INTRODUCTION:
Acute renal failure is characterized by a rapid fall in glomerular filtration rate, clinically manifest as an abrupt and sustained rise in urea and creatinine. Life threatening consequences include volume overload, hyperkalaemia, and metabolic acidosis. Acute renal failure is both common and costly and carries a high morbidity and mortality. As it is often preventable, identification of patients at risk and institution of appropriate preventive measures are crucial. In incipient or established acute renal failure rapid recognition and treatment may prevent irreversible loss of nephrons. In most cases of acute renal failure initial management is by non-specialist clinicians, often comparatively junior ones. All clinicians should therefore be able to recognize the symptoms and signs of acute renal failure request and interpret initial investigations, initiate appropriate treatment, and know when, and how urgently, to consult a more experienced colleague or specialist. [1]

EPIDEMIOLOGY:
Acute renal failure is increasingly common, particularly in elderly people, although reported incidences vary according to the definition used and the population studied. In 1993 a community based study found an incidence of severe acute renal failure (serum creatinine > 500 µmol/l) of 172 per million adults per year, of whom 72% were over 70.1 Age related incidence rose from 17 per million per year in adults under 50 to 949 per million per year in the 80-89 age group. More recent prospective studies report an overall incidence of acute renal failure of almost 500 per million per year and an incidence of acute renal failure needing dialysis of more than 200 per million per year. [1-4] This is double the UK incidence of end stage renal disease needing dialysis and places high demands on healthcare resources. [5] Acute renal failure accounts for 1% of hospital admissions and complicates more than 7% of inpatient episodes, mostly in patients with underlying chronic kidney disease. [6, 7] When the condition is severe enough to need dialysis in-hospital mortality is around 50%, and it may exceed 75% in the context of sepsis or in critically ill patients. [3, 4, 8] According to recent publication from Institute of Medical Sciences IMMS, BHU in India, over a period of 26 years, while analyzing data the total case of acute renal failure studied were 2405 (male vs. female; 1375 vs.1030) with age range 1-95(mean 40.32) years. The incidence of ARF has increased from 1.95 per 1000 admission in 1983-1995 to 4.19 per 1000 admission in 1996-2008 (P<0.01). Obstetric ARF declined due to decreasing number of postabortal ARF. Surgical ARF decreased to 9.17% in 1996-2008 from 13.8% in 1983-1995 (P<0.01). Malarial ARF increased significantly from 4.70% in first half of the study 17% in later period (P<0.01). Diarrhea associated ARF has significantly decreased from 36.83% in 1983 -1995 to 19% in 1996-2008 (P<0.01). Sepsis related ARF has increased from 1.57% in 1983-1995 to 11.43% in 1996-2008 (P<0.01). Hemolytic uremic syndrome was common cause of ARF in children. Rifampicin and NSAIDs were the main cause of nephrotoxic ARF with increasing trend in recent years (P<0.01). Liver disease related ARF increased from 1.73% in 1983-1995 to 3.17% in 1996-2008 (P<0.01). Myeloma associated ARF constitute 1.25% of total ARF cases in the period 1996-2008. Incidence of renal cortical necrosis has decreased significantly from 5.80% in 1983-1995 to 1.30% in 1996-2008 (P<0.01). However, during the same period ARF due to ATN, AGN and AIN has remained unchanged. The overall mortality from ARF has decreased significantly from 20% in 1983-1995to 10.98% in 1996-2008 (P<0.01). [9]
DEFINITION AND CLASSIFICATION:

Acute renal failure (ARF) has traditionally been defined as the abrupt loss of kidney function that results in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes. The loss of kidney function is most easily detected by measurement of the serum creatinine which is used to estimate the glomerular filtration rate (GFR).

Three problems are associated with the use of the serum creatinine to quantitatively define ARF:

Serum creatinine does not accurately reflect the GFR in a patient who is not in steady state. In the early stages of severe acute renal failure, the serum creatinine may be low even though the actual (not estimated) GFR is markedly reduced since there may not have been sufficient time for the creatinine to accumulate.

Creatinine is removed by dialysis. As a result, it is usually not possible to assess kidney function by measuring the serum creatinine once dialysis is initiated. One exception is when the serum creatinine continues to fall on days when hemodialysis is not performed, indicating recovery of renal function.

