Acute Renal Failure (ARF) is a common and a potentially devastating disorder with a higher prevalence in the intensive care units. ARF occurs in 10 to 15% of critically ill patients with a mortality of 78 to 90%. The estimates can differ due to the lack of consensus on the definition of ARF itself. They can prove conservative in the face of the aging population with increased comorbidities and the increasing number of patients supported for multiorgan failure. Nevertheless, ARF is potentially reversible if appropriately managed and preventable with a better understanding of its etiology and pathophysiology. Various novel therapies have been experimented but their practical validity is yet to be established. Early dialysis along with aggressive supportive measures will enable us to reduce the mortality in ARF. Continuous renal replacement therapy (CRRT) has its advantages in the hemodynamically unstable ARF. Yet, our approach should be primarily directed to prevent ARF.

Classically ARF is described by oliguria with urine output less than 400ml/day or less than 18 ml/hour. Azotemia and decreased urine output are hallmarks of ARF. However the incidence of nonoliguric ARF is on the increase. The consequences of acute derangement in extracellular uid balance, acid base, electrolytes and divalent cation regulation in ARF affects all organ systems. This has entertained the possibility of ARF as a syndrome than a disease by itself.

While the incidence of ARF is about 1% of hospitalized patients, in the ICU set up it is nearly 20%. ARF in the ICU is associated with high mortality of upto 90% in some studies. In the ICU set up ARF is usually associated with other organ failure (69% Vs 8% of isolated ARF). Thus many ICU patients die probably with ARF than due to ARF. Approximately 30% of ARF patients require renal replacement therapy (RRT). The mortality among patients requiring RRT is 79%. The outcome of ARF is also related to the severity of the underlying disease. It is 30% in ischemic renal failure against 10% in nephrotoxic ARF. Predictors of mortality in ARF are mechanical ventilation, hypoalbuminemia, hyperbilirubinemia and increased lactate levels.

In the ICU setting the most common cause of ARF is ATN. Renal hypoperfusion due to insufficient cardiac output, hypovolemia and vasodilatation coupled with other nephrotoxic insults are the most common causes of prerenal insufficiency that progress to ATN. Sepsis is the commonest cause of intrinsic ATN. In a prospective multicentric study, 75.9% of ARF in ICU was due to ATN of which 48% was due to sepsis. and 20% to toxic insults. Common drugs at risk of precipitating ARF are ACEI,
NSAID, radiocontrast dyes, antibiotics- gentamicin and amphotericin.

Loss of autoregulation of blood ow in the prerenal setting renders the kidneys severely hypoxic. The tubules get injured leading to cellular swelling and obstruction of lumen. The resultant increased tubular pressure offsets the ultrafiltration pressure and cause fall in glomerular filtration rate (GFR). Tubular cell injury allows the glomerular uid to leak back into peritubular capillaries causing further hemodynamic compromise via the tubuloglomerular feedback and other in ammation in the glomeruli. Various in ammatory mediators and neuroendocrine mechanisms are involved in sepsis mediated ARF. Important mediators of the hemodynamic response are tumor necrosis factor (TNF), platelet activating factor (PAF), endothelin-1, thromboxane A2 and leukotrienes. Others are the renin angiotensin system, kallikrein-kinin system, atrial natriuretic peptide (ANP), interleukin-1, adenosine and catecholamines. These mediators also activate the complement system, the coagulation and fibrinolysis cascade causing intrarenal coagulation.4

Prevention of ARF

Prevention of ARF is centred on improving the renal blood ow, decreasing the vasoconstriction through the various mediators, improving the tubular back leak by regrowing and renourishing the tubules that have been freshly injured and exerting anti-in ammatory effect on the interstitial in ammation. Restoration of the volume in patients at risk of volume depletion and hypotension is a time honoured effective measure to prevent ARF. It thus improves renal perfusion and increases the ow at which the injurious substances move through the tubules with les likelihood to cause ischemic or toxic damage. Osmotic agents like mannitol have thus been considered to aid incorporation of more uid in the extracellular space.5 It has proved effective in cardiac surgery but not in other cases of human ARF.

Avoiding nephrotoxic drugs like aminoglycoside is important. One third of patients on aminoglycosides can still get ARF despite ideal therapeutic levels. Using liposomal preparation of amphotericin and hydrating the patient well when on cisplatinum reduces incidence of ARF by as much as 50%.

