruction, transtubular backleak of the filtrate, and interstitial inflammation. New concepts such as sublethal cell injury, apoptosis, and cell repair after injury are emerging.

This section briefly summarises selected features of the pathophysiology of sepsis-related and postischaemic types of acute tubular necrosis. The cellular mechanisms of toxic acute tubular necrosis show similarities with the pathophysiology of postischaemic acute tubular necrosis; a recent review of this topic gives more specific details.⁴⁷

Sepsis-related acute tubular necrosis

Some advances in elucidation of the pathophysiology and genetic basis for the host response to sepsis have changed understanding of the syndrome. The prevailing theory was that sepsis represents an uncontrolled inflammatory response, but the individual immunological response to infection is now known to be determined by many factors, including the virulence of the organism, the size of the inoculum, and the patient's coexisting illnesses, age, and polymorphisms in genes for cytokines. The initial immune response is hyperinflammatory, but the response rapidly progresses to hypoinflammatory. In critically ill patients, the initial hyperinflammatory response can even be blunted and there is long-lasting

depression of immune function, culminating in death.⁴⁸

The haemodynamic hallmark of sepsis is generalised arterial vasodilatation with an associated decrease in systemic vascular resistance, resulting in arterial underfilling, which is associated with activation of the neurohumoral axis and an increase in cardiac output secondary to the decreased cardiac afterload. Activation of the sympathetic nervous system and the renin-angiotensin-aldosterone axis, the non-osmotic release of vasopressin, and an increase in cardiac output are essential in maintaining the integrity of the arterial circulation in patients with severe sepsis and septic shock, but these haemodynamic changes can lead to acute renal failure.¹⁴ The arterial vasodilatation that accompanies sepsis is mediated, at least partly, by cytokines that upregulate the expression of inducible nitric oxide synthase in the vasculature.⁴⁹

In contrast to the systemic vasodilatation, there is evidence that early in sepsis-related acute renal failure the predominant pathogenetic factor is renal vasoconstriction with intact tubular function, as shown by increased reabsorption of tubular sodium and water. Renal vasoconstriction in sepsis seems to be due, at least partly, to the ability of tumour necrosis factor α to release endothelin.⁵⁰ When endotoxin is present in the blood, endothelin can also cause general leakage of fluid from the capillaries and thereby diminish plasma volume.⁵¹ Endothelial damage occurs during sepsis and can be associated with microthrombi and high concentrations of von Willebrand factor in the circulation.⁵² Sepsis-related impairment of the endothelium can also attenuate or abolish the normal effect of endothelial nitric oxide synthase in the kidney to counteract the vasoconstrictor effects of norepinephrine, endothelin, and angiotensin II.⁵³

Ischaemic acute tubular necrosis

Figure 2 summarises the crucial factors in postischaemic acute tubular necrosis.⁵⁴ The molecular and cellular features have been established in animal models.⁵⁴⁻⁵⁸ The reported animal data are quite consistent, but their relevance to human ischaemic or nephrotoxic acute tubular necrosis is still questionable.⁵⁹⁻⁶¹

Histology

The typical histological features of human acute tubular necrosis include vacuolation, loss of brush border in proximal tubular cells, and sloughing of tubular cells into the lumen, leading to cast obstruction. Interstitial oedema with mild to moderate leucocyte infiltration can produce widely spaced tubules. Although the disorder is named necrosis, frankly necrotic cells are not a common finding and histological evidence of injury is limited in many cases despite striking functional impairment.^{62,63} With advanced injury, tubular epithelial cells detach from the basement membrane and contribute to

intraluminal aggregation of cells and proteins resulting in tubular obstruction.⁶⁴

Renal blood supply

The kidneys receive normally 25% of cardiac output, but renal blood flow is not uniformly distributed within the organs. Most of the blood supply is directed to the renal cortex where the tissue partial pressure of oxygen (pO_2) is 6.65–13.3 kPa. By contrast, in the outer medulla and medullary rays, countercurrent oxygen exchange occurs leading to a progressive fall in pO_2 from cortex to medulla. This process results in borderline chronic oxygen deprivation with a pO_2 as low as 1.3–2.9 kPa for the cells in the S₃ segment of the proximal tubule and the medullary thick ascending limbs, despite their high metabolic activity due to the activity of the basolateral sodium/potassium ATPase.⁶⁵

In established acute tubular necrosis, renal blood flow is decreased by 30–50%,^{66–68} and there is evidence of a selective reduction in blood supply to the outer medulla. Several vasoconstrictors have been implicated in the reduced renal blood flow, including angiotensin II, thromboxane A₂, prostaglandin H₂, leukotrienes C4 and D4, endothelin 1, and adenosine as well as increased sympathetic-nerve stimulation.⁶⁹

Evidence for dysfunction of cortical endothelial cells in ischaemia–reperfusion has come from the partial functional protection observed when human umbilical-vein endothelial cells or human embryonic kidney cells expressing endothelial nitric oxide synthase were implanted in the kidney.⁷⁰

Until recently, the evolution of clinical acute tubular necrosis was somewhat arbitrarily divided into initiation, maintenance, and recovery phases. A fourth extension phase has been described, connecting the initiation and maintenance phases.^{57,71} This phase is characterised by continued hypoxia and an inflammatory response,⁷² which are both more pronounced at the level of the corticomedullary junction. Although the proximal tubule cells in the outer cortex undergo cellular repair after return of the blood flow to near-normal values, cells in the S₃ proximal tubule and thick ascending limbs, as well as endothelial cells, continue to undergo injury, necrosis, and apoptosis, so the GFR continues to fall.

Inflammation has a major role in the pathophysiology of acute renal failure resulting from ischaemia; endothelial and epithelial cells as well as leucocytes and T cells contribute to this inflammatory response. The inflammatory cells are recruited during reperfusion and release chemokines and cytokines that further increase the inflammatory cascade.^{72–74}

Tubular factors

Renal ischaemia results in rapid loss of cytoskeletal integrity and cell polarity with shedding of the proximal tubule brush border, mislocalisation of adhesion molecules and other membrane proteins such as the

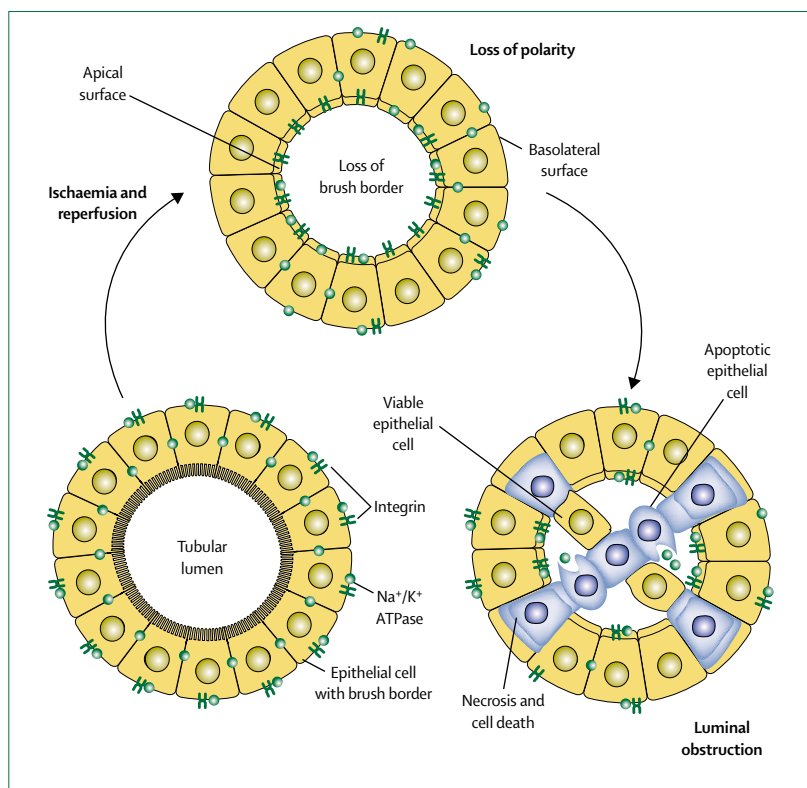


Figure 3: Tubular changes in the pathophysiology of ischaemic acute tubular necrosis