Numerous epidemiologic studies and clinical trials have used different cut-off values for serum creatinine to quantitatively define ARF [10].

The lack of consensus in the quantitative definition of ARF, in particular, has hindered clinical research since it confounds comparisons between studies. Some definitions employed in clinical studies have been extremely complex with graded increments in serum creatinine for different baseline serum creatinine values. [10, 11] As an example, in a classic study of the epidemiology of hospital-acquired acute renal failure, ARF was defined as a 0.5 mg/dl increase in serum creatinine if the baseline serum creatinine was ≤1.9 mg/dl, an 1.0 mg/dl increase in serum creatinine if the baseline serum creatinine was 2.0 to 4.9 mg/dl, and a 1.5 mg/dl increase in serum creatinine if the baseline serum creatinine was ≥5.0 mg/dl. [11]

CAUSES OF ARF:

The causes of acute renal failure can be broadly grouped into three major categories. These are decreased renal blood flow (pre-renal causes; 40-70% of cases), direct renal parenchymal damage (intrinsic renal causes; 10-50% of cases), and obstructed urine flow (post-renal or obstructive causes; 10% of cases).

PRE-RENAL FAILURE

Changes in pre-glomerular and post-glomerular arteriolar resistance enable renal blood flow and glomerular filtration rate to remain roughly constant across a wide range of mean arterial pressures. However, below a mean arterial pressure of 70 mm Hg autoregulation is impaired and glomerular filtration rate falls proportionately. Renal autoregulation chiefly depends on a combination of pre-glomerular arteriolar vasodilatation, mediated by prostaglandins and nitric oxide, and post-glomerular arteriolar vasoconstriction, mediated by angiotensin II. Drugs that interfere with these mediators—namely, non-steroidal anti-inflammatory drugs or selective cyclo-oxygenase 2 inhibitors, and angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists—may provoke pre-renal acute renal failure in particular clinical settings. People at high risk include elderly patients with atherosclerotic cardiovascular disease, patients with pre-existing chronic kidney disease, and patients with renal hypoperfusion, caused by volume depletion, hypotension, or renal artery stenosis.[1]

INTRINSIC RENAL FAILURE

Intrinsic acute renal failure may be caused by diseases affecting the glomeruli, renal tubules, interstitium, or vasculature. Overall, the most common cause is acute tubular necrosis, resulting from continuation of the same pathophysiological processes that lead to pre-renal hypoperfusion. Intrinsic acute renal failure is often multifactorial; in intensive care the most common cause is sepsis, often accompanied by multi-organ failure. Postoperative acute
tubular necrosis accounts for up to 25% of cases of hospital acquired acute renal failure, mostly resulting from prerenal causes. The third most common cause of hospital acquired acute renal failure is acute radio contrast nephropathy. [1]

POST-RENAL FAILURE
Obstructive nephropathy presents as acute renal failure relatively infrequently but is important to recognise, as rapid diagnosis and prompt intervention can result in improvement or even complete recovery of renal function. At risk populations include older men with prostate disease and patients with intra abdominal, particularly pelvic, malignancy. An important clinical consequence is the substantial diuresis that generally occurs once obstruction is relieved, which needs careful monitoring and appropriate fluid replacement to avoid volume depletion. [1]

RIFLE CRITERIA:
An expert panel under the auspices of the Acute Dialysis Quality Initiative (ADQI) has developed the RIFLE classification of AKI. [12-14] The acronym RIFLE defines three grades of increasing severity of ARF (risk, injury, and failure, respectively, R, I, and F) and two outcome variables (loss and end-stage kidney disease, respectively, L and E). A unique feature of the RIFLE classification is that it provides for three grades of severity of renal dysfunction on the basis of a change in serum creatinine, reflecting changes in GFR or duration and severity of decline in urine output from the baseline. The RIFLE criteria have the advantage of providing diagnostic definitions for the stage at which kidney injury still can be prevented (risk stratum), the one when the kidney has already been damaged (injury), and the one when renal failure is established (failure). The RIFLE criteria have been tested in clinical practice and seem to be at least coherent with regard to outcome of the patient with AKI. [15-18]