Adenosine antagonists like theophylline or acetycysteine have produced mixed results in contrast nephropathy. Multiple animal studies have shown promise by stimulating regrowth of ischemically injured tubular cells with growth factors such as insulin like growth factor (IGF-1), hepatocyte growth factor, transforming growth factor α.6 However in a multicentric trial of 72 patients IGF-1 did show significant change in the course of ARF. The vasodilatory effect of atrial natriuretic peptide (Anaritide) has been shown to improve urinary ow.7 Of three human trials, 2 trials failed to demonstrate any preventive or significant benefit. Prolonged use for more than 21 days has been successful in preventing dialysis. Fenaldopam - a specific dopamine agonist stimulates postsynaptic peripheral dopamine −1 receptors has been tried at 0. 02 to 0. 5 mg /kg/minute to increase the renal blood ow and as a renoprotective agent in high risk patients undergoing cardiac surgery, vascular surgery, transplant surgery and patients exposed to radiocontrast agents, cyclosporine and amphotericin B toxicity.7 The NORASEPT II Study 1999 concluded that renal dose dopamine does not prevent ARF in patients with septic shock and oliguria.7 The Australian and New Zealand Intensive Care Society (ANZICS) clinical trial involved 328 patients admitted to 23 participating ICU.5 No difference in the outcome was observed between the dopamine and placebo groups. If low dose renal dopamine (LDRD) is arranged, the response is based on increased diuresis and should be assessed within 6 hours. If there is no improvement or if rhythm disturbances occur it should be discontinued.

Diuretics should be considered only after renal perfusion has been maximized. Clinical situations that may warrant use of diuretics in early course of ARF are volume replete patients with endogenous heme pigment injury, forced diuresis in the setting of renally excreted toxins such as lithium, theophylline, salicylates and toxic alcohol ingestion or in patients with tumor lysis syndrome.7
Anti ICAM antibodies to improve blood ow in ischemic injury and antioxidants including acetylcysteine have been tried with no proven benefit.9

Management of ARF
The goal of treatment is immediate correction of reversible causes. Recognition and relief of urinary outlet obstruction should be given the highest priority, especially for patients with anuria. Support of renal perfusion with either volume expansion with uids or therapeutics that improve renal oxygen delivery should be considered before any other attempt to improve urinary ow. Urinary indices should be assessed before administration of diuretics. Therapy to correct the pathophysiological derangements of ARF can be broadly categorised into nondialytic and dialytic therapies.

Nondialytic therapies : Mannitol Boluses of 20 gm in not less than 30 minutes upto a maximum of 80 gm/day, to be stopped if oliguria persists, are safe.7 Bradykinin inhibitors, anti thrombin3, anti TNF monoclonal antibody and activated protein kinase C (PKC) besides thromboxane receptor and endothelin receptor antagonists have been tried.

Protein kinase is only useful agent in systemic in ammatory reaction syndrome induced ARF in ICU.10 The backbone of treatment of ARF remains adequate supportive care, maintenance of renal perfusion pressure (MAP > 80 mm Hg), avoidance of future nephrotoxic insults and provision of renal replacement therapy. Most of the post-operative or post transplant ARF has evidence of hypovolemia.

Adjuvant Measures : Restriction of potassium (60 Meq/day), sodium (90 Meq/day) and phosphorus (800 mg/day) should be recommended for most patients with ARF. Calorie requirements of atleast 35 cal/kg day and protein supplementation of 0.6 to 1.4 g/kg/day is required to minimize protein catabolism, depending on whether dialysis is required.2 Severe protein restriction to avoid dialysis is controversial. The current medication regimen, especially medication dosing should be adjusted to the residual renal function. Further potential nephrotoxins have to be avoided. Anemia due to ARF is better corrected with erythropoietin (EPO). It seems to play an important role in prevention renal tubular injury.11

Life threatening hyperkalemia may complicate ARF. Urgent measures to stabilise cardiac cellular membrane repolarisation is with calcium gluconate or chloride. Especially when ECG changes are present. Induction of intracellular shifting of potassium (K+) by intravenous dextrose and insulin administration is the next priority till measures to remove K+ by dialysis is arranged.

