ESSAY

CRITICAL CARE NEPHROLOGY

Presented by/ Doaa Hussein El Rouby

(M.B.B.ch.)

Submitted In Partial Fulfillment of M.Sc.Degree in Internal Medicine

Supervisors

Prof. Dr. / Dawlat Belal

Professor of Internal Medicine, Cairo university

Dr./ Manal El Deib

Lecturer of Internal Medicine, Cairo university

Dr./ Dalia Roshd Ahmad Abdel Rahman

Lecturer of Internal Medicine, Cairo university

ABSTRACT

This is a review of article of critically ill renal patients. We discussed severe acute renal failurewhich is seen predominantly in ICU's.

At first, we discussed definitions of acute renal failure with special emphasis on universal one and we reviewed different cases of ARF among ICU patients, which include sepsis, hepatorenal syndrome, rhabdomyolysis, haemolytic uraemic syndrome, post operative cases, contrast nephropathy and drug induced nephropathy. In each case, definition, epidemiology, pathophysiology and treatment were discussed.

In the chapter conserning conservative management of critically ill renal patients, we studied different vasoactive drugs and their renal effect. We discussed also the rolw of diuretics, and we studied acid –base disturbances in these patients.

At last, we reviewed the renal replacement therapy, its dose, when to start it, how to choose its type and differences between them.

Keywords: acute renal failure- critically ill renal patients-sepsis-renal replacement therapy.

Acknowledgment

I would like to thank Professor Dr. Dawlat Belal, professor of internal medicine, Cairo University, for her outstanding effort, encouraging, guiding and supervision.

I would like to thank Dr. Manal El Deib, lecturer of internal medicine, Cairo University, for the great effort she did and for the fruitful ladvice she gave.

I would like to thank Dr. Dalia Roshd Ahmad, lecturer of internal medicine, Cairo University, for her encouragement and support.

Finally, my hearty thanks to my family who constantly encouraged me to go forwards…...

Contents

Abbreviations

ACEIs: Angiotensin converting enzyme inhibitors
ADH: anti- diuretic hormone
ANP: atrial natriuretic peptide
APACHE: acute physiology and chronic health evaluation
ARA: Angiotensin II receptor antagonists
ARF: acute renal failure
ATN: acute tubular necrosis
BUN: blood urea nitrogen
CABG: coronary artery bypass graft
cAMP cyclic adenosine monophosphate
cGMP: cyclic guanosine mono-phosphate
CH: continuous haemofiltration
CHD: continuous haemodialysis
CHDF: continuous haemodiafiltration
CK: creatine kinase
CLrrt: drug clearance of renal replacement therapy
CN: contrast nephropathy
CO: cardiac output
COP: colloidal oncotic pressure
Cox: cyclo-oxygenase
CRRT: continuous renal replacement therapy
CVVHF: continuous veno-venous haemofiltration
EHEC: enterohhemorrhagic Escherichia coli
FE_{Na}: fractional excretion of sodium
GFR: glomerular filtration rate
HITTS: heparin induced thrombocytopenia and thrombosis
HRS: hepatorenal syndrome
HUS: haemolytic uraemic syndrome
ICU: intensive care unit
IGF: insulin growth factor
IHD: intermittent haemodialysis
LDL: low density lipoprotein
MAP: mean arterial pressure
MARS: molecular adsorption recirculating system
MIC: minimum inhibitory concentration
NAC: N- acetylcysteine

NE: noreepinephrine
NSAID: non-steroidal anti inflammatory agents
PAE: post antibiotic effect
PEEP: positive end expiratory pressure
RAAS: rennin angiotensin aldosterone system
RBF: renal blood flow
RRT: renal replacement therapy
SCUF: slow continuous ultrafiltration
SGA: subjective global assessment
SLEDD: slow low efficiency daily dialysis
STx: shiga toxin
SVR: systemic vascular resistance
TALH: thick ascending loop of Henle
TNF: tumour necrosis factor
UNA: urea nitrogen appearance
Vd: volume distribution
VP: vasopressin

INTRODUCTION

Intensive or critical care medicine is currently a well established medical speciality with specific therapies, publications, practical and cognitive skills, and associated procedures. The evolution of the ICU has had significant implications for clinical nephrologists especially in relation to the nature, epidemiology, and management of severe acute renal failure (ARF). Severe ARF, in fact, is now seen predominantly in ICUs (R Bellomo et al,1996), is usually associated with the dysfunction of other organ systems and is often accompanied by sepsis. This type of ARF is typically multifactorial and has a very high mortality. Its management requires complex knowledge and skills that are neither fully acquired as part of the standard training in intensive care medicine , nor are they part of standard nephrological training.(Claudio Ronco et al,1998).

DEFINITION OF ARF:

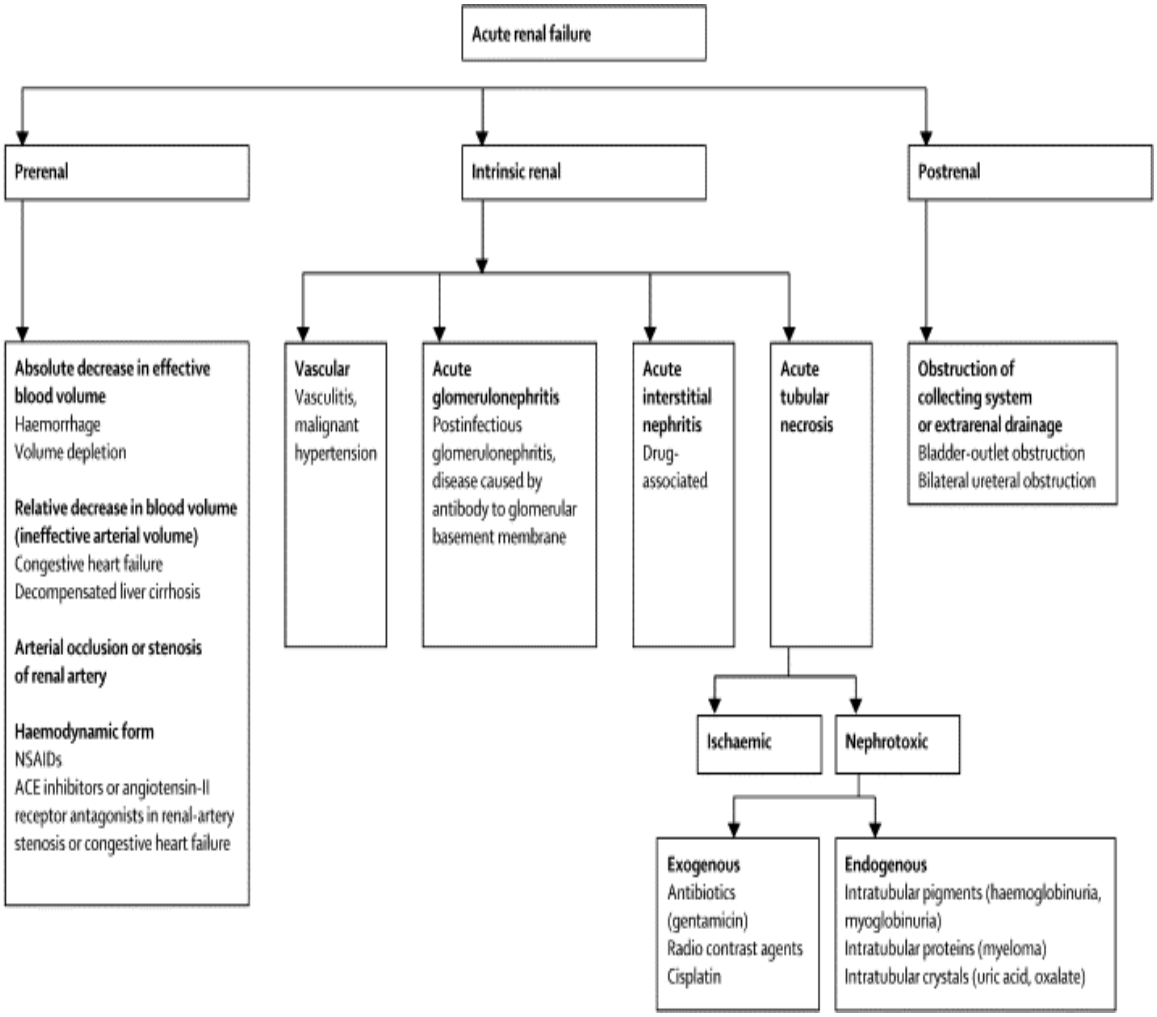
Acute renal failure (ARF) is characterized by an abrupt decline in renal function resulting in an inability to excrete metabolic wastes and maintain proper fluid and electrolyte balance. Although there is no universal laboratory definition, it is reasonable to define ARF as an increase in serum creatinine for 2 weeks or less of 0.5 mg/dL (44.2 μmol/L) if the baseline is less than 2.5 mg/dL (221 μmol/L) or an increase in serum creatinine by more than 20% if the baseline is more than 2.5 mg/dL (221 μmol/L). (Naveen Singri et al,2003). One must be cautious when making the diagnosis of ARF in critically ill patients on the basis of a change in urine output, BUN or creatinine concentration alone, as blood urea nitrogen (BUN) may be elevated in a number of conditions common in critical care patients in absence of renal failure, also, creatinine can be elevated without ARF in patients after acute muscle injury, and in individuals with a decreased intake of sodium or protein, less urine will be required daily for solute excretion, So, an abrupt change in urine output, rather than any specific quantity of urine output, should be the clue to the presence of ARF (Allen R. Nissenson ,1998). The Acute Dialysis Quality Initiative group lately proposed the RIFLE system , classifying acute renal failure into three severity categories (risk, injury, and failure) and two clinical outcome categories (loss and end-stage renal disease). (R Bellomo et al, 2004) .

	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 μmol/L when there was an acute rise of >44 μmol/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	

CAUSES OF ACUTE RENAL FAILURE:

Causes of acute renal failure can be broadly divided into three categories . 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. (Norbert Lameire et al,2005) .



EPIDEMIOLOGY OF ARF IN ICU PATIENTS:

Approximately 5% of a hospital's patient population may develop acute renal failure (ARF). This prevalence is even greater among patients in intensive care units (ICUs), where it may reach 16%. (Schwilk B et al, 1997). 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. (A de Mendonca et al, 2000).

In the intensive care unit (ICU), patients with ARF carry the highest mortality rate of 50% to 70%. This rate has remained unchanged during the past 50 years, because patients in the ICU have more complicated ARF and may be elderly with multiple comorbidities (Brivet G et al,1996) .

The subset of patients who develop ARF during the first 24 hours after cardiogenic shock from a myocardial infarction have a mortality rate of 87% vs 53% in those patients who did not develop ARF (Maria koreny et al 2002) .

Acute renal failure occurs in approximately 19 percent of patients with moderate sepsis, 23 percent with severe sepsis, and 51 percent with septic shock when blood cultures are positive (Riedemann NC et Al 2003) .

The combination of acute renal failure and sepsis is associated with a 70 percent mortality, as compared with a 45 percent mortality among patients with acute renal failure alone.(Schrier R. W. and Wei Wang,2004).

In the study by Brivet et al. drawn from 20 French multidisciplinary intensive care units (ICUs), the type of ARF was prerenal in 17%, renal (usually acute tubular injury) in 78%, and postrenal in 5% . (Brivet G et al, 1996).

A recent study showed that neither patient characteristics (age, gender, comorbid conditions), severity of illness (APACHE III, number of failed organs) nor mode and duration of renal replacement therapy were related to recovery of renal function, and concluded that if critically ill patients with normal renal function prior to the renal insults survive the precipitating cause of ATN, the overwhelming majority will recover sufficient renal function. [Helmut Schiffl, 2006).

CAUSES OF ARF IN ICU:

*Pre-renal (renal hypoperfusion):

- Intravascular volume depletion (e.g. dehydration, blood loss, redistribution of fluid between body compartements)

-Severe hypotension (e.g. sepsis, drugs)

-Reduced cardiac output (e.g. pump failure post myocardial infarction, myocardial ischaemia)

*Intrinsic renal failure :

-Acute tubular necrosis (ATN)

1-Ischaemic (the extreme end of pre-renal failure, also seen in pancreatitis, burns, sepsis)

2-Exogenous toxins (e.g. radiocontrast, nephrotoxic drugs)

3- Endogenous toxins (e.g. rhabdomyolysis, massive haemolysis, tumour lysis syndrome)

-Hepatorenal syndrome

-Acute glomerulonephritis or interstitial nephritis

-Increased intra-abdominal pressure

-Vascular (malignant hypertension, atheroembolic conditions)

* Obstructive renal failure: unusual to be main cause of ARF in ICU.

PATHOPHYSIOLOGY OF ARF IN ICU PATIENTS:

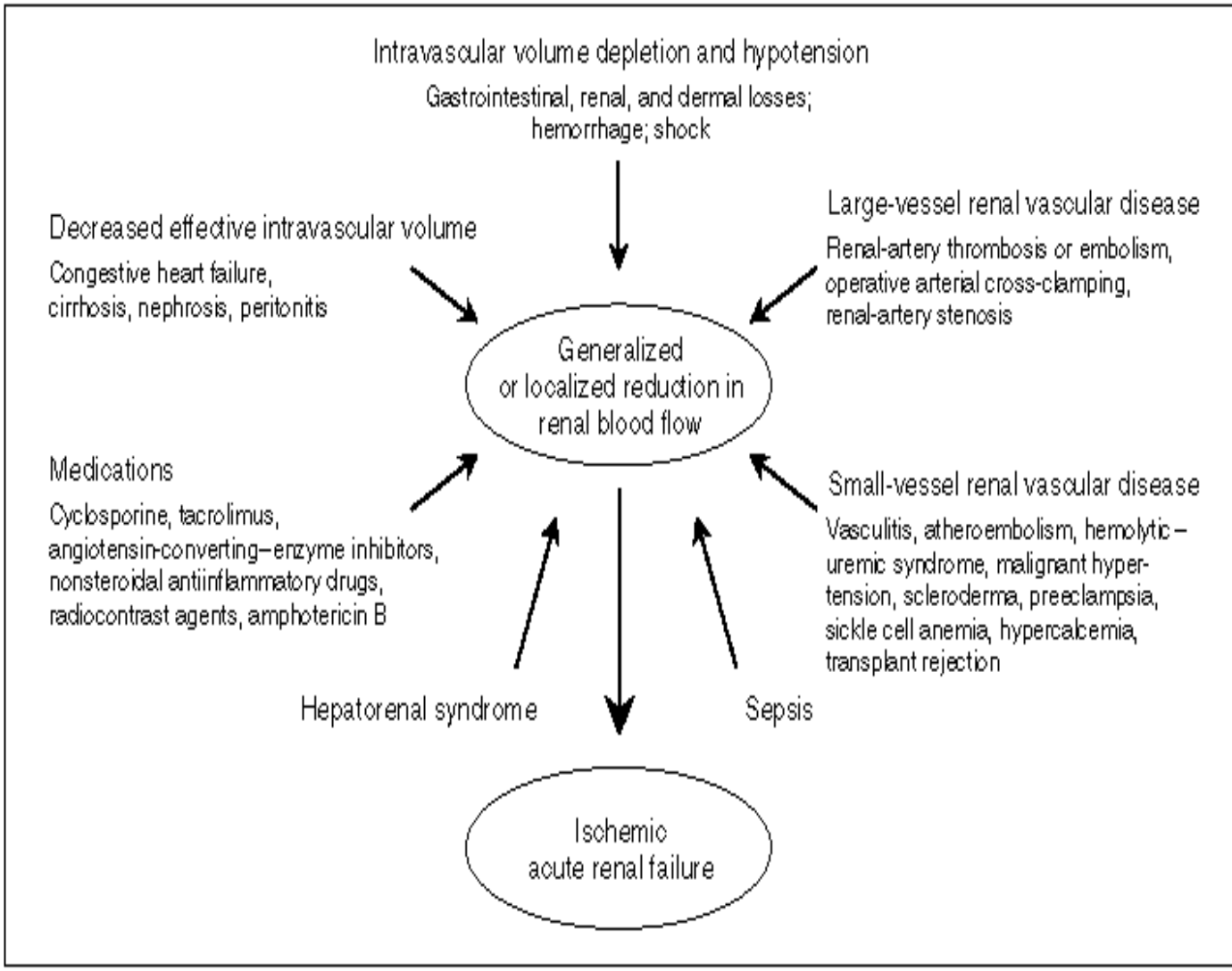
ARF in ICU patients is due to toxic or ischaemic cause. (Allen R. Nissenson, 1998) .

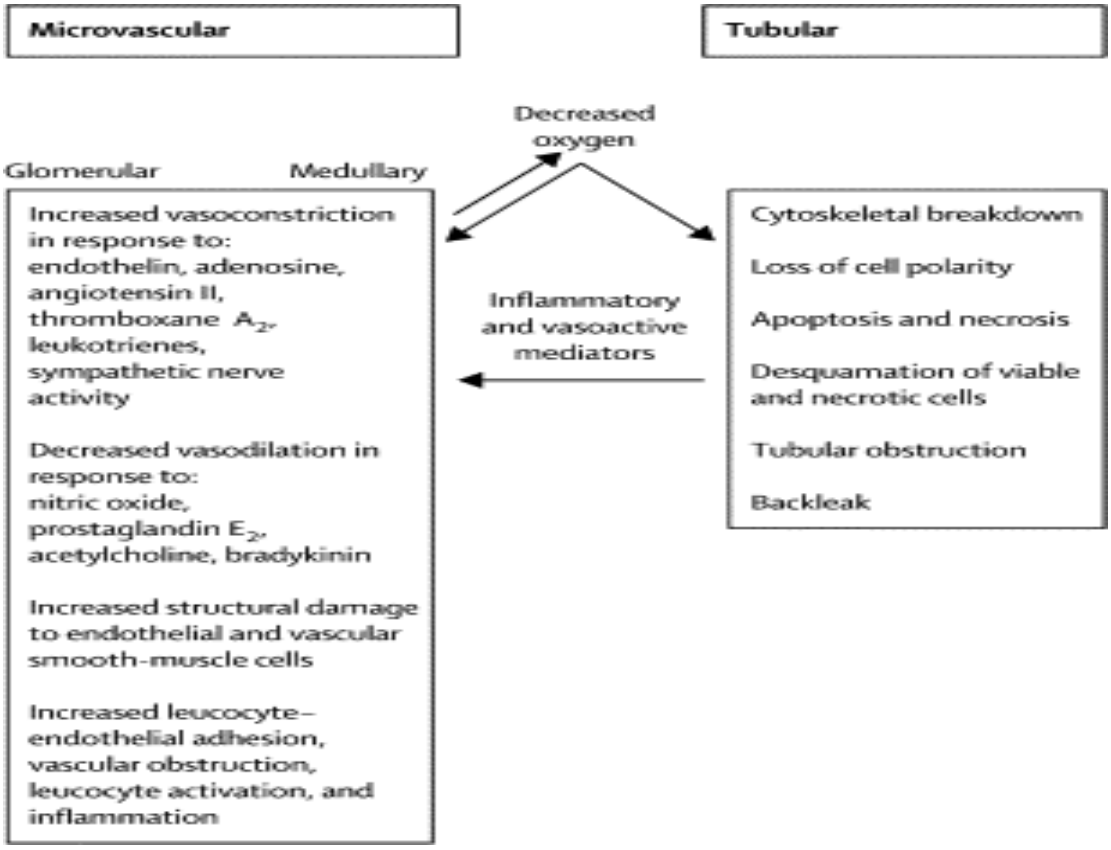
Ischemia and toxins often combine to cause acute renal failure in severely ill patients with conditions such as sepsis, hematologic cancers, or the acquired immunodeficiency syndrome(Rao TK and Friedman EA, 1995).

* Ischemic acute tubular necrosis:

Prerenal azotemia and ischemic tubular necrosis represent a continuum, with the former leading to the latter when blood flow is sufficiently compromised to result in the death of tubular cells. Many clinical conditions can lead to kidney ischemia as a result of either extrarenal or intrarenal factors that

compromise renal blood flow. Although most cases of ischemic acute renal failure are reversible if the underlying cause is corrected, irreversible cortical necrosis can occur if the ischemia is severe, especially if the disease process includes microvascular coagulation such as may occur with obstetrical complications, snake bites, or the hemolytic–uremic syndrome (Ravi Thadhani et al,
1996).





Pathophysiology of ischaemic acute renal failure (JV Bonventre and J M Weinberg, 2003).

*<u>Sepsis related acute tubular necrosis:</u>

In septic conditions, endotoxemia stimulates the induction of nitric oxide synthase, which leads to nitric oxide–mediated arterial vasodilatation. The resultant arterial underfilling is sensed by the baroreceptors and results in an increase in sympathetic outflow and the release of arginine vasopressin from the central nervous system, with activation of the renin–angiotensin–aldosterone system (RAAS). These increases in renal sympathetic and angiotensin activities lead to vasoconstriction with sodium and water retention and a predisposition to acute renal failure. (Ravi Thadhani et

al,1996).

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. When endotoxin is present in the blood, endothelin can also cause general leakage of fluid from the capillaries and thereby diminish plasma volume.(JG Filep,2000). Endothelial damage occurs during sepsis and can be associated with microthrombi and high concentrations of von Willebrand factor in the circulation.(K Reinhart et al,2000). 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.(D Schwartz et al, 1997).

* Renal tubular cell injury:

Renal tubular cell injury after a toxic or ischaemic insult results in sloughing of tubular debris and cells into the tubular lumen with eventual obstruction of tubular flow, increased intra-tubular pressure, and back leak of tubular filtrate out of the tubule and into the interstitium and renal venous blood. Studies have shown that in both toxic and ischaemic ARF, the cells of the straight portion of the proximal tubule are the most severely affected, undergoing extensive necrosis, while more superficial tubular cells are generally spared (Allen R. Nissenson ,1998) .

There are four factors that have been considered the most important in the initiation and maintenance of ARF:

- persistent vasoconstriction due to an imbalance between vasoconstrictive and vasodilatory mediators .
- vascular obstruction caused by endothelial-leukocyte interactions .
- tubuloglomerular feedback in response to increased solute delivery to the macula densa.
- tubular obstruction caused by detachment of tubular epithelial cells from the basement membrane and back-leak of glomerular filtrate as a consequence of disruption of the epithelial cell layer . (Babu J. Padanilam**,** 2003) .

Renal tubular cells that are lethally injured after an acute ischemic or nephrotoxic insult to the kidney can die by necrosis or apoptosis. Necrosis is usually the result of overwhelming and severe cellular ATP depletion. In contrast, there are many potential causes of apoptosis in acute renal failure (ARF). These include cytotoxic events not severe enough to induce necrosis, a relative deficiency of renal growth factors, and loss of cell-matrix or cell-cell adhesive interactions. In some situations, receptor-mediated events induced by tumor necrosis factor-alpha (TNF-alpha) or Fas (CD95) may play a role in apoptosis in ARF.

In experimental models of ARF in vivo, apoptosis of renal tubular cells has been shown to occur in two distinct phases. The first phase of apoptosis occurs early on, between 12 and 48 hours after the acute ischemic or nephrotoxic insult. The second phase of apoptosis occurs many days later, during the recovery phase of ARF. Tubular cell apoptosis occurring shortly after the acute insult probably contributes to tubular cell loss and the tubular

dysfunction associated with ARF.

In contrast, the apoptosis associated with the recovery phase has been postulated to contribute to the remodeling of injured tubules and to facilitate their return to a normal structural and functional state. Therapeutic interventions that inhibit or promote apoptosis of renal tubular cells have the potential for minimizing renal dysfunction and accelerating recovery after ARF. (Leiberthal W et al, 1998) .

*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. 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 for the cells in the S_3 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.

In established acute tubular necrosis, renal blood flow is decreased by 30–50%,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 A_2, prostaglandin H_2, leukotrienes C4 and D4, endothelin 1, and adenosine as well as increased sympathetic-nerve stimulation.(JD Conger,2001).

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. This phase is characterised by continued hypoxia and

an inflammatory response, which are both more pronounced at the level of the corticomedullary junction.(TA Sutton et al,2002).

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.(JV Bonventre et al, 2004).

*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. 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.. 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. (PM Price et al, 2004).
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. (Q Al Awqati et al, 2002).

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.

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. This plasticity of stem cells could be useful in therapeutic strategies designed to improve tissue regeneration after severe organ injury.(MB Rookmaaker et al, 2004).

DIAGNOSIS OF ARF IN ICU PATIENTS:

-History Taking and Physical Examination

Evaluation of the patient's history and physical examination often reveals the cause of renal dysfunction. For example, a history of exposure to nephrotoxic medication, a recent history of angiography, and physical findings of volume depletion all provide important diagnostic information. Other diagnostic clues can be ischemia in an arm or leg, which suggests the

presence of rhabdomyolysis, and anuria, which suggests postrenal acute renal failure**.** . (Ravi Thadhani et al,1996)**.**

-*Urine analysis*

Typical Urine Findings in Conditions That Cause Acute Renal Failure.

Condition	Dipstick Test	Sediment Analysis	Urine Osmolality	Fractional Excretion of Sodium
			mOsm/kg	%
Prerenal azotemia	Trace or no proteinuria	A few hyaline casts possible	>500	<1
Renal azotemia				
Tubular injury				
Ischemia	Mild-to-moderate proteinuria	Pigmented granular casts	<350	>1
Nephrotoxins*	Mild-to-moderate proteinuria	Pigmented granular casts	<350	>1
Acute interstitial nephritis	Mild-to-moderate proteinuria; hemoglobin; leukocytes	White cells and white-cell casts; eosinophils and eosinophil casts; red cells	<350	>1
Acute glomerulonephritis†	Moderate-to-severe proteinuria; hemoglobin	Red cells and red-cell casts; red cells can be dysmorphic	>500	<1
Postrenal azotemia‡	Trace or no proteinuria; can have hemoglobin, leukocytes	Crystals, red cells, and white cells possible	<350	>1

*In some conditions that lead to nonoliguric acute renal failure (e.g., exposure to radiocontrast agents and rhabdomyolysis), the initial fractional excretion of sodium can be <1 percent.

†When glomerulonephritis (e.g., post-streptococcal glomerulonephritis) is associated with tubulointerstitial abnormalities, the urine osmolality is <350 mOsm per kilogram and the fractional excretion of sodium is >1 percent.

‡Early in the course of obstruction, before tubular damage has occurred, the fractional excretion of sodium can be <1 percent.

Fractional excretion of sodium (FE_{Na}) has been used in the diagnosis of acute renal failure (ARF) to distinguish between the two main causes of ARF, prerenal state and acute tubular necrosis (ATN). However, many patients with prerenal disorders receive diuretics, which decrease sodium reabsorption and thus increase FE_{Na}. In contrast, the fractional excretion of urea nitrogen (FE_{UN}) is primarily dependent on passive forces and is

therefore less influenced by diuretic therapy. Low FE_{UN} (≤35%) was found to be a more sensitive and specific index than FE_{Na} in differentiating between ARF due to prerenal azotemia and that due to ATN,especially if diuretics have been administered. (Carvounis C.P et al, 2002).

-Blood Tests

Other blood tests in addition to the measurement **of** urea nitrogen and creatinine in serum help in the differential diagnosis of acute renal failure**.** 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. (J Coresh et al, 2002).

The presence of hypercalcemia and hyperuricemia can point to a malignant condition as a cause, elevated creatine kinase levels may indicate rhabdomyolysis, abnormal serum immunoelectrophoresis results suggest myeloma. (Ravi Thadhani et al,1996) .

Among newer markers, serum cystatin C has not yet been well validated as a GFR indicator in acute renal failure. (O Schuck et al, 2004).However, some

studies have found it to be an early and reliable marker of acute renal failure in patients in intensive-care units. (P Delanaye et al, 2004) .

-Biomarkers

Several biomarkers have been proposed for the early diagnosis of acute renal failure and are currently under study. These include urinary interleukin 18 (CR Parikh et al, 2004) and tubular enzymes, such as the intestinal form of alkaline phosphatase, N-acetyl-β-glucosaminidase, and alanine aminopeptidase. (J Westhuyzenet al,2003). 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.(WK Han et al, 2002).

-Evaluation of Obstruction

In the early evaluation of acute renal failure it is important to rule out urinary tract obstruction, especially in patients who present with severe oliguria or anuria. Simple bladder catheterization can rule out urethral obstruction. Renal ultrasound examination is a useful means of diagnosing obstruction, but its sensitivity may be only 80 to 85 percent. A nondilated collecting system does not necessarily exclude the possibility of obstruction, especially when the condition is acute, in the setting of retroperitoneal fibrosis, or in patients with hypovolemia. (Ravi Thadhani et al, 1996).

Role of Renal Biopsy in Acute Renal Failure

In general**,** renal biopsy is not necessary in the evaluation and therapy of patients with acute renal failure. However, when the history, clinical features, laboratory and radiologic investigations have excluded prerenal and postrenal causes and suggest a diagnosis of primary renal disease other than ischemic or toxin-related acute renal failure, a kidney biopsy may establish the diagnosis and guide therapy (Ravi Thadhani et al, 1996*)*. However, ARF in ICU patients is most commonly due to toxic or ischaemic cause. (Allen R. Nissenson, 1998).

CASES OF ARF AMONG ICU PATIENTS

I} Hepatorenal syndrome

-Definition:

Hepatorenal syndrome is a reversible and functional renal failure which occurs in patients with advanced liver disease and portal hypertension. It is characterized by a marked decrease in glomerular filtration rate (GFR) and renal plasma flow (RPF) in the absence of other identifiable causes of renal

-Pathophysiology:

Portal hypertension is the initial event in the pathogenesis of HRS inducing arterial vasodilation probably due to increased levels of vasodilator substances such as, nitric oxide, carbon monoxide, cytokines and other vasodilators. The vasodilation, which occurs mainly in the splanchnic circulation, induces a decreased effective arterial blood volume and an increased activity of vasoconstrictor systems(Monica Guevara & Juan Rodés, 2005).

