Acute kidney injury

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Acute kidney injury (formerly known as acute renal failure) is a syndrome characterised by the rapid loss of the kidney's excretory function and is typically diagnosed by the accumulation of end products of nitrogen metabolism (urea and creatinine) or decreased urine output, or both. It is the clinical manifestation of several disorders that affect the kidney acutely. Acute kidney injury is common in hospital patients and very common in critically ill patients. In these patients, it is most often secondary to extrarenal events. How such events cause acute kidney injury is controversial. No specific therapies have emerged that can attenuate acute kidney injury or expedite recovery; thus, treatment is supportive. New diagnostic techniques (eg, renal biomarkers) might help with early diagnosis. Patients are given renal replacement therapy if acute kidney injury is severe and biochemical or volume-related, or if uraemic-toxaemia-related complications are of concern. If patients survive their illness and do not have premorbid chronic kidney disease, they typically recover to dialysis independence. However, evidence suggests that patients who have had acute kidney injury are at increased risk of subsequent chronic kidney disease.

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Introduction

Acute kidney injury is the new consensus term for acute renal failure.[1] It refers to a clinical syndrome characterised by a rapid (hours to days) decrease in renal excretory function, with the accumulation of products of nitrogen metabolism such as creatinine and urea and other clinically unmeasured waste products. Other common clinical and laboratory manifestations include decreased urine output (not always present), accumulation of metabolic acids, and increased potassium and phosphate concentrations.

The term acute kidney injury has replaced acute renal failure to emphasise that a continuum of kidney injury exists that begins long before sufficient loss of excretory kidney function can be measured with standard laboratory tests. The term also suggests a continuum of prognosis, with increasing mortality associated with even small rises in serum creatinine, and additional increases in mortality as creatinine concentration rises.

Epidemiology

The described notions have led to a consensus definition of acute kidney injury by the Acute Dialysis Quality Initiative. These RIFLE (risk, injury, failure, loss, end stage) criteria (figure 1)[1] have been broadly supported with minor modifications by the Acute Kidney Injury Network,[2] and both definitions have now been validated in thousands of patients[3] and seem to work similarly to each other. A new consensus definition merging the RIFLE criteria and the Acute Kidney Injury Network definition has emerged from the Kidney Disease: Improving Global Outcomes (K-DIGO) group.[3]

Acute kidney injury is a common and important diagnostic and therapeutic challenge for clinicians.[4] Incidence varies between definitions and populations, from more than 5000 cases per million people per year for non-dialysis-requiring acute kidney injury, to 295 cases per million people per year for dialysis-requiring disease.[5] The disorder has a frequency of 1·9% in hospital inpatients[4] and is especially common in critically ill patients, in whom the prevalence of acute kidney injury is greater than 40% at admission to the intensive-care unit if sepsis is present.[6] Occurrence is more than 36% on the day after admission to an intensive-care unit,[6] and prevalence is greater than 60% during intensive-care-unit admission.[7]

Some causes of acute kidney injury are particularly prevalent in some geographical settings. For example, cases associated with hypovolaemia secondary to diarrhoea are frequent in developing countries, whereas open heart surgery is a common cause in developed countries. Furthermore, within a particular country, specific disorders are common in the community, whereas others arise only in hospitals. Thus, any diagnostic approach to the cause or trigger of acute kidney injury must take into account the local context and epidemiology.

Key ideas

Most clinicians are familiar with two key ideas related to acute kidney injury—namely, acute tubular necrosis and prerenal azotaemia. Acute tubular necrosis describes a form of intrinsic acute kidney injury that results from severe and persistent hypoperfusion of the kidneys (ie, prerenal acute kidney injury), although the term secondary acute kidney injury might be more appropriate. This definition is widely accepted and used in textbooks and by clinicians. However, we have some serious concerns about its use.

Search strategy and selection criteria

We searched PubMed and Medline between Jan 6, 2011, and Sept 13, 2011, for articles in English with the terms "acute kidney injury", "acute renal failure", "continuous hemofiltration", "continuous renal replacement therapy", and "haemodialysis". We combined the terms "continuous hemofiltration", "continuous renal replacement therapy", and "haemodialysis" with "acute kidney injury" and "acute renal failure". We did not restrict articles by date of publication. We identified 5523 potentially relevant titles.

All titles were scanned. We selected 398 potentially relevant articles. We reviewed the abstracts of these papers and chose the most suitable references. Additional references were selected from relevant articles and chapters of recent textbooks in the specialty.