PATHOGENESIS:
Renal blood flow is 25% of cardiac output but some areas are particularly sensitive to ischaemic damage. Most of the blood flow supplies the cortex, which contains the glomeruli and convoluted tubules, areas that require good perfusion to achieve filtration and reabsorption, the latter with high energy demands. The outer medulla is comparatively starved of oxygen, its blood supply first traversing the glomerular capillary bed, and losing hydrostatic pressure (in essence, a portal circulation), and then on entering the medulla, losing oxygen by countercurrent exchange with the venous vasa recta. These features are essential to maintain the osmotic gradients within the medulla and thus generate concentrated urine, but render the outer medulla very susceptible to variations in blood flow. [19] This area contains the thick ascending limb of the loop of Henle and S3 segment of the proximal tubule, both with high oxygen requirements. Impaired tubular sodium reabsorption attributable to reduced perfusion causes constriction of the afferent arteriole and a further reduction in glomerular filtration rate (GFR). This compensatory mechanism (tubulo-glomerular feedback), designed to protect the downstream nephron, may cause injury if prolonged, or if normal regulation of the arterial tone is blocked (for example, by non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs). Reduced blood flow in the peritubular capillaries produces ischaemic damage in vascular endothelial cells, resulting in cell swelling and the expression of cell adhesion molecules—reducing flow further and leading to leukocyte activation. Adherent leukocytes further impede blood flow and produce cytokines and reactive oxygen species that damage endothelial and tubular epithelial cells. Tubular cells swell, lose their brush border, and develop cytoskeletal abnormalities with abnormal localisation of cell membrane components (for example, Na+/K+2ATPase), changes in cellular polarity, and loss of cell-cell and cell-basement membrane attachment. These swollen, detached cells obstruct the tubular lumen, and backleak of filtrate occurs through the damaged basement membrane. In the classic histological appearance of ATN, tubules are surrounded by flattened, denuded epithelium, and the lumen filled by cell debris, with congested peritubular capillaries and an extensive inflammatory cell infiltrate. [20-22] Cell death occurs predominantly by necrosis, although apoptosis also contributes—especially in the thick ascending limb and late in the process. [21] A remarkable feature of the kidney is its ability to regain normal structure and function after such injury. Once renal perfusion and oxygen supply are normalised, viable cells still adherent to the tubular basement membrane can spread to cover denuded areas, and then differentiate to reproduce normal tubular architecture, and function. The return of glomerular filtration aids clearance of tubular debris and relief of obstruction. A period may exist where glomerular filtration has normalised, but tubular function remains deranged, hence the polyuric phase of ATN, where urine output is often excessive without normal homeostasis. The anuric phase of ATN classically lasts 7–21 days, and recovery to pre-insult levels of renal function can be expected, although some impairment of function may persist, particularly if there is a background of chronic renal insufficiency.

MANAGEMENT:
Despite our best therapeutic efforts, ARF is a serious condition that carries a considerable mortality, about 40%–70% depending on the population studied and definitions used. [23-30] This mortality rate has remained constant over the past 40 years, perhaps because the lower thresholds for high risk diagnostic and therapeutic interventions in those with increased comorbidity, and the reduction in the numbers of patients with “simple” ARF (for example, related to obstetric complications), have negated the effect of therapeutic advances on prognosis. [31-32] Immediate prognosis is worse with increasing age and comorbidity. A significant proportion fails to recover renal function and require long term renal replacement therapy (up to 17% of survivors in one study)—this proportion is much higher in those with pre-existing renal impairment. [25-26] Recovery of renal function is often incomplete and chronic renal failure may result, with its
associated increased cardiovascular mortality and attendant risks of later progression to end stage disease. [24]

As physicians, we should pay more attention to the prevention of ARF, recognising that our sick patients are at high risk of developing renal impairment, and seeking to avoid perturbations in cardiovascular status, the prescription of nephrotoxic drugs, and use of procedures that increase the risk. Once ARF is established, a precise diagnosis should be sought and appropriately treated, and further insults avoided. The cornerstone of effective management remains regular reassessment of the patient’s clinical and biochemical status, and recognition of the need for additional intervention, including timely and effective renal replacement therapy.

REFERENCES: