Acute kidney injury

The diagnosis of acute kidney injury relies on decreased glomerular filtration rate, increased serum creatinine or cystatin C, or oliguria. The consensus definition and classification RIFLE system is a mnemonic for three levels of severity—Risk, Injury, and Failure—and two outcomes—persistent acute renal failure termed Loss and End-stage kidney disease. The AKIN workgroup to refine the RIFLE criteria resulted in only modest differences, and for all practical purposes RIFLE and AKIN criteria are the same.[1,2]

Measurement of biomarkers released into the blood or urine by the injured kidney at an early stage of damage can lead to earlier starting of specific therapies to repair or prevent progression. Early diagnosis before glomerular filtration rate falls will be most cost-effective in patients at risk (figure).[3] An ideal biomarker should differentiate incipient acute tubular necrosis from other forms of acute renal dysfunction (volume responsive acute kidney injury, acute glomerular, vascular, and interstitial diseases, and obstructive nephropathies), allow monitoring of the effects of treatment, and predict the need for dialysis, long-term kidney outcome, and mortality. In a few clinical conditions, some of these biomarkers (eg, interleukin 18, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, liver fatty-acid-binding protein) increase in urine before the increase in serum creatinine (figure).[3]

Optimisation of the haemodynamic status (mainly perfusion pressure) has a salutary effect on kidney function, and helps to minimise further injury. Renal perfusion pressure can be improved by all or some of: increasing cardiac output, replenishing the circulating volume, enhancing cardiac inotropy, and inducing vasoconstriction.

Acute kidney injury is characterised by a continuum of volume responsiveness, starting from previously called prerenal acute kidney injury and up to unresponsiveness. Although the preferred type of fluid in the critically ill patient at risk for acute kidney injury is unclear, the SAFE study showed that albumin is safe but not more effective than saline in preventing death or need for dialysis.[4] A recent Cochrane review[5] concluded that there is no difference in outcome between colloids and crystalloids, a conclusion which is further corroborated in patients with sepsis in whom resuscitation with pentastarch was even associated with higher rates of acute kidney injury and need for dialysis.[6]

Most crystalloid fluids (hypotonic [0·45%] and isotonic saline [0·9%], and isotonic bicarbonate) have been tested in the prevention of contrast-induced nephropathy or cardiac surgery. Because of methodological differences in design, patients' charac-