	GFR criteria	Urine output criteria
Risk	1·5-fold increase in S_{creat} or GFR decrease ≥25%	UO <0·5 mL/kg/h for 6 h
Injury	Two-fold increase in S_{creat} or GFR decrease >50%	UO <0·5 mL/kg/h for 12 h
Failure	Three-fold increase in S_{creat}, GFR decrease >75%, S_{creat} ≥4 mg/dL, or acute rise in S_{creat} ≥0·5 mg/dL	UO <0·3 mL/kg/h for 24 h or anuria for 12 h
Loss	Complete loss of kidney function >4 weeks	
ESKD	End-stage kidney disease (>3 months)	

Figure 1: **RIFLE criteria for acute kidney injury**
Adapted from Bellomo and colleagues.[1] As GFR or UO deteriorate, the patient moves from risk (class R) to failure (class F). Class R has a high sensitivity and class F a high specificity for acute kidney injury. RIFLE=risk, injury, failure, loss, end stage. GFR=glomerular filtration rate. S_{creat}=serum creatinine concentration. UO=urine output. ESKD=end-stage kidney disease.

Our first concern is that the term acute tubular necrosis combines a histological diagnosis (tubular necrosis) that is rarely confirmed by biopsy[8] and thus is not scientifically verifiable, with a complex clinical syndrome (typically acute kidney injury of >72 h). In many cases, this syndrome has not been convincingly linked with the specific histopathological finding of acute tubular necrosis neither in animals nor in human disease.[8]

Second, acute tubular necrosis is believed to represent the consequence of sustained or severe prerenal azotaemia, which is not thought to be associated with histopathological changes (and is therefore not classified as intrinsic acute kidney injury). Such prerenal azotaemia can be expected to resolve in 2–3 days. Unfortunately, the term is conceptually flawed[8–10] because it implies that clinicians can know with a sufficient degree of certainty that no histopathological injury is present in the tubules by taking a history, examining the patient, and doing urine and blood tests. Such a state is not scientifically verifiable unless a renal biopsy sample is taken.

Finally, we are concerned that the terms prerenal azotaemia and acute tubular necrosis are biologically flawed because they imply that acute kidney injury does not represent a continuum of injury. For these reasons, such terms are increasingly being challenged.[9,10]

Pathophysiology

The pathogenesis of inflammatory diseases of the kidney parenchyma (eg, glomerulonephritis and vasculitis) is complex and implicates almost all aspects of the innate inflammatory system and antibody-mediated and immune-cell-mediated mechanisms.[11–17] In this Seminar, we focus on acute kidney injury secondary to prerenal factors because this form is the most common in developed countries, in hospital inpatients, and particularly in critically ill patients.

Much of our understanding of the pathophysiology of prerenal acute kidney injury is derived from work in animals.[18,19] Studies of models of acute ischaemia induced by acute occlusion of the renal artery show the many pathways that are probably implicated and the mechanisms of organ injury.[20,21] The coagulation system is locally activated,[22] leucocytes infiltrate the kidney,[23] endothelium is injured[24] and adhesion molecules are expressed,[25] cytokines are released,[26] toll-like receptors are induced,[27] intrarenal vasoconstrictor pathways are activated,[28] and apoptosis is induced.[29] Associated changes also occur in tubular cells with loss or inversion of polarity[30] and loss of adhesion to the basement membrane.[20] Renal injury seems able to trigger organ injury elsewhere (so-called organ cross-talk)[31] through unclear pathways, further emphasising the complexity of the biological response to acute kidney injury.

Unfortunately, this ischaemic model has little clinical relevance to illnesses such as sepsis.[32,33] Sepsis is the most common trigger of acute kidney injury in hospital inpatients and in those in the intensive-care unit. The model is also of little relevance to periods of decreased perfusion, as can happen during major surgery, since 80% renal-artery occlusion for 2 h does not lead to sustained renal dysfunction.[34]

Thus, many of the principles that clinicians use to guide their understanding of acute kidney injury are of questionable relevance to patients in modern hospitals or intensive-care units.[35] In such patients, sepsis, major surgery (especially open heart surgery), and acute decompensated heart failure are the most common triggers of acute kidney injury. The renal artery is not occluded in any of these situations. More relevant models are needed.

In view of the uncertainties associated with animal models of acute kidney injury, pursuit of pathogenetic investigations in people seems logical. However, such investigations are difficult because taking of renal biopsy samples to investigate acute tubular necrosis is unwarranted in the absence of available therapeutic interventions. Thus, histopathological assessment is used only for rapid post-mortem assessment, which adds major confounders such as selection bias and premortem hypoxia and ischaemia.

Despite the development of promising new techniques,[36] assessment of perfusion (ie, renal blood flow) is similarly difficult and confined to invasive techniques.[37] Such data should be interpreted with caution because they show renal blood flow in patients with established acute kidney injury when organ oedema, tubular injury, backleak, and increased tubular luminal pressure[38] could be present and the cause of the measured changes. Reported decreases in renal blood flow could be a result of, rather than the cause of, acute kidney injury.

