DISSERTATION ON

CYSTATIN-C IN ACUTE KIDNEY INJURY

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations
for the award of the degree of

M.D. DEGREE IN GENERAL MEDICINE

BRANCH – I

THANJAVUR MEDICAL COLLEGE,

THANJAVUR - 613 004

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI - 600 032
APRIL -2013

CERTIFICATE

This is to certify that this dissertation entitled 'CYSTATIN –C IN ACUTE KIDNEY INJURY'' is the bonafide original work of Dr.JAGANATHAN .P in partial fulfilment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu Dr.M.G.R. Medical University to be held in APRIL - 2013. The period of the study was from April – 2012 to November - 2012.

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DECLARATION

I, **Dr. JAGANATHAN .P**, solemnly declare that dissertation titled **" DISSERTATION ON CYSTATIN-C IN ACUTE KIDNEY INJURY"**is a bonafide work done by me at Thanjavur Medical College, Thanjavur, during April - 2012 to November - 2012 under the guidance and supervision of **Prof.Dr.S.MANOHARAN, M.D.,** Unit Chief M-IV, Thanjavur Medical College, Thanjavur.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University towards partial fulfilment of requirement for the award of **M.D. Degree (Branch - I) in General Medicine**.

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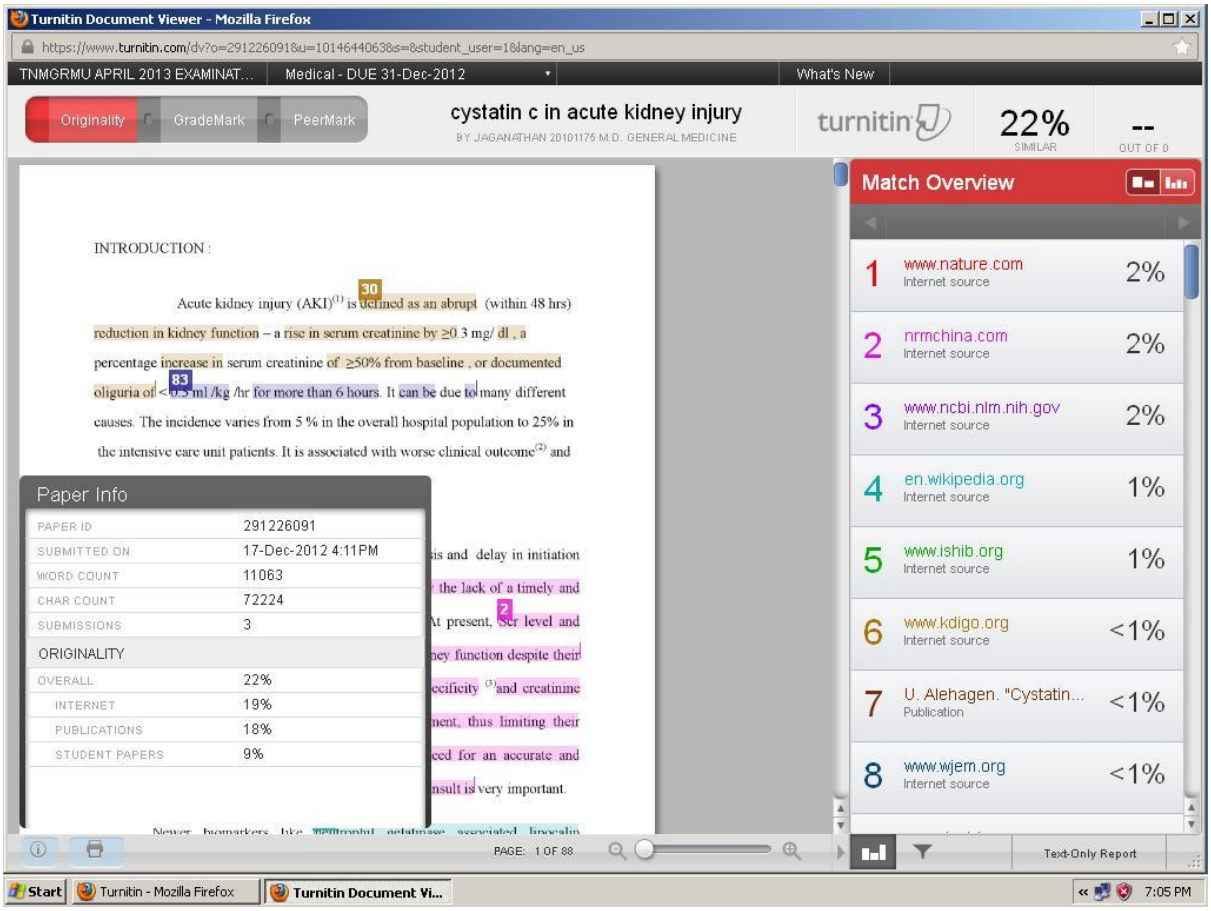
INTRODUCTION : Acute kidney injury (AKI) (1) is defined as an abrupt (within 48 hrs) reduction in kidney function – a rise in serum creatinine by ≥0.3 mg/ dl , a percentage increase in serum creatinine of ≥50% from baseline , or documented oliguria of < 0.5 ml /kg /hr for more than 6 hours. It can be due to many different causes. The incidence varies from 5 % in the overall hospital population to 25% in the intensive care unit patients. It is associated with worse clinical outcome (2) and high mortality ranging from 45 % to 60 %. The poor outcome is due to delay in diagnosis and delay in initiation of dialysis. The delay in initiation of dialysis is in part by the lack of a timely and...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CONTENTS