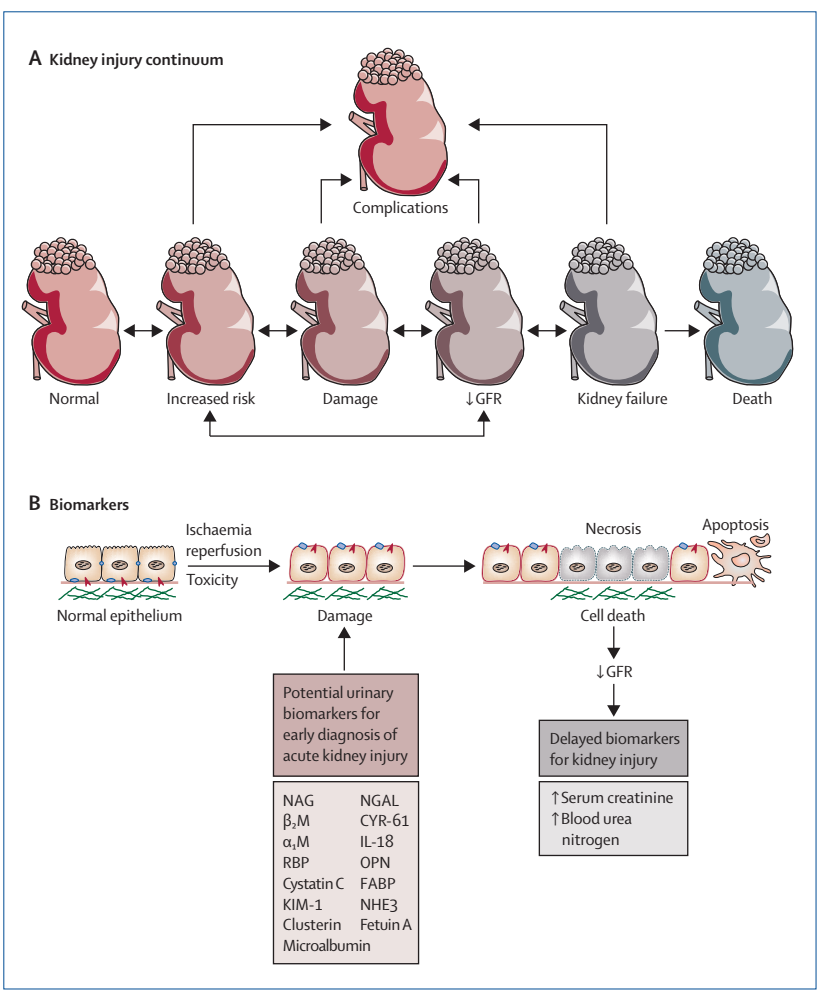

Figure: **Acute kidney injury and its biomarkers**
NAG=N-acetyl-β-glucosaminidase. β_2M=β_2-microglobulin. α_1M=α_1-microglobulin. RBP=retinol-binding protein. KIM-1= kidney injury molecule-1. NGAL=neutrophil gelatinase-associated lipocalin. CYR-61=cysteine-rich protein. IL-18=interleukin 18, OPN=osteopontin. FABP=fatty-acid-binding protein. NHE3=sodium/hydrogen exchanger isoform. (A) Continuum of acute kidney injury. Process can be divided into various reversible stages depending on severity of insult, starting from increased risk to damage followed by decrease in glomerular filtration rate (GFR), further progressing to kidney failure and death. (B) Biomarkers of acute kidney injury. Traditionally used markers, such as blood urea nitrogen and serum creatinine, are insensitive, non-specific, and do not adequately differentiate between different stages of acute kidney injury. Delay in diagnosis prevents timely decisions about management of patients, including administration of putative therapeutic agents. Urinary biomarkers of acute kidney injury will facilitate earlier diagnosis and specific preventive and therapeutic strategies, ultimately resulting in fewer complications and improved outcomes. From reference 3 with permission.

teristics, dose of contrast, and surgery compared with imaging, interpretation of results is difficult. By contrast with earlier reports, recent single-centre studies[7,8] concluded that isotonic bicarbonate compared with isotonic saline is not more efficient in preventing contrast-induced nephropathy. Both studies used iso-osmolal iodixanol as contrast medium which is probably more renal friendly than the classically used low osmolal molecules. The use of sodium bicarbonate to prevent contrast-induced nephropathy needs further evaluation.

In the acute setting, the two most significant threats to renal perfusion pressure are systemic arterial hypotension and increased intra-abdominal pressure (including abdominal compartment syndrome). Vasopressors such as norepinephrine should be used only to treat hypotension after intravascular volume has been restored. There is no evidence that norepinephrine is associated with increased risk of acute kidney injury, and a recent observational study[9] suggested that other vasopressors, such as dopamine, are associated with poor survival.

For the patient with septic shock and at risk of acute kidney injury, guidelines advocate the use of aggressive and early fluid resuscitation and, if hypotension persists, administration of norepinephrine.[10] In view of the low circulating concentrations of vasopressin in sepsis, low-dose vasopressin added to norepinephrine was recently compared with norepinephrine alone,[11] but no differences in 28-day or 90-day mortality and incidence of acute kidney injury were found. Norepinephrine plus dobutamine was be as effective as epinephrine, but is easier to manage.[12]

The independent effectiveness of N-acetylcysteine in the prevention of contrast-induced nephropathy is debatable. Meta-analyses consistently found that N-acetylcysteine along with hydration decreases incidence of contrast-induced nephropathy compared with hydration alone, at least in high-risk patients,[13] although the effect between studies was heterogeneous. Many other drugs (eg, renal vasodilators, diuretics, statins, vitamin C) have been used to prevent acute kidney injury but are not convincingly effective.