Dialysis
Initiation of renal replacement therapy (RRT) is recommended when severe derangements in electrolyte concentration (potassium, sodium), volume overload, acid base imbalance, pronounced azotemia (BUN more then 100 mg/dl), urid symptoms of uremia (pericarditis, encephalopathy, bleeding, nausea-vomiting) are noted. Options available are peritoneal dialysis (PD), intermittent hemodialysis (IHD) extended daily dialysis (EDD), slow low efficiency dialysis (SLED) and continuous renal replacement therapy (CRRT). PD is less preferred due to poor delivery of dialysis dose and difficulty in managing ultra filtration. However some trials have shown that continuous peritoneal dialysis has given better results in reducing morbidity and mortality in ICU ARF and is less injurious to ischemic kidney. IHD has proved to be beneficial in many of the controlled trials inspite of the fact that it may aggravate the renal injury due to fall in blood pressure.12

Extended daily hemodialysis and SLED seems to be superior to hemofiltration in effectively reversing the biochemical abnormality and the mortality is lower when compared to hemofiltration. In situation of hypovolemia, hypotension and multiorgan failure (MOF), CRRT by hemofiltration or hemodiafiltration is preferred. Critically ill patients who are hypercatabolic, anuric and uid overloaded may also need this procedure.
Role of CRRT\textsuperscript{13}: CRRT has potential benefits by an increased hemodynamic tolerance of dialysis, improved ability to manage fluid and electrolyte balance, improved dialytic dose delivery and use of more biocompatible high flux membranes. It maintains consistent homeostasis through slow gradual shifts in volume status and serum osmolality, permits continuous control of fluid balance, reduces need to restrict fluid administration, requires a lower volume of blood to be circulating outside the bag, has less effect on complements or leucocytes and has greater clearance of middle molecular weight solutes. This process is done by specially designed ultrafiltration cell or high flux dialyser which is connected by blood lines to large artery or vein. Blood pump is not necessary in continuous arteriovenous hemofiltration (CAVH). Ultrafiltration is driven by the patient’s arterial pressure. Fluid removal is about 5 to 15 ml/mt which amounts to about 20 litres/day as the process is continuous. CAVHD (continuous arteriovenous hemodialysis), CAVHDF (continuous arteriovenous hemodiafiltration), CVVH (continuous venovenous hemofiltration), CVVHD (Continuous venovenous hemodialysis), CVVHDF (Continuous venovenous hemodiafiltration) SCUF (slow continuous ultrafiltration) are different modes of CRRT. No particular form of CRRT has yet been shown as a superior option. Inspite of the advantages of CRRT, IHD remains a more practical option (except in select clinical situations of hemodynamically unstable ARF patients) in our Indian scenario considering the additional costs involved in CRRT. However IHD should utilize more biocompatible membranes such as polysulphones or polyacrilonitrile and should be extended for daily dialysis.\textsuperscript{6} This improves the outcome of ARF by decreasing complement activation and production of leukotrienes and other cytokines. Timing of RRT and adequate dosing of the delivery determines the outcome. RRT at lower levels of azotemia has a better outcome including shorter hospitalization. Besides hemofiltration and hemodiafiltration has the disadvantage of causing bleeding.

ARF is a multisystemic disorder with an increasing prevalence in ICU. A structured approach to the evaluation of ARF will facilitate early diagnosis and initiation of appropriate therapy. While understanding the pathophysiology of ARF has paved way for treatment with newer therapies, none of them have been found to be uniformly effective. Efforts should be maximum to prevent ARF. Maintaining renal perfusion by correcting hypovolemia, avoidance of nephrotoxins and close monitoring of patients at risk of developing ARF will yield better results than initiation of aggressive management after onset of ARF. In SIRS induced ARF appropriate antibiotic should be given in adequate amount. Use of activated protein C in SIRS induced ARF, has reduced the mortality to a significant extent. In ARF with MOF appropriate therapy to protect other organs such as ventilatory support in respiratory distress syndrome, should be provided along with other treatment modality for ARF. Non invasive respiratory support is preferred to endotracheal intubation. Prone ventilatory support appears to be better than than conventional supine respiratory assistance.\textsuperscript{14} In case of hepatorenal failure due to end stage liver disease MARS dialysis to support both liver and kidney will give a better result.

References
10. Abraham E. Sepsis / multiorgan failure. 2001 World Congress of Nephrology San Francisco.