ABSTRACT

INTRODUCTION

Acute kidney injury is associated with increased mortality of around 45% to 60%. Early diagnosis and initiation of dialysis can prevent progression and decrease mortality in patients with acute kidney injury. However, serum creatinine , the standard marker to detect AKI demonstrates major limitations. In this study, We prospectively evaluated the role of cystatin C in detection of AKI and whether it can detect AKI earlier than serum creatinine.

AIMS AND OBJECTIVES

1. To evaluate the role of cystatin-C as a biomarker for the early detection of AKI.
2. To compare the predictive ability of cystatin-C with serum creatinine level in early prediction of AKI.
3. To assess the correlation of cystatin-C level with the severity and outcome of AKI.

MATERIALS AND METHODS

Single Center, prospective observational study at Thanjavur Medical College. 60 patients at risk of developing AKI were studied.

RESULTS

Following results were obtained,

- Cystatin C levels predicts AKI better than serum creatinine level.
- Cystatin C levels can predict AKI earlier than serum creatinine value. It can predict AKI atleast 1 or 2 days earlier than serum creatinine.

CONCLUSION

Serum cystatin C is a sensitive bio-marker for AKI and it can predict AKI earlier than serum creatinine.

KEY WORDS

Acute kidney injury, cystatin C, creatinine.

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ETHICAL COMMITTEE

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INTRODUCTION

Acute kidney injury (AKI)[1] is defined as an abrupt (within 48 hrs) reduction in kidney function – a rise in serum creatinine by ≥0.3 mg/ dl , a percentage increase in serum creatinine of ≥50% from baseline , or documented oliguria of < 0.5 ml /kg /hr for more than 6 hours. It can be due to many different causes. The incidence varies from 5 % in the overall hospital population to 25% in the intensive care unit patients. It is associated with worse clinical outcome[2] and high mortality ranging from 45 % to 60 %.

The poor outcome is due to delay in diagnosis and delay in initiation of dialysis. The delay in initiation of dialysis is in part by the lack of a timely and accurate biomarker to predict the occurrence of AKI. At present, Scr level and urine output are the standard indicatiors of decreased kidney function despite their known limitations. They have limited sensitivity and specificity [3]and creatinine level change is delayed in response to kidney impairment, thus limiting their usefulness in early detection of AKI. Therefore, the need for an accurate and timely biomarker to predict AKI development after renal insult is very important.

Newer biomarkers like neutrophil gelatinase associated lipocalin (NGAL), kidney injury molecule -1(KIM-1), interleukin -18(IL-18) and Cystatin-C are being evaluated in a number of studies for their utility in detecting AKI.

Among them, cystatin-C is considered to be good biomarker of kidney function because,

1. It is produced at a relatively constant rate and released in to plasma[4].
2. >99% is filtered by glomeruli .
3. There is no significant protein binding.

Cystatin-C is a 13 kDa endogenous cysteine proteinase inhibitor.

Numerous studies have evaluated the role of cystatin-C as an endogenous marker of kidney function in population at risk of or with chronic kidney disease, showing that cystatin-C is superior to the serum creatinine level in the discrimination of normal from impaired kidney function. Recently, studies started evaluating the diagnostic accuracy of cystatin-C level in predicting AKI.