After ischaemia and reperfusion, morphological changes occur in the proximal tubules, including loss of polarity, loss of the brush border, and redistribution of integrins and sodium/potassium ATPase to the apical surface. Calcium and reactive oxygen species also have roles in these morphological changes, in addition to subsequent cell death resulting from necrosis and apoptosis. Both viable and non-viable cells are shed into the tubular lumen, resulting in the formation of casts and luminal obstruction and contributing to the reduction in the GFR. Reproduced with permission from Schrier et al.⁵⁸

sodium/potassium ATPase, apoptosis, and necrosis.⁵⁴ With severe injury, viable and non-viable cells are desquamated, leaving regions where the basement membrane remains the only barrier between the filtrate and the peritubular interstitium. Backleak of the filtrate can then occur, especially when the pressure in the tubule is increased owing to intratubular obstruction.⁷⁵

Figure 3 shows the most important tubular changes in the pathophysiology of ischaemic acute tubular necrosis.⁵⁸ Many biochemical pathways are activated by severe cell injury and lead to cell necrosis. These pathways include severe depletion of cell energy stores (ATP); increased tissue concentrations of reactive oxygen species; intracellular acidosis; raised concentrations of cytosolic calcium; increased activity of phospholipases; release of proteases from the tubular-cell brush border; and loss of lipid and transmembrane protein polarity in the tubular-cell apical and basolateral surface membranes.^{54,55} One of the consequences is that, owing to disruption of the cortical-cell actin cytoskeleton,^{76,77} the basolateral sodium/potassium ATPase relocates to the apical cell membrane.⁷⁸

The dual role of nitric oxide in the pathogenesis of ischaemic acute renal failure was summarised by Goligorsky and Noiri.⁷⁹ Acute renal ischaemia induces increased expression of inducible nitric oxide synthase; blockade of the enzyme by antisense oligonucleotides affords functional protection, at least in rats.⁸⁰ Scavenging of nitric oxide produces peroxynitrite, which causes tubule damage during ischaemia.⁸¹

In hypoxia, integrins, mediating cell–cell adhesion, move from a predominantly basolateral location to the apical cell membrane, which leads to tubular-cell desquamation,^{82,83} the integrin receptors on the apical cell membrane further lead to adhesion of desquamated cells to the cells remaining *in situ* and, after binding to the RGD sequence of the Tamm-Horsfall protein, promote tubule cast formation, distal tubular obstruction, and decreased GFR.⁸⁴

Damaged cells die not only from necrosis but also from apoptosis.^{85,86} Changes typical of apoptosis include condensation of the cell and of the nuclei, DNA fragmentation into nucleosomal units of 200 bp fragments, chromatin condensation, generation of evulsed membrane segments (zeiosis), formation of apoptotic bodies, cellular shrinkage, and disintegration of mitochondria. Unlike necrosis, apoptotic cell death is an active process that requires participation of the dying cell and changes in cellular biochemistry. Because apoptosis does not lead to the release of intracellular material into the extracellular space, it does not result in an inflammatory response.⁸⁷ Almost all apoptotic stimuli induce the activation of specific proteases, called caspases, which cleave target proteins at asparagine residues. An important function in apoptosis is also played by sphingomyelinases and ion channels. Apoptosis is most commonly seen in distal tubular cells, both in animals and in allografts of patients with biopsy-confirmed acute tubular necrosis.⁸⁸

Repair of renal injury

Proximal tubules can undergo repair, regeneration, and proliferation after damage. In the outer cortex, most of the cells are sublethally injured and undergo repair after adequate reperfusion. The first phase of this regeneration process consists of the death and exfoliation of the proximal tubular cells and is characterised by expression of stress response genes and the accumulation of mononuclear cells. Shortly after the experimental induction of acute renal failure, many normally quiescent kidney cells enter the cell cycle. The cell undergoing these changes can either check the progression of the cycle and repair damage before proceeding or enter a pathway destined to cell death. This decision point is carefully regulated, and cyclin-dependent kinase inhibitors, especially p21, are important in the regulation. Investigation of the effects on acute renal failure of selected gene knock-outs in mice has contributed to the recognition of many previously unappreciated molecular

pathways. The interface between the repair pathways and the cell-death pathways is emerging, but phosphorylation events crucial to cell function reside in the cyclin-dependent kinases and the kinases, phosphatases, inhibitors, and activators that regulate their activities.⁸⁹

Growth factors could play a part in determining the fate of the epithelial cells and might contribute to the generation of signals that result in neutrophil and monocyte infiltration. In the second phase, poorly differentiated epithelial cells appear; they are thought to represent a population of stem cells residing in the kidney.⁹⁰ This stage is therefore a dedifferentiation stage.

In the third phase, there is a pronounced increase in proliferation of the surviving proximal tubule cells, and growth factors could have an important role in this response.⁹¹ In this last phase, the regenerative tubular cells regain their differentiated character and produce a normal proximal-tubule epithelium.

Stem-cell research has shown that haemopoietic and other tissue-specific stem cells can cross tissue and even germ-line barriers and give rise to a wide range of cell types.^{92,93} This plasticity of stem cells could be useful in therapeutic strategies designed to improve tissue regeneration after severe organ injury. Traditionally, stem cells were thought to be organ specific.^{94,95} Experiments with transplantation of whole bone marrow showed that bone-marrow-derived stem cells could populate the renal tubular epithelium.^{96,97} Injection of mesenchymal stem cells derived from male bone marrow protected cisplatin-treated syngeneic female mice from renal functional impairment and severe tubular injury.⁹⁸ However, mobilisation of haemopoietic stem cells is associated with important granulocytosis, which could aggravate the intrarenal inflammation and impair renal recovery.⁹⁹

Diagnostic approach

The diagnostic approach to acute renal failure includes a careful history and record review, a thorough physical examination, and the judicious interpretation of laboratory data, including examination of the urinary sediment and other urinary chemistry, and appropriate ultrasonographic and radiological investigations.^{100,101}

Serum creatinine

In acute renal failure, renal function is commonly monitored by following the daily variations in serum creatinine concentration. However, this variable has limitations as a marker of GFR in patients with acute renal failure. The serum creatinine concentration depends not only on urinary clearance of creatinine but also on the rate of production and the volume of distribution. Furthermore, serum creatinine concentration does not accurately reflect GFR in the non-steady-state condition of acute renal failure. Correct interpretation of serum creatinine concentrations is hampered by the variation in calibration of the different creatinine assays.^{102–104}

Serum cystatin C

Among newer markers, serum cystatin C has not yet been well validated as a GFR indicator in acute renal failure.^{105,106} However, some studies have found it to be an early and reliable marker of acute renal failure in patients in intensive-care units.^{107–109}

Urine volume

Acute anuria or severe oliguria are quite specific indicators of acute renal failure, although severe acute renal failure can exist despite normal urine output. Changes in urine output can occur long before biochemical changes are apparent. Prerenal forms of acute renal failure nearly always present with oliguria (<400 mL/day), although non-oliguric forms have been reported.¹¹⁰ Postrenal and renal forms of acute renal failure can present with any pattern of urine flow ranging from anuria to polyuria.

Urinary indices (table 2)

As long as tubular function remains intact, renal vasoconstriction during the initiation phase of acute tubular necrosis is associated with increased tubular sodium reabsorption and the fractional excretion of filtered sodium:

$$\frac{\text{Urine sodium} \times \text{plasma creatinine}}{\text{Plasma sodium} \times \text{urine creatinine}} \times 100$$

will be less than 1%. Prerenal disorders also result in low fractional excretion of uric acid and lithium (each <7%). An exception to this physiological response is when the patient receives a diuretic, including mannitol, or has glucosuria. Carvounis and colleagues¹¹¹ found that a low fractional excretion of urea (<35%) is more sensitive and specific than the fractional excretion of sodium in differentiating between prerenal and renal causes of acute renal failure, especially when diuretics have been administered.¹¹¹

Biomarkers

Several biomarkers have been proposed for the early diagnosis of acute renal failure and are currently under study.^{112,113} These include urinary interleukin 18¹¹⁴ and tubular enzymes, such as the intestinal form of alkaline phosphatase, N-acetyl-β-glucosaminidase, and alanine aminopeptidase.¹¹⁵ Kidney injury molecule 1, a type-1 transmembrane protein, is extensively expressed in proximal tubule cells in biopsy samples from patients with confirmed acute tubular necrosis, and the normalised concentrations of this protein were significantly higher in ischaemic acute tubular necrosis than in other forms of acute renal failure or chronic renal disease.¹¹⁶

Identification of urinary proteins expressed during acute renal failure might lead to the identification of

	Prerenal	Renal
Urinalysis	Hyaline casts	Abnormal
Specific gravity	1-020	1-010
Osmolality (mmol/kg)	>500	>300
Sodium (mmol/L)	<20	>40
Fractional excretion of sodium (%)	<1	>2
Fractional excretion of urea (%)	<35	>35
Fractional excretion of uric acid (%)	<7	>15
Fractional excretion of lithium (%)	<7	>20
Low-molecular-weight proteins	Low	High
Brush-border enzymes	Low	High

Table 2: The most important urinary variables in the differential diagnosis between prerenal and renal acute renal failure

novel targets for early diagnosis and therapy. Hampel and co-workers¹¹⁷ found that after radiocontrast administration, protein expression differed between patients with normal renal function and those with impaired renal function at baseline.

Prevention and non-dialysis treatment

Progress in elucidation of the pathophysiology has led to development and testing of many therapeutic drug and other interventions in animal and human forms of acute tubular necrosis.^{118–121} The disorder can be prevented in some patients by careful attention to volume status and cardiac output, and the avoidance of nephrotoxic agents. These measures are more important when renal blood flow might already be compromised, such as in elderly patients or those with heart failure, liver disease, previous renal insufficiency, renal-artery stenosis, or diabetes mellitus. Agents that impair autoregulation of renal blood flow, such as NSAIDs, ACE inhibitors, or angiotensin-II-receptor blockers should be used with caution, as discussed earlier. Nephrotoxic agents should be limited and plasma concentrations should be measured to guide dosing of aminoglycosides and ciclosporin. Allopurinol and the recently introduced rasburicase, a recombinant urate oxidase preparation, decrease synthesis of uric acid in patients with leukaemia and lymphoma who are prone to uric-acid nephropathy.¹²² Forced alkaline diuresis prevents blockage of renal tubules by uric acid or methotrexate in these malignant diseases and by casts in rhabdomyolysis.

Discussion of the pharmacological treatments that have been tested in sepsis and related acute renal failure are beyond the scope of this seminar, but they have been discussed elsewhere.^{14,48,123,124}

Volume expansion

The preventive and therapeutic value of volume expansion alone is not easy to estimate, because fluids are commonly included as part of the overall management of patients in clinical studies, together with the administration of diuretics, dopamine, or both. The value of volume therapy and the nature of fluids

(crystalloids or colloids) to be used in critically ill patients with or without acute renal failure are controversial.^{125–127}

The SAFE trial found that fluid resuscitation with saline or with albumin gave similar results in critically ill patients.¹²⁸ Hydration has been suggested to prevent postsurgery acute tubular necrosis and that induced by contrast media, platinum, or amphotericin B, as well as the intrarenal tubular precipitation of crystals after high doses of methotrexate, sulphonamides, and aciclovir.¹²¹ Mueller and colleagues¹²⁹ found that hydration with isotonic saline is superior to the routinely recommended half-isotonic hydration in the prevention of contrast-media-associated nephropathy. Overzealous fluid administration can lead to pulmonary oedema, especially in patients with oliguria or anuria.

Use of diuretics and dopamine

Assessment of furosemide, mannitol, and low-dose dopamine in the prevention or reversal of acute tubular necrosis has given inconsistent results.^{130,131} Mannitol prevented acute renal failure only in rhabdomyolysis and kidney-transplant surgery. With adequate circulating volume, loop diuretics promote diuresis in some forms of oliguric acute renal failure,^{131,132} but some studies have suggested that their administration is associated with a higher risk of death and delayed recovery of renal function.^{133,134} However, a large multicentre study¹³⁵ did not confirm that diuretics adversely affect survival.

Low-dose dopamine ($1\text{--}3\ \mu\text{g kg}^{-1}\ \text{min}^{-1}$, intravenously) is a renal vasodilator and has frequently been used alone or in combination with furosemide, particularly in patients in intensive care. Prospective controlled trials and careful meta-analysis have led to the conclusion that dopamine does not reduce mortality or promote the recovery of renal function.^{136–139} The risks associated with dopamine in critically ill patients have been summarised elsewhere.¹²¹

N-acetylcysteine

Three meta-analyses during the past 2 years^{140–142} have concluded that, compared with periprocedural hydration alone, oral acetylcysteine with hydration significantly lowers the risk of contrast nephropathy in patients with chronic renal insufficiency. We should emphasise that acetylcysteine without adequate hydration is not sufficient and that in some of these studies the individual contribution of acetylcysteine is difficult to delineate. However, every meta-analysis also found studies showing no benefit. Furthermore, acetylcysteine seems to affect the tubular handling of creatinine directly, so a decrease in serum creatinine concentration with this drug does not necessarily lead to a protective effect on the GFR.¹⁴³

Calcium-channel blockers

Some investigators have shown that the prophylactic administration of calcium-channel blockers protects

Panel 1: Management priorities in patients with acute renal failure

- Search for and correct prerenal and postrenal factors
- Review medications and stop administration of nephrotoxins
- Optimise cardiac output and renal blood flow
- Restore and/or increase urine flow
- Monitor fluid intake and output; measure bodyweight daily
- Search for and treat acute complications (hyperkalaemia, hyponatraemia, acidosis, hyperphosphataemia, pulmonary oedema)
- Provide early nutritional support
- Search for and aggressively treat infections
- Expert nursing care (management of catheter care and skin in general; psychological support)
- Initiate dialysis before uraemic complications emerge
- Give drugs in doses appropriate for their clearance

against post-transplant delayed graft failure.¹²¹ However, meta-analysis¹⁴⁴ suggested that the issue of renal protection with calcium-entry blockers in the prevention of post-transplant acute tubular necrosis is not settled. In other settings of acute renal failure¹⁴⁵ and after cardiac surgery,¹⁴⁶ the preventive role of calcium-channel blockers was more promising.

Other therapeutic measures

Various other therapeutic agents, both established and novel, have been investigated for potential use in acute tubular necrosis, including atrial natriuretic peptide, theophylline, epidermal and insulin-like growth factors, antibodies to adhesion molecules, scavengers of oxygen free radicals, aminoacid infusions, and prostaglandins. Remarkable protection against renal ischaemia-reperfusion injury was observed with administration of a single dose of erythropoietin.¹⁴⁷ A direct tubular-cell effect by prevention of caspase activation in vivo and reduction of apoptotic cell death was shown. To date, two randomised, placebo-controlled trials with insulin-like growth factor I, one in critically ill patients and one in renal transplantation, have had negative results.^{148,149} None of these experimental therapies has yet been proven to be safe or effective for use in human acute renal failure.¹²¹

Supportive treatment of acute renal failure

The management of patients with established acute tubular necrosis is summarised in panel 1. Current therapy is aimed mainly at prevention and treatment of the associated complications. Hyperkalaemia was a frequent cause of death in the past but has become less common with greater access to dialysis and with development of rapid, accurate laboratory procedures to monitor the clinical course. Restriction of potassium in the diet and infusions and avoidance of potassium-containing drugs are especially important. Serum potassium concentrations can increase rapidly in

patients with oliguria, anuria, hypercatabolism, or rhabdomyolysis. Emergency treatment of hyperkalaemia, primarily dictated by changes in the electrocardiogram, includes the use of intravenous calcium, driving potassium into cells with sodium bicarbonate, an infusion of glucose and insulin, or both. These emergency measures do not remove potassium from the body, and additional therapy with a sodium-potassium exchange resin such as sodium polystyrene sulfonate (Kayexalate) or by dialysis will be needed as a second step. Haemodialysis is the most rapid way to remove potassium.

Abnormalities in water and sodium metabolism need careful management in acute renal failure. Bodyweight should be measured daily, and daily intake and output recorded. An oliguric patient's daily fluid intake should be limited to 400 mL plus the previous day's urinary output unless there are physical signs of volume depletion or volume overload. Dietary sodium should be restricted to 2 g (87 mmoles) per day. A patient with acute tubular necrosis, if not receiving hyperalimentation, is expected to lose 0.3–0.5 kg bodyweight per day. If this loss does not occur or if there is weight gain, fluid therapy should be reassessed. Hyponatraemia might necessitate stringent free-water restriction.

Acidosis is common in acute renal failure.¹⁵⁰ Small amounts of sodium bicarbonate can be given if the serum bicarbonate concentrations falls below 15–18 mmol/L, although the potential for volume overload should be recognised. Hyperphosphataemia should be treated with calcium carbonate or other phosphate binders. Hypermagnesaemia can occur after an exogenous load of magnesium, and magnesium-containing antacids should be avoided. Severe hyperphosphataemia or hypermagnesaemia can be treated with dialysis.

Nutritional support is an important part of the treatment of acute renal failure. It should be designed to give adequate calories without excessive volume. The caloric requirement in acute renal failure is high, especially in patients who are hypercatabolic. Carbohydrate intake should be sufficient (more than 100 g per day) to avoid breakdown of endogenous protein for glucose. The protein requirements depend on the clinical status. With oral feeding, an initial diet of 40 g/day high-quality protein can be given, and the protein content increased if deemed necessary. Provision of the nutritional needs of the patient might not be possible without dialysis, which allows larger quantities to be given. Enteral or parenteral alimentation might be necessary in postoperative patients or in those with anorexia or vomiting. The use of essential aminoacids or their keto analogues in postoperative or trauma patients has been suggested but not proven to improve the outcome of acute renal failure.

Attention has lately been given to the adverse effects of hyperglycaemia,¹⁵¹ and an extensive controlled trial showed a reduction in mortality and morbidity of

Panel 2: Proposed criteria for initiation of renal replacement therapy in critically ill patients with acute renal failure

Oliguria: urine output <200 mL in 12 h
 Anuria: urine output <50 mL in 12 h
 Hyperkalaemia: potassium concentration >6.5 mmol/L
 Severe acidemia: pH <7.0
 Azotaemia: urea concentration >30 mmol/L
 Uraemic encephalopathy
 Uraemic neuropathy/myopathy
 Uraemic pericarditis
 Plasma sodium abnormalities: concentration >155 mmol/L or <120 mmol/L
 Hyperthermia
 Drug overdose with dialysable toxin

critically ill patients with strict control of blood glucose concentration.¹⁵² Multivariate analysis showed that the lowered blood glucose concentration rather than the insulin dose was related to lower mortality, critical-illness neuropathy, bacteraemia, and inflammation.¹⁵³

Since infections are a common cause of death in these critically ill patients,⁵⁸ expert nursing care of catheter sites and skin is very important. Doses of several drugs must be altered in acute renal failure, especially those that are renally excreted or those with pharmacokinetics that are changed in azotaemia or dialysis.

Renal replacement therapy

There are no absolute rules as to when dialysis should begin, but too soon is better than too late, and the treatment should be started before complications occur.¹⁵⁴ Indications for immediate treatment in critically ill patients with acute renal failure include hyperkalaemia (causing significant electrocardiographic changes), severe pulmonary oedema, uraemic acidosis (causing cardiac compromise), and gross uraemia (panel 2).

	Intermittent haemodialysis	Continuous renal replacement therapy
Advantages	<ul style="list-style-type: none"> Lower risk of systemic bleeding More time available for diagnostic and therapeutic interventions More suitable for severe hyperkalaemia Lower cost 	<ul style="list-style-type: none"> Better haemodynamic stability Fewer cardiac arrhythmias Improved nutritional support Better pulmonary gas exchange Better fluid control Better biochemical control Shorter stay in intensive-care unit
Disadvantages	<ul style="list-style-type: none"> Availability of dialysis staff More difficult haemodynamic control Inadequate dialysis dose Inadequate fluid control Inadequate nutritional support Not suitable for patients with intracranial hypertension No removal of cytokines Potential complement activation by non-biocompatible membranes 	<ul style="list-style-type: none"> Greater vascular access problems Higher risk of systemic bleeding Long-term immobilisation of patient More filter problems (ruptures, clotting) Greater cost

Table 3: Advantages and disadvantages of intermittent versus continuous renal replacement therapy

Table 3 summarises the advantages and disadvantages of intermittent haemodialysis and continuous renal replacement therapies such as continuous venovenous haemofiltration. There are no evidence-based guidelines on the optimum dialysis treatment of acute renal failure.^{155,156} Continuous renal replacement therapy was claimed to be superior to intermittent haemodialysis. Many controlled studies^{157–161} and a recent meta-analysis¹⁶² have not found differences in outcome. In specific conditions, however, one of the dialysis modalities is an absolute preference: for example, continuous therapy in patients with cerebral oedema or liver failure, or intermittent haemodialysis in patients with increased bleeding risk.

A landmark study underscored the importance of the dose of dialysis in continuous renal replacement therapy.¹⁶³ Patients undergoing continuous venovenous haemofiltration had better outcomes with filtration rates of 35 mL kg⁻¹ h⁻¹ or 45 mL kg⁻¹ h⁻¹ than those treated at the lower rate of 20 mL kg⁻¹ h⁻¹. Although no comparable study has been done in intermittent haemodialysis,¹⁶⁴ daily dialysis resulted in better control of uraemia, fewer hypotensive episodes during dialysis, and more rapid resolution of acute renal failure.¹⁶⁵ Classic dialysis adequacy indices, such as Kt/V urea (clearance×time of dialysis session/distribution volume of urea) should be used with caution because they need an estimate of total body water, which is conventionally based on anthropometric values that may be incorrect in critically ill patients with acute renal failure.¹⁶⁶

Meta-analyses have further shown that the use of biocompatible membranes might influence survival positively, however, without effect on recovery of renal function.^{167–170} Slow extended daily dialysis emerged as a hybrid modality of renal replacement therapy and has promising features because it combines the advantages of both continuous and intermittent approaches.^{156,171–173}

Prognosis

When acute renal failure is severe enough to necessitate renal replacement therapy, in-hospital mortality is high, exceeding 50%.^{9,12,174} Mortality is extremely high in critically ill patients who have multiorgan failure.^{10,175,176} Mortality rates have changed little over the past few decades despite significant advances in supportive care; however, this lack of improvement may be more apparent than real because patients nowadays are older and have more pre-existing chronic health problems.¹⁷⁷ Certain combinations of gene polymorphism are related to the risk of death among patients with acute renal failure who need dialysis.^{178,179} The combination of a high concentration of tumour necrosis factor α and a genotype leading to low production of interleukin 10 was associated with a higher risk of death than for patients with low concentrations of tumour necrosis factor α and genotypes conferring intermediate or high production of interleukin 10.

The long-term effects of acute renal failure are unclear and controversial because of the diverse (and in many cases multiple) causes of the disorder and the paucity of long-term follow-up studies. Nevertheless, the view that renal recovery is complete is simplistic, and progressive renal dysfunction after severe acute renal failure is commonly observed.^{180–183} Acute renal failure is irreversible in 5% of patients, but in elderly people this proportion is as high as 16%.¹⁸⁴ Recent reports on children suggest that residual damage after acute renal failure develops into progressive renal failure by adolescence or early adulthood.^{180–183}

Conflict of interest statement

Norbert Lameire has received fees for speaking and research funding from several companies, including Novartis, Fresenius, Baxter, Gambro, Roche, and Amgen. Raymond Vanholder has received fees for speaking and research funding from several companies, including Fresenius, Baxter, and Roche. Wim Van Biesen has received fees for speaking and research funding from several companies, including Fresenius, Baxter, and Gambro.

References

- Singri N, Ahja SN, Levin ML. Acute renal failure. *JAMA* 2003; **289**: 747–51.
- Kellum JA, Levin N, Bouman C, Lameire N. Developing a consensus classification system for acute renal failure. *Curr Opin Crit Care* 2002; **8**: 509–14.
- Mehta RL, Chertow GM. Acute renal failure definitions and classification: time for change? *J Am Soc Nephrol* 2003; **14**: 2178–87.
- Bellomo R, Ronco C, Kellum JA, Mehta R, Palevsky P, and the ADQI 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* 2004; **8**: R204–12.
- Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis* 2002; **39**: 930–36.
- Feest TG, Round A, Hamad S. Incidence of severe acute renal failure in adults: results of a community based study. *BMJ* 1993; **306**: 481–83.
- Khan IH, Catto GR, Edward N, MacLeod AM. Acute renal failure: factors influencing nephrology referral and outcome. *QJM* 1997; **90**: 781–85.
- Stevens PE, Tamimi NA, Al Hasani MK, et al. Non-specialist management of acute renal failure. *QJM* 2001; **94**: 533–40.
- Metcalfe W, Simpson M, Khan IH, et al. Acute renal failure requiring renal replacement therapy: incidence and outcome. *QJM* 2002; **95**: 579–83.
- Brivet FG, Kleinknecht DJ, Loirat P, Landais PJ. Acute renal failure in intensive care units: causes, outcome, and prognostic factors of hospital mortality: a prospective, multicenter study. *Crit Care Med* 1996; **24**: 192–98.
- de Mendonca A, Vincent JL, Suter PM, et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. *Intensive Care Med* 2000; **26**: 915–21.
- Liano F, Junco E, Pascual J, Madero R, Verde E. The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. *Kidney Int Suppl* 1998; **66**: S16–24.
- Metnitz PGH, Krenn CG, Steltzer H, et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit Care Med* 2002; **30**: 2051–58.
- Schrier RW, Wang W. Acute renal failure and sepsis. *N Engl J Med* 2004; **351**: 159–69.
- Mehta RL, Pascual MT, Soroko S, et al. Spectrum of acute renal failure in the intensive care unit: the PICARD experience. *Kidney Int* 2004; **66**: 1613–21.
- Blantz RC. Pathophysiology of pre-renal azotemia. *Kidney Int* 1998; **53**: 512–23.
- Badr KF, Ichikawa I. Prerenal failure: a deleterious shift from renal

- compensation to decompensation. *N Engl J Med* 1988; **319**: 623–29.
- 18 Baylis C, Brenner BM. Modulation by prostaglandin synthesis inhibitors of the action of exogenous angiotensin II on glomerular ultrafiltration in the rat. *Circ Res* 1978; **43**: 889–98.
 - 19 Dzau VJ, Packer M, Lilly LS, Swartz SL, Hollenberg NK, Williams GH. Prostaglandins in severe congestive heart failure: relation to activation of the renin-angiotensin system and hyponatremia. *N Engl J Med* 1984; **310**: 347–52.
 - 20 De Nicola L, Blantz RC, Gabbai FB. Nitric oxide and angiotensin II: glomerular and tubular interaction in the rat. *J Clin Invest* 1992; **89**: 1248–56.
 - 21 Brater DC. Anti-inflammatory agents and renal function. *Semin Arthritis Rheum* 2002; **32** (suppl 1): 33–42.
 - 22 Gambaro G, Perazella MA. Adverse renal effects of anti-inflammatory agents: evaluation of selective and nonselective cyclooxygenase inhibitors. *J Intern Med* 2003; **253**: 643–52.
 - 23 Schepkens H, Vanholder R, Billiouw JM, Lameire N. Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. *Am J Med* 2001; **110**: 438–41.
 - 24 Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; **351**: 543–51.
 - 25 MacDowall P, Kalra PA, O'Donoghue DJ, Waldek S, Mamtara H, Brown K. Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. *Lancet* 1998; **352**: 13–16.
 - 26 Franklin SS, Smith RD. A comparison of enalapril plus hydrochlorothiazide with standard triple therapy in renovascular hypertension. *Nephron* 1986; **44** (suppl 1): 73–82.
 - 27 Bhandari S, Johnston P, Fowler RC, Joyce A, Turney JH. Non-dilated bilateral ureteric obstruction. *Nephrol Dial Transplant* 1995; **10**: 2337–39.
 - 28 Chapman ME, Reid JH. Use of percutaneous nephrostomy in malignant ureteric obstruction. *Br J Radiol* 1991; **64**: 318–20.
 - 29 Yarger WE. Obstructive urinary tract disease in the elderly. In: Martinez-Maldonado M, ed. Hypertension and renal disease in the elderly. Boston: Blackwell Scientific Publications, 1992: 272–308.
 - 30 Klahr S. Obstructive uropathy. In: Seldin DW, Giebisch G, eds. The kidney: physiology and pathophysiology, 3th edn. Philadelphia: Lippincott Williams & Wilkins, 2000: 2473–512.
 - 31 Barsoum RS. Tropical acute renal failure. *Contrib Nephrol* 2004; **144**: 44–52.
 - 32 Sever MS, Ereik E, Vanholder R, et al. Lessons learned from the catastrophic Marmara earthquake: factors influencing the final outcome of renal victims. *Clin Nephrol* 2004; **61**: 413–21.
 - 33 Lameire N, Mehta R, Vanholder R, Sever M. The organization and interventions of the ISN Renal Disaster Relief Task Force. *Adv Ren Replace Ther* 2003; **10**: 93–99.
 - 34 Cole L, Bellomo R, Silvester W, Reeves JH. A prospective, multicenter study of the epidemiology, management, and outcome of severe acute renal failure in “closed” ICU system. *Am J Respir Crit Care Med* 2000; **162**: 191–96.
 - 35 Hoste EA, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JM, Colardyn FA. Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. *J Am Soc Nephrol* 2003; **14**: 1022–30.
 - 36 Breen D, Bihari D. Acute renal failure as a part of multiple organ failure: the slippery slope of critical illness. *Kidney Int Suppl* 1998; **66**: S25–33.
 - 37 Carmichael P, Carmichael AR. Acute renal failure in the surgical setting. *Aust NZ J Surg* 2003; **73**: 144–53.
 - 38 Deman A, Hoste E, Van Biesen W, Vanholder R, Lameire N. Insuffisance rénale aigue postopératoire: épidémiologie, causes, pronostic et traitement. In: Lesavre P, Drucke T, Legendre C, Niaudet P, eds. Actualités néphrologiques Jean Hamburger. Paris: Flammarion, 2004: 227–54.
 - 39 Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality: a cohort analysis. *JAMA* 1996; **275**: 1489–94.
 - 40 Gruber SJ, Shapiro CJ. Nephropathy induced by contrast medium. *N Engl J Med* 2003; **348**: 2257–59.
 - 41 Dillon JJ. Nephrotoxicity from antibacterial, antifungal, and antiviral drugs. In: Molitoris BA, Finn WF, eds. Acute renal failure: a companion to Brenner and Rector's the kidney, 1st edn. Philadelphia: WB Saunders, 2001: 349–64.
 - 42 Agraharkar M, Guba SC, Safirstein RL. Acute renal failure associated with cancer chemotherapy. In: Molitoris BA, Finn WF, eds. Acute renal failure: a companion to Brenner and Rector's the kidney, 1st edn. Philadelphia: WB Saunders, 2001: 365–75.
 - 43 Boccacandro F, Anderson HV. Contrast-induced nephropathy: back to basics. *J Invasive Cardiol* 2003; **15**: 317–18.
 - 44 Evenepoel P. Acute toxic renal failure. *Best Pract Res Clin Anaesthesiol* 2004; **18**: 37–52.
 - 45 Bach PH. Acute renal failure associated with occupational and environmental settings. In: Molitoris BA, Finn WF, eds. Acute renal failure: a companion to Brenner and Rector's the kidney, 1st edn. Philadelphia: WB Saunders, 2001: 414–24.
 - 46 Turney JH. Acute renal failure associated with recreational drug use. In: Molitoris BA, Finn WF, eds. Acute renal failure: a companion to Brenner and Rector's the kidney, 1st edn. Philadelphia: WB Saunders, 2001: 397–405.
 - 47 Kaushal GP, Portilla D, Megyesi E, Price PM, Safirstein RL. Cellular mechanisms of nephrotoxicity. In: De Broe ME, Porter GA, Bennet WM, Verpooten GA, eds. Clinical nephrotoxins, 2nd edn. Dordrecht: Kluwer Academic Publishers, 2003: 65–76.
 - 48 Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med* 2003; **348**: 138–50.
 - 49 Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med* 2001; **345**: 588–95.
 - 50 Kon V, Badr KF. Biological actions and pathophysiologic significance of endothelin in the kidney. *Kidney Int* 1991; **40**: 1–12.
 - 51 Filep JG. Role for endogenous endothelin in the regulation of plasma volume and albumin escape during endotoxin shock in conscious rats. *Br J Pharmacol* 2000; **129**: 975–83.
 - 52 Reinhart K, Bayer O, Brunkhorst F, Meisner M. Markers of endothelial damage in organ dysfunction and sepsis. *Crit Care Med* 2002; **30** (suppl): S302–12.
 - 53 Schwartz D, Mendonca M, Schwartz I, et al. Inhibition of constitutive nitric oxide synthase (NOS) by nitric oxide generated by inducible NOS after lipopolysaccharide administration provokes renal dysfunction in rats. *J Clin Invest* 1997; **100**: 439–48.
 - 54 Bonventre JV, Weinberg JM. Recent advances in the pathophysiology of ischemic acute renal failure. *J Am Soc Nephrol* 2003; **14**: 2199–210.
 - 55 Lameire NH, Vanholder R. Pathophysiology of ischaemic acute renal failure. *Best Pract Res Clin Anaesthesiol* 2004; **18**: 21–36.
 - 56 Molitoris BA. Transitioning to therapy in ischemic acute renal failure. *J Am Soc Nephrol* 2003; **14**: 265–67.
 - 57 Molitoris BA, Sutton TA. Endothelial injury and dysfunction: role in the extension phase of acute renal failure. *Kidney Int* 2004; **66**: 496–99.
 - 58 Schrier RW, Wang W, Poole B, Mitra A. Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. *J Clin Invest* 2004; **114**: 5–14.
 - 59 Lieberthal W, Nigam SK. Acute renal failure II: experimental models of acute renal failure—imperfect but indispensable. *Am J Physiol Renal Physiol* 2000; **278**: F1–12.
 - 60 Heyman SN, Lieberthal W, Rogiers P, Bonventre JV. Animal models of acute tubular necrosis. *Curr Opin Crit Care* 2002; **8**: 526–34.
 - 61 Rosen S, Heyman SN. Difficulties in understanding human “acute tubular necrosis”: limited data and flawed animal models. *Kidney Int* 2001; **60**: 1220–24.
 - 62 Bohle A, Christensen J, Kokot F, et al. Acute renal failure in man: new aspects concerning pathogenesis: a morphometric study. *Am J Nephrol* 1990; **10**: 374–88.
 - 63 Racusen LC. The morphologic basis of acute renal failure. In: Molitoris BA, Finn WF, eds. Acute renal failure: a companion to Brenner and Rector's the kidney, 1st edn. Philadelphia: WB Saunders, 2001: 1–12.
 - 64 Thadhani R, Pascual M, Bonventre JV. Acute renal failure. *N Engl J Med* 1996; **334**: 1448–60.

- 65 Brezis M, Rosen S. Hypoxia of the renal medulla—its implications for disease. *N Engl J Med* 1995; **332**: 647–55.
- 66 Hollenberg NK, Epstein M, Rosen SM, Basch RI, Oken DE, Merrill JP. Acute oliguric renal failure in man: evidence for preferential renal cortical ischemia. *Medicine (Baltimore)* 1968; **47**: 455–74.
- 67 Hollenberg NK, Adams DF, Oken DE, Abrams HL, Merrill JP. Acute renal failure due to nephrotoxins: renal hemodynamic and angiographic studies in man. *N Engl J Med* 1970; **282**: 1329–34.
- 68 Reubi FC. The pathogenesis of anuria following shock. *Kidney Int* 1974; **5**: 106–10.
- 69 Conger JD. Vascular alterations in acute renal failure: roles in initiation and maintenance. In: Molitoris BA, Finn WF, eds. *Acute renal failure: a companion to Brenner and Rector's the kidney*, 1st edn. Philadelphia: WB Saunders, 2001: 13–29.
- 70 Brodsky SV, Yamamoto T, Tada T, et al. Endothelial dysfunction in ischemic acute renal failure: rescue by transplanted endothelial cells. *Am J Physiol Renal Physiol* 2002; **282**: F1140–49.
- 71 Sutton TA, Fisher CJ, Molitoris BA. Microvascular endothelial injury and dysfunction during ischemic acute renal failure. *Kidney Int* 2002; **62**: 1539–49.
- 72 Bonventre JV, Zuk A. Ischemic acute renal failure: an inflammatory disease? *Kidney Int* 2004; **66**: 480–85.
- 73 Ysebaert DK, De Greef KE, De Beuf A, et al. T cells as mediators in renal ischemia/reperfusion injury. *Kidney Int* 2004; **66**: 491–96.
- 74 Rabb H. The T cell as a bridge between innate and adaptive immune systems: implications for the kidney. *Kidney Int* 2002; **61**: 1935–46.
- 75 Zuk A, Bonventre JV, Matlin KS. Expression of fibronectin splice variants in the postischemic rat kidney. *Am J Physiol Renal Physiol* 2001; **280**: F1037–53.
- 76 Atkinson SJ, Molitoris BA. Cytoskeletal alterations as a basis of cellular injury in acute renal failure. In: Molitoris BA, Finn WF, eds. *Acute renal failure: a companion to Brenner and Rector's the kidney*, 1st edn. Philadelphia: WB Saunders, 2001: 119–31.
- 77 Molitoris BA. Actin cytoskeleton in ischemic acute renal failure. *Kidney Int* 2004; **66**: 871–83.
- 78 Alejandro VS, Nelson WJ, Huie P, et al. Postischemic injury, delayed function and Na⁺/K⁺-ATPase distribution in the transplanted kidney. *Kidney Int* 1995; **48**: 1308–15.
- 79 Goligorsky MS, Noiri E. Duality of nitric oxide in acute renal injury. *Semin Nephrol* 1999; **19**: 263–71.
- 80 Noiri E, Peresleni T, Miller F, Goligorsky MS. In vivo targeting of inducible NO synthase with oligodeoxynucleotides protects rat kidney against ischemia. *J Clin Invest* 1996; **97**: 2377–83.
- 81 Noiri E, Nakao A, Uchida K, et al. Oxidative and nitrosative stress in acute renal ischemia. *Am J Physiol Renal Physiol* 2001; **281**: F948–57.
- 82 Gailit J, Colflesh D, Rabiner I, Simone J, Goligorsky M. Redistribution and dysfunction of integrins in cultured renal epithelial cells exposed to oxidative stress. *Am J Physiol* 1993; **264**: F149–57.
- 83 Romanov V, Noiri E, Czerwinski G, Finsinger D, Kessler H, Goligorsky MS. Two novel probes reveal tubular and vascular Arg-Gly-Asp (RGD) binding sites in the ischemic rat kidney. *Kidney Int* 1997; **52**: 93–102.
- 84 Wangsiripaisan A, Gengaro PE, Edelstein CL, Schrier RW. Role of polymeric Tamm-Horsfall protein in cast formation: oligosaccharide and tubular fluid ions. *Kidney Int* 2001; **59**: 932–40.
- 85 Dagher PC. Apoptosis in ischemic renal injury: roles of GTP depletion and p53. *Kidney Int* 2004; **66**: 506–09.
- 86 Kaushal GP, Basnakian AG, Shah SV. Apoptotic pathways in ischemic acute renal failure. *Kidney Int* 2004; **66**: 500–06.
- 87 Bonegio R, Lieberthal W. Role of apoptosis in the pathogenesis of acute renal failure. *Curr Opin Nephrol Hypertens* 2002; **11**: 301–08.
- 88 Oberbauer R, Rohrmoser M, Regeler H, et al. Apoptosis of tubular epithelial cells in donor kidney biopsies predicts early renal allograft function. *J Am Soc Nephrol* 1999; **10**: 2006–13.
- 89 Price PM, Megyesi J, Safirstein RL. Cell cycle regulation: repair and regeneration in acute renal failure. *Kidney Int* 2004; **66**: 509–14.
- 90 Al Awqati Q, Oliver JA. Stem cells in the kidney. *Kidney Int* 2002; **61**: 387–95.
- 91 Hammerman MR, Miller SB. Therapeutic use of growth factors in renal failure. *J Am Soc Nephrol* 1994; **5**: 1–11.
- 92 Rookmaaker MB, Verhaar MC, Van Zonneveld AJ, Rabelink TJ. Progenitor cells in the kidney: biology and therapeutic perspectives. *Kidney Int* 2004; **66**: 518–22.
- 93 Krause DS, Theise ND, Collector MI, et al. Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell. *Cell* 2001; **105**: 369–77.
- 94 Verfaillie CM, Pera MF, Lansdorp PM. Stem cells: hype and reality. *Hematology (American Society of Hematology Education Program)* 2002: 369–91.
- 95 Ito T. Stem cells of the adult kidney: where are you from? *Nephrol Dial Transplant* 2003; **18**: 641–44.
- 96 Poulsom R, Forbes SJ, Hodivala-Dilke K, et al. Bone marrow contributes to renal parenchymal turnover and regeneration. *J Pathol* 2001; **195**: 229–35.
- 97 Kale S, Karihaloo A, Clark PR, Kashgarian M, Krause DS, Cantley LG. Bone marrow stem cells contribute to repair of the ischemically injured renal tubule. *J Clin Invest* 2003; **112**: 42–49.
- 98 Morigi M, Imberti B, Zoja C, et al. Mesenchymal stem cells are renotropic, helping to repair the kidney and improve function in acute renal failure. *J Am Soc Nephrol* 2004; **15**: 1794–804.
- 99 Tögel F, Isaac J, Westenfelder C. Hematopoietic stem cell mobilization-associated granulocytosis severely worsens acute renal failure. *J Am Soc Nephrol* 2004; **15**: 1261–67.
- 100 Anderson RJ, Barry DW. Clinical and laboratory diagnosis of acute renal failure. *Best Pract Res Clin Anaesthesiol* 2004; **18**: 1–20.
- 101 Kieran N, Brady HR. Clinical evaluation, management, and outcome of acute renal failure. In: Johnson RJ, Feehally J, eds. *Comprehensive clinical nephrology*, 2nd edn. Edinburgh: Mosby, 2003: 183–206.
- 102 Wuyts B, Bernard D, Van Den Noortgate N, et al. Reevaluation of formulas for predicting creatinine clearance in adults and children, using compensated creatinine methods. *Clin Chem* 2003; **49**: 1011–14.
- 103 Delanghe JR. Standardization of creatinine determination and its consequences for the clinician. *Acta Clin Belg* 2002; **57**: 172–75.
- 104 Coresh J, Astor BC, McQuillan G, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis* 2002; **39**: 920–29.
- 105 Schuck O, Teplan V, Jabor A, Stollova M, Skibova J. Glomerular filtration rate estimation in patients with advanced chronic renal insufficiency based on serum cystatin C levels. *Nephron Clin Pract* 2003; **93**: c146–51.
- 106 Schuck O, Teplan V, Sibova J, Stollova M. Predicting the glomerular filtration rate from serum creatinine, serum cystatin C and the Cockcroft and Gault formula with regard to drug dosage adjustment. *Int J Clin Pharmacol Ther* 2004; **42**: 93–97.
- 107 Delanaye P, Lambermont B, Chapelle JP, Gielen J, Gerard P, Rorive G. Plasma cystatin C for the estimation of glomerular filtration rate in intensive care units. *Intensive Care Med* 2004; **30**: 980–83.
- 108 Herget-Rosenthal S, Marggraf G, Husing J, et al. Early detection of acute renal failure by serum cystatin C. *Kidney Int* 2004; **66**: 1115–22.
- 109 Rickli H, Benou K, Ammann P, et al. Time course of serial cystatin C levels in comparison with serum creatinine after application of radiocontrast media. *Clin Nephrol* 2004; **61**: 98–102.
- 110 Miller PD, Krebs RA, Neal BJ, McIntyre DO. Polyuric prerenal failure. *Arch Intern Med* 1980; **140**: 907–09.
- 111 Carvounis CP, Nisar S, Guro-Razuman S. Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure. *Kidney Int* 2002; **62**: 2223–29.
- 112 Finn WF, Porter GA. Urinary biomarkers and nephrotoxicity. In: De Broe ME, Porter GA, Bennet WM, Verpooten GA, eds. *Clinical nephrotoxins renal injury from drugs and chemicals*, 2nd edn. Dordrecht: Kluwer Academic Publishers, 2003: 622–55.
- 113 Hewitt SM, Dear J, Star RA. Discovery of protein biomarkers for renal diseases. *J Am Soc Nephrol* 2004; **15**: 1677–89.

- 114 Parikh CR, Jani A, Melnikov VY, Faubel S, Edelstein CL. Urinary interleukin-18 is a marker of human acute tubular necrosis. *Am J Kidney Dis* 2004; **43**: 405–14.
- 115 Westhuyzen J, Endre ZH, Reece G, Reith DM, Saltissi D, Morgan TJ. Measurement of tubular enzymuria facilitates early detection of acute renal impairment in the intensive care unit. *Nephrol Dial Transplant* 2003; **18**: 543–51.
- 116 Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney injury molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. *Kidney Int* 2002; **62**: 237–44.
- 117 Hampel DJ, Sansome C, Sha M, Brodsky S, Lawson WE, Goligorsky MS. Toward proteomics in uroscopy: urinary protein profiles after radiocontrast medium administration. *J Am Soc Nephrol* 2001; **12**: 1026–35.
- 118 Conger JD. Interventions in clinical acute renal failure: what are the data? *Am J Kidney Dis* 1995; **26**: 565–76.
- 119 Dishart MK, Kellum JA. An evaluation of pharmacological strategies for the prevention and treatment of acute renal failure. *Drugs* 2000; **59**: 79–91.
- 120 Kellum JA. What can be done about acute renal failure? *Minerva Anestesiol* 2004; **70**: 181–88.
- 121 Lameire NH, De Vriese AS, Vanholder R. Prevention and nondialytic treatment of acute renal failure. *Curr Opin Crit Care* 2003; **9**: 481–90.
- 122 Ribeiro RC, Pui CH. Recombinant urate oxidase for prevention of hyperuricemia and tumor lysis syndrome in lymphoid malignancies. *Clin Lymphoma* 2003; **3**: 225–32.
- 123 De Vriese AS, Bourgeois M. Pharmacologic treatment of acute renal failure in sepsis. *Curr Opin Crit Care* 2003; **9**: 474–80.
- 124 De Vriese AS. Prevention and treatment of acute renal failure in sepsis. *J Am Soc Nephrol* 2003; **14**: 792–805.
- 125 Choi PT, Yip G, Quinonez LG, Cook DJ. Crystalloids vs colloids in fluid resuscitation: a systematic review. *Crit Care Med* 1999; **27**: 200–10.
- 126 Ragaller MJ, Theilen H, Koch T. Volume replacement in critically ill patients with acute renal failure. *J Am Soc Nephrol* 2001; **12** (suppl 17): S33–39.
- 127 Waikar SS, Chertow GM. Crystalloids versus colloids for resuscitation in shock. *Curr Opin Nephrol Hypertens* 2000; **9**: 501–04.
- 128 Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; **350**: 2247–56.
- 129 Mueller C, Buerkle G, Buettnner HJ, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 2002; **162**: 329–36.
- 130 Kellum JA. Use of diuretics in the acute care setting. *Kidney Int Suppl* 1998; **66**: S67–70.
- 131 Schetz M. Should we use diuretics in acute renal failure? *Best Pract Res Clin Anaesthesiol* 2004; **18**: 75–89.
- 132 Shilliday IR, Quinn KJ, Allison ME. Loop diuretics in the management of acute renal failure: a prospective, double-blind, placebo-controlled, randomized study. *Nephrol Dial Transplant* 1997; **12**: 2592–96.
- 133 Mehta RL, Pascual MT, Soroko S, Chertow GM. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. *JAMA* 2002; **288**: 2547–53.
- 134 Mehta RL, Chertow GM. Diuretics in critically ill patients with acute renal failure. *JAMA* 2003; **289**: 1379–81.
- 135 Uchino S, Doig GS, Bellomo R, et al. Diuretics and mortality in acute renal failure. *Crit Care Med* 2004; **32**: 1669–77.
- 136 Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. *Lancet* 2000; **356**: 2139–43.
- 137 Denton MD, Chertow GM, Brady HR. “Renal-dose” dopamine for the treatment of acute renal failure: scientific rationale, experimental studies and clinical trials. *Kidney Int* 1996; **50**: 4–14.
- 138 Kellum JA, Decker M. Use of dopamine in acute renal failure: a meta-analysis. *Crit Care Med* 2001; **29**: 1526–31.
- 139 Lassnigg A, Donner E, Grubhofer G, Presterl E, Druml J, Hiesmayr M. Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. *J Am Soc Nephrol* 2000; **11**: 97–104.
- 140 Alonso A, Lau J, Jaber BL, Weintraub A, Sarnak MJ. Prevention of radiocontrast nephropathy with N-acetylcysteine in patients with chronic kidney disease: a meta-analysis of randomized, controlled trials. *Am J Kidney Dis* 2004; **43**: 1–9.
- 141 Birck R, Krzossok S, Markowitz F, Schnulle P, van der Woude FJ, Braun C. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. *Lancet* 2003; **362**: 598–603.
- 142 Isenbarger DW, Kent SM, O'Malley PG. Meta-analysis of randomized clinical trials on the usefulness of acetylcysteine for prevention of contrast nephropathy. *Am J Cardiol* 2003; **92**: 1454–58.
- 143 Hoffmann U, Fischereder M, Kruger B, Drobnik W, Kramer BK. The value of N-acetylcysteine in the prevention of radiocontrast agent-induced nephropathy seems questionable. *J Am Soc Nephrol* 2004; **15**: 407–10.
- 144 Ladefoged SD, Andersen CB. Calcium channel blockers in kidney transplantation. *Clin Transplant* 1994; **8**: 128–33.
- 145 Lumlertgul D, Wongmekiat O, Sirivanichai C, et al. Intrarenal infusion of gallopamil in acute renal failure: a preliminary report. *Drugs* 1991; **42** (suppl 1): 44–50.
- 146 Piper SN, Kumle B, Maleck WH, et al. Diltiazem may preserve renal tubular integrity after cardiac surgery. *Can J Anaesth* 2003; **50**: 285–92.
- 147 Sharples EJ, Patel N, Brown P, et al. Erythropoietin protects the kidney against the injury and dysfunction caused by ischemia-reperfusion. *J Am Soc Nephrol* 2004; **15**: 2115–24.
- 148 Hirschberg R, Kopple J, Lipssett P, et al. Multicenter clinical trial of recombinant human insulin-like growth factor I in patients with acute renal failure. *Kidney Int* 1999; **55**: 2423–32.
- 149 Hladunewich MA, Corrigan G, Derby GC, et al. A randomized, placebo-controlled trial of IGF-1 for delayed graft function: a human model to study postischemic ARF. *Kidney Int* 2003; **64**: 593–602.
- 150 Bellomo R, Naka T, Baldwin I. Intravenous fluids and acid-base balance. *Contrib Nephrol* 2004; **144**: 105–18.
- 151 Schetz M, Van Den BG. Glucose control in the critically ill. *Contrib Nephrol* 2004; **144**: 119–31.
- 152 Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; **345**: 1359–67.
- 153 Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med* 2003; **31**: 359–66.
- 154 D'Intini V, Ronco C, Bonello M, Bellomo R. Renal replacement therapy in acute renal failure. *Best Pract Res Clin Anaesthesiol* 2004; **18**: 145–57.
- 155 Lameire N, Van Biesen W, Vanholder R. Dialysing the patient with acute renal failure in the ICU: the emperor's clothes? *Nephrol Dial Transplant* 1999; **14**: 2570–73.
- 156 Van Biesen W, Vanholder R, Lameire N. Dialysis strategies in critically ill acute renal failure patients. *Curr Opin Crit Care* 2003; **9**: 491–95.
- 157 John S, Griesbach D, Baumgartel M, Weihprecht H, Schmieder RE, Geiger H. 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* 2001; **16**: 320–27.
- 158 Manns B, Doig CJ, Lee H, et al. Cost of acute renal failure requiring dialysis in the intensive care unit: clinical and resource implications of renal recovery. *Crit Care Med* 2003; **31**: 449–55.
- 159 Mehta RL, McDonald B, Gabbai FB, et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int* 2001; **60**: 1154–63.
- 160 Sandy D, Moreno L, Lee J, Paganini E. A randomized stratified dose equivalent comparison of continuous veno-venous hemodialysis vs intermittent hemodialysis support in ICU acute renal failure patients. *J Am Soc Nephrol* 1998; **9**: 225A (abstr).
- 161 Uehlinger DE, Jacob S, Eichelberger M. A randomized, controlled single center study for the comparison of continuous renal replacement therapy with intermittent hemodialysis in critically ill patients with acute renal failure. *J Am Soc Nephrol* 2001; **12**: 278A (abstr).
- 162 Tonelli M, Manns B, Feller-Kopman D. Acute renal failure in the intensive care unit: a systematic review of the impact of dialytic modality on mortality and renal recovery. *Am J Kidney Dis* 2002; **40**: 875–85.

- 163 Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet* 2000; **356**: 26–30.
- 164 Lameire N, Van Biesen W, Vanholder R, Hoste E. Intermittent hemodialysis for acute renal failure patients: an update. *Contrib Nephrol* 2004; **144**: 255–63.
- 165 Schiff H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 2002; **346**: 305–10.
- 166 Ikizler TA, Sezer MT, Flakoll PJ, et al. Urea space and total body water measurements by stable isotopes in patients with acute renal failure. *Kidney Int* 2004; **65**: 725–32.
- 167 Jaber BL, Lau J, Schmid CH, Karsou SA, Levey AS, Pereira BJ. Effect of biocompatibility of hemodialysis membranes on mortality in acute renal failure: a meta-analysis. *Clin Nephrol* 2002; **57**: 274–82.
- 168 Subramanian S, Venkataraman R, Kellum JA. Influence of dialysis membranes on outcomes in acute renal failure: a meta-analysis. *Kidney Int* 2002; **62**: 1819–23.
- 169 Teehan GS, Liangos O, Jaber BL. Update on dialytic management of acute renal failure. *J Intensive Care Med* 2003; **18**: 130–38.
- 170 Teehan GS, Liangos O, Lau J, Levey AS, Pereira BJ, Jaber BL. Dialysis membrane and modality in acute renal failure: understanding discordant meta-analyses. *Semin Dial* 2003; **16**: 356–60.
- 171 Marshall MR, Golper TA, Shaver MJ, Alam MG, Chatoth DK. Sustained low-efficiency dialysis for critically ill patients requiring renal replacement therapy. *Kidney Int* 2001; **60**: 777–85.
- 172 Marshall MR, Ma T, Galler D, Rankin AP, Williams AB. Sustained low-efficiency daily diafiltration (SLEDD-f) for critically ill patients requiring renal replacement therapy: towards an adequate therapy. *Nephrol Dial Transplant* 2004; **19**: 877–84.
- 173 Kumar VA, Yeun JY, Depner TA, Don BR. Extended daily dialysis vs continuous hemodialysis for ICU patients with acute renal failure: a two-year single center report. *Int J Artif Organs* 2004; **27**: 371–79.
- 174 Karsou SA, Jaber BL, Pereira BJ. Impact of intermittent hemodialysis variables on clinical outcomes in acute renal failure. *Am J Kidney Dis* 2000; **35**: 980–91.
- 175 d'Avila DO, Cendoroglo NM, dos Santos OF, Schor N, de Figueiredo CE. Acute renal failure needing dialysis in the intensive care unit and prognostic scores. *Ren Fail* 2004; **26**: 59–68.
- 176 Guerin C, Girard R, Selli JM, Ayzac L. Intermittent versus continuous renal replacement therapy for acute renal failure in intensive care units: results from a multicenter prospective epidemiological survey. *Intensive Care Med* 2002; **28**: 1411–18.
- 177 McCarthy JT. Prognosis of patients with acute renal failure in the intensive-care unit: a tale of two eras. *Mayo Clin Proc* 1996; **71**: 117–26.
- 178 Jaber BL, Rao M, Guo D, et al. Cytokine gene promoter polymorphisms and mortality in acute renal failure. *Cytokine* 2004; **25**: 212–19.
- 179 Jaber BL, Liangos O, Pereira BJ, Balakrishnan VS. Polymorphism of immunomodulatory cytokine genes: implications in acute renal failure. *Blood Purif* 2004; **22**: 101–11.
- 180 Finn WF. Recovery from acute renal failure. In: Molitoris BA, Finn WF, eds. *Acute renal failure: a companion to Brenner and Rector's the kidney*, 1st edn. Philadelphia: WB Saunders, 2001: 425–50.
- 181 Alon US. Neonatal acute renal failure: the need for long-term follow-up. *Clin Pediatr (Phila)* 1998; **37**: 387–89.
- 182 Polito C, Papale MR, La Manna A. Long-term prognosis of acute renal failure in the full-term neonate. *Clin Pediatr (Phila)* 1998; **37**: 381–85.
- 183 Shaw NJ, Brocklebank JT, Dickinson DF, Wilson N, Walker DR. Long-term outcome for children with acute renal failure following cardiac surgery. *Int J Cardiol* 1991; **31**: 161–65.
- 184 Bhandari S, Turney JH. Survivors of acute renal failure who do not recover renal function. *QJM* 1996; **489**: 415–21.