A systematic review[14] showed reduction in mortality with strict control of blood glucose with intensive insulin treatment in critically ill patients, but with a four-fold or greater increase in the risk of hypoglycaemia. The positive outcome results have been contradicted[6,15,16] and one meta-analysis[17] showed that tight glycaemic control did not significantly reduce mortality or dialysis need in critically ill patients. There was, however, a beneficial effect on risk of septicaemia and, not unexpectedly, a higher risk of hypoglycaemia.[17] Stringent protocols for blood-glucose control in critically ill patients should only be applied with great caution.

About 4% of all critically ill patients with acute kidney injury will require dialysis. No single dialysis method modality (continuous haemodialysis, intermittent haemodialysis, or slow extended daily but intermittent) is superior to another. The best timing for dialysis also remains unclear. Early initiation might be associated with improved survival,[18] but the discussion is blurred by the lack of a robust marker of renal function. The same applies to the discussion on the correct dose of dialysis.[19] In continuous haemofiltration, most experts recommend a minimum dose of 35 mL^{-1} kg^{-1} h^{-1}. However, some recent studies demonstrated that the potential side-effects of this high-volume treatment often offset its benefits, so that this dose should not be aimed for in every patient.[20,21]

The adequate dose in intermittent haemodialysis has even been more controversial and has ranged from 3 h to 4 h of dialysis thrice weekly to daily. By contrast with previous belief, a multicentre trial found no effect of dialysis intensity on mortality, recovery of kidney function, or reduction in the rate of non-renal organ failure in critically ill patients with acute renal failure.[20] Daily intermittent haemodialysis is recommended when needed but should be adapted to avoid side-effects.

The addition of renal tubule cell therapy to continuous veno-venous haemofiltration resulted not only in a substantive beneficial effect on survival of patients with sepsis and acute kidney injury compared with conventional continuous renal replacement therapy, but also in an acceptable safety profile.[22] More trials are needed to evaluate this new therapeutic approach further.

Although the treatment of patients with acute renal failure is largely supportive, basic research keeps providing the clinician with many, albeit still unproved, approaches to future therapies. Additional experimental models that better reflect the multifactorial causes are

needed because no single intervention therapy will probably be effective. We should not be discouraged by negative results from the many trials, but should continuously think and rethink the basic and clinical strategies to improve the grim prognosis of this disease.

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China's barefoot doctor: past, present, and future

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China's long struggle with rural coverage for health care goes back to the early part of the 20th century. However, these early efforts were seen at that time as unsuccessful.[1] Although the Government tried to draft private practitioners into the rural medical service corps,[2] delivery of health care was still scarce after 1949. Health-care expenditure for 8·3 million urban citizens covered by the state was more than that for 500 million peasants in 1964.[3] After Mao Zedong criticised the urban bias of medical services and pointed out the stress placed on rural areas in 1965,[4] mobile teams of doctors from urban hospitals were sent to deliver health care and train indigenous paramedics.

In 1968, the programme of barefoot doctors was introduced by the journal *Red Flag* as a national policy focused on quickly training paramedics to meet rural needs.[5] Most barefoot doctors, who graduated from secondary school education, practised after training at the county or community hospital for 3–6 months. Hence medical coverage in the countryside rapidly expanded (figure).[6,7] However, the barefoot doctors, who generated their work points with medical services just like agricultural work (ie, their income was counted by transferring time for medical service to similar time for agricultural work,) were not at par with the regularly trained doctors and their incomes were 50% lower .

Despite a low level of service in terms of technique and medical instruments, the barefoot doctor programme effectively reduced costs and provided timely treatment to the rural people.[8] The programme also provided other