Some natural models of human acute kidney injury exist, when injury is expected and the timing of such injury is known—eg, cardiac surgery[39] and renal

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transplantation.[40] Cardiac surgery has not yet yielded insights into pathogenesis and does not allow tissue assessment. Renal transplantation has been well studied and allows tissue assessment. However, it is affected by the use of nephrotoxic drugs and is an infrequent cause of acute kidney injury. Moreover, we believe that extrapolation of insights gained from a non-perfused, cold-solution-preserved organ outside the body to common clinical triggers of acute kidney injury such as sepsis, bleeding, or major surgery is difficult.

Neurohormonal mechanisms

Sympathetic system activation[41] and neurohormonal responses unique to the kidney are activated in acute kidney injury.[42] The renin–angiotensin–aldosterone system,[43] renal sympathetic system,[42] and tubuloglomerular feedback system[43] are activated. Knowledge of these changes has led to schemata of how acute kidney injury can be precipitated in human beings (figure 2). These frameworks show that, in situations such as sepsis, infection leads to induction of nitric oxide synthase and nitric-oxide-mediated vasodilation, which in turn causes arterial underfilling and baroreceptor activation. These circulatory changes trigger activation of the sympathetic system, which induces increased renin–angiotensin–aldosterone activity and renal vasoconstriction. Simultaneously, arginine vasopressin is released and contributes to water retention.[42]

These frameworks do not provide information about which particular pathway of injury has primacy in terms of importance or timing, and do not guide the development of new therapeutic interventions. Whether neurohormonal changes lead to intrarenal shunting, or whether such shunting contributes not only to decreased glomerular filtration rates, but also to ischaemia of the renal medulla is unknown. Shunting can be coupled with changes in the microcirculation; thus, even if overall renal blood flow could be measured with reasonable accuracy, understanding of acute kidney injury will remain poor unless the microcirculation is also assessed.

Hepatorenal syndrome is perhaps the most extensively studied form of acute kidney injury in terms of neurohormonal changes,[44–46] and provides useful mechanistic insights. In this syndrome, as in experimental sepsis, acute kidney injury seems to occur without histopathological renal changes and thus is essentially functional in nature. The intense renal vasoconstriction associated with substantial renin–angiotensin–aldosterone activation is the characteristic finding in patients with hepatorenal syndrome,[39] suggesting that neurohormonal events bring about the development of the disorder. Although the mechanisms that cause such activation are debated, decreased systemic blood pressure secondary to splanchnic vasodilation is judged a key event.[47] The neurohormonal response to such vasodilation supports the systemic circulation, but renal circulation can be adversely affected. Whether a similar state occurs in other diseases associated with hypotension and systemic vasodilation (eg, inflammation and sepsis) remains unknown. Thus, increases in norepinephrine, renin, and angiotensin II concentrations can contribute to other forms of acute kidney injury, suggesting that, at least in some situations, neurohormonal renal vasoconstriction could be a fundamental mechanism of loss of excretory function.

Diagnosis

Because acute kidney injury is asymptomatic until extremes of loss of function are reached and has no characteristic clinical findings, diagnosis typically occurs in the context of another acute illness. Although oliguria is a helpful sign, it is neither specific nor sensitive.[48] Under most circumstances, acute kidney injury is diagnosed in high-risk contexts (eg, sepsis, major surgery, bleeding, volume losses) by laboratory tests. Creatinine and urea concentrations are the standard diagnostic analytes.

When a patient presents with raised serum creatinine concentrations, to establish whether the patient has acute kidney injury, chronic kidney disease, or a bout of acute illness superimposed on chronic disease is important. Usually, the clinical context provides clues. Abnormal serum creatinine before presentation; relevant risk factors (eg, hypertension or diabetes); a slow clinical course for the presenting illness; high serum concentrations of creatine or phosphate, or both; and normocytic anaemia all suggest the presence of chronic

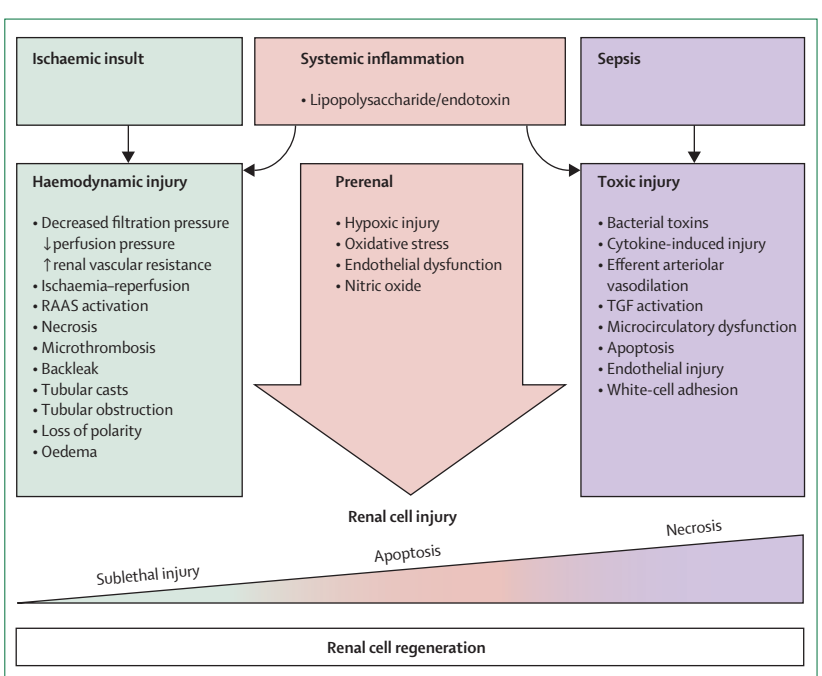

Figure 2: **Key potential pathways implicated in pathogenesis of acute kidney injury due to ischaemia or sepsis**
The timing of activation of each pathway, their interaction, and the hierarchy of these pathways remain unknown. RAAS=renin–angiotensin–aldosterone system. TGF=tubuloglomerular feedback.

kidney disease. Renal ultrasonography might show small kidneys and provide evidence of chronic disease.

In some cases, acute kidney injury has a sudden and easily identifiable cause (eg, pneumonia with septic shock, cardiac surgery, trauma with haemorrhagic shock, diarrhoea), which makes the presence of obstruction unlikely. In some situations, the presence of substantially increased intra-abdominal pressure as a trigger is easily suspected because of the clinical context and raised bladder pressure.[49] In other situations, however, presentation is less clear and the possibility of obstruction as a cause of acute kidney injury or acute-on-chronic kidney disease should be considered. In any case, renal ultrasonography could be of use.

Although most cases of intrinsic acute kidney injury are associated with prerenal triggers and typically thought to be due to acute tubular necrosis, in some patients the illness is secondary to inflammatory parenchymal disease. Of these cases, diseases such as vasculitis, glomerulonephritis, and interstitial nephritis are the most common. Clinical features might suggest one of these diagnoses—eg, systemic manifestations in vasculitis, the presence of macroscopic haematuria in glomerulonephritis, or the recent initiation of treatment with a drug known to cause interstitial nephritis. Other common causes of parenchymal acute kidney injury are malignant hypertension, pyelonephritis, bilateral cortical necrosis, amyloidosis, malignant disease, and nephrotoxins.

Often, patients present with acute kidney injury in the absence of obstruction or a clear prerenal cause. In such patients, urinary microscopy frequently suggests glomerular pathological changes, with haematuria; proteinuria; or fragmented red cells, red-cell casts, white-cell casts, or granular casts; or any combination of these factors. When interstitial nephropathy is suspected, urine samples should be tested for eosinophils. However, the sensitivity of the test is poor. Urine biochemical analysis is of little use, especially in sepsis.[50–53] Measurement of variables such as the fractional excretion of sodium or urea has not been consistently shown to have a clear correlation with histopathological findings in systematic reviews of work in animals, or in people.[50–53] Biochemical investigations have little association with biomarkers of injury, clinical course, or prognosis in critically ill patients.[54]

Albuminuria, however, is a strong risk factor for the development of acute kidney injury[55] and a potential biomarker of the disease.[56] The relation between histopathology and urine microscopy (a possible surrogate measure of tubular injury) is unknown. However, the urinary microscopy score (based on the quantification of tubular cells and casts) correlates with biomarkers of injury, worsening acute kidney injury, need for renal replacement therapy, and hospital mortality.[54,57] The therapeutic implications of any urinary findings are unknown.[58]

Blood tests can detect evidence of an unexplained inflammatory state, and specific tests for autoantibodies can show patterns suggestive of specific types of vasculitis. If deemed clinically appropriate, a renal biopsy might show diagnostic changes.

Nephrotoxic drugs

Drug-induced acute kidney injury is important because the offending drug can often be identified and removed or substituted for one that is non-nephrotoxic or less nephrotoxic. Additionally, many affected patients present with polyuric acute kidney injury, and thus a high index of suspicion is crucial for diagnosis. Drugs seem to contribute to acute kidney injury in roughly 20% of patients, especially in critically ill patients.[59,60] Panel 1 shows a list of frequently prescribed drugs that are known to contribute to acute kidney injury. For several nephrotoxic drugs (eg, aminoglycosides, angiotensin-converting-enzyme inhibitors, calcineurin inhibitors, non-steroidal anti-inflammatory drugs) administration can be suspended, the pattern of administration changed, or another less toxic or non-toxic drug used instead, but this strategy cannot be used for all drugs.