-Diagnosis

The diagnosis of HRS is based on the exclusion of other possible causes of renal failure. In 1996 the International Ascites Club recommended the following criteria for the diagnosis of HRS:

*All the following major criteria must be present to make the diagnosis:

1. Chronic or acute liver disease with advanced hepatic failure and portal hypertension.
2. Low glomerular filtration rate, as indicated by serum creatinine of >1.5 mg/dL or 24-h creatinine clearance <40 mL/min.

3. Absence of shock, ongoing bacterial infection, fluid loss and current or recent treatment with nephrotoxic drugs.
4. No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or less or increase in creatinine clearance to 40 mL/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline.
5. Proteinuria <500 mg/day.
6. No ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.

*These criteria are frequently present in patients with HRS but are not necessary for the diagnosis:
1. Urine volume <500 mL per 24 h,
2. Urine sodium <10 meq/L.
3. Urine osmolality > plasma osmolality.
4. Red blood cells in urine <50 per high-power field.
5. Serum sodium concentration <130 meq/L (Monica Guevara & Juan Rodés, 2005).

-Types:

The HRS is classified into two types, type 1 and type 2; Type 1 HRS is characterized by severe and rapidly progressive renal failure defined as doubling of serum creatinine reaching a level greater than 2.5 mg/dL in less than 2 weeks. Type 2 HRS is characterized by moderate and steady renal failure. It is associated with relatively preserved liver function and its main clinical consequence is the development of refractory ascites (Monica Guevara & Juan Rodés, 2005) .

-Treatment:

Liver transplantation is the treatment of choice for candidate patients with HRS .Patients with HRS who undergo transplantation have more complications, spend more days in the intensive care unit, and have a higher in-hospital mortality rate than transplanted patients without HRS. However, long-term survival is only moderately reduced compared with patients transplanted without HRS (Guevara & Juan Rodés, 2005) .

-Treatment of type 1 HRS:

*** *Vasoconstrictors*:**

Several studies have shown that the administration of vasoconstrictor drugs, analogues of vasopressin, and albumin are effective in patients with HRS (Ortegw R et al, 2002). The administration of vasopressin analogues plus albumin is followed by a marked improvement in renal function in most patients with HRS. This improvement commonly occurs several days after the initiation of therapy. The concurrent systemic vasoconstriction may potentially cause ischemic side effects, the appearance of which is infrequent and reversible after discontinuation of the treatment (Arroyo et al, 2002) .

***Transjugular intrahepatic portosystemic shunt (TIPS):**

Useful in the treatment of HRS (Guevara et al, 1998) . The main limitation of this treatment is that it is considered to be contraindicated in patients with severe liver failure (Child-Pugh score >12) or severe hepatic encephalopathy because of the risk of inducing irreversible liver failure or chronic disabling hepatic encephalopathy. (Monica Guevara & Juan Rodés, 2005) .

***Hemodialysis** is not effective in the treatment of HRS and should only be used in patients with specific clinical indications (hypervolemia, tubular acidosis, hyperkalemia). (Monica Guevara & Juan Rodés, 2005)

*** Extracorporeal albumin dialysis** :

The molecular adsorbent recirculating system (MARS) represents a cell-free, extracorporeal, liver assistance method for the selective removal of albumin-bound substances. Moreover, it enables the removal of excess water and water-soluble substances via an inbuilt dialysis step.. Diseases treated with MARS included acute exacerbation of chronic hepatic failure, hepatorenal syndrome, acute hepatic failure, and primary nonfunction/poor function after liver transplantation and major liver resection. Treatments were well tolerated The removal of albumin-bound toxins resulted in decreases in hepatic encephalopathy, increases in mean arterial pressure, and improvements in kidney and liver function.. It is concluded that the MARS method can contribute to the treatment of critically ill patients with liver failure and different underlying diseases. (Steffen R. Mitzner et al, 2001)

-Treatment of type 2 HRS:

The management of these patients should be focused on the treatment of the refractory ascites that is usually associated with this condition . Treatment is by repeated paracentesis plus I.V. albumin or by TIPS. It was found that repeated paracentesis plus I.V. albumin is better that TIPS (Gines et al, 2002).

<u>-Prevenrtion of HRS:</u>

The administration of albumin (1.5 g/kg i.v. at infection diagnosis and 1 g/kg i.v. 48 h later) together with cefotaxime in patients with cirrhosis and spontaneous bacterial peritonitis markedly reduced the incidence of impairment in circulatory function and the occurrence of type 1 HRS as compared to a control group of patients receiving cefotaxime alone. (Sort P. et al, 1999). The administration of the tumor necrosis factor inhibitor pentoxyfilline (400 mg t.i.d.) to patients with severe acute alcoholic hepatitis reduced the occurrence of HRS (Akriviadis et al., 2000).

II} SEPSIS

Acute renal failure occurs in approximately 19 percent of patients with moderate sepsis, 23 percent with severe sepsis, and 51 percent with septic shock when blood cultures are positive. The combination of acute renal failure and sepsis is associated with a 70 percent mortality, as compared with a 45 percent mortality among patients with acute renal failure alone.
(Schrier R.W. and Wei Wang, 2004).

-Clinical definitions of sepsis:

1-Moderate sepsis:

*Temperature < 36 degree or > 38 degree.

* Heart rate > 90/min.

* Respiratory rate > 20/min. or $PaCO_2$ < 20.

* White blood cell count > 12.000/cmm or > 10%

Immature bands.

2- Severe sepsis:

Sepsis associated lactic acidosis, oliguria or acute alteration in mental status.

3- Septic shock:

Sepsis associated with hypotension (i.e. systolic blood pressure < 90) inspite of adequate fluids resuscitation.
(Riedemann NC et al, 2003).

- Haemodynamics and hormones:

The hemodynamic hallmark of sepsis is generalized arterial vasodilatation with an associated decrease in systemic vascular resistance. Arterial underfilling due to arterial vasodilatation occurs in several clinical circumstances, including sepsis, and 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 nonosmotic 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 may lead to acute renal failure.
(Schrier RW and Abraham WT, 1999)

Vascular resistance to the pressor response to norepinephrine and angiotensin II occurs during sepsis and is attributable to:

- The potent vasodilatory effect of nitric oxide.(Landry DW and Oliver JA ,2001) .
- An increase in plasma concentrations of hydrogen ions and lactate and a decrease in ATP in vascular smooth-muscle cells during septic shock activate the ATP-sensitive potassium channels (K_{ATP} channels). The resultant potassium efflux through the K_{ATP} channels causes hyperpolarization of the vascular smooth-muscle cells with closure of the voltage-gated calcium channels in the membrane. Since the vasoconstrictor effects of norepinephrine and angiotensin II depend on open calcium channels so vascular resistance to these pressor hormones can occur along with lactic acidosis in patients with sepsis. (Keung EC et al , 1991) .

- The high endogenous levels of these vasoactive hormones during sepsis may be associated with down-regulation of their receptors, which would result in a lessening of their effects on the vasculature.

There is evidence that the administration of arginine vasopressin in patients with sepsis-related vasodilatory shock may help maintain blood pressure despite the relative ineffectiveness of other vasopressor hormones such as norepinephrine and angiotensin II (Morales D et al , 1999) :

- Arginine vasopressin may inactivate the K_{ATP} channels and thereby lessen vascular resistance to norepinephrine and angiotensin II.
- Arginine vasopressin also decreases the synthesis of nitric oxide (as a result of a decrease in the expression of inducible nitric oxide synthase) as well as cyclic guanosine monophosphate (cGMP) signaling by nitric oxide.
- Arginine vasopressin is also known to be synergistic with the pressor hormones norepinephrine and angiotensin II, since all three hormones have in common intracellular signaling that involves an increase in the cytosolic calcium concentration.
- The sites of major arterial vasodilatation in sepsis which are the splanchnic circulation, the muscles, and the skin , are vascular beds that contain abundant V_{1a} arginine vasopressin receptors.
- Glomerular filtration is determined by the net difference in arterial pressure between the afferent and efferent arterioles across the glomerular capillary bed (termed transcapillary filtration pressure). Norepinephrine profoundly constricts the glomerular afferent arteriole, dropping the filtration pressure, and thus may contribute to and prolong the course of acute

renal failure in patients with sepsis. In contrast, arginine vasopressin has been shown to constrict the glomerular efferent arteriole and therefore can increase the filtration pressure and, consequently, the glomerular filtration rate.

Initially, in septic or hemorrhagic shock, the plasma arginine vasopressin concentrations increase to 200 to 300 pg per milliliter, but after approximately an hour, the neurohypophysial stores of vasopressin are depleted and plasma concentrations may fall to approximately 30 pg per milliliter.(Landry DW et al , 1997).

At that time and in the presence of unoccupied V_{1a} receptors, the administration of exogenous arginine vasopressin can increase blood pressure by 25 to 50 mm Hg by returning the plasma concentrations of antidiuretic hormones to their earlier high levels. (Kaufmann H et al, 1991).

The decision to use arginine vasopressin as a pressor agent, however, must involve consideration of several additional physiological properties:

- Increased concentrations of arginine vasopressin constrict the coronary arteries and have been reported to cause myocardial infarction.
- In contrast to norepinephrine and angiotensin II, arginine vasopressin does not have a cardiac inotropic effect; thus, the increase in cardiac afterload during the infusion of arginine vasopressin can decrease cardiac output.
- Since arginine vasopressin is a very potent venoconstrictor that decreases splanchnic compliance, excessive fluid that is administered

is distributed more centrally, including in the lung, and therefore can lead to noncardiogenic pulmonary edema.

-Experimental Models of Endotoxemia and Sepsis:

Vasoactive Hormones

There is experimental evidence that early in sepsis-related acute renal failure, the predominant pathogenetic factor is renal vasoconstriction with intact tubular function, as demonstrated by increased reabsorption of tubular sodium and water. Thus, intervention at this early stage may prevent progression to acute tubular necrosis. Plasma concentrations of catecholamines and activation of the renin–angiotensin–aldosterone system are known to be heightened in cases of sepsis and septic shock. In an experimental model renal denervation afforded considerable protection against the decrease in the glomerular filtration rate during the initial 16 hours of endotoxemia. Such study indicate that the effects of these vasoactive hormones on the kidney are, at least in some measure, neurally mediated and may contribute to the acute renal failure seen in cases of sepsis. (Benedict CR and Rose JA, 1992).

Endothelial and Inducible Nitric Oxide Synthases

The vasodilatory effect of constitutive endothelial nitric oxide synthase within the kidney might be expected to lessen the renal vasoconstriction induced by norepinephrine, angiotensin II, and endothelin during sepsis. When cytokines activates inducible nitric oxide synthase not only did the plasma nitric oxide concentration increase, but also the expression of

inducible nitric oxide synthase increased in the renal cortex. In association with this increased expression of inducible nitric oxide synthase, a progressive increase in cGMP in the renal cortex occurred during the initial 16 hours after exposure to endotoxin. At 24 hours, however, the plasma nitric oxide concentration remained high, though renal cGMP had decreased. Since cGMP is the secondary messenger for nitric oxide–mediated arterial vasodilatation, the down-regulation of this enzyme at 24 hours may also contribute to renal vasoconstriction during sepsis. (Knotek M et al, 2001). Sepsis-related impairment of the endothelium may 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. The study of knockout mice(in which the expression of either endothelial nitric oxide synthase or inducible nitric oxide synthase has been ablated) showed that a small dose of endotoxin, which did not alter the glomerular filtration rate in the control mice, caused a profound decrease in the glomerular filtration rate in these knockout mice.(Reinhart K et al, 2002).

Endotoxemia

- Tumor Necrosis Factor $\alpha$and Reactive Oxygen Species:

The role of tumor necrosis factor αin endotoxin-related acute renal failure has been tested in both animal and human studies. knockout mice still have a decrease in the glomerular filtration rate after receiving endotoxin, suggesting that cytokines such as tumor necrosis factor αcan cause renal vasoconstriction even in the absence of inducible nitric oxide synthase. Although a soluble tumor necrosis factor receptor (TNFsRp55) afforded

renal protection in murine endotoxemia (Knotek Met al, 2001), a prospective, randomized study of a monoclonal antibody against tumor necrosis factor α(the MONARCS [Monoclonal Anti-TNF: A Randomized Controlled Sepsis] trial) did not show any improvement in the survival of patients.(Reinhart K and Karazai W, 2001).

Endotoxemia is known to be associated with the generation of oxygen radicals and thus may contribute to the early vasoconstrictor phase of acute renal failure. Endogenous scavengers of reactive oxygen species can attenuate renal tubular injury or renal vascular injury (or both) that is caused by reactive oxygen species during endotoxemia. Exogenous oxygen-radical scavengers were shown to protect against acute renal failure in this normotensive mouse model of endotoxemia. Furthermore, the decrease in endothelial nitric oxide synthase in the kidney when there is oxidant-related endothelial damage may contribute to the early vasoconstrictor phase of acute renal failure. (Wang W et al 2003) .

- Nonspecific Inhibitors of Nitric Oxide Synthase :

Studies in animals and humans have further examined the role of nitric oxide synthase in the decrease in the glomerular filtration rate during endotoxemia. No renal protection was found with the administration of a nonspecific inhibitor of nitric oxide synthase. (Lopez A et al, 2004) . Further studies with an inhibitor specific for inducible nitric oxide synthase, which would preserve any renal protective effect of endothelial nitric oxide synthase, were undertaken in the rat model appeared to be protective experimentally.(Schwartz D et al, 1997).

- Cytokines, Chemokines, and Adhesion Molecules

The complex composed of a lipopolysaccharide and the lipopolysaccharide-binding protein activates the membrane-CD14 and toll-like receptors on cells, which up-regulate nuclear factor-κB (NF-κB), a nuclear transcription factor for the promoters of multiple cytokines, chemokines, and adhesion molecules. (Schor N ,2002) .Activation of NF-κB may therefore be a critical factor in the proinflammatory phase that involves a cytokine, chemokine, and adhesion molecule "storm," which leads to acute renal failure and an increased rate of death. Blocking agents for NF-κB exist that could protect against endotoxemia better than targeting any individual cytokine, chemokine, or adhesion molecule. Complement pathways are activated during sepsis by bacterial products such as lipopolysaccharide, C-reactive protein, and other stimuli. Complement C5a that is generated during sepsis seems to have procoagulant properties, and blocking C5a and C5a receptor in a rodent model of sepsis has been shown to improve survival. (Riedemann NC et al 2002).

Disseminated Intravascular Coagulation

Sepsis can be viewed as a procoagulant state that can lead to disseminated intravascular coagulation with consumptive coagulopathy, thrombosis, and ultimately, hemorrhage. Disseminated intravascular coagulation has been associated with glomerular microthrombi and acute renal failure. A major prospective, randomized study showed that recombinant human activated protein C (drotrecogin alfa) significantly

improved survival in patients with severe sepsis, as compared with those given placebo.(Bernard GR et al, 2001).

-TEATMENT:

Patients must be referred promptly to an intensive care unit where management includes careful nursing, immediate control of infection and haemodynamic status, and support to failing organs and to immune, neuroendocrine, and haemostasis responses.

- Rapid removal of infected tissues or devices combined with antibiotic treatment is the key to ensuring survival.
- To manage shock and organ dysfunction, fluid resuscitation should be initiated promptly and guided by monitoring of the central venous oxygen saturation, a surrogate of global tissue dysoxia, in addition to clinical signs. Fluid challenges can be repeated until cardiac output increases by more than 10% and as long as central venous pressure increases less than 3 mm Hg.(SM Hollenberg,2004).
  A trial of fluid replacement in 7000 critically ill patients showed no difference in mortality between crystalloids and albumin. (S Finfer,2004).
- Dopamine or norepinephrine is recommended as the first-line drug, although phase II trials have yielded conflicting results. Norepinephrine, indeed, reduces RBF in healthy animals and humans. The ultimate effect of norepinephrine on renal perfusion depends, however, on a complex interplay of its actions on different vascular beds and the underlying condition of the patient. Norepinephrine increases BP by an $alpha_1$-mediated increase in systemic vascular

resistance and a beta $_1$-mediated increase in cardiac output. An excessive rise in systemic vascular resistance with an increase in cardiac afterload may have a potential negative impact on cardiac output. The net effect on renal vascular resistance hinges on (*1*) the increase in systemic BP with a decreased renal sympathetic tone through a baroreceptor response, resulting in vasodilatation; (*2*) an autoregulatory vasoconstriction owing to a rise in renal perfusion pressure; (*3*) a direct alpha$_1$-mediated renal vasoconstriction, which is of minor importance. Thus, in a patient with sepsis, characterized by systemic vasodilatation and impaired renal autoregulation, norepinephrine administration may be expected to improve RBF. Several non-controlled studies in patients with sepsis have, indeed, shown that norepinephrine augmented urine output and GFR (Schetz M,2002). A prospective observational study in 97 patients with septic shock found a lower mortality in patients treated with norepinephrine than in those treated with other vasopressors — mainly high-dose dopamine (Martin C et al,2000).

- In a randomized placebo-controlled trial in 328 critically ill patients with early renal dysfunction sufficiently powered to detect a small benefit, there was no effect of low-dose dopamine on renal function, need for dialysis, ICU or hospital length of stay, or mortality (R Bellomo et al ,2000).
- Arginine vasopressin administration in 16 patients with septic shock and hyporesponsiveness to catecholamines increased BP, systemic vascular resistance, and urine output (Tsuneyoshi I et al, 2001). A randomized trial in 24 patients with septic shock demonstrated that a 4-h infusion of arginine vasopressin improved urine output and

creatinine clearance with similar effects on BP and cardiac output, as compared with norepinephrine (Patel BM et al,2002).

- Vasopressors should be titrated to quickly restore systemic mean arterial pressure to 60–90 mm Hg, depending on whether the patient had pre-existing hypertension. Secondary endpoints that need monitoring include cardiac performance, tissue dysoxia (eg, lactate), and microcirculation as assessed by capillary refilling time or by sublingual capnography. Optimisation of haemodynamic status could require blood transfusion. . (E Rivers,2001).
- Hyperglycemia impairs the function of leukocytes and macrophages, Recent studies support the importance of controlling blood glucose in critically ill patients but suggest a less stringent goal of maintaining blood glucose at a level of 145 mg per deciliter (8.0 mmol per liter) or less.(Finney SJ et al, 2003).
- Patients should be treated with oxygen, and when they have acute lung injury or acute respiratory distress syndrome, with invasive mechanical ventilation with a tidal volume of 6–7 mL/kg of ideal body weight.
- Glucocorticoids have been known to enhance the pressor effects of catecholamines, but older studies in which septic shock was treated with large doses of glucocorticoid hormones for a short period of time did not show any benefit.(Lefering R and Neugebauer EA, 1995) . However, a more recent study in patients with septic shock showed that patients without a response to corticotropin (as defined by a rise in plasma free cortisol of less than 9 μg per deciliter at 30 or 60 minutes) who were treated for 7 days with intravenous boluses of 50 mg of hydrocortisone every 6 hours plus daily oral fludrocortisone (a

50-µg tablet) had a decrease in mortality at 28 days as compared with the placebo group.(Annane D et al, 2002).

- High-dose loop diuretics are commonly used in critically ill patients with early or established ARF. The rationale for their use rests heavily on the assumption that they decrease oxygen consumption in the tubular cells by inhibiting transcellular sodium transport and thus prevent or limit ischemic cell injury. In addition, loop diuretics may vasodilatate cortical blood vessels and improve oxygenation. Finally, augmentation of tubular flow may reduce intratubular obstruction and backleak of filtrate, thereby accelerating resolution of ARF. Prophylactic administration of loop diuretics in patients at high risk for ARF contra-intuitively appeared to be deleterious to renal function (Solomon R et al, 1994). Although no specific information on septicemic patients is available, physicians should be discouraged from using diuretics in these patients in an effort to prevent ARF. In patients with established ARF, several studies have found no benefit of loop diuretics. More particularly, loop diuretics did not accelerate renal recovery, reduce the need for dialysis, or decrease mortality. Most of these studies were, however, relatively small and lacked statistical power to entirely rule out a beneficial effect of diuretics. Loop diuretics may convert oliguria to diuresis in a subset of patients with ARF. The mortality rate of non-oliguric ARF was found to be lower than that of oliguric ARF There were, however, no significant differences in the clinical characteristics, the severity of renal failure, and the mortality rate between spontaneously non-oliguric patients and patients becoming non-oliguric after furosemide (Shilliday IR et al, 1997). These observations imply that patients responding to loop

diuretics are characterized by a less severe form of renal failure, rather than a beneficial effect of therapy. In a recent retrospective survey of critically ill patients with ARF, diuretic use was associated with an increased risk of death and non-recovery of renal function(Mehta RL et al, 2002).

*In conclusion, in the absence of data from a sufficiently powered multicenter randomized trial, high-dose loop diuretics should be used cautiously in critically ill patients with ARF. Intravascular volume depletion should be carefully corrected before and during administration of diuretics, as an already damaged kidney may be profoundly injured by a relatively mild decrease in perfusion pressure. In patients with sustained oliguria despite high doses of loop diuretics, this treatment should be withdrawn. In responders, continuous infusions are preferred because they are more effective and associated with less toxicity than bolus administrations (Martin SJ and Danziger LH, 1994).

- **Dialytic Treatment will be discussed later.**

III} RHABDOMYOLYSIS

Rhabdomyolysis is a common disorder which may result from a large variety of diseases, trauma, or toxic insults to skeletal muscle. It may be defined as a clinical and biochemical syndrome resulting from an injury which damages the integrity of the sarcolemma of skeletal muscle, leading to the release of potentially toxic muscle cell components into the circulation. This may result in potential life-threatening complications including myoglobinuric acute renal failure, hyperkalaemia and cardiac arrest, disseminated intravascular coagulation, and more locally, compartment syndrome.(Zager R.A., 1996).

-CAUSES:(John M. Sauret and George Marinides, 2002) .

I. Exogenous Causes
   - A. Limb ischemia
   - B. Carbon Monoxide Poisoning
   - C. Trauma
     1. Lightning strike or third-degree burns
     2. Crush injury
     3. Snake Bite
   - D. Heat Injury
     1. Heat Stroke
     2. Malignant hyperthermia
     3. Neuroleptic malignant syndrome
   - E. Physical exertion
     1. Marathon Running
     2. Overexertion
        - a. Deconditioned athletes
        - b. Sickle Cell Anemia

II. Endogenous Causes
    A. Hypoxia
    B. Polymyositis or Dermatomyositis
    C. Acute Infection
        1. Viral: HIV, Influenza virus A or B
        2. Bacterial: Legionella, Salmonella, Streptococcus
    D. Endocrine causes
        1. Thyroid disease
        2. Diabetic Ketoacidosis
        3. Electrolytes (Hypophosphatemia, Hypokalemia)
III. Medication Causes
    A. HMG-CoA Reductase Inhibitors
    B. Cyclosporine
    C. Itraconazole
    D. Erythromycin
    E. Colchicine
    F. Zidovudine
    G. Corticosteroids
IV. Alcohol or Drug Use Causes
    A. Alcohol
    B. Cocaine
    C. Amphetamine
    D. LSD

-Diagnosis:

The primary diagnostic indicator of rhabdomyolysis is an elevated serum creatine phosphokinase (CK) to at least five times the normal value. This elevation is generally to such a degree that myocardial infarction and other causes of a raised CK are excluded. Additionally, the CK-MM isoenzyme predominates in rhabdomyolysis, comprising at least 98% of the total value.

The other important finding frequently seen in rhabdomyolysis is myoglobinuria. Myoglobin, a haem protein which functions as an oxygen store in type 1 skeletal muscle fibres, normally has a rapid renal clearance which maintains a low plasma level up to a certain serum concentration . As myoglobin is released into the circulation from necrotic muscle cells it first becomes detectable in the urine at serum concentrations ranging from 300ng/ml to 2 g/ml and produces visible pigmenturia (classically a "coca-cola" coloured urine) at concentrations exceeding 250 g/ml.

Other important biochemical findings in rhabdomyolysis include hyperkalemia, hypocalcaemia, hyperphosphataemia, hyperuricaemia, and raised levels of other muscle enzymes including lactate dehydrogenase, aldolase, aminotransferases, and carbonic anhydrase III (which is a very specific marker for skeletal muscle injury). Metabolic acidosis may result from release of phosphate, sulphate, uric acid, and lactic acid from the muscle cell.

-Rhabdomyolysis as a cause of ARF:

Acute renal failure due to rhabdomyolysis has several causes, including direct tubular toxicity of myoglobin, formation of myoglobin casts within tubules, and vasoconstrictive effects of myoglobin . In addition,

rhabdomyolysis is frequently associated with hypotension, in part due to fluid sequestration in damaged muscles, exacerbating renal hypoperfusion .(Zager R.A., 1996).

-Prevention of rhabdomyolysis and myoglobinuric ARF:

In animal models of myoglobinuria, volume depletion and an acidic urine pH predispose to the development of ARF, whereas volume repletion, high urine flow rates, and an alkaline pH are protective. These experimental observations form the basis for the management of myoglobinuria in humans. In a retrospective study of 20 patients with myoglobinuria, all of whom had oliguria and azotemia despite the correction of volume deficits, the administration of mannitol and sodium bicarbonate was associated with increases in urinary output and prompt resolution of renal failure (Eneas JF et al, 1979). Homsi and coworkers performed a retrospective analysis of 24 patients with rhabdomyolysis admitted to an ICU, 15 of whom were treated with saline, mannitol, and sodium bicarbonate, and the remainder with saline alone (Homsi E et al, 1997). There were no significant differences between the two treatment groups in the evolution of the serum creatinine, leading the investigators to suggest that mannitol and bicarbonate are unimportant components of therapy.

IV} HAEMOLYTIC URAEMIC SYNDROME

Enterohaemorrhagic Escherichia coli (EHEC) are the pathogenic subgroup of Shiga toxin (Stx)-producing E. coli. EHEC can cause non-bloody and bloody diarrhoea, and the haemolytic uraemic syndrome (HUS).

-Clinical manifestations of HUS:

The clinical manifestations of EHEC infections are best characterized for illnesses caused by EHEC O157:H7. After a typical incubation period of 3–4 days, patients develop watery diarrhoea accompanied by abdominal cramping pain for 1–3 days. During the next several days, watery diarrhoea changes to bloody diarrhoea in about 90% of culture-confirmed cases. Antibiotics should not be administered to patients with definite or possible EHEC infections, because antibiotic use during E. coli O157:H7 infections has been associated with an increased risk of developing complications (S Dundas et al., 2001).

HUS develops in approximately 15% of patients under 10 years of age with a diagnosed E. coli O157:H7 infection. HUS occurs 5–13 days after the onset of diarrhoea, and consists of microangiopathic haemolytic anaemia, thrombocytopaenia, and renal insufficiency. The following are finite criteria for HUS: an haematocrit below 30%, with evidence of the destruction of erythrocytes on a peripheral blood smear, a platelet count <150,000/mm^3, and a serum creatinine concentration that exceeds the upper limit of the normal range for age (A. Gerber et al., 2002). Central nervous system manifestations, including irritability, lethargy, seizures, stupor, coma, and stroke occur in a significant proportion of patients with HUS .

Cardiac dysfunction was demonstrated in about 10% of children with HUS.

Intestinal complications during acute HUS consist of bowel perforation, necrosis, and pancreatitis. Pulmonary consequences include fluid overload, pleural effusions, and adult respiratory distress.

Most patients recover from the acute episode, but in some survivors, there are chronic renal sequelae (A.X.Garg et al., 2003). Other post-HUS sequelae include diabetes mellitus, neurological disorders, hypertension, colonic strictures, biliary lithiasis, and urinary abnormalities of uncertain clinical significance.

- Pathophysiology of HUS:

Enteric STEC infections are almost never accompanied by bacteraemia. Presumably, systemic complications, such as HUS, arise from lesions caused by circulating Shiga toxin. Shiga toxins bind to the glycosphingolipid globotriaosylceramide,which occurs on renal glomerular endothelial, mesangial, and tubular epithelial cells. The profound haematological abnormalities during and before HUS and histopathological analyses show that the basis of HUS is thrombotic, not vasculitic. (HM Tsai et al,2001). Even if vascular occlusion is not the underlying major lesion in HUS, thrombosis-independent thrombin-mediated host mechanisms could cause renal injury after E coli O157:H7 infections(MA Cunningham et al ,2000). The plasma of patients with HUS shows fibrinolysis inhibition manifest by increased activity of plasminogen activator inhibitor 1 (PAI-1), presumed increased intravascular generation of fibrin, as shown by high concentrations of D-dimers, and generation of thrombin. On or before day 4 of diarrhoea, many patients infected with E coli O157:H7 have similar abnormalities, even those who do not develop HUS.(WL Chandler et al, 2002).

- Management of HUS:

* Management of patients with suspected or confirmed E coli O157:H7 infections:(PI Tarr and MA Neill,2001).

Do not give antibiotics, antimotility agents, narcotic opioids, or non-steroidal anti-inflammatory drugs.

Bolus with intravenous normal saline, 20 mL/kg, on presentation, if there is no evidence of cardiopulmonary overload.

Continue intravenous maintenance fluid in the form of isotonic crystalloid (normal saline, normal saline with 5% dextrose, or lactated Ringer's solution), and not hypotonic crystalloid.

Potassium can be added to the intravenous fluids if the serum potassium concentration is normal or low.

Most patients can eat or drink, though appetite tends to be diminished during the acute infection.

Repeat boluses of normal saline (10–20 mL/kg) if there is any question of diminished urine output, and the patient is not showing signs of central volume overload.

Daily laboratory tests should include complete blood count, electrolytes, and serum urea nitrogen and creatinine concentrations.

The patient should be admitted to an institution skilled in the age-appropriate monitoring of fluid status.

The HUS risk period is past when the platelet count rises, or if the platelet count is stable, and symptoms are resolved or resolving. We also repeat laboratory tests 1 day after discharge.

As the creatinine concentration rises, patients should be monitored even more assiduously for hypertension or signs of cardiopulmonary overload and transferred, if necessary, to a centre where acute renal failure can be managed and treated.

At the first indication of hypertension or cardiopulmonary overload, fluids should be restricted. Diuretics, sometimes given during early HUS, rarely avert anuria. If their use does lead to urine production, intravascular volume depletion might be inadvertently exacerbated, and thrombus development facilitated; these processes could further compromise renal blood flow. Use of diuretics should be restricted to severe clinically consequential central volume overload, but dialysis is likely to be more effective.

Vasodilators (JJ Corrigan Jr and FG Boineau,2001), are the preferred agents for the treatment of hypertension. Avoid inhibitors of angiotensin-converting enzyme as they might exacerbate kidney injury by diminishing renal perfusion (AC Schoolwerthet al , 2001).
Most patients with early renal insufficiency and a diminishing urine output who do not respond to boluses of isotonic crystalloid progress to oligoanuric renal failure. HUS patients whose hourly urine output remains above 0·5 mL/kg beyond day 10 of illness (with the first day of illness being the first day of diarrhoea) generally do not become anuric.

Oliguric or anuric patients might need potassium restriction to prevent hyperkalaemia (though this electrolyte abnormality is uncommon despite haemolysis and renal failure) and phosphate restriction and phosphate binders to prevent hyperphosphataemia..

HUS patients can become profoundly and rapidly anaemic, and the usual indications for erythrocyte transfusion (largely cardiovascular or respiratory compromise) apply; about 80% of patients with HUS need erythrocyte transfusions.Blood transfusions should, however, be administered cautiously, because rapid intravascular expansion can cause hypertension.

Indications for dialysis in HUS are similar to those in other forms of acute renal failure.(R Bhimma et al, 2001).

Many approaches have been unsuccessful in HUS, and are not commonly used today, corticosteroids (N Perez al,1998) , aspirin and dipyridamole , plasmapheresis or plasma infusion , Synsorb Pk (an oral agent that binds

Shiga toxin) (H Trachtman et al, 2003) proved all to be ineffective approaches in typical HUS.

V} CONTRAST NEPHROPATHY

Contrast-induced nephropathy (CN) has become an important cause of iatrogenic acute renal impairment. In fact, CN is the third leading cause of new acute renal failure in hospitalized patients

-Defintion and clinical features:

CN defined as an acute decline in renal function following the administration of intravenous contrast in the absence of other causes, a definition such as a rise in serum creatinine ≥25 or 50% above the baseline value is often used, serum creatinine generally peaks at 3 to 5 days and returns to baseline value by 7 to 10 days (Solomon R,1998).

The acute renal failure is nonoliguric in most cases. Urinalysis often reveals granular casts, tubular epithelial cells, and minimal proteinuria, but in many cases may be entirely bland. Most, but not all, patients exhibit low fractional excretion of sodium, The diagnosis of CN is frequently obvious if the typical course of events follows the administration of contrast

-Pathogenesis:

CN appears to be the result of a synergistic combination of direct renal tubular epithelial cell toxicity and renal medullary ischemia. The nature of the contrast, associated ions, concentration, and concomitant hypoxia are all important to the degree of cellular damage, while the osmolality of the solution seems to be of secondary importance. The injection of contrast induces a biphasic hemodynamic change in the kidney, with an initial, transient increase and then a more prolonged decrease in renal blood flow. Alterations in the metabolism of prostaglandin, nitric oxide, endothelin, or adenosine may play a role. [Barrett BJ,1994).

-Risk factors:

Mild, transient decreases in GFR occur after contrast administration in almost all patient. A multivariate analysis of prospective trials has shown that baseline renal impairment, diabetes mellitus, congestive heart failure, and higher doses of contrast media increase the risk of CN Other risk factors include reduced effective arterial volume (*e.g.*, due to dehydration, nephrosis, cirrhosis) or concurrent use of potentially nephrotoxic drugs such as nonsteroidal anti-inflammatory agents and angiotensin-converting enzyme inhibitors. Of all these risk factors, preexisting renal impairment appears to

be the single most important; patients with diabetes mellitus and renal impairment, however, have a substantially higher risk of CN than patients with renal impairment alone.(Rudnick MR et al, 1995).

-Prevention of contrast induced nephropathy:

A variety of specific measures have been used in an attempt to decrease the risk of CN, particularly in high-risk patients.

**Nonionic and Low-Osmolality Media:*

These alternative forms of contrast media, which have approximately one-half to one-third the osmolality of standard agents, were developed at great expense in an attempt to reduce the incidence of complications associated with radiocontrast agents. Unfortunately, they are also capable of inducing CN, although perhaps less frequently than high-osmolality contrast agents. The apparent lack of difference between high- and low-osmolality media in those with normal renal function may reflect the very low risk of CN in such patients. It makes sense to consider nonionic low-osmolality contrast for patients with renal impairment, especially due to diabetic nephropathy, to minimize CN. It is not necessary to use nonionic media to reduce CN in patients with normal renal function who are at very low risk of clinically important changes in renal function.

Isoosmolar contrast media have recently become commercially available and are expected to reduce the incidence of CN. The currently available data, however, are conflicting. Though some studies have shown their use to be associated with lower incidence of CN compared to low osmolar contrast

media, meta-analyses have not found the benefit to be consistent.(Aspelin Pet al,2003).

Gadolinium chelates, intended as intravenous contrast media for magnetic resonance imaging, was regarded as nonnephrotoxic and it was thought that it could replace iodinated contrast media for radiographic examinations. However, studies in mice have shown them to be more nephrotoxic than iodinated contrast media at equivalent X-ray attenuating doses. There are no randomized studies comparing nephrotoxic effects of gadolinium-based and iodinated contrast media at equal X-ray attenuating concentrations and doses. These contrast media are hypertonic, having osmolality 2-7 times that of plasma. Currently, gadolinium- based contrast media are not approved for radiographic examinations. (Nyman U et al, 2002).

**Fluid Administration:*

The administration of intravenous fluids has long been used to reduce the likelihood of CN for high-risk patients. The rationale for this approach is that giving fluids before the study may correct subclinical dehydration, whereas hydration for a period of time afterward may counter an osmotic diuresis resulting from the contrast. Even if only modestly beneficial, however, this approach is simple and carries minimal risks of adverse effects if appropriate care is taken, *i.e.*, close monitoring of the patient's fluid balance and clinical status. A reasonable starting protocol might use intravenous 0.45% saline at a rate of 1 ml/kg per h, beginning 1 to 2 h before contrast and continuing for up to 24 h, depending on the duration of the attendant diuresis. The protocol

should be flexible to allow an increase in rate if a negative fluid balance seems to be developing. For outpatient procedures, a protocol using oral hydration before the procedure and intravenous 0.45% saline for 6 h afterward has been shown to be as successful as inpatient hydration in preventing CN. (Taylor AJ et al, 1998).

*Hydration with forced diuresis:

Most studies have found that hydration alone is better than hydration combined with a diuretic. In the landmark study by Solomon et al. 78 patients with serum creatinine >1.6 mg/dl were randomized to three groups: hydration alone, hydration with mannitol (25 g) and hydration with furosemide (80 mg). Half-isotonic saline (0.45%) was used for hydration. CN occurred in 11%, 28% and 40% of patients in the three groups, respectively , thus showing that forced diuresis is of no benefit in preventing CN. (Solomon R et al, 1994).

* Dopamine:

Dopamine infusion in low dose (2-5 μg/kg/ min) results in increased renal blood flow that leads to increased glomerular filteration rate. Therefore it was thought to be of benefit in preventing CN. However, studies of low dose dopamine have produced conflicting results, with no clear benefit for prevention of CN. Probably, in low dose dopamine nonselectively interacts with D_1, D_2 and adrenergic receptors leading to increased perfusion to renal cortex but not to medulla, the site which is vulnerable to contrast-induced damage.

Dopamine receptor agonists: Fenoldopam, a selective dopamin-1 receptor

agonist, increases renal blood flow in both cortex and medulla. It was shown to be beneficial in preventing CIN in early studies in humans. (Tumlin JA et al, 2002).

However, a recently reported large randomized controlled trial did not find significant benefit with fenoldopam. The possible additive effects of fonoldopam or other vasodilators in conjunction with Nacetyl cysteine or other anti-oxidants remains to be tested. (Stone GW et al , 2003) .

*N-Acetylcysteine:

There has been a great increase in interest regarding NAC's antioxidant properties. Oxidative stress occurs as a result of an imbalance between ROS and the body's native antioxidant systems .

NAC is one of a large group of exogenous antioxidant drugs that may protect against oxidative tissue injury. The antioxidant effects of NAC may be directly related to the drug itself or to the secondary induction of glutathione production. Reactive oxygen species have been implicated in pathogenesis of CN.

A study comparing Nacetyl cysteine and hydration with hydration alone to prevent CN in patients with CRF. Administration of N-acetyl cysteine and hydration significantly reduced the relative risk of CN by 56% (p=0.02) in patients with CRF.(Birck R et al,2003).

Even intravenous N-acetyl cysteine given 30 min before and 4 hours after the procedure has been shown to reduce CIN in patients with stable renal dysfunction. This may be considered when time constraints preclude adequate oral prophylaxis.N-acetyl cysteine is usually recommended, as it is inexpensive, has low risk and is likely to be of benefit in preventing CIN in high risk patients. However, as the need for dialysis rates was not reduced by

N-acetyl cysteine, a hard clinical benefit needs to be demonstrated, before it can be universally recommended for preventing CIN. (Baker C et al, 2003). It would seem that the Tepel administration protocol (600 mg orally twice daily on the day before and on the day of the procedure) is a reasonable treatment approach.(Tepel M et al, 2000).

* Calcium channel blockers:

Despite substantial evidence that calcium channel blockers reduce vasoconstriction and maintain GRF following contrast exposure, several studies were done giving conflicting results as they were all quite small and do not include high risk patients with renal insufficiency. Additional large scale randomized trials are necessary, particularly in high risk patients, before Ca channel blockers can be recommended for the prevention of CN. (Sean W. Murphy et al, 2000)

*Theophylline:

Adenosine is a vasodilator of most vascular beds. A_1 receptor stimulation causes cortical vasoconstriction while A_2 receptor stimulation results in medullary vasodilatation. Human studies have shown conflicting results , as a benefit of use of theophylline over saline hydration alone has not been proven (Kapoor A et al, 2002).

* Atrial natriuretic peptide:

Initial reports suggested that atrial natriuretic peptide **(**ANP) prevents fall in creatinine clearance after contrast exposure. However, a randomized, double blind, placebo-controlled trial showed that intravenous anaritide did not reduce the incidence of CN in patients with preexisting chronic renal failure, with or without diabetes mellitus.(Kurnik BR et al, 1998).

VI} CARDIAC PATIENTS

- Congestive heart failure:

Acute renal failure in patients with congestive heart failure occurs because of decreased renal blood flow. This decrease is due to hypovolemia from overdiuresis or hypervolemia that causes elevated filling pressures of the left ventricle and leads to decreased cardiac output. Patients in the former group may respond to the discontinuation of diuretics and gentle hydration. Patients in the latter group are treated with diuretics and may need inotropes

and vasodilators. Invasive hemodynamic monitoring may be required for fluid management.

- Cardiac Surgery :

ARF after cardiac surgery is a well recognized complication that generally occurs in 1 to 10% of patients(Bove T et al, 2004). Patients who develop ARF have higher rates of mortality and resource utilization, with the worst values seen in dialyzed patients. Loef *et al.* describe the long-term outcomes of a cohort of cardiac surgery patients treated with cardiopulmonary bypass at a single European center. Patients with postoperative ARF (defined as >25% change in serum creatinine corresponding to a 20% reduction in Cockroft-Gault GFR from baseline within 1 week post-surgery) not only had an increase in in-hospital mortality, confirming previous studies, but also had higher mortality rates >5 yr later. The long-term effect persisted even if the creatinine levels had returned to baseline at hospital discharge. (Loef B et al, 2005).
Similar effects have been reported in patients with ARF after percutaneous coronary interventions, where 1-yr mortality is significantly higher. (Gruberg L et al, 2000).

Low-dose dopamine is known to result in renal artery dilatation, natriuresis, and diuresis. This is mediated, at least in part, by activation of the DA-1 receptor. Low-dose dopamine continues to be widely used to protect against ARF and ameliorate established ARF. Similarly, in a randomized, controlled trial in patients undergoing cardiac surgery, there was no effect of low-dose dopamine on either renal function or mortality.(Lassnigg A et al, 2000).

Diuretics, including mannitol and furosemide, have been advocated as preventive agents in the setting of cardiovascular surgery. This is based on their potential ability to decrease renal oxygen consumption and to prevent the accumulation of intraluminal debris that may cause obstructing casts. Mannitol may have the additional property of scavenging free oxygen radicals. In a small study of cardiac surgery patients, prophylactic use of furosemide infused at 0.5 μg/kg/min was associated with significant worsening of renal outcome compared with placebo. .(Lassnigg A et al, 2000).

Atrial natriuretic peptide (ANP) is a potent diuretic and natriuretic substance that can increase glomerular filtration rate (GFR), reverse renal vasoconstriction, and block sodium reabsorption. In 11 patients who developed ARF after cardiac surgery, a 48-h infusion of ANP was found to improve renal blood flow and GFR . (Sward K et al, 2001). None of the patients required dialysis, and hemodynamic measurements were similar both during and after ANP infusion, suggesting that the hypotensive effect of the medication can be safely managed.

Unfortunately, there is currently no established pharmacologic intervention to prevent renal failure in cardiovascular surgery patients. As intravascular volume depletion is believed to exacerbate renal hypoperfusion and accentuate the risk for postoperative ARF, close attention to volume status is important. The use of dopamine as a prophylactic agent should be abandoned, and its use should be limited to those settings in which it will exert a desirable hemodynamic effect. Likewise, the use of furosemide should be limited to those circumstances in which the induction of diuresis is desirable. The role of mannitol should be more limited and probably

confined to the circumstance of rhabdomyolysis. It is important to note that although dopamine, furosemide, and mannitol can induce diuresis and convert an oliguric state to a nonoliguric state, and this may facilitate fluid and electrolyte management, there remains an absence of evidence that this conversion is associated with a mortality benefit. Further investigation of the effect of ANP is warranted, but there is insufficient evidence at present to support its routine use. (Clay A. and Harold L. Manning, 2002).

- Post myocardial infarction cardiogenic shock:

A study found that among patients with cardiogenic shock, 13% of patients treated with early revascularization and 24% of patients treated with initial medical therapy developed acute renal failure.(J.S. Hochman et al 1999). Although acute renal failure is often considered to be a marker of serious underlying disease, with few direct effects on mortality, studies have suggested that impaired renal function is an independent predictor of mortality.

Acute renal failure in cardiogenic shock is believed to result from inadequate perfusion of the kidney. Renal injury is minimal if blood flow can be restored quickly. However, severe and persistent hemodynamic compromise may lead to ischemic tubular necrosis. Not surprisingly, it was found that a greater incidence of acute renal failure in patients who had a low cardiac index or who required high doses of epinephrine and dobutamine.
Neither treatment with dopamine and norepinephrine, nor intraaortic balloon counterpulsation, was associated with the incidence of acute renal failure.

Elderly patients and diabetic patients are particularly prone to develop acute renal failure, and an association between mechanical ventilation and renal failure has also been described.
Neither hemofiltration nor early revascularization were associated with survival benefit . (Maria Koreny MD et al, 2002).

VII} MECHANICALLY VENTILATED PATIENTS

A number of mechanisms have been proposed to explain the effects of positive-pressure ventilation on renal function, including:
(1) a reduction in cardiac output.
(2) redistribution of intrarenal blood flow.
(3) stimulation of sympathetic and hormonal pathways.
(4) release of systemic inflammatory mediators as a consequence of ventilator-induced lung injury.

1) Cardiovascular changes:

Cardiovascular effects of respiratory support result from a complex interaction between intrathoracic pressure, intravascular volume and cardiac performance. Positive intrathoracic pressure from mechanical ventilation inhibits venous return and increases inferior vena caval pressure, resulting in a decrease in effective circulating volume (pre-load). Positive-pressure ventilation also compresses pulmonary and mediastinal vasculature, resulting in increased right ventricular afterload. These alterations in cardiopulmonary haemodynamics could potentially decrease cardiac output, which would result in a decrease in renal function secondary to decreased renal perfusion.

Increased renal vein pressures have been shown to directly decrease RBF and urinary sodium excretion and have been postulated to be another potential explanation for ventilator-induced renal dysfunction.

More recently, it has become clear that changes in cardiopulmonary haemodynamics with mechanical ventilation vary with intravascular volume and pulmonary and cardiac status. This perhaps explains the contradictory findings of previous studies and suggests that haemodynamic effects of mechanical ventilation probably do not entirely explain ventilator-induced renal dysfunction.(Neesh Pannu et al, 2004).

2)Intrarenal changes:

Hall et al suggested that redistribution of intrarenal blood flow from the cortical to juxtamedullary nephrons secondary to the release of vasoactive mediators induced by positive-pressure ventilation may be an important contributory factor in initiating depression of renal function during PEEP

therapy. Although they reported no change in RBF, Hall et al found a redistribution in blood flow from the cortical to juxtamedullary nephrons, measured by the krypton 85 washout technique. A follow-up study failed to show redistribution of RBF during ventilation with PEEP. (Neesh Pannu et al, 2004).

3) Hormonal changes:

-Early investigators postulated that ADH was responsible for the decrease in urine volume and free-water clearance because the majority of studies noted an increase in serum and urine ADH levels during positive-pressure ventilation. The most likely stimulus for ADH release in this setting is relative intravascular volume depletion induced by positive-pressure ventilation, although the mechanism by which this happens remains unexplained. Investigators have been unable to correlate ADH levels with observed changes in urine flow associated with PEEP. If ADH was the primary mechanism of the observed decline in urine volume, one would expect an associated increase in urine osmolality, which generally has not been reported.

- Increased plasma renin activity has been reported during positive-pressure ventilation. It seems most likely that the sodium retention commonly observed in ventilated patients is caused by a sympathetically mediated increase in renin activity, which decreases GFR by both decreasing blood flow and stimulating aldosterone.

- Recent studies suggest that the reduced urine volume and sodium content associated with mechanical ventilation may be mediated by a decrease in

atrial natriuretic peptide (ANP). ANP is released by the atria in response to increased transmural pressure and has potent diuretic and natriuretic properties. (Neesh Pannu et al, 2004). ANP levels correlated significantly with atrial transmural filling pressure, which declined with PEEP.

4) Activation of inflammatory mediators:

Studies have shown that an inflammatory response may be elicited by mechanical ventilation, resulting in worsening of pre-existing lung injury and ventilator-induced lung injury. (D. Dreyfuss and G. Saumon, 1998). Ventilator-induced lung injury includes mechanical complications of positive-pressure ventilation such as pneumothorax, air leaks and increases in endothelial and epithelial cell permeability, as well as increases in pulmonary and systemic inflammatory mediators.
Recent trials looking at low tidal volume high PEEP ventilation in patients with acute lung injury and ARDS show that 'protective' ventilation strategies are associated with decreased serum cytokine and chemokine activity, decreased organ dysfunction and decreased mortality
Apoptosis is regulated by inflammatory cytokines so it seems reasonable that the altered cytokine milieu induced by positive-pressure ventilation could result in end-organ epithelial cell apoptosis and induce organ injury. (Y. Imai et al, 2003).

*The effect of renal injury on lung function:

A strong association has been repeatedly observed between the development of acute renal failure and non-cardiogenic pulmonary oedema.

(H. Rabb et al, 2001).

The direct effect of renal injury on pulmonary vascular permeability has been demonstrated in rat models of renal ischaemia/reperfusion injury. (A.A. Kramer et al,1999). Down-regulation of epithelial sodium channels (EnaC) and aquaporins are believed to account for much of this altered vascular permeability. However, it was concluded that these regulatory changes are the result of uraemia, not simply ischaemia/reperfusion injury. (Neesh Pannu et al, 2004).

VIII} PERIOPERATIVE ARF

Perioperative ARF is among the most common aetiologies of ARF in hospitalized patients and markedly increases perioperative morbidity and mortality. Post-operative ARF is associated with an increased risk of perioperative infection, further complicating the post-operative course and increasing mortality.(C.V. Thakar et al, 2003).

The incidence of perioperative ARF varies with the type of surgery; cardiac, vascular and major abdominal surgery are the highest-risk procedures. Elective surgery has a lower risk compared to emergent surgery. Multiple risk factors, including old age, chronic renal insufficiency, cardiac disease,

sepsis, and concurrent use of nephrotoxic agents (radiocontrast dye, non-steroidal anti-inflammatory agents [NSAIDs]) predispose patients to perioperative renal failure. (Ignatius Y. Tang PharmD et al, 2004)

Pathogenesis of perioperative ARF:

Most perioperative ARF is caused by either pre-renal azotaemia (reversible renal insufficiency due to renal hypoperfusion) or acute tubular necrosis (ATN). ATN results from a variety of ischaemic and nephrotoxic insults, often in additive or synergistic combination.
Severe or sustained perioperative hypotension may result in ischaemic ATN. Other causes of decreased perioperative renal hypoperfusion include hypovolaemia (bleeding, anaesthetic-induced vasodilation), decreased effective circulating volume (ECV) (pre-operative cardiac dysfunction, perioperative myocardial infarction, cirrhosis and sepsis), cardiopulmonary bypass.

Increased intra-abdominal pressure in major abdominal surgery, including liver transplantation and even laparoscopic surgery , can also lead to renal hypoperfusion. (B. Ben-David et al, 1999).
Perioperative atrial fibrillation can lead to ARF because of renal artery embolization.
Obstructive uropathy due to mechanical blockage of the urinary tract, or neurogenic bladder caused by anaesthetics , diabetic neuropathy etc. should always be considered(Ignatius Y. Tang PharmD et al, 2004).

Prophylactic strategies in patients at risk of perioperative ARF:

1- Optimizing renal perfusion:-

Adequacy of renal perfusion is determined by the balance of RBF, intrarenal blood flow distribution, and parenchymal oxygen consumption. There are three main determinants of RBF: (1) cardiac output (CO), (2) renal perfusion pressure (RPP, proportional to mean arterial pressure (MAP), within the autoregulatory range), and (3) glomerular haemodynamic factors (primarily afferent and efferent arteriolar tone) (Ignatius Y. Tang PharmD et al, 2004).

*Cardiac output:-

Decreased CO due to hypovolaemia or cardiac dysfunction diminishes renal perfusion both directly and indirectly. Decreased CO not only directly lowers RBF but also activates a number of renal vasoconstrictor systems. Volume loading to prevent hypovolaemia is probably the most effective preventive measure to avoid pre-renal azotaemia as well as ischaemic and nephrotoxic ATN. It remains unresolved whether crystalloids or colloids are the preferred fluids to use. Crystalloids can be given initially to maintain adequate pre-load. However, in patients with severe hypovolaemia and capillary leak due to severe inflammation, colloids may be used.(M.J.R. Ragaller et al, 2001).

*Renal perfusion pressure:-

Autoregulation maintains RBF and GFR within a narrow range at MAP between 85 and 180 mmHg; this regulatory process is achieved by modulation of afferent arteriolar tone by two influences: a local myogenic reflex in the afferent arteriolar wall and a process called TGF. Standard

recommendations suggest that fluids and vasoactive drugs should be titrated to maintain a MAP of 60 mmHg.
Autoregulation is impaired by conditions such as sepsis and cardiopulmonary bypass. Furthermore, if renal injury does result in ATN, abundant experimental data suggest that autoregulation is lost and that RBF becomes linearly pressure-dependent, resulting in fresh ATN lesions with subsequent hypotension and hypoperfusion insults.
Vasopressin deficiency may play a role in post-cardiopulmonary bypass hypotension, and a small study suggested that prophylactic vasopressin administration reduces post-bypass hypotension and use of other vasconstrictors.(D.L. Morales et al,2003).

*Optimization of glomerular haemodynamics:-

Renal vasoconstriction occurs in shock through multiple mechanisms. The importance of renal vasoconstriction and regional hypoperfusion in causing perioperative ARF has not been precisely defined. Nevertheless, theoretically, any agent which offsets renal vasoconstriction might decrease the incidence of pre-renal azotaemia and ATN in high-risk patients. (Ignatius Y. Tang PharmD et al, 2004).

2- Dopamine:-

Despite the lack of evidence that dopamine is efficacious in preventing perioperative ARF, it is still commonly used in the surgical and critical care

setting. There is also the misconception that dopamine is a benign agent even though it may not be efficacious. Indeed, even low-dose dopamine is not without side-effects. These include tachyarrhythmia, myocardial ischaemia, intestinal ischaemia, which may result in bacterial translocation, and tissue necrosis when extravasated. There is also evidence that dopamine may worsen renal tubular injury, as indicated by elevated urinary retinol-binding protein.

In fact, the renal effects of dopamine may not necessarily be beneficial to patients in shock because it appears that dopamine preferentially increases cortical blood flow without augmenting perfusion to the medulla. This phenomenon may explain the failure of low-dose dopamine prophylaxis to achieve benefit in studies to date, despite the documented capacity to increase RBF. Also, if renal tubular injury (ATN) has already developed, increased RBF theoretically stresses subcritically injured nephron segments by requiring oxygen consumption for re-absorption of filtered sodium. . (Ignatius Y. Tang PharmD et al, 2004).

3- Fenoldopam:-

Fenoldopam is a pure and potent dopaminergic agonist, acting only at DA-1 (not DA-2) receptors, without eliciting α- or β-adrenergic effects at any dose. It is a potent parenteral anti-hypertensive agent. (I. Singer and M. Epstein, 1998).

Fenoldopam also causes renal vasodilation at low doses (<0.1 μg/kg/minute) which have no effect on systemic blood pressure in healthy. (V.S. Mathur et al , 1999).

Fenoldopam was additionally shown to reverse cyclosporine-induced renal vasoconstriction in renal transplant recipients , and radiocontrast-induced

vasoconstriction in dogs. (G.L. Bakris et al,1999).
In contrast to dopamine, experimental data suggest that renal vasodilation with fenoldopam preferentially augments medullary blood flow.
In addition to systemic and renal vasodilation, fenoldopam has other regional circulatory effects. Limited data from animals and human subjects suggest that fenoldopam is a mesenteric and coronary vasodilator .
Pilot studies suggested that fenoldopam might be effective in the prevention of radiocontrast nephropathy and might be potentially useful for perioperative renoprotection during high-risk cardiovascular surgical procedures. It is important to emphasize that, because fenoldopam caused dose-dependent systemic vasodilation (beginning at a dose of approximately 0.1 μg/kg/minute), renal vasodilation may be accompanied by hypotension, and extreme caution must be exercised in the experimental or therapeutic use of this drug in critically ill patients. (Ignatius Y. Tang PharmD et al, 2004).

4-Diuretics:

loop diuretics have been used in the management of ATN. It is thought that increasing tubular flow with diuretics may 'wash out' the intraluminal cell debris that causes obstruction Furthermore, by inhibiting the Na–K–2Cl co-transporter in the TALH, medullary oxygen consumption could be reduced, thereby decreasing medullary ischaemia.(S. Garwood , 2000) .
Loop diuretics, such as furosemide and torsemide, were shown to convert an oliguric to a non-oliguric state in patients with less severe ATN. However, the course of ATN was not altered. Its prophylactic use in the perioperative setting may actually be detrimental.(I.R. Shilliday et al, 1997) .

Like loop diuretics, mannitol has not been convincibly shown to be effective in the prevention of ARF in the surgical setting. (J.A. Kellum,1997).

5-Natriuretic peptides:

Atrial natriuretic peptide has been shown to cause afferent arteriolar vasodilation and efferent arteriolar vasoconstriction, thereby increasing the GFR. It also blocks tubular re-absorption of sodium chloride, re-distributes renal medullary blood flow, disrupts TGF and reverses endothelin-induced vasoconstriction. .(S. Garwood , 2000) .

One of these natriuretic peptides, urodilatin, which is produced by renal tubular cells, was found to have the same renal haemodynamic effect but was devoid of systemic hypotensive effects. (W.G. Forssmann et al , 2001). Urodilatin has been shown to improve the course of established post-operative ARF.

However, in another small, placebo-controlled study of 24 patients who underwent orthotopic heart transplant, the incidence of ARF was the same, six of 12 in each group. Interestingly, the cumulative duration of haemofiltration was significantly shorter and the frequency of haemodialysis less in those who received urodilatin.. (P. Brenner et al, 1995).

6- Calcium channel blockers:

Calcium channel blockers cause afferent arteriole vasodilation and natriuresis. They also reduce intracellular calcium influx and act as a free radical scavenger.

Among the calcium channel blockers, diltiazem has been the most studied in patients who underwent non-transplant surgery. It was shown to preserve

renal tubule integrity (measured by urinary alpha-glutathione S-transferase) in patients who underwent cardiac surgery. (S.N. Piper et al, 2003).
While the use of diltiazem in patients with renal insufficiency appears promising, its efficacy remains to be proven in larger studies. (A.S. Bergman et al, 2002).

7- Prostaglandins:-

In addition to being an afferent arteriole vasodilator, prostaglandins also have been shown to inhibit pro-inflammatory cytokines during cardiac surgery. (A.S. Bergman et al, 2002).
Morgera et al. evaluated the use of low-dose prostacyclin perioperatively to preserve renal function after CABG in a group of patients with decreased cardiac function (ejection fraction <40%) but normal renal function. The mean creatinine clearance changed from 91 ml/minute pre-operatively to 103 ml/minute in patients who received prostacyclin. In contrast, the mean creatinine clearance decreased from 100 to 68 ml/minute. (S. Morgera etal, 2002).

8- Adenosine antagonist:-

Adenosine A1 receptor mediates haemodynamic changes in ischaemia-induced ATN. The non-specific adenosine receptor antagonist, theophylline, was studied in a double-blind, placebo-controlled trial of 56 patients with normal pre-operative renal function who underwent elective CABG. No difference in the incidence of acute rise in creatinine was found between patients who received aminophylline (4 mg/kg intravenous bolus, followed

by 0.25 mg/kg/hour infusion for up to 96 hours) versus saline. (B.K. Kramer et al, 2002).

9- Antioxidants:-

Because of the generation of reactive oxygen species during ATN, antioxidants have been studied to prevent perioperative ARF.
In a prospective, randomized, placebo-controlled study of 100 patients with normal baseline renal function who underwent major abdominal surgery, patients who received acetylcysteine were shown to have a reduced serum C-reactive protein concentration, compared to those who received dextrose solution. However, there was no difference in the post-operative renal function between the two groups.(Z. Molnar et al, 2003).

10- Anti-inflammatory agents:-

Because of the pro-inflammatory state of surgery, pentoxyfylline, a phosphodiesterase inhibitor which promotes prostacyclin release and inhibits TNF-alpha, was evaluated in a group of elderly patients who underwent cardiac surgery.It was found to reduce the production of inflammatory proteins. However, no difference in renal function was shown between the treatment and the control groups. (J. Boldt et al, 2001).

11- Insulin like growth factor I(IGF-1):-

IGF-1 may be useful in the prophylaxis against perioperative ARF. In 58 patients with pre-operative GFR of 50-60 ml/minute who underwent vascular surgery, 22% of patients who received IGF-1 versus 33% of those who received placebo showed an increase in serum creatinine 24 hours post-surgery. However, no patient in either group developed ARF. (S.C. Franklin et al, 1997) .

12- Prophylactic dialysis :-

Optimization of renal function prior to surgery might reduce the risk of perioperative ARF. In 56 patients with pre-operative serum creatinine >3 mg/dl who underwent elective CABG surgery, one of 21 patients who received haemodialysis twice within 72 hours before surgery developed ARF, compared to 14 of 23 patients who did not. Furthermore, the stay in the intensive care unit and the hospital was shorter and the mortality rate lower in those who received pre-operative dialysis. (I. Durmcaz et al, 2003)

IX} DRUG-INDUCED NEPHROPATHIES

A possible contribution of drugs should be considered in every type of renal failure. A large number of drugs may compromise renal function**.**

1. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (ARA) are usually well-tolerated and highly effective antihypertensive drugs. As compared to other antihypertensives, drugs that

interrupt the rennin–angiotensin axis may be associated more commonly with renal dysfunction, because any decline in intraglomerular pressure due to blood pressure lowering will be exaggerated by concomitant vasodilatation of the efferent side of the glomerular circulation. There are several conditions in which the use of ACEIs or ARAs may cause an exaggerated or progressive decline in renal function, including renal-artery stenosis, polycystic kidney disease when the renal arteries are extrinsically compressed by large cysts, decreased absolute or effective arterial blood volume, use of non-steroidal anti-inflammatory drugs and sepsis. (B.F. Palmer,2002).

2. Non-steroidal anti-inflammatory drugs

NSAIDs have been associated with several types of renal dysfunction. ARF occurring relatively quickly (3–7 days) after the beginning of treatment without proteinuria or abnormalities of the urinary sediment suggests a haemodynamic disorder, which is related to inhibition of renal prostaglandin synthesis. The products of arachidonic acid metabolism have diverse roles in the kidney, including the regulation of renal plasma flow (RPF) (prostaglandins PGI_2 and PGE_2 vasodilate; thromboxane A_2 vasoconstricts), salt and water handling, and renin release by the juxtaglomerular apparatus. Renal prostaglandin synthesis is low in healthy subjects and plays a minor role in the maintenance of RPF. Under these conditions, inhibition of prostaglandin synthesis by NSAIDs appears to cause no clinically significant adverse effects.

However in subjects dependent on increased prostaglandin synthesis for maintenance of RPF and fluid and electrolyte homeostasis, inhibition of cyclo-oxygenase by NSAIDs may have profound adverse renal effects.

Thus, the risk of adverse renal effects is increased by any condition that results in low circulating blood volume or increased renin production, for example, plasma volume contraction, congestive cardiac failure, cirrhosis and ascites, diabetes mellitus and old age. If the NSAID-induced vasoconstriction is sufficiently intense and of extended duration, ATN may ensue. (W.L. Bennet and J.S. Henrich,1996).

Acute interstitial nephritis may be another cause of NSAID-related ARF.. Affected patients typically present with haematuria, pyuria, white cell casts, proteinuria, and an acute rise in the plasma creatinine concentration. More than 80% of patients with acute interstitial nephritis related to NSAIDs develop a nephrotic syndrome. Spontaneous recovery generally occurs within weeks to a few months after therapy is discontinued. A course of prednisone may be considered in patients whose renal failure persists more than 1–2 weeks after the NSAID has been discontinued.

Current evidence indicates that the selective COX-2 inhibitors may not offer distinct clinical advantages over other non-selective COX-inhibitors with respect to renal regulation of sodium excretion, blood pressure and glomerular filtration rate. (M.A. Perazella and J. Eras,2000).

3. Aminoglycoside antibiotics

Aminoglycoside antibiotics, despite their nephrotoxicity, continue to be a mainstay in the clinical management of Gram-negative infections. The incidence of ARF with aminoglycoside therapy varies with the definition used, but ranges from 5 to 25%. Aminoglycosides produce tubular cell necrosis, which is largely confined to the proximal convoluted tubule and pars recta. The precise mechanism(s) of aminoglycoside nephrotoxicity remains largely unknown. Aminoglycoside nephrotoxicity is typically

associated with non-oliguric renal failure. Decline in glomerular filtration rate and elevations of serum creatinine usually are not apparent until after 5–10 days of aminoglycoside treatment. The urine sediment is benign or shows granular and epithelial cell casts. A variety of risk factors have been identified that increase the risk of aminoglycoside nephrotoxicity; these include the dose and duration of drug treatment, pre-existing renal insufficiency or liver disease, elderly age, volume depletion and sepsis, potassium and magnesium depletion.

Once established, aminoglycoside-induced ARF must be handled like any other type of ARF, with stringent fluid and electrolyte management and, if necessary, dialysis. After cessation of the aminoglycoside therapy, the plasma creatinine concentration usually returns to the prior baseline level within 21 days.

There is some evidence that divided-dose regimens are more likely to produce toxicity than once-daily regimens.

Irreversible damage, however, may occur, especially with prolonged therapy, even in low doses. (J.M. Prins et al, 1993).

4. Vancomycin

The exact incidence of vancomycin nephrotoxicity is uncertain. Most studies have noted that 5–15% of patients treated with vancomycin alone develop an acute decline in renal function, defined as a rise in the plasma creatinine concentration of at least 0.5 mg/dl. The degree of renal insufficiency is relatively mild in most cases unless excessive doses are given. Pharmacokinetic monitoring and dosage adjustment are effective methods for reducing the toxicity of vancomycin in intensive care patients,

especially for those receiving concomitant nephrotoxins. (W. Darko et al, 2003).

5. Antifungals

A common complication of amphotericin B therapy is renal dysfunction. The clinical manifestations include renal insufficiency and various electrolyte disorders (hypokalaemia, hypomagnesaemia, renal tubular acidosis, nephrogenic diabetes insipidus). The mechanism by which renal insufficiency occurs is incompletely understood. It has been proposed that both direct tubular toxicity and renal vasoconstriction play an important role. Risk factors for amphotericin B-associated nephrotoxicity include total cumulated dose, duration of therapy, dehydration and diuretic use, abnormal baseline renal function, and association with other nephrotoxins. Slow recovery of renal function follows drug withdrawal but recovery is often incomplete; magnesium wasting, in particular, may be chronic. (K. Furrer et al, 2002).

Finally, recent literature indicates that the ecchinocandins, a novel class of antifungal agents, may represent a valuable alternative in patients with amphotericin B-induced renal function impairment or in patients at increased risk.(T.R. Rogers, 2001).

6. Acyclovir and sulphonamides

Opportunistic infections are increasingly common in intensive care units and now represent more than 10% of all nosocomial infections. Several antimicrobials used to treat these infections—notably acyclovir and sulphonamides—are associated with the production of crystals that are

insoluble in human urine. Intratubular precipitation of these crystals can lead to acute renal insufficiency. Many patients who require treatment with these medications have additional risk factors, such as true or effective intravascular volume depletion and underlying renal insufficiency, that increase the likelihood of drug-induced intrarenal crystal deposition. Acute renal failure in this setting may be preventable if it is anticipated by appropriate drug dosing, volume expansion with high urinary flow, and alkalinization of the urine when appropriate. (M.A. Perazella,1999).

7. Colloids

Absolute and relative blood volume deficits often occur in patients undergoing surgery and in the intensive care unit. The pre-operative medical status of the patient, medication, anaesthesia, surgical trauma, and inflammatory reactions may all alter intravascular volume status. Appropriate intravascular volume replacement is a fundamental component of critical care management because failure to treat hypovolaemia may lead to multiple organ dysfunction syndrome or death. There is controversy as to whether crystalloids or colloids are preferred for intravascular volume replacement.(J. Boldt and H.J. Priebe,2003).

Information on the influence of the different colloids (human albumin, dextran, gelatin or different hydroxyethyl starch solutions) on renal function is fairly incomplete. All colloids, including hyperoncotic human albumin, may induce ARF by increasing the plasma colloid osmotic pressure. This has been termed ‘hyperoncotic ARF’. The dehydrated patient who receives considerable amounts of colloids is especially at risk for developing ‘hyperoncotic ARF’. Thus, it may be advisable (although not evidence-

based) to administer colloids in addition to, rather than in lieu of, crystalloids.

CONSERVATIVE AND SUPPORTIVE MANAGEMENT OF CRITICALLY ILL RENAL PATIENTS

I} VASOACTIVE DRUGS

-The rationale for vasoactive drugs in ICU

In patients with cardiogenic shock and vasodilatory shock maintenance of an adequate mean arterial pressure and cardiac output is fundamental to ensure adequate vital organ perfusion and function. In many ICU patients, plasma volume expansion is sufficient to achieve these goals. In many others

it is not. In these patients, vasoactive drugs (many of which have both inotropic and vasopressor properties) are used to augment either cardiac output or perfusion pressure, or both. However, many aspects of their use remain controversial. One particular area of controversy relates to their renal effects.

- Vasoactive drugs

Catecholamines are by far the most common vasoactive drugs used in the ICU. They can reverse cardiogenic shock through their inotropic effects (β-adrenergic receptors), and distributive shock through their vasoconstrictive effects (α-adrenergic receptors and β-adrenergic receptor-mediated renin and then angiotensin II generation) or both.

1. Dopamine

***** Cardiovascular effects:-

Dopamine has cardiac β_1-adrenergic effects (threshold ~3.0 and maximal dose ~10 μg/kg/minute) and peripheral α_1-adrenergic receptor agonist activity (threshold ~5.0 and maximal ~20 μg/kg/minute), which increase myocardial contractility, heart rate and systemic vascular resistance (SVR) and, in turn, blood pressure. Dopamine is also well known to have non-selective dopaminergic effects at lower doses (1–2 μg/kg/minute). Stimulation of peripheral dopamine-1 receptors is believed to produce renal, coronary, and mesenteric arterial vasodilationif given at (3–8 μg/kg/minute),

dopamine would prove to be beneficial to kidney function remains unknown. At such doses, dopamine increases cardiac output (and at times, mean arterial blood pressure) through a beta-adrenergic agonist effect much the same way as dobutamine or adrenalin (epinephrine) would. Thus, such an effect would not be unique to dopamine. (J.D. Sandham et al, 2003).

* Renal effects of dopamine:-

1)Natriuresis: Dopamine exerts its natriuretic effect by inhibition of baso-lateral Na–K-ATPase activity in the proximal tubule, medullary thick ascending limb of the loop of Henle and cortical collecting duct epithelial cells through engagement of DA-1 and probably DA-2 receptors Dopamine also promotes renal excretion of free water, probably by inhibiting central antidiuretic hormone (ADH) .

2)Blood flow: Dopamine at low dose also induces a dose-dependent (threshold ~0.5 and maximal ~3.0 μg/kg/minute) increase in the renal plasma flow in animals and healthy humans and to a lesser extent in disease states. (S. Mousdale et al, 1988).

* Preventive role of low-dose dopamine:-

A few early small and uncontrolled studies in the 1980s and early 1990s showed beneficial effects of low-dose dopamine on oliguric renal failure. In patients with oliguria and/or acute renal failure or hepatorenal syndrome despite normal intra-vascular volume, low-dose dopamine with/without furosemide infusion produced a diuresis , higher fractional excretion of sodium, reduced serum creatinine levels, and reduction of plasma renin activity. Studies done later on septic patients contradicted these results. In

oliguric septic patients with or without shock, dopamine failed to reverse oliguria and hypotension and did not significantly affect the incidence of acute renal failure. Low-dose dopamine also failed to improve survival or obviate the need for dialysis (P.E. Marik and J. Iglesias,1999).

Although an increase in RBF with dopamine was demonstrated in animal studies and human volunteers, this effect in septic and critical ill patients with incipient or established acute renal failure might be different from that in the normal state. The renal haemodynamic effects of low-dose dopamine in septic shock are uncertain. The sensitivity of tubular epithelial cells and vessels to the drug may be only partial or even absent when renal lesions are established. This is supported by the observation that, in a number of trials, some agents were effective only in the less severe cases. Even if RBF could be increased by low-dose dopamine, it is not clear that increased blood flow at the pre-glomerular level per se is useful or even desirable to achieve meaningful clinical end points. Finally, there is uncertainty whether acute renal failure of critical illness is predominantly due to a decrease in renal blood supply or an increased oxygen demand or a toxic effect of sepsis on tubular cells, or a combination of these, and whether hypoperfusion is present in septic renal failure at all. (C.L. Holmes and K.R. Walley, 2003).

In summary, The effect of dopamine on renal blood flow remains controversial. If dopamine does increase renal blood flow, the vascular anatomy of the kidney would limit its effectiveness. Rather than improving renal function, dopamine has been shown to impair renal oxygen kinetics, inhibit feedback systems that protect the kidney from ischemia, and may worsen tubular injury. Dopamine has not been proven useful in the prevention or alteration of the course of acute renal failure as a result of heart failure, cardiac surgery, abdominal aortic surgery, sepsis, and

transplantation. Dopamine has been associated with multiple complications involving the cardiovascular, pulmonary, gastrointestinal, endocrine, and immune systems. (Schenarts PJ et al, 2006).

2. Fenoldopam

Fenoldopam is a selective dopamine receptor-1 (DA-1) agonist that causes DA-1 receptor-mediated vasodilatation and does not stimulate DA-2 or adrenergic α- or β-receptors, even at high doses. The peripheral vasodilatatory effect of fenoldopam causes reduction of mean arterial pressure while its renal vasodilatatory effect, being more than six times as potent as dopamine, appears preferentially directed at efferent arterioles. As with dopamine, there has been some expectation that fenoldopam might protect the kidney owing to its renal vasodilatatory and natriuretic effect. The results of studies on the prophylactic use of fenoldopam in contrast-induced nephropathy and cardiovascular surgery seem promising but are not conclusive.Results in other areas are either equivocal or discouraging.(R. Sheinbaum et al, 2003). A recent study concluded that In critically ill patients, a continuous infusion of fenoldopam at 0.1 microg/kg/min does not cause any clinically significant hemodynamic impairment and improves renal function compared with renal dose dopamine. In the setting of acute early renal dysfunction, before severe renal failure has occurred, the attempt to reverse renal hypoperfusion with fenoldopam is more effective than with low-dose dopamine. (Brienza N et al, 2006).

3. Norepinephrine (noradrenalin)

* Cardiovascular effects:-

Norepinephrine (NE) (noradrenalin) has a moderate β_1- and β_2-adrenergic effect but strong alpha-adrenergic effects, which causes vasoconstriction in all vascular beds, including the renal circulation.

* Renal effects :-

Two studies done on healthy volunteers with NE infusion at mean of 0.1 μg/kg/minute with and without dopamine showed that NE increased renal vascular resistance ,decreased effective RBF, however, GFR was increased modestly or remained unchanged. .Even though NE may be a mild renal vasoconstrictor when given intravenously its effect on blood pressure/perfusion pressure would be such that overall RBF should be at least preserved .(M. Richer et al, 1996).

There are insufficient data to define the effect of NE on the kidney, either in normal subjects or under septic condition. The data available suggest that restoration of an adequate blood pressure by means of NE infusion in patients with septic shock is associated with increased diuresis, but whether this could be achieved or even bettered with any other drug that also improved blood pressure to a similar degree is unknown. The same is probably true for NE's effects on RBF and GFR. Importantly, however, there appears to be no reason to avoid NE administration because of concerns that it would have a specific adverse effect on renal function. Given its greater efficacy in restoring MAP compared to high-dose dopamine, NE is the

vasopressor of choice in vasodilated hypotensive states with preserved or increased cardiac output. (Raymond Wai Chuen Lee et al, 2004).

4. Epinephrine (adrenalin)

*Cardiovascular effects

As with norepinephrine (noradrenalin), epinephrine (Epi) (adrenalin) exerts combined α- and β-adrenergic effects. In low dose, it has predominantly β-adrenergic effects, which lead to an increase in cardiac output. In higher dose, its α-adrenergic effect causes vasoconstriction, particularly in the splanchnic and renal vascular bed.

* Renal effects

Day et al (N.P.J. Dayet al, 2000) showed that epinephrine (adrenalin) infusion was associated with a significant increase in renal vascular resistance and a decrease in RBF as a fraction of cardiac output. Absolute RBF index and renal oxygen consumption, creatinine clearance and urine output remained constant.
The presence or absence of renal failure did not significantly influence the effects of epinephrine. Thus, the effect of epinephrine (adrenalin) on the kidney remains largely unknown.

5. Phenylephrine

*Cardiovascular effects

Phenylephrine is a predominant α_1-adrenergic receptor-mediated agonist. As a result, it increases blood pressure mainly by increasing systemic

vascular resistance (SVR). Studies in both cardiac and septic patients show that blood pressure, central venous pressure and heart rate increase significantly while cardiac index and stroke index decrease in cardiac patients but increase in septic patients.(G. Lema and R. Canessa,1996).

*Renal effects

Besides increasing SVR, phenylephrine also constricts the renal vasculature and decreases RBF. However, it increases renal perfusion pressure in the presence of a low SVR. Phenylephrine is not as commonly used as other drugs in septic shock. Thus, little evidence is available on its renal effects in this setting.(S. Bennett et al, 1996).

6.Dobutamine

*Cardiovascular effects

The additive effect of the cardiac α_1- and β_1-agonist activity gives dobutamine a strong inotropic action, which increases myocardial contractility. Although it has opposing peripheral α_1- (vasoconstriction) and peripheral β_2-(vasodilation) adrenergic effects, the reflex reduction in sympathetic nervous system tone in response to the increased myocardial contractility and stroke volume leads to a reduction in total peripheral vascular resistance. In combination to its β_2 vasodilatory effects, dobutamine

causes hypotension, which may preclude its use as a single agent. It also has a weak chronotropic effect.

* Renal effects

The specific renal effects of dobutamine are probably dependent on its ability to augment cardiac output. In human studies, RBF was increased by dobutamine in some reports but not changed in others. There is little information on any specific effects of dobutamine on RBF or function. It is likely that dobutamine would have a beneficial renal effect in patients with a low cardiac output state by increasing cardiac output and overall organ perfusion. Its addition to pressor treatment of septic shock patients with renal dysfunction in order to further augment an already high cardiac output seems unlikely to benefit the kidneys. There is insufficient information to recommend its use for renal protection. (Raymond Wai Chuen Lee et al, 2004).

7.Dopexamine

*Cardiovascular effect

This relatively new catecholamine has predominantly β_2 and dopaminergic receptor activity but no α-effect. It has a direct inotropic action in low cardiac output states. It increases cardiac index and heart rate and decreases SVR.

*Renal effects

Its powerful dopaminergic effect is believed to induce splanchnic vasodilatation and increased gut and renal perfusion.
Ralph et al conducted probably the largest prospective, randomized controlled clinical trial on 102 critically ill patients concerning the effect of dopexamine on organ functions, including the kidney. The result showed no benefit in creatinine clearance or incidence of acute renal failure requiring renal replacement therapy. (C.J. Ralph et al, 2002).

8. Milrinone (amrinone/enoximone)

Milrinone (and other similar drugs such as amrinone and enoximone) is a short-acting phosphodiesterase inhibitor which increases cAMP activity resulting in a positive inotropic effect and systemic vasodilatory effect. There has been no clinical human study on critically ill patients focusing on the renal effect of milrinone or other agents of the same class such as amrinone and enoximone. Although there is no information about the positive renal effect of milrinone, there are reports of mild elevations in serum creatinine owing to milrinone-induced hypotension.(G. Saab et al,2002).

9.Vasopressin

Vasopressin exerts its vasoconstrictive effect via vascular V_1-receptors and its anti-diuretic effect through renal tubular V_2-receptors. Stimulation of V_1-receptor causes arterial vasoconstriction in non-vital organs, such as skin, skeletal muscle and bowel, in a dose-dependent manner. The main effect is increased SVR and blood pressure. On the other hand, low-dose vasopressin

causes vasodilatation in the renal, pulmonary, cerebral and mesenteric vasculature, probably due to nitric oxide release by the endothelium. vasopressin decreases cardiac output in the normal heart or mild heart failure. In addition, vasopressin also modulates the baroreflex response, causing a more prominent reduction in heart rate for a given increase in blood pressure.(C.L. Holmes et al, 2001).

V_2-receptor stimulation increases renal free water re-absorption. It also increases the medullary concentration gradient by activating a distinct urea transporter, further concentrating the urine. However, under some conditions such as haemorrhage or sepsis, vasopressin increases urine output.

The mechanisms of this diuretic effect of vasopressin have not been fully explained yet. Although the pressor effect of VP in septic shock patients may increase renal perfusion pressure sufficiently to improve flow and function, these effects may be achievable with other pressor agents. It remains unclear whether the unique properties of VP offer any clinically significant advantages over the use of any other pressor agent or whether a combination of low-dose VP infusion and NE (norepinephrine, noradrenalin) infusion represents the best pressor combination for the septic kidney. (Raymond Wai Chuen Lee et al, 2004).

10.Terlipressin

Terlipressin is a long-acting analogue of vasopressin. It has a higher affinity than vasopressin for vascular receptors.

While the vast majority of studies of terlipressin have concentrated on cirrhotic patients with hepatorenal syndrome and variceal haemorrhage, only one study concerning the use of terlipressin in septic patients has been reported showing that terlipressin was associated with a progressive increase

in mean arterial pressure. In two patients with oliguria, urine output increased after administration of terlipressin without obvious complication. (A. O'Brien et al, 2002). As terlipressin is a relatively new drug used in critically ill patients, more studies are necessary before a clear view emerges of its renal effects outside of the field of hepatorenal syndrome.

II} NUTRITION

Nutritional status has been considered to be one of the possible determinants of mortality rates in cases of acute renal failure (ARF). However, most studies evaluating possible mortality indicators in ARF cases have not focused on the nutritional status, possibly because of the difficulties involved in assessing the nutritional status of critically ill patients

ENERGY METABOLISM

Even under hypercatabolic conditions, such as sepsis or organ dysfunction, the energy requirements rarely exceed 1.3 times the baseline energy expenditure. In ARF cases, an energy intake of 25 to 35 kcal/kg/day is recommended, according to the associated degree of catabolism. (Druml W,2002).

PROTEIN METABOLISM

The most marked alteration in nutritional status among ARF patients is the presence of hypercatabolism with a negative nitrogen balance. Several factors may contribute towards the increased catabolism in ARF cases. Inflammatory mediators, including interleukins and tumour necrosis factor, activate the protein metabolism in the same way as in other conditions like sepsis that are observed among critically ill patients. Data obtained from animal studies suggest that uremia is associated with increased gluconeogenesis, with increased protein catabolism and reduced protein synthesis.Hormonal and metabolic changes, such as insulin resistance, increased glucagon concentrations, secondary hyperparathyroidism and metabolic acidosis have also been correlated with malnutrition among ARF patients.Dialysis procedures cause nutrient loss and stimulate protein catabolism. (Druml W,1998).

NUTRITIONAL ASSESSMENT IN ACUTE RENAL FAILURE

INSULIN-LIKE GROWTH FACTOR-1

Insulin-like growth factor-1 Insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-2 (IGF-2) are structurally related to insulin. Human IGFs, generically called somatomedins. Somatomedins are secreted

at the same time as they are produced, and consequently they are not concentrated in any organ. Therefore, although the liver is the major source of circulating somatomedins, their highest concentration is observed in the blood. IGFs are produced in several organs and are biologically active in most cell types.

In humans, serum IGF-1 levels are reduced after protein-energy deprivation, and return to normal levels within few days after food intake is resumed. IGF-1 is a reliable marker for nutritional status and has been shown to be better than other biochemical markers for assessing nitrogen balance in severely ill and hypercatabolic patients. (Sérgio Mussi Guimarães et al, 2005).

ALBUMIN

Serum albumin levels decrease markedly in response to stress and inflammation, and may not accurately reflect nutritional status changes in severely ill patients.

TRANSFERRIN

Transferrin has a shorter half-life (8 days) than albumin, but it lacks sensitivity for evaluating the short-term effects of refeeding.Transferrin concentration is significantly influenced by patients' serum iron levels. (Sérgio Mussi Guimarães et al, 2005).

PREALBUMIN

Serum prealbumin is a nutritional marker with a half-life of 1 to 2 days and a good response to nutritional supplementation. Similarly to albumin, its serum levels decrease in response to stress and inflammation.It is excreted mainly by the kidneys. Prealbumin concentrations may be falsely high in patients with ARF. (Goldstein-Fuchs DJ,2002).

BODY COMPOSITION ANALYSIS

Fat storage and the quantification of somatic proteins are usually evaluated by anthropometric measurements. The use of these methods in ARF cases has limited value, due to the frequent fluid variations observed in this type of patients.

SUBJECTIVE GLOBAL ASSESSMENT

Subjective global assessment (SGA) is a technique used for evaluating nutritional status. It assesses the nutritional status based on clinical experience and includes the medical and nutritional history, physical examination and functional assessment of the patients. Since SGA is a subjective technique, it does not measure visceral proteins and does not provide follow-up for nutritional therapy. Moreover, because it requires information from patients, this methodology may not always be applicable to ARF patients in the ICU, due to their decreased consciousness levels caused by their underlying disease or by the use of sedatives, or because of the use of mechanical ventilation. . (Sérgio Mussi Guimarães et al, 2005).

TOTAL CHOLESTEROL

Serum cholesterol is an independent predictor for mortality among hemodialysis patients. Hypocholesterolemia and decreased low density lipoprotein (LDL) have been described in severely ill surgical patients in the ICU with evidence of sepsis.

NUTRITIONAL THERAPY

The use of adequate nutritional therapy among patients suffering from different diseases is required in order to maintain protein storage and regulate lean body mass deficits. The objectives of nutritional therapy among ARF patients are no different from those under other hypercatabolic conditions.

Urea nitrogen appearance rate (UNA) measurements, which reflect protein catabolism,and the assessment of energy requirements are not routine practice. The formulae usually used to calculate energy requirements may underestimate these requirements among ARF patients, since they are based on healthy individuals with normal body fluid distribution.

The undesirable effects of nutritional therapy are another limitation on its use. Excessive supplementation of proteins increases the end products of protein metabolism. The provision of large amounts of nutrients requires the infusion of considerable quantities of fluids, carbohydrates and lipids, and this may cause volume overload and undesirable electrolytic and metabolic changes.

Nutritional programs must be individually designed for each ARF patient. In clinical practice, patients may be divided into three groups, according to the degree of catabolism, which may be evaluated by calculating the UNA rate:

GROUP I: Low UNA rate. These patients are mildly catabolic, i.e. those whose ARF was caused by nephrotoxins alone (aminoglycosides, contrast

media and others). Dialysis is seldom required and the use of nutritional therapy containing 25 kcal/kg/day and 0.6 g/kg/day of proteins rich in essential amino acids is usually sufficient. Such patients are usually fed orally and the prognosis for the recovery of renal function and survival is excellent.

GROUP II: Moderate UNA rate. These are ARF patients with moderate catabolism, frequently suffering from infectious or surgical complications. The use of enteral or parenteral nutrition and dialysis is often required. These patients should receive essential and non-essential amino acids at a dose of 0.8 to 1.2 g/kg/day and calorie intake of 25 to 30 kcal/kg/day. The mortality rate in this population is approximately 60%.

GROUP III: High UNA rate. These are patients who develop ARF in association with severe trauma, severe burn injuries and sepsis. The treatment for this population is complex and includes parenteral nutrition and dialysis. Ventilatory and hemodynamic support are often required. The nutritional requirements for reducing catabolism and minimizing protein depletion are high. The energy requirement is approximately 25 to 35 kcal/kg/day and the protein requirement is 1.0 to 1.5 g/kg/day. The mortality rate in this group is greater than 80%.
It should be stressed that, in groups II and III, even early and optimized use of nutritional support will hardly be able to offset the marked negative nitrogen balance observed in such patients. (Druml W ,2002).

Urea nitrogen appearance (UNA) (g/day)
=urinary urea nitrogen excretion + change in urea nitrogen pool
$= (Uun \times V) + (BUN_2 - BUN_1)\ 0.006 \times BW + + (BW_2 - Bw_1) \times BUN_2 / 100$

[Uun = urinary urea nitrogen concentration in grams/day; V = urinary volume in liters ; BUN_2 & BUN_1 = blood urea nitrogen in mg nitrogen/dl on days 2 and 1 ; BW_2 & Bw_1 = body weights in Kg on days 2 and 1]

III} PHARMACOKINETICS AND

ANTIBIOTICS THERAPY

Critically ill patients often have multi-organ dysfunction, sepsis, or other conditions that require complex drug therapy and may influence drug concentrations through changes in absorption, distribution, metabolism and

elimination. The addition of renal replacement therapy (RRT) may further complicate drug therapy.

- Influence of ARF and critical illness on pharmacokinetic parameters:

The effective concentration of a drug is the free fraction at the site of action, and this concentration reflects a complicated interplay between dose, absorption, protein binding, volume of distribution (Vd), and clearance (metabolism and elimination). Total body clearance of a drug is the sum of clearances from different sites in the body that may include hepatic, renal and other metabolic pathways. It is the contribution of renal clearance to total body clearance that is the major determinant of the need for dosing adjustments in renal failure. If the renal clearance of a drug is normally less than 25–30% of total body clearance, impaired renal function is unlikely to have clinically significant influence on drug removal. Similarly, drug removal by RRT will have little influence on total body clearance and dosing adjustments do not have to be considered.

Only the unbound fraction of a drug is available for filtration, and drugs with a high protein binding are poorly cleared by RRT.

The influence of ARF on protein binding is not well described. Critically ill patients often have low albumin levels which may increase the unbound fraction of many drugs with possible deleterious effects, as documented for phenytoin. These patients also often have increased levels of acid α_1-glycoprotein (an acute-phase protein) which may increase protein binding of some drugs. (D.F. Driscoll et al, 1988).

The Vd is a mathematical reflection of the volume in which a drug would need to be dissolved to obtain the observed blood concentration, assuming homogenous mixing in the body. A large Vd reflects a drug that is highly

tissue bound, and consequently only a small proportion actually resides in the vascular compartment available for clearance by endogenous or extracorporeal routes. The overall response to critical illness includes increased capillary permeability, fluid shifts, and third space losses resulting in large extravascular, interstitial fluid accumulation , and these changes may increase the Vd of many drugs used in the intensive care setting. (P. Gosling et al, 1994).

Renal and hepatic impairment result in decreased drug clearance and increase the risk of drug accumulation and overdosing. Liver failure may increase the contribution of renal clearance and hence the contribution of RRT to total body clearance, making drug-dosing adjustments necessary during RRT for drugs that in healthy individuals mainly undergo hepatic degradation. Similarly, renal failure may alter extrarenal clearance of drugs that are normally excreted by the kidney, and the critically ill patient with severe ARF may have a residual clearance that is often remarkable. (U.F. Kroh et al, 1996).

- RRT drug clearance and dosing adjustments:

The critically ill patient with renal failure is at risk for drug accumulation and overdose, but also for underdosing that may be life-threatening, such as in the case of insufficient antibiotic treatment. An increased Vd and greater than expected elimination either from RRT or from residual endogenous clearance are probably the main reasons for underdosing, whereas underestimated organ dysfunction is the main cause of overdosing. When making drug-dosing adjustments during RRT our goal is to compensate for the drug clearance of RRT (CL_{RRT}). This clearance can be measured as:

$$CL_{RRT}=Q_E C_E/C_P$$

where C_E and C_P are drug concentrations in effluent fluid and plasma, respectively. Q_E is the effluent flow rate, which is the sum of ultrafiltration flow rate (Q_{UF}) and dialysate flow rate (Q_D). However, apart from some exceptions and individual variations, Golper and Marx found that, for a large series of drugs frequently used in critically ill patients, the filtered fraction during CRRT correlated well with the unbound fraction in healthy subjects. (T.A. Golper and M.A. Marx, 1998).

-Critical illness and pharmacological principles for antibiotic prescription:
The goal of antibiotic treatment is to achieve effective active drug concentrations that result in clinical cure while avoiding or minimalizing drug-associated toxicity.

1. Aminogycosides

The bactericidal effect of the aminoglycosides is concentration-dependent. A high peak concentration provides better and faster bacterial killing and is associated with better clinical response. Aminoglycosides exhibit a significant post-antibiotic effect (PAE) , which refers to continued suppression of bacterial growth despite no measurable concentration of the antibiotic.
Elimination is dependent on glomerular filtration, and plasma half-life increases in accordance with the reduction in GFR. Dose adjustments have to be performed during ARF, and increasing the dosing interval according to the reduction in renal function without reducing each single dose seems to be a reasonable approach, and is supported by clinical investigations.RRT

has a significant impact on aminoglycoside elimination. (J.W. Mouton et al, 2000).

2. β-Lactam antibiotics

Bacterial killing by β-lactam antibiotics is slow and continuous, and is almost entirely related to the time the drug levels in tissue and plasma exceed the minimum inhibitory concentration (MIC). Except for the carbapenems, which exibit some, other β-lactam antibiotics lack any clinically relevant PAE and bacterial growth resumes as soon as the concentration of the antibiotic is too low. (J.D. Turnidge,1998). The best correlate for therapeutic efficacy is the percentage of the dosing interval for which drug concentrations remain above MIC, whereas the development of resistance seems to be related to the percentage of the dosing interval with levels below MIC. Maximal killing effects occur at levels four to five times MIC with no additional effect of higher levels (A.S. Benko et al, 1996).
The situation may become a little bit more complex for drugs containing two compounds such as imipenem and cilastatin. Renal failure results in more accumulation of cilastatin than imipenem and this dysequilibrium is attenuated by RRT. Meropenem is therefore the preferred carbapenem in RRT patients.
Compared to aminoglycosides, β-lactam antibiotics have much less toxicity and when using estimated RRT clearances to perform drug-dosing adjustments, doses can safely be increased 30% above estimates to secure adequate dosing.(U.F. Kroh, 1995).

3. Fluoroquinolones

Bacterial killing by fluoroquinolones is both concentration- and time-dependent , and these antibiotics exhibit PAE. The Vd for ciprofloxacin does not significantly change in the critically ill. Renal elimination normally amounts to 60% of total body clearance , and ciprofloxacin dosing has to be reduced in ARF. Both individual dose reductions and/or extension of the dosing interval seem to be reasonable approaches. RRT significantly increases ciprofloxacin elimination depending on the RRT mode used, and elimination is less with standard low-flux IHD than with CRRT. (S.C. Wallis et al, 2001). Levofloxacin elimination is nearly completely dependent on intact renal routes of excretion, and dosage has to be substantially reduced in renal failure.

4. Vancomycin

Vancomycin does not exhibit concentration-dependent killing, and exceeding the MIC more than four- to fivefold does not result in increased activity. Recent data suggest that optimal vancomycin therapy may be achieved by sustained therapeutic concentrations without high peaks, and vancomycin therapy given as continuous infusion demonstrates comparable efficacy and tolerance. (M. Wysocki et al, 2001). Vancomycin is poorly protein-bound and distributes into the extravascular space. The Vd is increased in the critically ill, and higher doses are required to achieve appropriate concentrations in these patients. Vancomycin is almost entirely eliminated by glomerular filtration, and in ARF the dose has to be reduced in proportion to the reduction in GFR.(J.H. Reeves and W.W. Butt, 1995). A recent study showed that High efficiency haemodialysis with cellulose triacetate dialyzer removes significant amount of vancomycin, and

recommended a loading dose of 1 g, and 500 mg after every subsequent high efficiency haemodialysis. (Klansuwan N et al, 2006).

5. Fluconazole

Fluconazole is a well-tolerated drug for treatment of serious infections caused by Candida species Protein binding of fluconazole is approximately 12%. Protein binding in the critically ill with ARF is unknown. The kidney eliminates 80% of the drug and this elimination is proportional to GFR. The low molecular weight (306 Da) and low protein binding of fluconazole indicate high extracorporeal diffusive and convective clearances. The higher extracorporeal compared with renal clearances are related to an important tubular re-absorption of fluconazole in the normal kidney. (E. Muhl et al, 2000). Serious fungal infections have high mortality, and underdosing increases the risk of therapeutic failure. Fluconazole seems to have a wide therapeutic range, and doses should be increased above standard during CRRT. A recent study showed that at least the fluconazole concentrations desirable on the basis of in vitro susceptibility testing can be reached in critically ill patients on CVVHF in an ICU setting. However, in these patients, 800 mg fluconazole/day are necessary to achieve fungicidal drug concentrations. (Raoul Bergner et al,2006).

IV} ACID- BASE STATUS AND ELECTROLYTES DISTURBANCES

*Acid- base status:

The typical acid–base picture of ARF of critical illness is one of mild acidemia due to moderate metabolic acidosis. Such acidosis is the result of the net balance of acidifying forces due to the accumulation of unmeasured anions, phosphate, and the attenuating effect of metabolic alkalosis secondary to hypoalbuminemia. In ARF patients, the compensatory responses are inadequate both at a respiratory level and at a metabolic level. (Jens Rocktaeschel,2003).

The major adverse consequences of severe acidemia (blood pH, <7.20) include decreased cardiac output, decreased arterial blood pressure, decreased hepatic and renal blood flow.Reentrant arrhythmias and a reduction in the threshold for ventricular fibrillation can occur, while the defibrillation threshold remains unaltered.

Acidemia triggers a sympathetic discharge but also progressively attenuates the effects of catecholamines on the heart and the vasculature; thus, at pH values below 7.20, the direct effects of acidemia become dominant. Although metabolic demands may be augmented by the associated sympathetic surge, acidemia decreases the uptake of glucose in the tissues by inducing insulin resistance and inhibits anaerobic glycolysis. This effect can have grave consequences during hypoxia, since glycolysis becomes the main source of energy for the organism..Acidemia causes potassium to leave the cells, resulting in hyperkalemia. Increased net protein breakdown and development of a catabolic state also occur in patients with acidosis. Brain metabolism and the regulation of its volume are impaired by severe acidemia, resulting in progressive obtundation and coma.

Alkali Therapy

Because the administration of sodium bicarbonate entails certain risks, it should be given judiciously in amounts that will return blood pH to a safer level of about 7.20. To accomplish this goal, plasma bicarbonate must be increased to 8 to 10 mmol per liter.

There is no simple prescription for reaching this target, since several ongoing, and at times competing, processes can affect the acid–base status (e.g., increased net lactic acid production, vomiting, or renal failure), and the apparent space of distribution of infused bicarbonate is variable. (The apparent space of distribution is calculated by dividing the administered alkali load, in millimoles per kilogram of body weight, by the observed change in the plasma bicarbonate concentration, in millimoles per liter, and multiplying the ratio by 100.)

Whereas patients with very low plasma bicarbonate concentrations can have a bicarbonate space of 100 percent of body weight or greater, others with less severe metabolic acidosis have a space closer to 50 percent of body weight, the normal value. Being mindful of overtreatment, we recommend that, as the starting point, bicarbonate space be taken to be 50 percent of body weight. Thus, to raise the plasma bicarbonate concentration from 4 to 8 mmol per liter in a 70-kg patient, one should administer 4 x 70 x 0.5, or 140, mmol of sodium bicarbonate.

Except in cases of extreme acidemia, sodium bicarbonate should be dispensed as an infusion (over a period of several minutes to a few hours) rather than a bolus. Follow-up monitoring of the patient's acid–base status will determine additional alkali requirements. About 30 minutes must elapse

after the infusion of bicarbonate is completed before its clinical effect can be judged.

Risks of Sodium Bicarbonate Therapy

The administration of sizable amounts of sodium bicarbonate is associated with certain risksas hypernatremia and hyperosmolality. This complication can be avoided by adding two 50-ml ampules of sodium bicarbonate (each containing 50 mmol of sodium bicarbonate) to 1 liter of 0.25 *N* sodium chloride or three ampules to 1 liter of 5 percent dextrose in water, thereby rendering these solutions nearly isotonic. Alkali therapy can lead to extracellular-fluid volume overload, especially in patients with congestive heart failure or renal failure. Administration of loop diuretics may prevent or treat this complication. If adequate diuresis cannot be established, hemofiltration or dialysis may be required. (Faber MD et al, 1994). Buffering of protons by bicarbonate releases carbon dioxide ($HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$) and can raise the prevailing partial pressure of carbon dioxide in body fluids. This effect can be consequential in patients with limited ventilatory reserve, those in advanced circulatory failure, or those undergoing cardiopulmonary resuscitation.

<u>*Electrolytes disturbances:</u>

In acute renal failure, the kidneys are unable to perform their normal excretory function leading to accumulation of renally-eliminated electrolytes.

In the case of sodium, this may not be reflected by hypernatremia (*i.e.*, elevated concentrations in the blood). In fact, hyponatremia is a relatively common complication of acute renal failure due to a dilution effect by retained water. Although patients are usually asymptomatic, seizures and encephalopathy may result with rapid decreases in plasma sodium concentrations(Fraser and Arieff, 1997). The method and rate of correction of the hyponatremia is dependent on the cause and duration of the lowered sodium concentrations. Since free water intake in excess of clearance is the usual cause of hyponatremia, the major intervention should be fluid restriction with or without concomitant dialysis. In cases of overt neurological complications such as seizures, administration of sodium-containing solutions such as isotonic or hypertonic saline solutions may also be required. Rapid correction (minutes to hours) of plasma sodium concentrations has been associated with a brain disorder called myelinolysis that may result in death, but this problem has usually occurred in patients with chronic hyponatremia(Laureno and Karp,1997).

Hyperkalemia in acute renal failure is usually caused by decreased elimination by the kidneys. The normal laboratory range for plasma potassium concentrations is approximately 3.5-5.5 mMol/L and concentrations greater than 6 mMol/L often require intervention due to potentially life-threatening arrhythmias. When interpreting an elevated potassium concentration in the blood, it is important to exclude potential causes of pseudohyperkalemia such as hemolysis, megarokaryocytosis, and fragile white blood cells as seen in some forms of leukemia.
The therapy of hyperkalemia should begin by stopping any external sources of potassium. Dialysis is a reliable method of removing potassium from the

blood in patients who are on dialysis because of acute renal failure. Several medications
are available that may be used until dialysis can be implemented,
or in patients who are not expected to require dialysis.These medications include IV calcium administration for patients with electrocardiographic changes consistent with hyperkalemia, and medications that temporarily reduce extracellular potassium concentrations by shifting the potassium to intracellular stores (*e.g.*, glucose/insulin, sodium bicarbonate, beta-adrenergic agents such as albuterol). In addition to dialysis, potassium-binding resins are available that remove potassium from the body. Therapies such as diuretics and saline infusions that are used to lower potassium concentrations in patients with normal renal function are usually not effective or entail too many risks in patients with acute renal failure.

Hyperphosphatemia is an extremely common and predictable occurrence in patients with acute renal failure due to decrease elimination. The elevation may be particularly high in patients with aggravating causes such as rhabdomyolysis . While mild hyperphosphatemia is of little consequence, increases in the calcium/phosphorus product (serum total calcium times serum phosphate concentrations, both in mg/dL) above 60-70 may result in deposition of the insoluble calcium phosphate salt into various tissues including the heart where it may result in conduction abnormalities or the lungs where it may cause respiratory insufficiency and death. Unfortunately, dialysis is not always effective in lowering the phosphate concentrations and phosphate binders such as aluminum hydroxide or calcium salts (*e.g.*, calcium carbonate) are usually needed.

The changes seen in serum calcium and magnesium concentrations are usually less pronounced then those of phosphate. The changes involved in calcium homeostasis in renal failure are complex, but the end result is usually asymptomatic hypocalcemia. While maintenance amounts of calcium are indicated in the diet or by IV solutions, therapeutic doses of calcium are usually reserved for symptomatic hypocalcemia (*e.g.*, tetany) since calcium may cause adverse cardiac effects.

With regards to magnesium, mild hypermagnesemia without symptoms is the usual pattern in acute renal failure, unless exogenous intake of this magnesium is excessive due to diet or magnesium-containing drugs.

V} DIURETICS

Experimentally, the effectiveness of diuretics in the prevention of ischemic ATN appears to be related to timing.(Stein JH, 1992). Once the time limit has passed, the intervention will be ineffective. This is because the unifying

principle is cytoprotection of the renal tubular cells which, if lethally injured, may only be `rescued' for a short time. The injury to the renal tubular cells has been attributed to four major factors: renal vasoconstriction, reduction of glomerular capillary permeability, tubular obstruction and transepithelial back-leak of filtrate . In theory, loop diuretics may be useful in combating each of these factors. These agents decrease the metabolic demand of the renal tubular cell, reducing its oxygen requirement and hence increasing its resistance to ischemia and perhaps to other toxic insults as well. A greater urine flow may also reduce the incidence of tubular obstruction and the higher hydraulic pressures may reduce the back-leak of filtrate (Shilliday I and Alison,1994).

In practical terms these data from animal studies offer little to guide practice in the care of patients, though they provide great insight into the various mechanisms of ATN. This is because it is not usually possible to anticipate the renal injury and act within the time required to have an effect. However, there are notable exceptions, such as aortic cross-clamping in aneurysm repair. The use of loop diuretics has become routine for this indication in many institutions. Nonetheless there appears to be no evidence in support of this approach.(J. A. Kellum, 1997)**.**

Additionally, there are some situations in which the renal injury is subacute or mild and sustained. Such is often the case in conditions such as rhabdomyolysis, drug-induced renal injury, hepatorenal syndrome, and ARF associated with cardiopulmonary bypass circulation in cardiac surgery (especially in patients with pre-operative renal impairment (Mangos GJ et al, 1995). In these conditions it is often possible to act in an attempt to prevent or reduce the renal injury as it evolves. Although the specifics of renal injury

vary somewhat between these forms of `subacute' renal failure, all are exacerbated by hypovolemia and, therefore, any consideration of the use of loop diuretics must include a provision for adequate volume replacement. This requirement makes it difficult to separate the effects of diuretics from the effects of the increased fluid given to prevent diuretic-induced hypovolemia.

Dramatic evidence exists from a case-controlled study to support the use of (`early and aggressive') hydration along with forced alkaline/osmotic diuresis (mannitol) for the treatment of ATN secondary to traumatic rhabdomyolysis . Delayed treatment in a series of seven patients was associated with a 100% incidence of ARF, while in another seven patients prompt treatment was 100% successful in avoiding this complication even though renal injury had already begun. Unlike loop diuretics, mannitol functions as an intravascular volume expander, at least initially. None of these patients received loop diuretics and, indeed, the authors have argued that hydration alone may have been sufficient to produce many of salutary effects of the osmotic diuresis .(Better OS and Stein JH, 1990).

Once ATN is established there are no therapies that have been proven to reverse it. The most a clinician can do is to manage the complications of ARF and limit further renal insult so as to assure the best chance of renal recovery. Diuretics can be both useful and harmful in this regard. The harm comes from reducing the circulating volume too much and adding a prerenal insult on top of the established ATN. The recovering kidney may be even more susceptible to this `second hit' and may be profoundly injured by a relatively mild decrease in perfusion, especially with the pre-existing renal disease. Clinicians may inadvertently produce this injury if diuretics are

dosed according to the amount of peripheral edema or body weight without consideration of intravascular volume. This may be of particular concern in many critically ill patients with hypoalbuminemia. These patients may have coexisting total body volume overload and intravascular volume depletion.

However, if volume status is monitored closely, diuretics can be useful in the conversion to nonoliguria. This goal may be reasonable in certain situations and patients are clearly easier to manage without volume overload and electrolyte imbalances. In this regard, loop diuretics appear to be more effective and less toxic when given as a continuous infusion rather than as a bolus. It is also important to note that large bolus doses of loop diuretics may cause transient renal vasoconstriction. Despite these potentially useful effects of diuretic therapy, there is no evidence that converting oliguria into nonoliguria is effective in reducing mortality or the need for dialysis. (Rudy DW et al, 1991).

VI} VOLUME REPLACEMENT

Acute tubular necrosis, primarily induced by ischemia and nephrotoxic substances (drugs), is the predominate cause of ARF. The risk factors for ARF are volume depletion, sepsis, septic shock, hemorrhagic shock, contrast

exposure, aminoglycoside therapy, age, and previous chronic renal disease or heart failure. The predominance of prerenal risk factors in the ICU setting highlights the importance of maintaining adequate renal perfusion for renal protection . Therefore, adequate volume replacement plays a crucial role in the treatment of critically ill patients with acute renal dysfunction or ARF.

Crystalloids

Isotonic crystalloid solutions (Ringer's lactate solution and 0.9% saline solution) are very commonly used to compensate for general losses of water and electrolytes and are usually the first choice for fluid replacement. Isotonic crystalloid solutions do not contain oncotically active macromolecules. Therefore, their effect on plasma volume expansion of approximately 200 ml for every 1000 ml administered, with an intravascular half-life of 20 to 30 min, is very limited (Kreimeier U& Peter K,1998). To substitute for blood loss, crystalloid solutions must be infused in four- to fivefold greater amounts, compared with colloid solutions, to exert the same volume effects. In the dynamic processes of SIRS or sepsis, with increased transmembrane fluid flux and low plasma colloidal on cotic pressure (COP), fluid shift from the intravascular compartment to the interstitial compartment is promoted if crystalloids are exclusively infused. In addition to their ineffectiveness in restoring sufficient tissue perfusion, this phenomenon increases the risk for tissue edema, particularly in the lung and gut mucosa . Crystalloids have no specific nephrotoxic effects and are the basic fluids to fulfill the requirements for water and electrolytes in critically ill patients. In cases of major intravascular hypovolemia or severe sepsis, the exclusive administration of crystalloids is not appropriate because they are not able to sufficiently restore microcirculation, which is the major pathogenic factor in

the development of multiple organ failure. Therefore, crystalloids should be used in conjunction with colloids to restore intravascular volume. (Kreimeier U& Peter K,1998).

Colloids

General Considerations

There is a controversy regarding the use of colloid or crystalloid solutions for volume resuscitation in critically ill patients . Because of their content of macromolecules, colloids are retained within the intravascular space to a much greater extent, resulting in a greater intravascular volume effect. The volume effect exerted by colloids and their volume-supporting capacity with time depend on their concentration, mol wt, molecular structure, COP, metabolism, and elimination rate.(Schierhout G &Roberts I, 1998).

Albumin

The administration of albumin, as the "natural colloid," has been the standard method for the treatment of hypovolemia in critically ill patients in past decades. However, albumin administration is expensive and offers no apparent advantage, with respect to outcomes, for patients with hypovolemia or hypoalbuminemia .Albumin, which is usually used in 5% or 20% solutions, is thought to increase COP, which prevents extravasation of fluid from the intravascular space. In contrast, in situations with increased capillary permeability, the shift of albumin into the interstitial space is enhanced, and albumin thus aggravates interstitial edema formation. With respect to the effect of albumin administration on patient outcomes, no evidence currently exists to support the use of albumin in patients in the ICU. (Boldt J, 2000).

Gelatin

Three different gelatin preparations (polypeptides from bovine raw material) are currently available, with a relatively low average mol wt of approximately 35,000. They contain a high proportion of low-mol wt components that are poorly retained in the intravascular space. Therefore, their effect on volume expansion is limited, and the duration of the effect does not exceed 2 h . Therefore, a colloid fluid regimen restricted to gelatin alone may be of limited value for patients with severe hypovolemia (Kreimeier U& Peter K,1998).

Studies demonstrated that gelatin compromises platelet function and the activity of the plasma von Willebrand's factor and interferes with the polymerization of fibrin monomers, thus reducing the quality of clot formation (Mardel SN et al, 1998).

Because of their capacity for histamine release, gelatin solutions are associated with a higher incidence of anaphylactoid reactions, compared with hydroxyethyl starch (HES) solutions .

Dextran

Dextran, a single-chain polysaccharide of bacterial origin, is still commonly used for plasma expansion in many countries. Dextran solutions have sufficient initial plasma volume expansion effects, as well as prolonged intravascular volume effects because of a high water-binding capacity (approximately 20 to 25 ml/g dextran). However, these solutions have been associated with serious side effects, such as coagulation abnormalities (dose, >1.5 g/kg per d) (Baron JF, 2000), anaphylactic/anaphylactoid reactions and the onset of oliguric or anuric renal failure . However, dextrans have well documented effects in the reduction of endothelial cell-blood cell

interactions, which are important for adequate capillary perfusion and may be of value in preventing excessive activation of inflammatory cascade systems (Haljamae H &Lindgren S, 2000). When the data on dextran solutions are summarized, the potential advantages are completely outweighed by the serious side effects. Therefore, the routine use of dextran solutions is no longer warranted for intravascular volume expansion in critically ill patients.

Hydroxyethyl Starches

The successful use of HES 200/0.5 for intravascular volume expansion has been demonstrated in several settings, such as isovolemic hemodilution, perioperative volume replacement, cardiac surgery, trauma, and sepsis Furthermore, experimental studies showed beneficial effects of HES solutions on inflammatory processes such as endothelial cell activation and monocyte chemotaxis or chemotactic cytokine release (Collis RE et al, 1994). Although HES seems to be very effective in correcting hypovolemia, potential side effects must also be stressed, such as coagulation disorders. Reduction of factor VIII and von Willebrand's factor activity, impairment of platelet function, or increases in the activated partial thromboplastin time were observed after repeated treatment with HES preparations. The risk of anaphylactic reactions, and severe anaphylactic reactions (grade III/IV) in particular, seems to be the lowest among all synthetic colloids. Lethal anaphylaxis has never been observed (Laxenaire MC et al, 1994).

Colloids and ARF

After the first description of ARF occurring after the infusion of dextran, additional case reports of ARF occurring after gelatin, 10% HES, 20%

mannitol, or concentrated (20%) albumin solution administration were published, as summarized by Baron . However, most cases of dextran-induced renal failure were associated with several other patient risk factors, such as age, arteriosclerosis, preexisting renal insufficiency, colloid use for nonsurgical reasons, and dehydration before colloid use. Three hypotheses are presented to explain the mechanisms of ARF associated with colloid use, i.e., accumulation of a low-mol wt fraction in the renal tubules, induction of osmotic nephrosis-like lesions (vacuolization of the proximal tubular cells), and hyperoncotic renal failure (Baron JF, 2000).

For patients with acute renal dysfunction, careful daily monitoring of renal function is required if colloids are used. The risk of hyperoncotic renal failure can be further reduced by the administration of adequate amounts of crystalloid solutions. The measurement of COP may facilitate safe fluid management in these cases. Of all colloids, gelatin and HES solutions with low in vivo mol wt should be preferred in these cases. On the basis of the currently very limited data regarding the specific situation of kidney transplantation, colloid solutions should be administrated in a restricted manner to organ donors and kidney recipients. (Maximilian J.R et al, 2001).

RENAL REPLACEMENT THERAPY

INTRODUCTION

RRT is a therapy which assumes all or part of the blood purification and water and electrolyte balance functions of the kidney. This term therefore incorporates all forms of 'artificial kidney' treatments which are divided into peritoneal and haemodialysis modes based on the location of the membrane that is used to simulate the natural glomerulotubular system.

The most basic aims of RRT are the optimization of fluid and electrolyte balance. There are two key principles that must be understood in order to differentiate between the increasing numbers of techniques that are on offer. These are **DIALYSIS**, which should strictly be used when referring to *diffusion*, and **ULTRAFILTRATION**, which is *convection. Diffusion* is the movement of solutes along an electrochemical gradient, from a compartment in which they are in a high concentration to one in which they are in a lower concentration. During these types of dialysis, an electrolyte solution runs in a counter-current direction to the patient's blood flowing on the opposite side of a semi-permeable filter. Small molecules in the blood, such as urea, move along the concentration gradient into the dialysate fluid. Larger molecules are poorly removed by this process. The rate of diffusion of a given solute depends on its charge and molecular weight (diffusion co-efficient), the surface area, membrane porosity, thickness and amount of protein binding, the blood flow rate and dialysate flow rate (which generates the concentration gradient) and the temperature of the system.

Conversely with **ULTRAFILTRATION**, solute is carried in solution across a semi-permeable membrane in response to a transmembrane driving pressure (also called solvent drag). This is a more effective method for removal of fluid and middle-sized molecules. The rate of ultrafiltration more simply depends on the hydraulic permeability co-efficient, transmembrane

pressure and the surface area of the membrane. (R. Bellomo and C. Ronco,2005).

Hemofiltration has many superficial similarities to hemodialysis. In both techniques, access to the circulation is required and blood passes through an extracorporeal circuit that includes either a dialyzer or a hemofilter. However, the mechanisms by which the composition of the blood is modified differ markedly. During dialysis, blood flows along one side of a semipermeable membrane as a solution of crystalloids is pumped along the other side of the membrane against the direction of the blood flow. Small molecules diffuse across the membrane from regions of greater concentration to regions of lesser concentration, and the composition of the dialysis fluid is designed to produce as near normalization of the plasma as possible. Thus, the sodium concentration of the dialysis fluid is physiologic, but the potassium concentration is lower than that of normal plasma in order to establish a gradient from plasma to the fluid that promotes the removal of potassium ions from the patient's blood. The concentrations of substances that are to be removed completely (such as urea, creatinine, and phosphate) are zero in the dialysis fluid. The removal of salt and water is achieved by the creation of a transmembrane pressure gradient (with lower pressure in the dialysis-fluid compartment). According to the laws of diffusion, the larger the molecule, the slower will be its rate of transfer across the membrane. A small molecule, such as urea (60 daltons), is cleared efficiently, and a larger molecule, such as creatinine (113 daltons), less well. Phosphate ions have such low rates of clearance that hyperphosphatemia is always a problem for patients on intermittent dialysis. Dialysis has no similarity to the normal physiologic processes of the kidney, but it is

effective, and many patients have lived for decades entirely dependent on intermittent hemodialysis.

Hemofiltration works in a different manner.In the simplest form of the procedure, blood under pressure passes down one side of a highly permeable membrane allowing both water and substances up to a molecular weight of about 20,000 to pass across the membrane by convective flow, as in glomerular filtration. During hemofiltration, in contrast to hemodialysis, urea, creatinine, and phosphate are cleared at similar rates, and profound hypophosphatemia may develop unless the patient's phosphate intake is supplemented. Larger molecules such as heparin, insulin, myoglobin, and vancomycin, which are cleared from the blood in only negligible quantities in a dialyzer, are cleared efficiently by the hemofilter.

In the kidney, the glomerular filtrate is selectively reabsorbed by the renal tubules, a process too complex to be artificially reproduced with current technology. Instead, during hemofiltration, the filtrate is discarded and the patient receives infusions (usually through the distal part of the hemofiltration circuit) of a solution in which the major crystalloid components of the plasma are at physiologic. If there is no need for the removal of fluid from the patient, the rate at which the replacement fluid is administered is matched exactly with the rate of production of hemofiltrate. Usually, however, there is a need to remove fluid, because of either fluid overload or the clinical need to administer fluids to a patient with oliguria. A net loss of extracellular fluid is achieved by replacing less fluid through infusion than is removed by hemofiltration.

1. Indications for RRT in acute renal failure

Patients with ARF differ from patients with chronic renal failure. Acute illness creates physiological fragility with severe homeostatic derangement that is exacerbated when associated with multiple organ dysfunction. Standard indications to initiate RRT are therefore inappropriate. Treatment considerations and targets should also be different. There is no consensus on exact indications for the initiation of RRT in ARF but general criteria have been proposed(R. Bellomo and C. Ronco,1998), this includes :-anuria or oliguria with urine output<200ml/12 hours,
hyperkalaemia, severe acideamia with PH>7.1,
azotemia with urea> 30 mmol/L, clinically significant organ oedema,
uraemic encephalopathy, uraemic pericarditis,
uraemic neuropathy or myopathy,
severe dysnatraemia with Na> 160 or < 115 mmol/L,
hyperthermia and drug overdose with a dialyzable product.
The timing of implementation of RRT may have an effect on outcome. A retrospective study showed an improved survival with earlier start of RRT in posttraumatic ARF.(L.G. Gettings, 1999). Despite the lack of prospective randomized trials, a trend to commence therapy earlier is emerging. Once a decision to initiate RRT is made, the next step is choosing the most favourable option for the individual clinical situation.

2- Optimal RRT in the critically ill

All types of RRTs have a role in the care of ICU patients at different stages of their admission and will therefore be practically evaluated.

-Peritoneal dialysis:

PD is the least useful, and probably least used RRT in the ICU population. Solute and volume clearance may be inefficient in haemodynamically unstable patients with dubious intestinal blood flow. A burden is placed on the respiratory system by a reduction in diaphragmatic excursion associated with the rise in intraabdominal volume caused by the dialysate. PD is contraindicated in individuals with intraabdominal pathologies and is associated with a significant risk of peritonitis. The risk of peritoneal leak is increased in these situations, where the peritoneal dialysate can leak into the abdominal wall or chest cavity if co-existing trauma is present. (P. O'Reilly and A. Tolwani, 2005).

-Intermittent haemodialysis:

IHD may be poorly tolerated by haemodynamically unstable patients due to the requirement of high blood flow rates. The significant advantages compared to CRRT, however, are superior solute clearance, more rapid removal of dialysable toxins, shorter sessions and less episodes of filter clotting. Over-rapid solute clearance may cause cerebral oedema and rapid correction of hyponatraemia may induce central pontine demyelinosis. (N. Lameire et al, 2005).

-Slow continuous therapies:

Each of these procedures involves slow, continuous passage of blood, taken from either an arterial or venous source, through a filter.

1- Continuous hemodialysis (CHD): In CHD, dialysis solution is passed through the dialysate compartment of the filter continuously and at a slow rate. In CHD, diffusion is the primary method of solute removal. The amount of fluid that must be ultrafiltered across the membrane is low (3-6L/day).

2-Continuous hemofiltration (CH): In CH, dialysis solution is not used. Instead, a large volume (about 25-50 L/day) of replacement fluid is infused into either the inflow or the outflow blood line (predilution or post dilution mode, respectively). With CH the volume of fluid that needs to be ultrafiltered across the membrane (on the order of 30-55L/day, representing replacement fluid plus removal of excess fluid) is much higher than with CHD, where the ultrafiltered fluid volume is on the order of 3-6 L/day.

3- Continuous hemodiafiltration (CHDF): This is simply a combination of CHD and CH. Dialysis solution is used, and a replacement fluid is also infused into either the in flow or the outflow blood line. The daily volume of fluid that is ultrafiltered across the membrane is high, but not as highas with CH, as the volume of replacement fluid used in CHDF (typically about 20 L/day) is lower than CH.

* In the previously mentioned therapies a venovenous blood access (i.e.CVV-D, CVV-H and CVV-HDF) or an arteriovenous blood access (i.e. CAV-D, CAV-H and CAV-HDF) can be used.

Use of a venovenous access avoids risks associated with arterial cannulation such as distal arterio-occlusive , atheroembolic complications , bleeding and continuous bed rest. Use of a roller pump with venovenous access assures a relatively rapid, constant blood flow rate. Pumpedblood flow may enhance dialyzer performance and may reduce the likelihood of clotting, as clotting may occur with an AV access due to temporary slowing of blood flow in the extra-corporeal circuit.

The disadvantages of a pumped venovenous extracorporeal blood circuit relate to the possibility of inadvertent disconnection of the lines, leading to hemorrhage or air embolism with continued pump operation. Also, lines are longer with pumped venovenous systems, thus predisposing to more line clotting. And risks included are exit site and catheter induced bacteremia and central vein thrombosis or stenosis.

4-Slow continuous ultrafiltration (SCUF): Neither diaysis solution nor replacement fluid is used. Daily ultrafitered fluid volume across the membrane is low (3-6 L/day) similar to CHD.

*Differences among CHD, CHDF and CH in clearance of small and large molecular weight solutes:

-Urea clearance with CHD and CHDF: In CHD and CHDF, once the blood flow rate is 100-150 mL/min or more, clearance of urea and other small molecules is determined primarily by the dialysis solution flow rate. As outflow dialysate is 90% or more saturated with urea (except when filters start to clot or when very high dialysate flow rates are used), urea clearance can be estimated simply by the total daily filter outflow volume (which includes dialysis solution used, replacement fluid infused plus any excess fluid removed). The standard dialysis solution inflow rate is now about 25-50 L/day. Thus taking into account an additional 5 L/day for excess fluid removal, it is easy to achieve urea clearance with CHD on the order of 30-55 L/day (20-38 mL/minute). With CHDF, the replacement fluid infused will add to the clearance as a comparable amount of fluid is removed by the filter. This is automatically taken into consideration if one starts the clearance computation from the total daily outflow volume.

- Urea clearance with continuous hemofiltration : CH is a purely convection based blood cleansing technique. As blood flows through the hemofilter, a transmembrane pressure gradient between the blood compartment and the ultrafiltrate compartment causes plasma water to be filtered across the highly permeable membrane. As the water crosses the membrane, it convects small and large molecules across the membrane and thus leads to their removal from the blood. The ultrfiltrate is replaced by a balanced electrolyte solution infused into either the inflow (predilution) or the outflow (postdilution) line of the hemofilter.

Typically about 25-50 L of replacement fluid is infused per day. The filter outflow or " drainage fluid" is nearly 100% saturated with urea when postdilution mode is used. At high replacement fluid infusion rates the blood flow rate needs to be increased from the usual 100-150 mL/min. to prevent excessive hemoconcentration (and resultant clotting) in the filter. When replacement fluid is given in predilution mode, the drainage fluid will not be 100% saturated, because levels of waste products in the blood entering the filter will be diluted.

- Solute removal with CH versus CHD: on a milliliter for milliliter basis (plasma ultrafitrate out versus dialysate out), CH is more efficient than CHD as a means for solute removal. With CHD, the dialysate is almost completely saturated with urea (at dialysate solution flow rates below 50 L/day and when clotting is not occurring). However, outflow dialysate is not completely saturated with higher molecular weight substances (because these moves slowly in solution and thus have a lower diffusive transfer across the dialyser membrane). With CH, the plasma ultrafiltrate is almost completely saturated with both low and middle molecular weight solutes (because the convective removal rates of small and larger molecular weight solutes are similar) and, hence, is more efficient if one considers larger molecules, such as inulin and vitamin B_{12} . However, the theoretical advantage of CH is not practically realizable, as it is very difficult to ultrafilter more than about 25L from patients using CH techniques. Fluid balance becomes very critical, as the replacement fluid infusion rate is high. Any slowing of blood flow rate will result in transient hemoconcentration in the hemofilter, with attendant risk of clotting. On the other hand, it is easy to perform CHD using dialysis

solution flow rates of 50 L per day.For this reason,in daily practice,plasma urea clearance with CH is often less than that with CHD. A recent study showed that analysis of clearance modification over time did not show significant modifications of urea, creatinine and beta$_2$microglobulin clearance in the first 48 hours during both treatments. In the CVVHD group, the only significant difference was found for beta2m between 72 hours and baseline clearance . (Ricci Z et al, 2006)

-Slow low efficiency dialysis (SLED):

This technique is very much like prolonged nocturnal IHD and uses the same machines and dialysates. The main difference is that longer sessions (usually 8–12 h) enable slower blood and dialysate flow rates. As with IHD this technique is excellent for solute clearance but fluid may also be removed. In the absence of evidence to support an outcome benefit of continuous techniques favouring ultrafiltration over dialysis, SLED has been favoured by some ICUs. It has the same advantages of CVVHDF with slower shifts in volume and electrolytes when compared to IHD. (Vincent D'Intini et al, 2004). A recent study concluded that SLED may be routinely performed without anticoagulation; it provides solute removal equivalent to CRRT at significantly lower cost. (Berbece AN and Richardson RM, 2006)

-Continuous high flux dialysis :

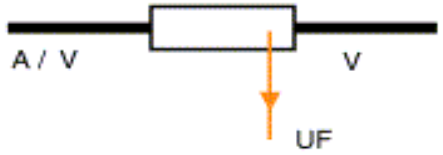
Uses a highly permeable dialysis membrane with blood and dialysate circulating in a counter-current fashion. The production of ultrafiltrate is controlled by pressure, and is reinfused by backfiltration in the blood system; therefore, a separate replacement fluid is not needed.

-Coupled plasmafiltration adsorption:

This is the use of activated charcoal sorbent cartridge placed in series with but downstream of the plasma filter. Filtered plasma is pumped through a charcoal cartridge such as Adsorba 150c and Adsrba 300c, respectively containing 150 and 300 gram of cellulose coated, haemoperfusion grade activated charcoal. Another type of carteidge made from resins has been shown to adsorb large quantities of tumour factor alpha and interlukin 1-beta. (HK Tan & G Hart, 2005).

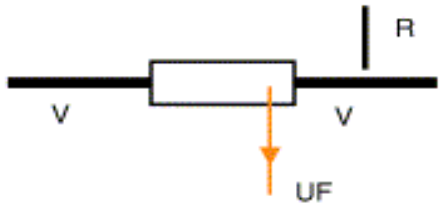
Ronco and co-workers has shown that CPFAmay be useful in the treatment of severe sepsis in critically ill patients. Another kind of sorbent cartridge is an immunosorbent column with mono or polyclonal antibody coated resin through which filtered plasma is pumprd. This set up is called coupled plasma filtration immunoadsorption. (Ronco C et al,2003).

SCUF - Slow continuous ultrafiltration (AV or VV)



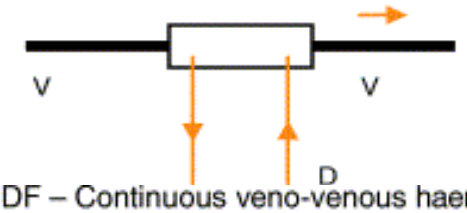
Technique used for fluid control only
Convective mechanism
Ultrafiltrate iso-osmotic to blood
Used in arteriovenous or venovenous mode
Qb = 50 – 100 ml/min
Ultrafiltration rate controlled

CVVH - Continuous veno-venous haemofiltration



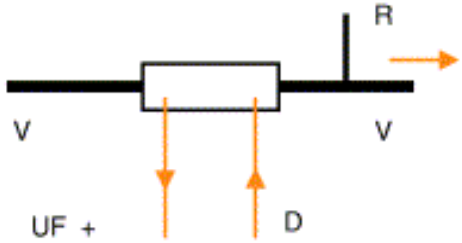
Convective blood purification through high permeability membrane
Ultrafiltration rate controlled
Ultrafiltrate replaced by replacement solution
Qf = 50 – 200 ml/min Qf = 8-25 ml/min
K = 12 – 36 L/24h
Can be used in arteriovenous mode

CVVHD - Continuous veno-venous haemodialysis



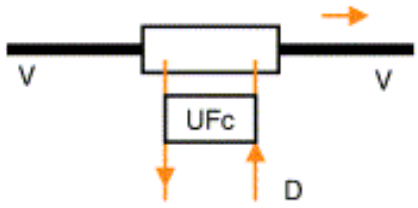
Diffufication blood purisive through low permeability dialyser
Dialysate solution in countercurrent flow
No replacement fluid used
Qb = 50 – 200 ml/min Qf = 2-4 ml/min
Qd = 10 – 20 ml/min K = 14 – 36 L/24h
Small molecule clearance only
Can be used in arteriovenous mode

CVVHDF – Continuous veno-venous haemodiafiltration



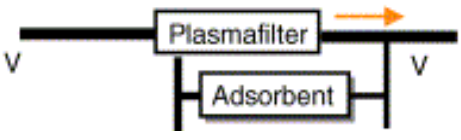
Diffusive and convective blood purification
Countercurrent dialysate flow
High permeability membrane utilized, thus small and middle molecules removed
Qb = 50 – 200 ml/min Qf = 8 - 12 ml/min
Qd = 10 – 20 ml/min K = 20 - 40 L/24h

CVVHFD – Continuous high flux dialysis



Diffusive and convective blood purification through a highly permeable membrane
Back diffusion occurs in membrane
Dialysate in countercurrent flow
Accessory pumps to control ultrafiltration
Replacement not required because fine regulation of filtration and backfiltration
Qb = 50 – 200 ml/min Qf = 2 - 8 ml/min
Qd = 50 – 200 ml/min K = 40 - 60 L/24h

CPFA – Continuous plasmafiltration adsorption



Ahighly permeable plasmafilter filters plasma allowing it to pass through a bed of adsorbent material (carbon or resins).
Fluid balance maintained.
Can be coupled with CVVH or CVVHD/F.
Qb = 50 – 200 ml/min Pf = 20 – 30 ml/min

**** Comparison between slow continuous therapies:***

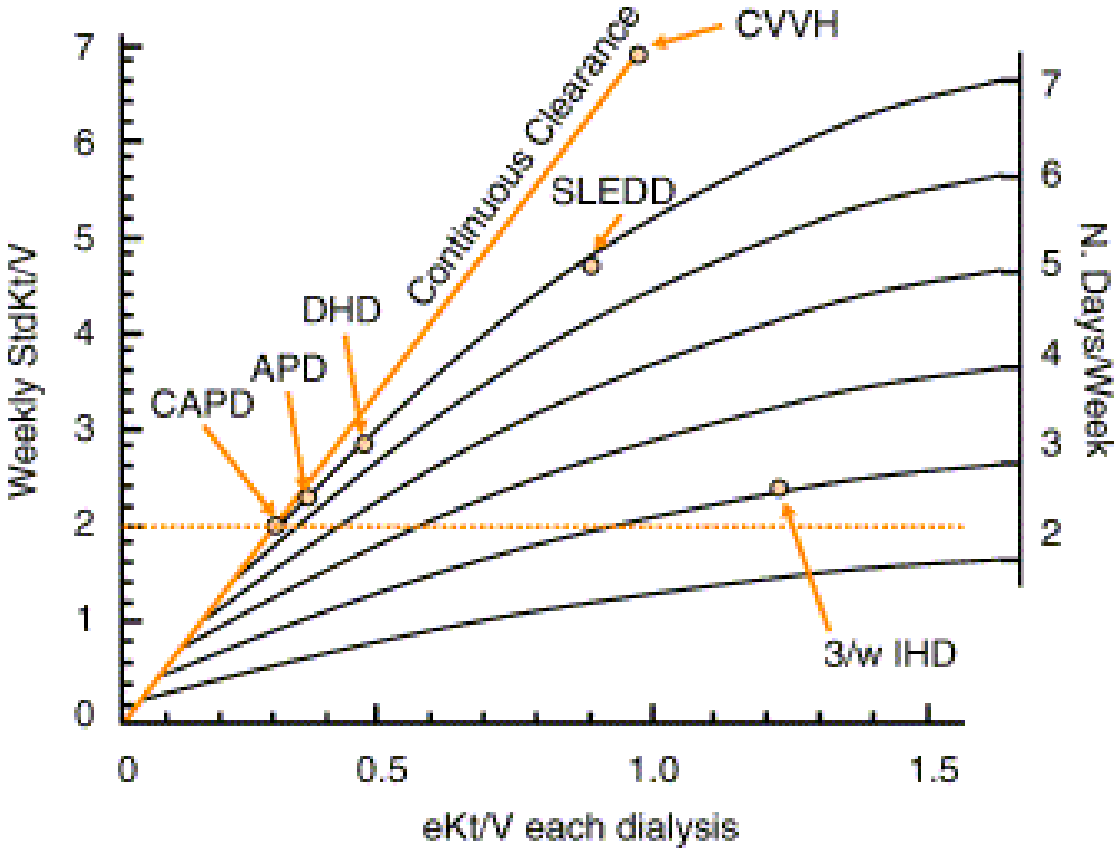
Technique	Diffusion	Convection	Replacement fluid	Dialysis fluid	Back filtration
Intermittent haemodialysis (IHD)	+++++	+	No	Yes	+
Daily haemodialysis (DHD)	+++++	+	No	Yes	+
Intermittent haemofiltration (HF)		+++++	Yes		
Intermittent haemodiafiltration (HDF)	+++	+++	Yes	Yes	+
Intermittent high flux dialysis (HFD)	++++	++	No	Yes	+++++
Sustained low efficiency dialysis (SLED)	+++	+	No	Yes	+
Continuous venovenous haemofiltration (CVVH)		+++++	Yes		
Continuous venovenous haemodialysis (CVVHD)	+++++	+	No	Yes	
Continuous venovenous haemodiafiltration (CVVHDF)	+++	+++	Yes	Yes	
Continuous venovenous high flux dialysis (CVVHFD)	++++	++	No	Yes	+++++
Intermittent ultrafiltration (UF)		+++++	No		
Slow continuous ultrafiltration (SCUF)		+++++	No		
Slow continuous ultrafiltration with dialysate (SCUF-D)	++	+++	No	Yes	
High volume haemofiltration (HVHF)		+++++	++++++		
Coupled plasmafiltration–adsorption (CPFA)[a]	–[a]	–[a]	–[a]	–[a]	–[a]

(Vincent D'Intini et al, 2004).

3- Treatment dose

RRT uses diffusive or convective solute transport across a semi-permeable membrane in order to remove toxins that are normally removed by the kidney. Whether IHD or CRRT is utilized, the patient must receive an adequate treatment dose. The dialytic dose has indeed been demonstrated to affect outcome in ARF. In the absence of a specific and measurable toxin for uraemia, urea and creatinine are still the surrogate markers used to measure the efficiency of RRT, despite failing evidence for a correlation between the levels of these solutes with outcome. Urea *Kt*/*V* (*K*, clearance, *t*, time and *V*, volume of distribution) is the fractional clearance related to the distribution volume of the solute. Unlike CRF patients, ARF patients are more catabolic and often have other failing organs. A standard dialysis dose in ARF would therefore be difficult to define. Recent studies suggest that more frequent dialysis is beneficial.(H. Schiffl et al, 2002).

Clearance or *Kt*/*V* are inadequate parameters to compare disparate therapies because they do not correlate with solute removal in intermittent techniques. Standardized *Kt*/*V* (*Kt*/*V* adjusted for frequency and duration of treatment) has been used for this purpose. The figure below demonstrates some values of standardized *Kt*/*V* reported with different dialytic techniques. CRRT provides superior efficiency over standard short IHD. Slow, low-efficiency daily dialysis (SLEDD), also provides exceptional clearances compared to standard methods. In continuous treatment, evidence has emerged that a minimum clearance of 35 ml/hour/kg of body weight should be delivered in acutely ill patients. This provides a level of efficiency by far superior to any previous standard therapy.(C. Ronco et al, 2000).



4- Membranes

In the extracorporeal circuit of RRT, membranes represent the largest artificial surface exposed to blood. Artificial kidney membranes have the potential to activate inflammatory cascades and affect cell function (bio-incompatibility).The selection of a membrane has to take into account the indication for RRT (small, middle or large solute removal) and the biocompatibility issue. Large-pore or high-flux membranes can remove larger molecules up to 30 000 Da, including drugs such as vancomycin and inflammatory mediators such as TNF. There are insufficient data to support the choice of a specific membrane in ARF patients.(S. Subramanian et al, 2002).

High-volume haemofiltration and general CRRT treatments mostly use synthetic membranes with larger solute removal (high flux). IHD and SLEDD treatments often utilize larger surface area filters to maximize small solute clearance. Although the role of special sorbent cartridges and membrane adsorption in eliminating a broader range of accumulated renal toxins is still under investigation, this approach seems to provide enhanced efficiency for a wide spectrum of molecules. (C. Ronco et al, 2001).

Filters have increasingly been recognized as exerting important adverse immunologic reactions with the patient's blood as well as being generators of reactive oxygen species. These interactions may contribute to short and longer term adverse complications including delayed renal recovery, anaphylactic reactions, impaired haemopoietic capacity, amyloidosis and reduced survival. Numerous studies have attempted to compare the utility of natural membrane materials such as cellulose (e.g. Cuprophane) with synthetic substances (e.g. polymethylmethacrylate, polyacrylonitrile, polysulfone, polyamide) which are regarded as more ‘biocompatible’. A recent Cochrane Database systematic review of 32 studies found no benefit of one membrane type over the other in terms of mortality or dialysis-related adverse symptoms. (Carole L. Foot and John F. Fraser, 2005).

5- **Dialysis fluids**

There is substantial loss of endogenous bicarbonate during RRT which must be replaced. A major difference between the available dialysates and replacement solutions in haemofiltration is the buffer base. This may be acetate, lactate or bicarbonate. Acetate is converted to on a 1:1 basis to bicarbonate by liver and skeletal muscle and lactate in a 1:1 ratio to

bicarbonate by the liver. A prospective cohort study of critically ill patients subjected to CVVHDF with any of the 3 buffers, found that those who received lactate or bicarbonate had a significantly higher serum bicarbonate and arterial pH with superior haemodynamics than those treated with acetate. (P. Heering et al, 1999). Because bicarbonate-containing fluids are significantly more expensive with a shorter shelf life, it is common practice to use lactate buffered fluids for the majority of patients in ICU and reserve bicarbonate buffered solutions for patients unable to effectively metabolize lactate (e.g. liver failure) or who are already generating high lactate loads (e.g. severe shock). A study evaluating the impact of lactate buffered high volume haemofiltration on 10 patients with septic shock and acute renal failure showed that persistent lactataemia (7 mmol/l) occurs but by 6 h the pH returns to 7.42 and these changes remain stable. This is attributed to a compensatory reduction in chloride ions and removal of unmeasured ions generated in renal failure. (L. Cole et al, 2003).

From this finding it has become practice for some clinicians to change to bicarbonate containing fluids for RRT only when the lactate exceeds 7 mmol/l. A larger randomized multi-centre study by Barenbrock et al. randomized over 100 patients who developed acute renal failure to receive either lactate or bicarbonate buffered replacement fluids and showed the bicarbonate supplemented group to have less hypotensive episode, better correction of pH and, using logistic regression, a reduced mortality in patients with previous cardiovascular disease or heart failure. (Barenbrock et al, 1995).

The other considerations when prescribing RRT fluids are that they are sterile and the concentration of other ions should be checked. Most dialysis fluids have a low concentration of potassium ions to facilitate treatment of

hyperkalaemia. Extra potassium may need to be added either to the bags or replaced systemically as levels usually start to fall once acidosis corrects and body compartment concentrations normalize. Phosphate ions which are initially high due to the renal failure are well dialysed across the concentration gradient and can become dangerously low, resulting in cardiac dysrhythmias and motor weakness unless levels are routinely monitored. This may be prevented by addition of phosphate ions to the dialysis bags to help prevent ongoing losses. In critically ill patients, the adverse effects of deranged sodium, potassium, magnesium, phosphate and calcium cannot be overstated. (Carole L. Foot and John L Fraser et al, 2005).

The hemofiltrate is collected in bags that are suspended on a strain gauge and weighed continuously. The bags of replacement fluid, suspended on a second strain gauge, are similarly weighed. A servomechanism drives the replacement-fluid pump at a rate computed either to balance the inflow and loss of fluid or to maintain a predetermined rate of fluid loss.

6- Vascular access

Most ICU patients requiring IHD, CVVH, CVVHDF or SLED require insertion of a temporary dialysis catheter. Issues that need to be considered are the individual characteristics of the catheter and the site and method of placement. For patients requiring longer term treatment or as 'bridging' access in patients whose other dialysis access has become unusable, semi-permanent tunnelled catheters are often a solution. The catheter size is determined by the patient's size and in general larger catheters perform better than smaller bore devices. The length of the catheter is important. Not only will it ensure that the device is located within a vein in the best position

for blood to enter and leave the device, but it also determines the amount of recirculation that can be expected.

Some catheter surfaces are treated with antimicrobial agents with the rationale that this reduces catheter-related infections.

It must be appreciated that even short-term haemodialysis catheters have a significant impact on the central veins in which they are placed and thus unnecessary catheter placement should be avoided. Subclavian vein catheters are more comfortable for the patients and have the lowest rate of infectious complications. Subclavian vein complications, however, may have more serious long-term adverse ramifications for the patient such as deep vein thrombosis and pulmonary thrombo-embolism, chronic limb oedema and contraindication to formation of arteriovenous fistulae for long-term dialysis. Femoral veins are favored for initial vascular access for CRRT, particularly in patients with impaired coagulation as there is the lowest rate of insertion-related complications. Subsequent catheters are rotated to the internal jugular veins to facilitate early mobilization and physiotherapy.

A significant number of patients who require RRT in the ICU will go on to require chronic therapy and the creation of an AV fistula at a later date, and subclavian vein thrombosis may exclude upper limbs as a site of fistula due to venous obstruction. Hence site and duration of dialysis catheterization has important long-term ramifications. (Carole L. Foot and John F. Fraser, 2005).

7- Anticoagulation and the filter

Blood flow through an extracorporeal circuit is associated with activation of the coagulation cascade. In order to prevent the filter from clotting specific consideration needs to be given to the patient, the vascular access and the circuit. An acceptable duration for an individual filter to survive is at least 24 h with CRRT and a single session with IHD or SLED.

A baseline assessment of the patient's coagulation status should be made prior to initiation of dialysis. This involves not only reviewing a recent blood coagulation profile but a complete picture of their medical problem list (e.g. liver dysfunction, procoagulant disorders) and medications (e.g. drugs with antiplatelet properties, consideration of heparin-induced thrombocytopenia and thrombosis (HITTS) if heparin has recently been administered). The most frequently encountered problems of blood flow are associated with adequacy, size and position of the venous access

The circuit has many design features that help to prevent clotting. These include a large size of the tubing with laminar flow characteristics and an absence of areas in contact with air, avoiding stagnant flow. High blood flow rates, facilitated by large bore vascular access in a large central vein also helps prevent clotting.

Despite all of these protective factors and the relative hypothermia resulting from extra-corporeal circulation, many patients still require anticoagulant drugs. There is no strong evidence in favour of aspirin though it is commonly used. The majority of centres commence an infusion of

unfractionated heparin following priming of the circuit with heparin and a systemic bolus dose of around 5000 units if no bleeding diathesis exists. The infusion can be administered in low dose pre-filter (<500 units/h), medium dose pre-filter (500–1000 units/h), full systemic heparinization with an unfractionated heparin infusion or as low molecular weight heparin. (S. Abramson and J.L. Niles, 1999). The selection of dose will depend on the patient's individual bleeding risk and the need for anticoagulation imposed by other pathologies (e.g. mechanical heart valves, pulmonary embolism).

Some patients will bleed despite low doses of heparin and may require a regional anticoagulation technique if filter clotting remains problematic. Regional heparinization can be achieved with pre-filter heparin being neutralized by the infusion of post-filter protamine in a 100 unit heparin: 1 mg protamine ratio. This has been shown to be a safe and valid technique when titrated to a systemic aPTT of <45 s and a circuit aPTT of >55 s with adjustments in the infusion rates of heparin and/or protamine of up to 20%. (S. Morabito et al, 2003). Regional citrate anticoagulation is an alternative to heparin whereby citrate is infused pre-filter, causing anticoagulation through chelation of calcium ions required for clotting. Calcium is infused post-filter to prevent profound hypocalcaemia. There are risks of metabolic alkalosis as citrate is converted by the liver to bicarbonate and conversely systemic hypocalcaemia with liver dysfunction. Some units are experienced with, and prefer, citrate regional anticoagulation over heparin (aPTT 45–65 s) and have shown both safety and improved filter survival with this technique. (D.J. Kutsogiannis et al, 2005).

Anticoagulation in the setting of HITTS is a special problem; as not only is there a critical requirement for anticoagulation but the alternatives to heparin

require careful adjustment of dosage in renal failure. Options include heparinoids such as danaparoid (anti-Xa and antithrombin effects) and recombinant hirudin molecules such as lepirudin (antithrombin effects). (B. Farner et al, 2001). Other potential anticoagulants include prostacyclin which is expensive and can cause bleeding, vasodilatation and hypotension. (S. Abramson and J.L. Niles, 1999).

8- Comparison between IHD and CRRT:

Because of lower blood flows and slower ultrafiltration over a prolonged period of time, CRRT and SLEDD are generally better tolerated than shorter and intense IHD treatments-and this without compromising the dialytic dose.

-Haemodynamics:

Compared to IHD, CRRT provides excellent fluid removal with minimal deviation of blood volume and mean arterial pressure (MAP). Recurrent episodes of hypotension and hypovolaemia during IHD may exacerbate tissue ischaemia-reperfusion damage, particularly in renal tubules.(M. Manns et al, 1997).

-Fluid balance:

The longer treatment duration in CRRT and SLEDD allows for a stricter and more flexible management of fluid balance, in turn allowing optimization of nutritional support without the concern of fluid overload.

-Nutrition:

With standard IHD, adequate azotaemic control is difficult and a degree of protein restriction is often applied to prevent uncontrolled uraemia. Such restrictions induce protein starvation and highly negative daily nitrogen balances. With CRRT, nitrogen balance is close to neutral and protein malnutrition is prevented. (R. Bellomo et al, 1991).
Amino acid losses through the filter do occur. However, even during total parenteral nutrition, they represent only approximately 10% of administered amino acids. Such losses are not appreciably greater than those seen during a session of IHD or during PD.

- Acidosis and electrolytes:

CRRT offers better control of metabolic acidosis and serum electrolyte levels compared to IHD. (S. Uchino et al,2001). However, due to the high phosphate clearance and the frequent simultaneous initiation of nutritional support, hypophosphataemia will develop during CRRT and thus should be monitored and treated.

-Intra- cranial pressure:

CRRT has beneficial effects in patients at risk of or with increased intracranial pressure (neurosurgical patients, patients with encephalitis or meningo-encephalitis or hepatic encephalopathy). CRRT has been demonstrated to prevent the surges in intracranial pressure associated with intermittent therapies that can perpetuate further injury. (A. Davenport et al, 1989).

-Solutes and cytokines:

There is a strong biological rationale for the efficient removal of uraemic toxins in ARF. The accumulation of toxins may have detrimental effects and blood purification treatments should look beyond simple urea and electrolyte clearance.CRRT modalities generally use middle- to high-flux membranes which have the ability to remove larger molecular weight molecules, including cytokines.(A.S. De Vriese et al, 1999). IHD generally uses standard low-flux membranes. CRRT provides various options to increase ultrafiltration volume (dialytic dose) which has been demonstrated to improve haemodynamics and survival. (L. Cole et al, 2001).

-Membranes biocompitability:

Many of the dialyzers used for CRRT contain synthetic membranes; the majority of these are biocompatible toward the complement and leukocyte systems. For IHD, both synthetic and cellulosic dialyzers are used. Unmodified cellulosic dialyzers are bioincompatible with respect to the complement and leukocyte responses. It has been hypothesized that this bioincompatibility of unmodified cellulose might slow the recovery of renal function, because of the induction of inflammatory responses and the intrarenal release of free radical species, and increase morbidity and mortality rates. At least as many studies, however, do not indicate an effect of biocompatibility on final outcomes . (Vanholder R& Lameire N, 1999).

* Despite the suggested benefits of CRRT, there are some significant controversies preventing the use of this technology:-

-To date, there is no definitive evidence that CRRT can improve mortality when compared to IHD in critically ill subjects with ARF. However, there is some evidence of better recovery of renal function using CRRT compared to IHD. Meta-analyses of all trials have conflicting conclusions , being in favour or showing no advantage of CRRT. (M. Tonelli et al, 2002).

-The need for continuous anticoagulation has been considered an important disadvantage of CRRT, with reported bleeding complications .Shorter IHD has less exposure to anticoagulation. CRRT can be efficiently implemented without any anticoagulation in patients at risk of bleeding. (W. Silvester, 1998).

-Studies comparing CRRT and IHD costs have shown much discordance. Considering replacement and dialysate solutions, dialysers, anticoagulation and monitoring, the overall costs of CRRT may seem greater, but the earlier recovery of renal function can offset such costs.(B. Manns et al, 2003). However, a recent study concluded that provided strict guidelines to improve tolerance and metabolic control are used, almost all patients with acute renal failure as part of multiple-organ dysfunction syndrome can be treated with intermittent haemodialysis. (Vinsonneau C et al, 2006)

SLEDD is a recent RRT gaining success because it shares the optimal characteristics of both CRRT and IHD modalities. Favourable haemodynamic tolerance, excellent volume control and an efficacious dialytic dose in a non-continuous treatment, which has the benefits of not anchoring a patient to the bed and without exposure to continuous anticoagulation, seems ideal. Lower material costs makes it cost-efficient, but this may be outweighed depending on nursing policies in individual units.

9-Septic shock, multiorgan failure, and renal replacement therapy

Many patients with ARF have severe sepsis, multiorgan dysfunction and a major systemic inflammatory response. In these patients, the blood purification achieved with CRRT may
provide additional advantages that go beyond renal replacement therapy *per se* and move into the area of immunomodulation. In fact, the demonstrated ability that CRRT has to remove or
adsorb putative mediators of organ dysfunction may represent yet another reason for its preferential application .
The effect of CRRT in sepsis may increase survival in
patients with sepsis-associated ARF (R Bellomo et al, 1995).

In response to these developments, investigators are now seeking to augment the blood purification efficacy of CRRT in a direction more clearly aimed at immune system modulation. Initial experience is accumulating in the treatment of severe sepsis with organ dysfunction using high volume

hemofiltration (Bellomo R et al, 1998) or coupled plasmafiltration with adsorption (Tetta C et al, 1998). Such experience suggests that, at the very least, these more aggressive approaches to blood purification can decrease the need for vasopressor therapy during septic shock.
The concept that convective CRRT in the form of CVVH is more effective at lowering circulating levels of soluble inflammatory mediators than diffusive CRRT in the form of CVVHD has been tested in a randomized,controlled study(JA Kellum et al,1998). This study demonstrated that for equal amounts of dialysate/replacement fluid administration rate, convective therapy achieves lower serum TNF concentrations than diffusive therapy. The findings of this study lend further support to the preferential use of convective therapy.

Another area where hemofiltration is proving remarkably useful is the control of fluid balance in patients requiring extracorporeal membrane oxygenation for cardiogenic shock after cardiac surgery. These patients often require massive amounts of clotting factors, which can only be given safely in the presence of continuous hemofiltration. Under such circumstances, fluid can be removed as the clotting factors are being administered and the development of ARDS/pulmonary edema can be prevented while the bleeding is controlled. Under such circumstances, hemofiltration can be performed without any need for circuit anticoagulation.

Hemofiltration is also used to treat patients with ARDS in whom attempts to induce a negative fluid balance with loop diuretics result in a water diuresis but not a salt diuresis. In such patients, hypernatremia develops and

extravascular lung water is not decreased. Continuous hemofiltration under these circumstances achieves the normalization of serum sodium levels and the removal of extravascular water while maintaining full hemodynamic stability. This process often achieves substantial improvements in gas exchange and lung compliance.(R. Bellomo and Claudio Ronco, 2001).

10- Hepatic patients and CRRT

Continuous renal replacement therapy (CRRT) has now been in use in the management of patients with combined renal and hepatic failure. CRRT remains the treatment of choice in this group of critically ill patients because of improved cardiovascular and intracranial stability when compared with conventional intermittent hemofiltration and/or dialysis and effective solute clearances when compared with forms of peritoneal dialysis. The technique has evolved with the introduction of pumped CRRT circuits, using machines that can accurately regulate fluid balance, and the commercial introduction of bicarbonate-based or "lactate- free" substitution fluids and/or dialysates. Whether continuous dialysis or hemofiltration is the mode of treatment choice remains unanswered, with greater amino acid and ammonia losses during dialysis, whereas hemofiltration leads to increased middle molecule and cytokine removal when compared with dialysis, the latter mainly caused by membrane adsorption.

Whether the improved cardiovascular stability observed during these techniques is due to the removal of inflammatory mediators or is related to cooling as a consequence of the technique remains to be determine .

However, The necessity for CRRT in patients after liver transplantation correlates with a high risk of death. Thus, more efforts have to be made to

prevent failure in patients after liver transplantation.(Peter Lütkes et al, 1998).

SUMMARY

The evolution of the intensive care unit (ICU) has had significant implications for clinical nephrologists especially in relation to the nature, epidemiology, and management of severe acute renal failure (ARF). Severe ARF, in fact, is predominantly seen in ICUs. Although there is no universal laboratory definition, it is reasonable to define ARF as an increase in serum creatinine for 2 weeks or less of 0.5 mg/dL (44.2 μmol/L) if the baseline is less than 2.5 mg/dL (221 μmol/L) or an increase in serum creatinine by more than 20% if the baseline is more than 2.5 mg/dL (221 μmol/L). In ICU, patients with ARF carry the highest mortality rate of 50% to 70%. ARF in ICU patients is due to toxic or ischaemic cause.

Cases of ARF among ICU patients include:

- Hepatorenal syndrome: which occurs in patients with advanced liver disease and portal hypertension, and its diagnosis is based on the exclusion of other possible causes of renal failure.
- Sepsis: The combination of ARF and sepsis is associated with a 70 percent mortality. In sepsis, generalized arterial vasodilatation with an associated decrease in systemic vascular resistance occurs. Activation of the neurohumoral axis and sympathetic nervous system essential in maintaining the integrity of the arterial circulation in patients with severe sepsis and septic shock but may lead to acute renal failure.
- Rhabdomyolysis: either due to exogenous causes (as limb ischaemia and crush injury), endogenous causes (as viral infections) or drug induced.
- Haemolytic uraemic syndrome.

- Contrast nephropathy: which is considered to be the third leading cause of new acute renal failure in hospitalized patients.
- Cardiac patients: specially after cardiac surgery and percutaneous coronary interventions.
- Peri-operative ARF: Post-operative ARF is associated with an increased risk of perioperative infection, further complicating the post-operative course and increasing mortality. Several prophylactic strategies in patients at risk of perioperative ARF are taken.
- Drug- induced nephropathies : A large number of drugs may compromise renal function such as certain antibiotics as aminoglycosides, non-steroidal anti-inflammatory drugs , …..

Conservative and supportive management of ARF patients in ICU includes:

- Use of vasoactive drugs: many of which have both inotropic and vasopressor properties and are used to augment either cardiac output or perfusion pressure, or both. However, many aspects of their use remain controversial. One particular area of controversy relates to their renal effects.
- Care of nutritional status: which is difficult to be assessed in such patients.
- Antibiotic therapy: difficult in such patients as drug concentrations is altered through changes in absorption, distribution, metabolism and elimination. The addition of renal replacement therapy (RRT) may further complicate drug therapy.
- Care of acid-base status and electrolytes disturbances.

- Use of diuretics: if volume status is monitored closely, diuretics can be useful in the conversion to nonoliguria. However, there is no evidence that converting oliguria into nonoliguria is effective in reducing mortality or the need for dialysis.
- Volume replacement: Which plays a crucial role in prevention of hypovolemic patients with pre-renal failure.

Renal replacement therapy in critically ill renal patients is indicated when there is oliguria with urine output<200ml/12 hours, hyperkalaemia, severe acideamia with PH>7.1, azotemia with urea> 30 mmol/L, clinically significant organ oedema, uraemic encephalopathy, uraemic pericarditis, uraemic neuropathy or myopathy, severe dysnatraemia with Na> 160 or < 115 mmol/L, hyperthermia and drug overdose with a dialyzable product. However, a trend to commence therapy earlier is emerging. . Once a decision to initiate RRT is made, the next step is choosing the most favourable option for the individual clinical situation. Because of lower blood flows and slower ultrafiltration over a prolonged period of time, continuous renal replacement therapy (CRRT) and slow low efficiency daily dialysis (SLEDD) are generally better tolerated in such patients than shorter and intense intermittent haemoialysis (IHD) treatments-and this without compromising the dialytic dose.

REFERENCES

1. A de Mendonca, JL Vincent and PM Suter et al., Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score, Intensive Care Med 26 (2000), pp. 915–921.
2. A.A. Kramer, G. Postler, K.F. Salhab et al., Renal ischemia/reperfusion leads to macrophage-mediated increase in pulmonary vascular permeability. Kidney International 55 (1999), pp. 2362–2367.
3. A. Davenport, R. Finn and A.J. Goldsmith, Management of patients with acute renal failure complicated by cerebral edema. Blood Purification 7 (1989), pp. 203–209.
4. A. Gerber, H. Karch, F. Allerberger, H.M. Verweyen and L.B. Zimmerhackl, Clinical course and the role of Shiga toxin-producing Escherichia coli infection in the hemolytic-uremic syndrome in pediatric patients, 1997–2000, in Germany and Austria: a prospective study, J. Infect. Dis. 186 (2002), pp. 493–500.
5. A. O'Brien, L. Clapp and M. Singer, Terlipressin for norepinephrine-resistant septic shock. Lancet 359 (2002), pp. 1209–1210.
6. A.S. Benko, D.M. Capelletty, J.A. Kruse and M.J. Rybak, Continuous infusion of versus intermittent administration of ceftazidime in critically ill patients with suspected Gram-negative infections. Antimicrobial Agents and Chemotherapy 40 (1996), pp. 691–695.
7. A.S. Bergman, I. Odar-Cederlof, L. Westman et al., Diltiazem infusion for renal protection in cardiac surgical patients with pre-existing renal dysfunction. Journal of Cardiothoracic and Vascular Anesthesia 16 (2002), pp. 294–299.
8. A.S. De Vriese, F.A. Colardyn, J.J. Philippe et al., Cytokine removal during continuous hemofiltration in septic patients. Journal of the American Society of Nephrology 10 (1999), pp. 846–853.
9. A.X. Garg, R.S. Suri, N. Barrowman, F. Rehman, D. Matsell, M.P. Rosas-Arellano, M. Salvadori, R.B. Haynes and W.F. Clark, Long-term renal prognosis of diarrhea-associated hemolytic uremic syndrome: a systematic review, meta-analysis, and meta-regression, JAMA 290 (2003), pp. 1360–1370.
10. AC Schoolwerth, DA Sica, BJ Ballermann and CS Wilcox, Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association, Circulation 104 (2001), pp. 1985–1991.

11. Akriviadis E., Botla, R., Briggs, W., Han, S., Reynolds, T. and Shakil, O.,. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology 119 (2000) , pp. 1637–1648.
12. Allen R. Nissenson. Acute renal failure: Definition and pathogenesis. Kidney Internationa Vol.53 (1998), Suppl. 66, pp. S-7-S-10.
13. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288 (2002):862-871.
14. ArroyoV., Guevara, M. and Gines, P. Hepatorenal syndrome in cirrhosis: pathogenesis and treatment. Gastroenterology 122 (2002), pp. 1658–1676.
15. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ, et al.Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med 348 (2003): 491-499.
16. B. Ben-David, M. Croitoru and L. Gaitini, Acute renal failure following laporoscopic cholecystectomy: a case report. Journal of Clinical Anesthesia 11 (1999), pp. 486–489.
17. B. Farner, P. Eichler, H. Kroll and A. Greinacher, A comparison of danaparoid and lepirudin in heparin-induced thrombocytopenia, Thromb Haemost 85 (2001), pp. 950–957.
18. B.F. Palmer, Renal dysfunction complicating the treatment of hypertension. New England Journal of Medicine 347 (2002), pp. 1256–1261.
19. B.K. Kramer, J. Preuner, A. Ebenburger et al., Lack of renoprotective effect of theophylline during aortocoronary bypass surgery. Nephrology Dialysis and Transplantation 17 (2002), pp. 910–915.
20. B. Manns, C.J. Doig, H. Lee et al., Cost of acute renal failure requiring dialysis in the intensive care unit: clinical and resource implications of renal recovery. Critical Care Medicine 31 (2003), pp. 449–455.
21. Babu J. Padanilam . Cell death induced by acute renal injury: a perspective on the contributions of apoptosis and necrosis. Am J Physiology- Renal Physiology vol. 284 (2003): F608-F627.
22. Baker C, Wragg A, Kumar S, De Palma R, Baker LR, Knight CJ. A rapid protocol for the prevention of contrast-induced renal dysfunction. The RAPPID study. J Am Coll Cardiol 41 (2003): 2114–2118.
23. Barenbrock M, Colmorgen U, Firschka E, Gellert J, Lippert J, Schroder K, Spieker C, Voigt-Ladner G, Wagner K, Neumayer HH, et al. A multicenter, randomized, double-blind, placebo-controlled, two-year trial

to study the effect of nitrendipine on chronic renal transplant function. Clin Nephrol. 43(6) (1995):388-91.
24. Baron JF: Crystalloids versus colloids in the treatment of hypovolemic shock. In: Yearbook of Intensive Care and Emergency Medicine, edited by Vincent J-L, Berlin, Springer,2000 , pp 443-466.
25. Barrett BJ: Contrast nephrotoxicity. J Am Soc Nephrol 5 (1994) :125 - 137, .
26. Benedict CR, Rose JA. Arterial norepinephrine changes in patients with septic shock. Circ Shock 38 (1992):165-172.
27. Berbece AN, Richardson RM. Sustained low-efficiency dialysis in the ICU: Cost, anticoagulation, and solute removal. Kidney Int. (2006) 70(5):963-8.
28. Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344 (2001):699-709.
29. Better OS, Stein JH: Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. N Engl J Med , 322 (1990):825-829.
30. Birck R, Krzossok S, Markowetz F, Schnulle P, van der Woude FJ, Braun C. Acetylcysteine for prevention of contrast nephropathy : meta-analysis. Lancet 362 (2003): 598–603.
31. Boldt J: Human albumine on the intensive care unit: Can we live without it. In: Yearbook of Intensive Care and Emergency Medicine, edited by Vincent J-L, Berlin, Springer,2000 , pp 467-475.
32. Bove T, Calabro MG, Landoni G, Aletti G, Marino G, Crescenzi G, Rosica C, Zangrillo A: The incidence and risk of acute renal failure after cardiac surgery. J Cardiothorac Vasc Anesth 18 (2004): 442–445.
33. Brienza N, Malcangi V, Dalfino L, Trerotoli P, Guagliardi C, Bortone D, Faconda G, et al. A comparison between fenoldopam and low-dose dopamine in early renal dysfunction of critically ill patients. Crit Care Med. (2006);34(3):707-14.
34. Brivet G et al. Acute renal failure in intensive care units: causes, outcome, and prognostic features of hospital mortality: a prospective, multicenter study. Crit Care Med.24 (1996):192-198.
35. C Ronco, Brendolan A, D'Intinin, Ricci z, Wratten ML, Bellemo R. Coupled plasma filtration adsorption: Rationale, technical development and early clinical experience. Blood purification 21 (2003), pp.409-16.
36. C. Ronco, A. Brendolan, M. Dan et al., Use of sorbents in acute renal failure and sepsis. Contributions to Nephrology 133 (2001), pp. 180–193.

37. C. Ronco, R. Bellomo, P. Homel et al., Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure. A prospective randomised trial. Lancet 356 (2000), pp. 26–30.
38. C. Ronco et al. Critical care nephrology: The time has come. Kidney International , Vol.53 (1998), Suppl. 66, pp. S-1-S-2.
39. C.J. Ralph, S.J. Tanser, P.D. MacNaughton et al., A randomised controlled trial investigating the effects of dopexamine on gastrointestinal function and organ dysfunction in the critically ill. Intensive Care Medicine 28 (2002), pp. 884–890.
40. C.L. Holmes and K.R. Walley, Bad medicine: low-dose dopamine in the ICU. Chest 123 (2003), pp. 1266–1275.
41. C.L. Holmes, B.M. Patel, J.A. Russell et al., Physiology of vasopressin relevant to management of septic shock. Chest 120 (2001), pp. 989–1002.
42. C.V. Thakar, J.P. Yared, S. Worley et al., Renal dysfunction and serious infections after open heart surgery. Kidney International 64 (2003), pp. 239–246.
43. Carole L. Foot and John F. Fraser. So you need to start renal replacement therapy on your ICU patient? Current Anaesthesia & Critical Care ,Volume 16, Issue 6 (2005), pp. 321-329
44. Carvounis C.P et Al (2002). Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure . Kidney international, Volume 62, Number 6 (2002), pp. 2223-2229(7).
45. CLAY A. BLOCK and Harold L. Manning. Prevention of acute renal failure in critically ill. Am. J. Respir. Crit. Care Med., Volume 165, Number 3 (2002), 320-324.
46. Collis RE, Collins PW, Gutteridge CN, Kaul A, Newland AC, Williams DM, Webb AR: The effect of hydroxyethyl starch and other plasma volume substitutes on endothelial cell activation: An in vitro study. Intensive Care Med 20 (1994):37 -41.
47. CR Parikh, A Jani, VY Melnikov, S Faubel and CL Edelstein, Urinary interleukin-18 is a marker of human acute tubular necrosis, Am J Kidney Dis 43 (2004), pp. 405–414.
48. D. Dreyfuss and G. Saumon, Ventilator-induced lung injury: lessons from experimental studies. American Journal of Respiratory & Critical Care Medicine 157 (1998), pp. 294–323.
49. D.F. Driscoll, M. McMahon, G.L. Blackburn and B.R. Bistrain, Phenytoin toxicity in a critically ill, hypoalbuminemic patient with normal serum drug concentrations. Critical Care Medicine 16 (1988), pp. 1248–1249.

50. D.J. Kutsogiannis, R.T. Ibney, D. Stollery and J. Gao, Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patents, Kidney Int 67 (2005), pp. 2361–2367.
51. D.L. Morales, M.J. Garrido, J.D. Madigan et al., A double-blind randomized trial: prophylactic vasopressin reduces hypotension after cardiopulmonary bypass. Annals of Thoracic Surgery 75 (2003), pp. 926–930.
52. D Schwartz, M Mendonca and I Schwartz 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 Inves 100 (1997), pp. 439–448.
53. Druml W. Nutritional support in acute renal failure. In: Handbook of nutrition and kidney. Mitch WE, Klahr S, editors. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 191-213.
54. Druml W. Protein metabolism in acute renal failure. Miner Electrolyte Metab. 24(1) (1998):47-54.
55. E. Muhl, T. Martens, H. Iven et al., Influence of continuous veno-venous haemodiafiltration and continuous veno-venous haemofiltration on the pharmacokinetics of fluconazole. European Journal of Clinical Pharmacology 56 (2000), pp. 671–678.
56. E Rivers, B Nguyen and S Havstad et al., Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock, N Engl J Med 345 (2001), pp. 1368–1377.
57. Eneas JF, Schoenfeld PY, Humphreys MH. The effect of infusion of mannitol-sodium bicarbonate on the clinical course of myoglobinuria. Arch Intern Med 139 (1979): 801-805.
58. Faber MD, Kupin WL, Heilig CW, Narins RG. Common fluid-electrolyte and acid-base problems in the intensive care unit: selected issues. Semin Nephrol 14 (1994):8-22.
59. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. JAMA 290 (2003):2041-2047.
60. Fraser, C.L. and Arieff, A.I., “Epidemiology, pathophysiology, and management of hyponatremic encephalopathy,” Am. J. Med., 102 (1997), pp.67- 77.
61. G. Lema and R. Canessa, Phenylephrine, dopamine, mannitol, and renal protection during cardiopulmonary bypass. Anesthesia and Analgesia 87 (1998), pp. 1459–1463.
62. G.L. Bakris, N.A. Lass and D. Glock, Renal hemodynamics in radiocontrast medium-induced renal dysfunction: a role for dopamine-1 receptors. Kidney International 56 (1999), pp. 206–210.

63. G. Saab, G. Mindel, G. Ewald et al., Acute renal failure secondary to milrinone in a patient with cardiac amyloidosis. American Journal of Kidney Diseases 40(2) (2002), p. E7.
64. Gines P., Uriz, J., Calahorra, B., Garcia-Tsao, G., Kamath, P.S., Del Arbol, L.R. et al.. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology 123 (2002), pp. 1839–1847.
65. Goldstein-Fuchs DJ. Assessment of nutritional status in renal diseases. In: Handbook of nutrition and kidney. Mitch WE, Klahr S, editors. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 42-92.
66. Gruberg L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, Pichard AD, Satler LF, Leon MB: The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol 36 (2000): 1542–1548.
67. Guevara M., Ginés, P., Bandi, J.C., Gilabert, R., Sort, P., Jimenez, W. et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. Hepatology 28 (1998), pp. 416–422.
68. H. Rabb, F. Chamoun and J. Hotchkiss, Molecular mechanisms underlying combined kidney–lung dysfunction during acute renal failure. Contrib Nephrol 132 (2001), pp. 41–52.
69. H. Schiffl, S.M. Lang and R. Fischer, Daily hemodialysis and the outcome of acute renal failure. New England Journal of Medicine 346 (2002), pp. 305–310.
70. H Trachtman, A Cnaan and E Christen et al., Effect of an oral Shiga toxin-binding agent on diarrhea-associated hemolytic uremic syndrome in children: a randomized controlled trial, JAMA 291 (2003), pp. 1337–1344.
71. Haljamae H, Lindgren S: Fluid therapy: Present controversies. In: Yearbook of Intensive Care and Emergency Medicine, edited by Vincent J-L, Berlin, Springer, 2000, pp429 -442 .
72. Helmut Schiffl. Renal recovery from acute tubular necrosis requiring renal replacement therapy: a prospective study in critically ill patients. Nephrology Dialysis Transplantation (2006) 21(5):1248-1252.
73. HK Tan & G Hart. Plasma filtration. Annals academy of medicine 34 (2005), 615-624.
74. HM Tsai, WL Chandler and R Sarode et al., von Willebrand factor and von Willebrand factor-cleaving metalloprotease activity in Escherichia

coli O157:H7-associated hemolytic uremic syndrome, Pediatr Res 49 (2001), pp. 653–659.
75. Homsi E, Barreiro MF, Orlando JM, Higa EM. Prophylaxis of acute renal failure in patients with rhabdomyolysis. Renal Failure 19 (1997): 283-288.
76. I.Durmcaz, T. Yagdi, T. Calkaur et al., Prophylactic dialysis in patients with renal dysfunction undergoing on-pump coronmary artery bypass surgery. Annals of Thoracic Surgery 75 (2003), pp. 859–864.
77. I.Singer and M. Epstein, Potential of dopamine A-1 agonists in the management of acute renal failure. American Journal of Kidney Disease 31 (1998), pp. 743–755.
78. I.R. Shilliday, K.J. Quinn and M.E.M. Allison, Loop diuretics in the management of acute renal failure: a prospective, double-blind, placebo-controlled randomized study. Nephrology Dialysis and Transplantation 12 (1997), pp. 2592–2596.
79. Ignatius Y. Tang PharmD,and Patrick T. Murray . Prevention of perioperative acute renal failure: what works?. Best Practice & Research Clinical Anaesthesiology ,Vol. 18, Issue 1 (2004) pp 91-111.
80. J Coresh, BC Astor and G McQuillan 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 39 (2002), pp. 920–929.
81. J Westhuyzen, ZH Endre, G Reece, DM Reith, D Saltissi and TJ Morgan, Measurement of tubular enzymuria facilitates early detection of acute renal impairment in the intensive care unit, Nephrol Dial Transplant 18 (2003), pp. 543–551.
82. J.A. Kellum, Systematic review: the use of diuretics and dopamine in renal failure: a systemic review of the evidence. Critical Care Medicine 1 (1997), pp. 53–59.
83. J A Kellum , Johnson JP, Kramer D, Palevsky P, Brady JJ, Pinsky MR. Diffusive vs. convective therapy: Effects on mediators of inflammation in patients with severe systemic inflammatory response syndrome. Crit Care Med 26 (1998): 1995–2000.
84. J. Boldt and H.J. Priebe, Intravascular volume replacement therapy with synthetic colloids: is there an influence on renal function. Anesthesia and Analgesia 96 (2003), pp. 376–382.
85. J. Boldt, C. Brosch, S.N. Piper et al., Influence of prophylactic use of pentoxyfylline on post-operative organ function in elderly cardiac surgery patients. Critical Care Medicine 29 (2001), pp. 952–958.

86. J.D. Sandham, R.D. Hull, R.F. Brant et al., A Randomized, controlled trial of the use of pulmonary-artery catheters in high risk surgical patients. New England Journal of Medicine 348 (2003), pp. 5–14.
87. J.D. Turnidge, The pharmacodynamics of beta-lactams. Clinical Infectious Diseases 27 (1998), pp. 10–22.
88. J.H. Reeves and W.W. Butt, A comparison of solute clearance during continuous hemofiltration, hemodiafiltration and haemodialysis using a polysulfone hemofilter. Asaio Journal 41 (1995), pp. 100–104.
89. J.M. Prins, H.R. Buller, E.J. Kuijper et al., Once versus thrice daily gentamicin in patients with serious infections. Lancet 341 (1993), pp. 335–339.
90. J.S. Hochman, L.A. Sleeper, J.G. Webb et al., Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators: Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. NEJM 341 (1999), pp. 625–634.
91. J.W. Mouton, D.J. Touzw, A.M. Horrevorts and A.A. Vinks, Comparative pharmacokinetics of the carbapenems: clinical implications. Clinical Pharmacokinetics 39 (2000), pp. 185–201.
92. JD Conger, Vascular alterations in acute renal failure: roles in inititation and maintenance (1st edn.). In: BA Molitoris and WF Finn, Editors, Acute renal failure: a companion to Brenner and Rector's the kidney, WB Saunders, Philadelphia (2001), pp. 13–29.
93. Jens Rocktaeschel, Hiroshi Morimatsu, Shigehiko Uchino, Donna Goldsmith, Stephanie Poustie, David Story, Geoffrey Gutteridge and Rinaldo Bellomo . Acid–base status of critically ill patients with acute renal failure: analysis based on Stewart–Figge methodology. Critical Care 7 (2003):R60-R66.
94. JG Filep.Role for endogenous endothelin in the regulation of plasma volume and albumin escape during endotoxin shock in conscious rats, Br J Pharmacol 129 (2000), pp. 975–983.
95. JJ Corrigan Jr and FG Boineau, Hemolytic-uremic syndrome, Pediatr Rev 22 (2001), pp. 365–369.
96. John M. Sauret and George Marinides . Rhabdomyolysis. Am Fam Physician 65(5) (2002):907-912.
97. JV Bonventre and A Zuk, Ischemic acute renal failure: an inflammatory disease?, Kidney Int 66 (2004), pp. 480–485.
98. JV Bonventre and JM Weinberg, Recent advances in the pathophysiology of ischemic acute renal failure, J Am Soc Nephrol 14 (2003) ,pp. 2199–2210.

99. K. Furrer, A. Schaffner, S.R. Vavricka et al., Nephrotoxicity of cyclosporine A, amphotericin B-deoxycholate as continuous infusion in allogeneic stem cell transplantation. Swiss Medical Weekly 132 (2002), pp. 316–320.
100. K Reinhart, O Bayer, F Brunkhorst and M Meisner, Markers of endothelial damage in organ dysfunction and sepsis, Crit Care Med 30 (2000) , pp. S302–S312.
101. Kapoor A, Kumar S, Gulati S Gambhir S, Sethi RS, Sinha N. The role of theophylline in contrast-induced nephropathy: A case-control study. Nephrol Dial Transplant 2002; 17: 1936–1941.
102. Kaufmann H, Oribe E, Oliver JA. Plasma endothelin during upright tilt: relevance for orthostatic hypotension? Lancet 338 (1991):1542-1545.
103. Keung EC, Li Q. Lactate activates ATP-sensitive potassium channels in guinea pig ventricular myocytes. J Clin Invest 88 (1991):1772-1777.
104. Klansuwan N, Ratanajamit C, Kasiwong S, Wangsiripaisan A. Clearance of vancomycin during high-efficiency hemodialysis. J Med Assoc Thai. (2006);89(7):986-91.
105. Knotek M, Rogachev B, Wang W, et al. Endotoxemic renal failure in mice: role of tumor necrosis factor independent of inducible nitric oxide synthase. Kidney Int 59 (2001):2243-2249.
106. Kreimeier U, Peter K: Strategies of volume therapy in sepsis and systemic inflammatory response syndrome. Kidney Int53 (1998) [Suppl 64]: S75-S79.
107. Kurnik BR, Allgren RL, Genter FC, Solomon RJ, Bates ER, Weisberg LS, et al. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. Am J Kidney Dis 31 (1998): 674–680.
108. L. Cole, R. Bellomo, D. Journois et al., High-volume haemofiltration in human septic shock. Int. Care Medicine 27 (2001), pp. 978–986.
109. L. Cole, R. Bellomo, I. Baldwin, M. Hayhoe and C. Ronco, The impact of lactate-buffered high-volume hemofiltration on acid-base balance, Intensive Care Med 29 (2003), pp. 1113–1120
110. L.G. Gettings, H.N. Reynolds and T. Scalea, Outcome in post-traumatic acute renal failure when continuous renal replacement therapy is applied early vs. late. Intensive Care Medicine 25 (1999), pp. 805–813.
111. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. New England Journal of Medicine 345 (2001):588-595.

112. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 95 (1997):1122-1125.
113. Lassnigg A, Donner E, Grubhofer G, Presterl E, Druml W, Hiesmayr M. Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. J Am Soc Nephrol 11 (2000): 97-104.
114. Laureno, R and Karp, B.I., "Myelinolysis after correction of hyponatremia," Ann. Intern. Med., 126 (1997), pp.57-62.
115. Laxenaire MC, Charpentier C, Feldman L: Anaphylactoid reactions to colloid plasma substitutes: Incidence, risk factors, mechanisms: A French multicenter prospective study. Ann Fr Anesth Reanim13(1994) : 301-310.
116. Lefering R, Neugebauer EA. Steroid controversy in sepsis and septic shock: a meta-analysis. Crit Care Med 23 (1995):1294-1303.
117. Lieberthal W et Al . Necrosis and apoptosis in acute renal failure. Seminar of nephrology 18(1998):505-518.
118. Loef B, Epema A, Smilde T, Henning R, Ebels T, Navis G, Stegeman C: Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. J Am Soc Nephrol 16 (2005) 196–201.
119. Lopez A, Lorente JA, Steingrub J, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. Crit Care Med 32 (2004):21-30.
120. M.A. Perazella, Crystal-induced acute renal failure. American Journal of Medicine 106 (1999), pp. 459–465.
121. M.A. Perazella and J. Eras, Are selective COX-2 inhibitors nephrotoxic?. American Journal of Kidney Diseases 35 (2000), pp. 937–940.
122. M.J.R. Ragaller, H. Theilen and T. Koch, Volume replacement in critically ill patients with acute renal failure. Journal of the American Society of Nephrology 12 (2001), pp. S33–S39.
123. M. Manns, M.H. Siegler and B.P. Teehan, Intradialytic renal hemodynamics—potential consequences for the management of the patient with acute renal failure. Nephrology Dialysis Transplantation 12 (1997), pp. 870–872.
124. M. Richer, S. Robert and M. Lebel, Renal hemodynamics during norepinephrine and low-dose dopamine infusions in man. Critical Care Medicine 24 (1996), pp. 1150–1156.

125. M. Tonelli, B. Manns and D. Feller-Kopman, Acute renal failure in the intensive care unit: a systematic review of the impact of dialytic modality on mortality and renal recovery. American Journal of Kidney Diseases 40 (2002), pp. 875–885.
126. M. Wysocki, F. Delatour, F. Faurisson et al., Continuous versus intermittent infusion of vancomycin in severe staphylococcal infections: prospective multicenter randomized study. Antimicrobial Agents and Chemotherapy 45 (2001), pp. 2460–2467.
127. MA Cunningham, E Rondeau, X Chen, SR Coughlin, SR Holdsworth and PG Tipping, Protease-activated receptor 1 mediates thrombin-dependent, cell-mediated renal inflammation in crescentic glomerulonephritis, J Exp Med 191 (2000), pp. 455–462.
128. Mangos GJ, Brown MA, Chan WY, Horton D, Trew P, Whitworth JA: Acute renal failure following cardiac surgery: incidence, outcomes and risk factors. Aust N Z J Med 25 (1995):284-289.
129. Mardel SN, Saunders FM, Allen H, Menezes G, Edwards CM, Ollerenshaw L, Baddeley D, Kennedy A, Ibbotson RM: Reduced quality of clot formation with gelatin-based plasma substitutes. Br J Anaesth 80 (1998): 204-207.
130. Maria Koreny ,Georg Delle Karth , Alexander Geppert , Thomas Neunteufl , Ute Priglinger , Gottfried Heinz and Peter Siostrzonek . Prognosis of patients who develop acute renal failure during the first 24 hours of cardiogenic shock after myocardial infarction. The americain journal of medicine vol.112 (2002), Issue 2, Pages 115-119 .
131. Martin C, Viviand X, Leone M, Thirion X: Effect of norepinephrine on the outcome of septic shock. Crit Care Med 28 (2000): 2758–2765.
132. Martin SJ, Danziger LH: Continuous infusion of loop diuretics in the critically ill: A review of the literature. Crit Care Med 22 (1994): 1323–1329.
133. Maximilian J.R., Ragaller, Hermann Theilen and Thea Koch. Volume Replacement in Critically Ill Patients with Acute Renal Failure. J Am Soc Nephrol 12 (2001):S33-S39.
134. MB Rookmaaker, MC Verhaar, AJ Van Zonneveld and TJ Rabelink, Progenitor cells in the kidney: biology and therapeutic perspectives, Kidney Int 66 (2004), pp. 518–522.
135. Mehta RL, Pascual MT, Soroko S, Chertow GM; PICARD Study Group: Diuretics, mortality, and nonrecovery of renal function in acute renal failure. JAMA 288 (2002): 2547–2553.

136. Mónica Guevara and Juan Rodés. Hepatorenal syndrome. The International Journal of Biochemistry & Cell Biology Volume 37, Issue 1 (2005), Pages 22-26.
137. Morales D, Madigan J, Cullinane S, et al. Reversal by vasopressin of intractable hypotension in the late phase of hemorrhagic shock. Circulation 100 (1999):226-229.
138. N. Lameire, W. VanBlesen and R. Vanholder, Acute renal failure, Lancet 365 (2005), pp. 417–430.
139. N Perez, F Spizzirri, R Rahman, A Suarez, C Larrubia and P Lasarte, Steroids in the hemolytic uremic syndrome, Pediatr Nephrol 12 (1998), pp. 101–104.
140. N.P.J. Day, N.H. Phu, N.T.H. Mai et al., Effects of dopamine and epinephrine infusions on renal hemodynamics in severe malaria and severe sepsis. Critical Care Medicine 28 (2000), pp. 1353–1362.
141. Neesh Pannu , and Ravindra L. Effect of mechanical ventilation on the kidney. Best Practice & Research Clinical Anaesthesiology , Volume 18, Issue 1 (2004) Pages 189-203.
142. Naveen Singri et al. Acute renal failure. JAMA ;289 (2003):747-751.
143. Norbert Lameire , Wim Van Biesen and ProfRaymond Vanholder MD .Acute renal failure. The lancet. Volume 365, Issue 9457 (2005), Pages 417-430.
144. Nyman U, Elmstahl B, Leander P, Nilsson M, Golman K, Almen T. Are gadolinium-based contrast media really safer than iodinated media for digital substraction angiography in patients with azotemia? Radiology 223 (2002): 311–318.
145. O Schuck, V Teplan, J Sibova and M Stollova, 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 42 (2004), pp. 93–97.
146. Ortegw R., Ginès, P., Uriz, J., Cardenas, A., Calahorra, B., De Las Heras, D. et al.. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome. Results of a prospective, non-randomised study. Hepatology 36(2002), pp. 941–948.
147. P Delanaye, B Lambermont, JP Chapelle, J Gielen, P Gerard and G Rorive, Plasmatic cystatin C for the estimation of glomerular filtration rate in intensive care units, Intensive Care Med 30 (2004), pp. 980–983.
148. P. Brenner, M. Meyer, H. Reichenspurner et al., Significance of prophylactic urodilatin (INN: ularitide) infusion for the prevention of

acute renal failure in patients after heart transplant. European Journal of Medical Research 1 (1995), pp. 137–143.
149. P. Gosling, K. Sanghera and G. Dickson, Generalized vascular permeability and pulmonary function in patients following serious trauma. Journal of Trauma 36 (1994), pp. 477–481.
150. P. Heering, K. Ivens and O. Thumer et al., The use of different buffers during continuous hemofiltration in critically ill patients with acute renal failure, Intensive Care Med 25 (1999), pp. 1244–1251.
151. P. O'Reilly and A. Tolwani, Renal replacement therapy III: IHD, CRRT, SLED, Crit Care Clin 21 (2005), pp. 367–378.
152. P.E. Marik and J. Iglesias, Low-dose dopamine does not prevent acute renal failure in patients with septic shock and oliguria. American Journal of Medicine 107 (1999), pp. 387–390.
153. Patel BM, Chittock DR, Russell JA, Walley KR: Beneficial effects of short-term vasopressin infusion during severe septic shock. Anesthesiology 96 (2002): 576–582.
154. Peter Lütkes, Jens Lutz, Jan Loock, Anton Daul, Christoph Broelsch, Thomas Philipp, and Uwe Heemann. Continuous venovenous hemodialysis treatment in critically ill patients after liver transplantation. Kidney International, 72 (1999):S71-4.
155. PI Tarr and MA Neill, Escherichia coli O157:H7, Gastroenterol Clin North Am 30 (2001), pp. 735–751.
156. PM Price, J Megyesi and RL Saf Irstein, Cell cycle regulation: repair and regeneration in acute renal failure, Kidney Int 66 (2004), pp. 509–514.
157. Q Al Awqati and JA Oliver, Stem cells in the kidney, Kidney Int 61 (2002), pp. 387–395.
158. R. Bellomo and C. Ronco, Acute renal replacement therapy: haemofiltration or haemodiafiltration or haemodialysis, Int J Intensive Care Med 12 (2005), pp. 30–37.
159. R. Bellomo and Claudio Ronco, 2001. An introduction to continuous renal replacement therapy.www.intl.elsevierhealth.com/e-books.
160. R. Bellomo and C. Ronco, Indications and criteria for initiating renal replacement therapy in the intensive care unit. Kidney International 66 supplement (1998), pp. S106–S109.
161. R Bellomo, C Ronco, JA Kellum, R Mehta, P Palevsky and the ADQI workgroup.Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Coference of the Acute Dialysis Quality Initiative (ADQI) Group, Crit Care 8 (2004), pp. R204–R212.

162. R Bellemo, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet 356 (2000): 2139-2143.
163. R Bellemo, Cole L, Baldwin I, Ronco C. Preliminary experience with high-volume hemofiltration in human septic shock. Kidney Int 53 (1998); Suppl 66: S182–S185.
164. R Bellemo et al . The changing pattern of severe acute renal failure. Nephrology 2 (1996): 149-154.
165. R Bellemo, Farmer M, Wright C, Parkin G, Boyce N. Treatment of sepsis-associated severe acute renal failure with continuous hemodiafiltration: clinical experience and comparison with conventional dialysis. Blood Purif 13 (1995): 246–254.
166. R. Bellomo, H. Martin, G. Parkin et al., Continuous arteriovenous haemodiafiltration in the critically ill: influence on major nutrient balances. Intensive Care Medicine 17 (1991), pp. 399–402.
167. R Bhimma, HM Coovadia, M Adhikari and CA Connolly, Re-evaluating criteria for peritoneal dialysis in “classical” (D+) hemolytic uremic syndrome, Clin Nephrol 55 (2001), pp. 133–142.
168. R. Sheinbaum, C. Ignacio, H.J. Safi et al., Contemporary strategies to preserve renal function during cardiac and vascular surgery. Reviews in Cardiovascular Medicine 4 supplement 1 (2003), pp. S21–S28.
169. Rao TK, Friedman EA . Outcome of severe acute renal failure in patients with acquired immunodeficiency syndrome. Am J Kidney Dis 25 (1995):390-398.
170. Raoul Bergner, Martin Hoffmann, Klaus-Dieter Riedel, Gerd Mikus, Dirk M. Henrich, Walter E. Haefeli, Michael Uppenkamp and Ingeborg Walter-Sack[2]. Fluconazole dosing in continuous veno-venous haemofiltration (CVVHF): need for a high daily dose of 800 mg . Nephrology Dialysis Transplantation (2006) 21(4):1019-1023
171. Ravi Thadhani et al . Acute renal failure. The New England journal of Medicine Vol. 334 (1996):1448-1460.
172. Raymond Wai Chuen Lee, David Di Giantomasso, Clive May r and Rinaldo Bellomo. Vasoactive drugs and the kidney.Best Practice & Research Clinical Anaesthesiology , Vol. 18, Issue 1(2004) Pp. 53-74.
173. Reinhart K, Karzai W. Anti-tumor necrosis factor therapy in sepsis: update on clinical trials and lessons learned. Crit Care Med 29 (2001):Suppl:S121-S125.

174. Reinhart K, Bayer O, Brunkhorst F, Meisner M. Markers of endothelial damage in organ dysfunction and sepsis. Crit Care Med 30 (2002):Suppl:S302-S312.
175. Ricci Z, Ronco C, Bachetoni A, D'amico G, Rossi S, Alessandri E, Rocco M, Pietropaoli P. Solute removal during continuous renal replacement therapy in critically ill patients: convection versus diffusion. Crit Care. (2006);10(2):R67.
176. Riedemann NC, Guo RF, Ward PA 2003. The enigma of sepsis. Journal of Clinical Investigations 112 (2003):460-467.
177. Riedemann NC, Guo RF, Neff TA, et al. Increased C5a receptor expression in sepsis. J Clin Invest 110 (2002):101-108.
178. Rudnick MR, Goldfarb S, Wexler L, Ludbrook PA, Murphy MJ, Halpern EF, Hill JA, Winniford M, Cohen MB, VanFossen DB: Nephrotoxicity of ionic and non-ionic contrast in 1196 patients: A randomized trial. Kidney Int 47 (1995): 254-261.
179. Rudy DW, Voelker JR, Greene PK, et al.: Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. Ann Intern Med 115 (1991):360-366.
180. S. Abramson and J.L. Niles, Anticoagulation in continuous renal replacement therapy, Curr Opin Nephrol Hypertens 8 (1999), pp. 701–707.
181. S. Bennett, J. McKeown and S. Griffin, Effect of angiotensin and phenylephrine on renal function in cardiac surgical patients. Heart 79 supplement 1 (1998), pp. 28–31.
182. S.C. Franklin, M. Moulton and G.A. Sicaro, Insulin-like growth factor-1 preserves renal function post-operatively. American Journal of Physiology 272 (1997), pp. F257–F259.
183. S.C. Wallis, D.V. Mullany, J. Lipman et al., Pharmacokinetics of ciprofloxacin in ICU patients on continous veno-venous haemodiafiltration. Intensive Care medicine 27 (2001), pp. 665–672.
184. S Finfer, R Bellomo and N Boyce et al., A comparison of albumin and saline for fluid resuscitation in the intensive care unit, N Engl J Med 350 (2004), pp. 2247–2256.
185. S. Dundas, W.T. Todd, A.I. Stewart, P.S. Murdoch, A.K. Chaudhuri and S.J. Hutchinson, The central Scotland Escherichia coli O157:H7 outbreak: risk factors for the hemolytic uremic syndrome and death among hospitalized patients, Clin. Infect. Dis. 33 (2001), pp. 923–931.
186. S. Garwood, New pharmacologic options for renal preservation. Anesthesiology Clinic of North America 18 (2000), pp. 753–771.

187. S. Morabito, I. Guzzo, A. Solazzo, L. Muzi, R. Luciani and A. Pierucci, Continuous renal replacement therapies: anticoagulation in the critically ill at high risk of bleeding, J Nephrol 16 (2003), pp. 566–571.
188. S. Morgera, R. Woydt, H. Kern et al., Low-dose prostacyclin preserves renal function in high risk patients after coronary bypass surgery. Critical Care Medicine 30 (2002), pp. 107–112.
189. S. Mousdale, P.A. Clyburn, A.M. Mackie et al., Comparison of the effects of dopamine, dobutamine, and dopexamine upon renal blood flow: a study in normal healthy volunteers. British Journal of Clinical Pharmacology 25 (1988), pp. 555–560.
190. S.N. Piper, B. Kumble, W.H. Maleck et al., Diltiazem may preserve renal tubular integrity after cardiac surgery. Canadian Journal of Anesthesia 503 (2003), pp. 285–292.
191. S. Subramanian, R. Venkataraman and J.A. Kellum, Influnece of dialysis membranes on outcomes in acute renal failure: a meta-analysis. Kidney International 62 (2002), pp. 1819–1823.
192. S. Uchino, R. Bellomo and C. Ronco, Intermittent versus continuous renal replacement therapy in the ICU: impact on electrolyte and acid–base balance. Intensive Care Medicine 27 (2001), pp. 1037–1043.
193. Schenarts PJ, Sagraves SG, Bard MR, Toschlog EA, Goettler CE, Newell MA, Rotondo MF. Low-dose dopamine: a physiologically based review. Curr Surg. (2006);63(3):219-25.
194. Schetz M: Vasopressors and the kidney. Blood Purif 20 (2002): 243–251.
195. Schierhout G, Roberts I: Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: A systemic review of randomised trials. Br Med J316 (1998) : 961-964.
196. Schor N. Acute renal failure and the sepsis syndrome. Kidney Int 61 (2002):764-776.
197. Schrier RW and Abraham WT,1999 . Hormones and hemodynamics in heart failure. NEJM 341 (1999):577-585.
198. Schrier R.W. and Wei Wang . Renal failure and sepsis. New England journal of medicine, Volume 351 (2004):159-169.
199. Schwilk B, Wiedeck H, Stein B, Reinelt H, Treiber H, Bothner U. Epidemiology of acute renal failure and outcome of haemodiafiltration in intensive care. Intensive Care Med. (1997);23(12):1204-11.
200. Sean W. Murphy, Brendad J. Barret and Patrick S. Parery. Contrast nephropathy. JASN 11 (2000) 177-182.

201. Sérgio Mussi Guimarães; José Paulo Cipullo; Suzana Margareth Ajeje Lobo; Emmanuel de Almeida Burdmann. Nutrition in acute renal failure. Sao Paulo Med. J. vol.123 no.3 (2005):143-7.
202. Shilliday I, Allison ME: Diuretics in acute renal failure. Ren Fail , 16 (1994):3-17.
203. 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 12 (1997): 2592–2596.
204. SM Hollenberg, TS Ahrens and D Annane et al., Practice parameters for hemodynamic support of sepsis in adults patients. 2004 update, Crit Care Med 32 (2004), pp. 1928–1948.
205. Solomon R: Nephrology forum: Contrast-medium-induced acute renal failure. Kidney Int 53 (1998):230 -242.
206. Solomon R, Werner C, Mann D, D'Elia J, Silva P: Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 331 (1994): 1416–1420.
207. Sort,P., Navasa, M., Arroyo, V., Aldeguer, X., Planas, R., Ruiz-del-Arbol, L. et al.. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. New England Journal of Medicine 341 (1999), pp. 403–409.
208. Steffen R Mitinzer et al . Extracorporeal detoxification using MRSA technique in critically ill patients with liver failure. J Am Soc Nephrol 12 (2001) :S75-S82.
209. Stein JH: Acute renal failure. Lessons from pathophysiology. West J Med 156 (1992):176-182.
210. Stone GW, McCullough PA, Tumlin JA, Lepor NE, Madyoon H, Murray P, et al. for CONTRAST Investigators. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: A randomized controlled trial. JAMA 290 (2003): 2284–2291.
211. Sward K, Valson F, Ricksten SE. Long-term infusion of atrial natriuretic peptide (ANP) improves renal blood flow and glomerular filtration rate in clinical acute renal failure. Acta Anaesthesiol Scand 45 (2001): 536-542.
212. T.A. Golper and M.A. Marx, Drug dosing adjustments during continuous renal replacement therapies. Kidney International 53 supplement 66 (1998), pp. S165–S168.
213. T.R. Rogers, Optimal use of existing and new antifungal drugs. Current Opinion in Critical Care 7 (2001), pp. 238–241.

214. TA Sutton, CJ Fisher and BA Molitoris, Microvascular endothelial injury and dysfunction during ischemic acute renal failure, Kidney Int 62 (2002), pp. 1539–1549.
215. Taylor AJ, Hotchkiss D, Morse RW, McCabe J: PREPARED: Preparation for Angiography in Renal Dysfunction. A randomized trial of inpatient vs outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. Chest 114 (1998):1570 -4574.
216. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W: Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. NEJM 343 (2000) : 180–184.
217. Tetta C, Cavaillon JM, Camussi G, Lonneman FG, Brendolan A, Ronco C. Continous plasma filtration coupled with absorbents. Kidney Int 1998; 53; Suppl 66: S186–S189.
218. Tsuneyoshi I, Yamada H, Kakihana Y, Nakamura M, Nakano Y, Boyle WA3rd: Hemodynamic and metabolic effects of low-dose vasopressin infusions in vasodilatory septic shock. Crit Care Med 29 (2001): 487–493.
219. Tumlin JA, Wang A, Murray PT, Mathur VS. Fenoldopam blocks reductions in renal plasma flow after radiocontrast dye infusion: a pilot trial in the prevention of contrast nephropathy. Am Heart J 143 (2002): 894-903.
220. U.F. Kroh, Drug administration in critically ill patients with acute renal failure. New Horizons 3 (1995), pp. 748–759.
221. U.F. Kroh, T.J. Holl and W. Steinhausser, Management of drug dosing in continuous renal replacement therapy. Seminars in Dialysis 9 (1996), pp. 161–165.
222. V.S. Mathur, S.K. Swan, L.J. Lambrecht et al., The effects of fenoldopam, a selective dopamine receptor agonist, on systemic and renal hemodynamics in normotensive subjects. Critical Care Medicine 27 (1999), pp. 1832–1837.
223. Vanholder R, Lameire N: Does biocompatibility of dialysis membranes affect recovery of renal function and survival? Lancet 354 (1999) : 1316-1318.
224. Vincent D'Intini , C. Ronco , Monica Bonello and Rinaldo Bellomo. Renal replacement therapy in acute renal failure. Best Practice & Research Clinical Anaesthesiology .Vol.18, Issue1(2004), pp.145-157.
225. Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, et al . Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ

dysfunction syndrome: a multicentre randomised trial. Lancet (2006)368(9533):379-85
226. W. Darko, J.J. Medicis, A. Smith et al., Mississippi mud no more: cost-effectiveness of pharmacokinetic dosage adjustment of vancomycin to prevent nephrotoxicity. Pharmacotherapy 23 (2003), pp. 643–650.
227. W.G. Forssmann, M. Meyer and K. Forssmann, The renal urodilatin system: clinical implications. Journal of Cardiovascular Research 51 (2001), pp. 456–462.
228. W.L. Bennet and J.S. Henrich, renal effects of nonsteroidal anti-inflammatory drugs; summary and recommendations. American Journal of Kidney Diseases 28 (1996), pp. S56–S62.
229. W. Silvester, Outcome studies of continuous renal replacement therapy in the intensive care. Kidney International 53 supplement 66 (1998), pp. S138–S141.
230. Wang W, Jittikanont S, Falk SA, et al. Interaction among nitric oxide, reactive oxygen species, and antioxidants during endotoxemia-related acute renal failure. Am J Physiol Renal Physiol 284 (2003):F532-F537.
231. WK Han, V Bailly, R Abichandani, R Thadhani and JV Bonventre, Kidney injury molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury, Kidney Int 62 (2002), pp. 237–244.
232. WL Chandler, S Jelacic and DR Boster et al., Prothrombotic coagulation abnormalities associated with Escherichia coli O157:H7 infections, N Engl J Med 346 (2002), pp. 23–32.
233. Y. Imai, J. Parodo, O. Kajikawa et al., Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA 289 (2003), pp. 2104–2112.
234. Z. Molnar, T. Szkany and T. Koszegi, Prophylactic N-acetylcysteine decreases serum CRP but not PCT levels and microalbuminuria following major abdominal surgery. A prospective, randomized, double-blinded, placebo-controlled clinical trial. Intensive Care Medicine 29 (2003), pp. 749–755.
235. Zager, R.A. Rhabdomyolysis and myohemoglobinuric acute renal failure. Kidney International 49 (1996): 314-326.

الملخص العربى

حالات الكلى الحرجة

يتناول هذا البحث حالات القصور الكلوى الحاد التى تعالج فى وحدات الرعاية الحرجة.

برغم عدم وجود معيار معملى ثابت لإعتبار حالة القصور فى وظائف الكلى كحالة فشل كلوى حاد ، إلا ان الفشل الكلوى الحاد يعرف على أنه إرتفاع نسبة الكرياتينين بالدم لمدة اسبوعين أو أقل بنسبة 0.5 مجم % (42.2 ميكرو مول / لتر) إذا كانت النسبة المبدئية أقل من 2.5 مجم % (221 ميكرومول / لتر)أو ارتفاعه بنسبة أكثر من 20% إذا كانت النسبة المبدئية أكثر من 2.5 مجم % (221 ميكرومول / لتر) هو التعريف الأكثر إستخداما.

إن أسباب حالات الفشل الكلوى الحاد بوحدات الرعاية المركزة كثيرة، وتشمل حالات إنتان الدم ، و المتلازمة الكبدية الكلوية، ومتلازمة إنحلال الدم اليوريمية و حالات القصور الكلوي بعد إستخدام بعض العقارات أو الصبغة المستخدمة فى الأشعة و أيضا قصور وضائف الكلى مع أجهزة التنفس الصناعي.

يشمل علاج حالات الكلى الحادة فى وحدات الرعاية المركزة إستخدام العقارات الفعالة في الأوعية و العقارات التى تزيد من قوة ضخ عضلة القلب. كما يلجأ للمضادات الحيوية فى حالة إنتان الدم و لمدرات البول فى حالة انقطاعه أو انخفاض كميته. ويحتاج هؤلاء المرضي للاهتمام الخاص بالتوازن الحمضى-القاعدى و كهارل الدم.

يلجأ للعلاج الكلوى التعويضى فى حالات الكلى الحرجة عند نقص كمية البول لأقل من 200 مل/12 ساعة، ارتفاع نسبة البوتاسيوم بالدم ، ارتفاع حموضة الدم ، الارتشاح العضوى ،

الاعتلال الدماغى اليوريمى ، ارتفاع نسبة البولينا لأكثر من 30 مل مول/لتر ، و أيضا فى حالات التسمم بأدوية قابلة للاستصفاء الدموى.

وبعد اتخاذ القرار ببدء العلاج الكلوى التعويضى ، يبقي اختيار نوعية هذا العلاج حسب حالة كل مريض ، و إن كان العلاج الكلوى التعويضى البطىء المستمر هو الأفضل مقارنة بالديال الدموى المتقطع وذلك لأن استخدام معدلات أقل لجريان الدم و ترشيح فائق أبطأ يتناسب بشكل أفضل مع الحالة العامة لهذه النوعية من المرضى

حالات الكلى الحرجة

رسالة

مقدمة من الطبيبة

دعاء حسين الروبى

توطئة للحصول علي درجة الماجستير في الأمراض الباطنة

تحت إشراف

أ.د/ دولت بلال
أستاذ امراض الباطنة
كلية الطب –جامعة القاهرة

د/ منال الديب
مدرس أمراض الباطنة
كلية الطب-جامعة القاهرة

د/ داليا رشد أحمد عبد الرحيم
مدرس أمراض الباطنة
كلية الطب –جامعة القاهرة

كلية الطب
جامعة القاهرة
2006