Iodinated radiocontrast agents are a unique and important cause of acute kidney injury[61] because of their use in angiography. Evidence from randomised controlled trials shows that contrast-induced nephropathy can be lessened by use of iso-osmolar contrast agents[62–65] and isotonic fluid loading.[66] The use of other protective interventions—eg, N-acetylcysteine—is controversial.[67] Similar amounts of uncertainty surround the use of bicarbonate[68–72] and other less extensively studied interventions.[73–78]

Laboratory assessment of renal function

The laboratory hallmarks of acute kidney injury are increased serum creatinine concentrations or raised plasma urea concentrations, or both. Unfortunately, these waste products are insensitive markers of glomerular filtration rate and are modified by nutrition, use of steroids, presence of gastrointestinal blood, muscle mass, age, sex, muscle injury, and aggressive fluid resuscitation. Furthermore, they become abnormal only when glomerular filtration rate decreases by more than 50% and do not show dynamic changes in filtration rates.[79] Despite these shortcomings, clinical monitoring remains based on the measurement of urea and creatinine concentrations. The use of sophisticated radionuclide-based tests is cumbersome and useful only for research purposes. However, new biomarkers of renal injury and function are emerging for the diagnosis of acute kidney injury.

Some biochemical test results are abnormal in patients with acute kidney injury and such tests are useful to establish whether renal replacement therapy should be started. For example, a high (>6 mmol/L) or rapidly rising potassium concentration increases the risk of

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life-threatening arrhythmias and requires both specific potassium-lowering treatment and possible early renal replacement therapy. Similarly, decompensated marked metabolic acidosis with acidaemia should prompt consideration for renal replacement therapy.

In specific situations, other investigations are necessary to establish the diagnosis, such as measurement of creatine kinase and free myoglobin to identify possible rhabdomyolysis.[80] Chest radiographs, blood films, measurement of non-specific inflammatory markers, and assays that detect specific antibodies (eg, those against glomerular basement membrane, neutrophil cytoplasm, DNA, or smooth muscle) are useful screening tests to help support the diagnosis of vasculitis, specific types of collagen disease, or glomerulonephritis. If thrombotic–thrombocytopenic purpura is suspected, concentrations of lactic dehydrogenase, haptoglobin, unconjugated bilirubin, and free haemoglobin should also be measured. The presence of microangiopathic haemolysis in blood smears is also crucial for this diagnosis. In some patients, specific findings—eg, cryoglobulins, Bence-Jones proteins—provide almost conclusive diagnosis. Rarely, clinical signs, laboratory investigations, and radiological investigations are not sufficient to make a causative diagnosis with certainty. In such patients a renal biopsy might be necessary.

Novel biomarkers

Investigators have used new search techniques based on proteomics to identify several novel biomarkers of acute kidney injury. Despite the novelty and dynamic nature of this new research specialty,[67–89] several key points can already be made. First, in patients who develop acute kidney injury, concentrations of these biomarkers seem to change earlier than do serum creatinine concentrations (figure 3).[82] Typically, these biomarkers have been most extensively assessed after cardiac surgery or on presentation to the emergency department.[83–85] Second, they seem to show different aspects of renal injury. For example, cystatin C concentrations seem to show changes in glomerular filtration rate,[86–89] whereas concentrations of neutrophil gelatinase-associated lipocalin are related to tubular stress or injury.[86–93]

Third, these biomarkers seem to change with treatment or recovery, which suggests that they can be used to monitor interventions.[94] Fourth, they can identify subpopulations of patients who do not have acute kidney injury according to creatinine-based criteria, but actually have a degree of kidney stress or injury that is associated with worse outcomes.[93] Finally, by identifying possible mechanisms of injury, novel biomarkers increase our understanding of the pathogenesis of acute kidney injury.

Although neutrophil gelatinase-associated lipocalin is the most studied renal biomarker,[95–99] several other biomarkers are under investigation.[100–104] Whether the additional cost (£5–20 per test) is worthwhile, or whether this research will yield therapeutic benefits has not been established.

Panel 1: **Drugs that contribute to acute kidney injury**

- Radiocontrast agents
- Aminoglycosides
- Amphotericin
- Non-steroidal anti-inflammatory drugs
- β-lactam antibiotics (specifically contribute to interstitial nephropathy)
- Sulphonamides
- Aciclovir
- Methotrexate
- Cisplatin
- Ciclosporin
- Tacrolimus
- Angiotensin-converting-enzyme inhibitors
- Angiotensin-receptor blockers

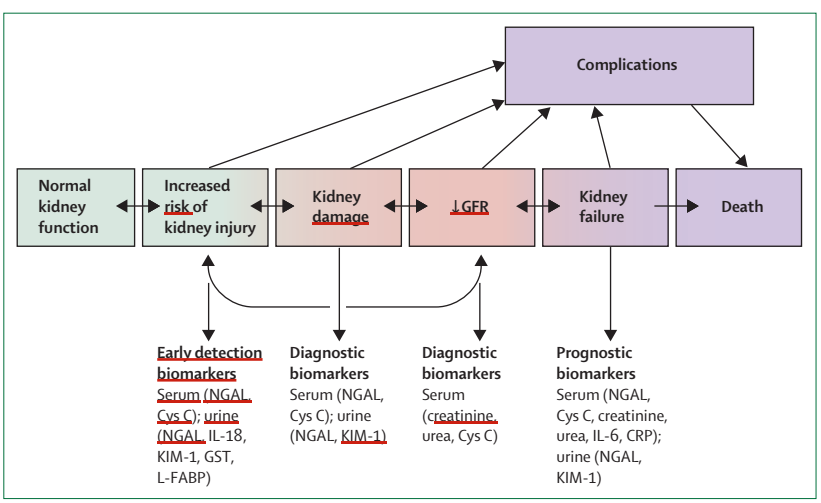

Figure 3: **Evolution of acute kidney injury**
Injury begins before excretory function is lost (ie, decreased GFR) and can in some cases be detected by the measurements of biomarkers. Such biomarkers can also be used for diagnostic and prognostic assessment. GFR=glomerular filtration rate. NGAL=neutrophil gelatinase-associated lipocalin. Cys C=cystain C. KIM-1=kidney injury molecule 1. IL-18=interleukin 18. GST=glutathione-S-transferase. L-FABP=liver fatty-acid-binding protein. CRP=C reactive protein. IL-6=interleukin 6.

Prevention

The fundamental principle of prevention of acute kidney injury is to treat the cause or trigger. If prerenal factors contribute, they should be identified, haemodynamic resuscitation quickly begun, and intravascular volume maintained or rapidly restored. In many patients, insertion of a peripheral intravenous catheter and rapid administration of intravenous fluids are sufficient to complete this process. The choice of fluid for such resuscitation is controversial. In particular, the possibility that fluids containing large-molecular-weight starch are nephrotoxic is of concern.[105] Whether fluids containing

novel low-molecular-weight starch are also nephrotoxic is the subject of a large double-blind randomised controlled trial in progress (NCT00935168).

Central volume status can be monitored by physical examination, neck vein inspection, and measurement of blood pressure and heart rate. However, if the patient is acutely ill, invasive haemodynamic monitoring (eg, central venous catheter, arterial cannula, and cardiac output monitoring in some cases) is often the best assessment. Adequate oxygenation and haemoglobin concentration (at least 70 g/L) should be maintained or immediately restored.[106] Once intravascular volume has been restored, some patients remain hypotensive (mean arterial pressure <65–70 mm Hg). In such patients, autoregulation of renal blood flow can be lost, contributing to acute kidney injury.[107] Restoration of a higher mean arterial pressure might raise the glomerular filtration rate and has no appreciable disadvantage. However, vasopressor drugs might be needed to bring about such increases in mean arterial pressure.

The nephroprotective role of additional fluid therapy in a patient with a normal or increased cardiac output and blood pressure is questionable. Despite resuscitation measures, acute kidney injury can still develop if cardiac output is inadequate. Inotropic drugs or the application of ventricular assist devices might be necessary to treat a low cardiac output state.

After haemodynamic resuscitation and removal of nephrotoxins, no specific drug-based intervention has been consistently and reproducibly shown to be protective. The alleged nephroprotective effect of so-called renal-dose or low-dose dopamine was refuted by findings from a multicentre, randomised, double-blind placebo-controlled trial.[108] Loop diuretics might protect the loop of Henle from ischaemia by decreasing its transport-related workload. However, no results from double-blind, randomised controlled studies of suitable size have shown that these agents reduce the incidence of acute kidney injury.[109] The usefulness of diuretics remains confined to the control of fluid status. Other drugs such as theophylline,[110] urodilatin,[111] fenoldopam,[110,111] bicarbonate,[72] and atrial natriuretic peptide[112] have been studied in different subgroups of patients and clinical contexts. However, such studies have been negative, too small, single centre, confined to a very specific group of patients, or have not yet been reproduced. Thus, no established pharmacotherapy exists for acute kidney injury.

Management of established disease

General management

The principles of management of established acute kidney injury are to treat or remove the cause and to maintain homoeostasis while recovery takes place. Complications can be prevented in some cases by actions that vary in complexity from fluid restriction to extracorporeal renal replacement therapy. Most experts recommend that nutritional support should be started early, contain adequate calories and protein, and be given as for other hospital inpatients or those in intensive-care units. No evidence shows that specific renal nutritional solutions are useful or necessary. The recommended daily allowance of vitamins and trace elements should be given. The enteral route is preferred to the use of parenteral nutrition.[113] Patients with hyperkalaemia (potassium concentrations >6 mmol/L) should be promptly given insulin and dextrose, a bicarbonate infusion (if acidosis is present), or nebulised salbutamol, or all three. If the serum potassium concentration is higher than 7 mmol/L or electrocardiographic signs of hyperkalaemia are present, 10 mL of 10% calcium gluconate solution should also be given intravenously.

These treatments are temporising actions while renal replacement therapy is set up. Metabolic acidosis is almost always present but rarely requires treatment per se (unless severe). Anaemia might need correction. Drug therapy should be adjusted to take into account the decreased clearance associated with loss of renal function. Stress-ulcer prophylaxis is advisable. Careful attention should be paid to the prevention of infection. Fluid overload can sometimes be prevented by the use of loop diuretics in patients with polyuria.

No specific recommendations exist for the management of fluids, and fluid restriction might be appropriate in some patients. However, we believe that the best way to avoid fluid overload in fluid-resuscitated critically ill patients with pronounced oliguria or anuria is to institute renal replacement therapy at an early stage. We recommend this strategy because some fluid overload already exists, and nutritional intake typically requires at least 1 L of fluid per day and drug intake another 500 mL per day. These fluid sources cannot be compensated for by insensible losses. The importance of fluid overload as a major contributor to increased risk of death in patients with acute kidney injury is increasingly recognised.[114] 10–20% overload can be sufficient to cause adverse clinical consequences.

Substantial azotaemia (suggested by urea concentrations >30 mmol/L or creatinine concentrations >300 µmol/L) is judged a marker of an undesirable toxic state. However, no recommendations state the severity of acute azotaemia that can be tolerated. We believe that this degree of azotaemia should probably be treated with renal replacement therapy unless recovery is imminent or already underway, or unless a return towards normal urea and creatinine concentrations is expected within 24–48 h. However, no randomised controlled trials have defined the ideal time for intervention with artificial renal support.

Hepatorenal syndrome

Hepatorenal syndrome is a form of acute kidney injury that arises in patients with severe liver dysfunction. Typically, patients present with progressive oliguria with a low urinary sodium concentration (<10 mmol/L).

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However, in patients with severe liver disease, other causes of acute kidney injury are much more common than is hepatorenal syndrome—eg, sepsis, paracentesis-induced hypovolaemia, diuretic-induced hypovolaemia, lactulose-induced hypovolaemia, cardiomyopathy, or any combination of these factors. Treatment of the trigger of deterioration and avoidance of hypovolaemia (preferably by albumin administration) can help to decrease the incidence of acute kidney injury.[115] Notably, findings from several studies suggest that the long-acting vasopressin derivative terlipressin can improve glomerular filtration rates and perhaps patient outcomes,[116,117] and this drug is becoming widely used.

Rhabdomyolysis

Rhabdomyolysis-associated acute kidney injury accounts for roughly 5–10% of cases of the disorder in intensive-care units, dependent on the setting. Prerenal, renal, and postrenal factors are implicated in its pathogenesis. Rhabdomyolysis-associated acute kidney injury is typically seen after major trauma, narcotics overdose, vascular embolism, or use of drugs that can induce major muscle injury. The principles of treatment are based on retrospective data, small series, and multivariate logistic regression analysis because no randomised controlled trials have been done. These principles include prompt and aggressive fluid resuscitation, elimination of causative drugs, correction of compartment syndrome, alkalinisation of urine (pH >6·5), and maintenance of polyuria (>300 mL/h). Typically, rhabdomyolysis is an issue of concern in scenarios such as mass disasters—eg, earthquakes or explosions. In such settings, the deployment of renal-protection and disaster teams with appropriate portable dialysis facilities can make a big difference to outcomes.

Cardiorenal syndrome

The changing demographics of patients in developed countries and the rising incidence of chronic heart failure and chronic kidney disease have led to an increase in patients with both heart disease and acute kidney injury. Acute kidney injury is often superimposed on chronic kidney disease and is frequently triggered by an acute decompensation of heart failure. A growing amount of published work focuses on so-called cardiorenal syndromes.[118] Although such investigations are quite new, initial insights are emerging—eg, the notion that a congestive state might contribute more to the pathogenesis of acute kidney injury than might low blood pressure and cardiac output.[119]

Renal replacement therapy

In some patients, acute kidney injury is severe enough to require renal replacement therapy. No one set of criteria exists to guide such intervention. However, when clinicians make this decision, they consider factors such as potassium, creatinine, and urea concentrations; fluid status; acid–base status; urine output; the overall course of the patient's illness; and the presence of other complications (panel 2).

The best time to start renal replacement therapy is controversial because the only studies linking timing with outcome are observational.[120,121] Three forms of renal replacement therapy are available: continuous, intermittent (either as intermittent haemodialysis or slow low-efficiency dialysis), and peritoneal dialysis. Continuous renal replacement therapy can involve filtration alone (eg, continuous venous–venous haemofiltration) or diffusion alone (eg, continuous veno–venous haemodialysis), or both (eg, continuous veno–venous haemodiafiltration). Peritoneal dialysis is associated with clearance limitations and difficulties with fluid removal (and potential complications), and is thus rarely used in adults in developed countries.

Should intermittent renal replacement therapy or continuous renal replacement therapy be used? No suitably powered randomised controlled trials have been done to address this question. However, results of small-to-medium-sized studies do not suggest a difference in patient survival. Thus, on the basis of patient survival, intermittent haemodialysis, slow low-efficiency dialysis, and continuous renal replacement therapy all seem to be acceptable options.[122]

The appropriate intensity of renal replacement therapy is uncertain, especially in critically ill patients, who most often need this treatment. A single-centre medium-sized study suggested that an increase of continuous renal replacement therapy from 20 mL/kg/h of effluent generation to greater than 35 mL/kg/h might be associated with increased survival.[123] In response to this finding, two large multicentre randomised controlled studies were designed: the Acute Renal Failure Trial Network (ATN) study[124] and the Randomised Evaluation of Normal versus Augmented Level of Renal Replacement Trial (RENAL) study.[125] Both showed no difference in survival rates with increasing intensity of renal

Panel 2: **Conventional criteria for initiation of renal replacement therapy in acute kidney injury**

1. Anuria (negligible urine output for 6 h)
2. Severe oliguria (urine output <200 mL over 12 h)
3. Hyperkalaemia (potassium concentration >6·5 mmol/L)
4. Severe metabolic acidosis (pH <7·2 despite normal or low partial pressure of carbon dioxide in arterial blood)
5. Volume overload (especially pulmonary oedema unresponsive to diuretics)
6. Pronounced azotaemia (urea concentrations >30 mmol/L or creatinine concentrations >300 μmol/L)
7. Clinical complications of uraemia (eg, encephalopathy, pericarditis, neuropathy)*

*Complications of uraemia should be prevented by avoidance of unnecessarily high degrees of azotaemia.

replacement therapy. These findings suggest that the prescribed dose of renal replacement therapy should be equivalent to 25–30 mL/kg/h, to take into account the effect of down time, and that a plateau in effectiveness is apparent at such doses. Moreover, nearly all patients with acute kidney injury who were on vasopressor support received continuous renal replacement therapy in the ATN and RENAL trials. Thus, by practice consensus, continuous renal replacement therapy was treated as the de-facto standard of care in haemodynamically unstable patients in both trials. Renal recovery was much greater in the RENAL trial (with almost exclusive use of continuous renal replacement therapy) than in the ATN trial (with substantial use of intermittent haemodialysis), suggesting that continuous therapy might help with renal recovery.[126–129] Therefore the cost-effectiveness of such therapies should be judged on the basis of their possible effect on recovery. In critically ill patients, the cost difference is small in the context of daily care and is dependent on region or institution.[129]

If continuous renal replacement therapy is given, anticoagulation of the circuit might be necessary. Either low-dose heparin (prefilter or systemic) or regional citrate anticoagulation is typically used. In selected patients at risk of bleeding, either no anticoagulation or citrate should be used.[130] Once renal replacement therapy is started, uncertainty exists about when to stop. No randomised controlled trials have addressed this issue. Findings from observational studies have suggested that urine output during treatment can be used to predict successful cessation of continuous renal replacement therapy. A spontaneous urine output of more than 500 mL per day seems to have sufficient discrimination to be used in a trial of therapy cessation.[131]

Research is increasing into acute-kidney-injury-related extracorporeal blood purification by means of adsorptive systems[132,133] and the use of tubular cells containing bioreactors.[134] Although early clinical studies offer some promise, much more work is needed before such treatments are widely applied.

Prognosis

Mortality from acute kidney injury remains high, particularly in critically ill patients, in whom mortality was 53% in the ATN trial and 44·7% in the RENAL trial. Several large epidemiological studies have linked acute kidney injury with the later development of chronic kidney disease, end-stage kidney disease, and mortality.[135–141] These results suggest that even a short episode of acute illness might contribute to long-term morbidity and mortality. Thus, the cost to the patient and to society of acute kidney injury might be greater than was previously thought. Whether this increased risk of chronic kidney disease shows the effect of acute kidney injury itself, or whether acute disease is a marker that identifies vulnerable patients, is unclear and requires further investigation as a public health priority.

Contributors

RB, JAK, and CR jointly developed the outline of the Seminar. RB wrote the first draft and searched for relevant articles. JAK and CR reviewed the choice of references, tables, and figures and edited the initial draft and every subsequent draft.

Conflicts of interest

RB and CR have received consultancy and speaking fees from Alere, Abbott Diagnostics, Gambro, Fresenius, B Braun, and Edwards Lifesciences. JAK has received consultancy and speaking fees from Alere, Abbott Diagnostics, Gambro, Baxter, and Fresenius.

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