In this study, we evaluated the role of cystatin-C as an early biomarker in predicting AKI in patients at risk of developing AKI. We also compared the diagnostic accuracy of cystatin-C with serum creatinine level in predicting AKI and also the correlation of cystatin-C level with severity and outcome of AKI is studied.

CLINICAL ANATOMY:-

Kidneys are paired retroperitoneal organs[5]. Each kidney weighs about 125 gm to 170 gm in adult male and 115gm to 155gm in adult female. It is surrounded by a tough fibrous capsule.

Dimensions:

Length – 11cm to 12cm.

Width – 5 cm to 7.5cm.

Thickness- 2.5cm to 3cm.

It is supplied by renal artery which arises directly from the abdominal aorta. The renal artery enters through renal pelvis and divides into an anterior branch and a posterior branch.

The anterior branch gives rise to three segmental or lobar branches that supply upper, middle and lower thirds of the anterior surface of the kidney. The posterior surface is supplied by the posterior branch. All are end arteries and there is no collateral circulation between individual branches.

Nephron:

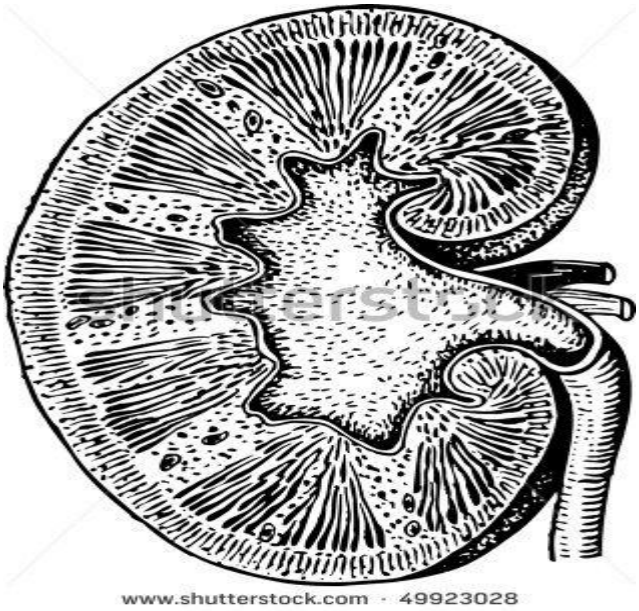
Nephron is the functional unit of the kidney. About 0.6×10^6 to 1.4×10^6 nephrons are there in each kidney. Each nephron contains,

1. Glomerulus
2. Proximal tubule
3. Loop of henle
4. Distal tubule
5. Collecting duct

Glomerulus:

It consists of a capillary membrane lined by single layer of endothelial cells. It also has a layer of visceral epithelial cells, a parietal layer and a central mesangium. Bowman's space is the narrow space between the visceral and parietal cells. Plasma is filtered through the glomerular capillaries to form an ultra filtrate. This is called glomerular filtration. The factors affecting the glomerular filtration are[(6)]:

- Size of the capillary bed
- Permeability of the capillaries
- Hydrostatic and osmotic pressure gradient across the capillaries.



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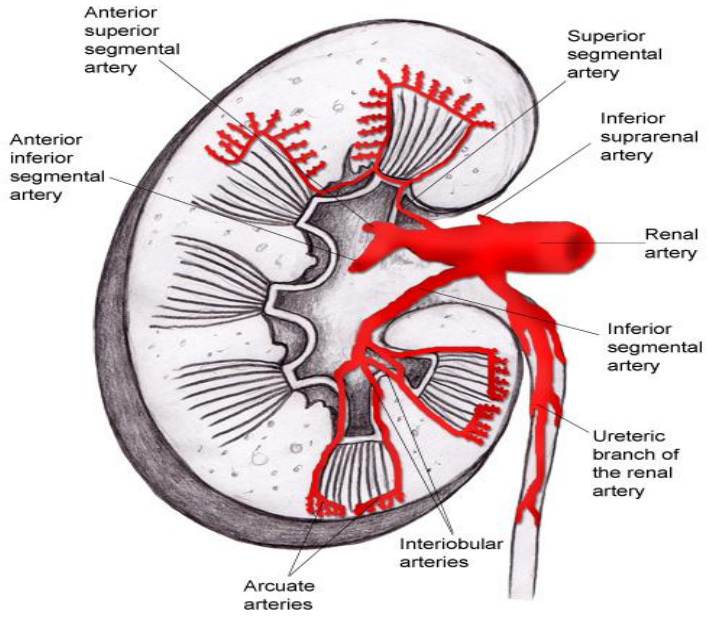
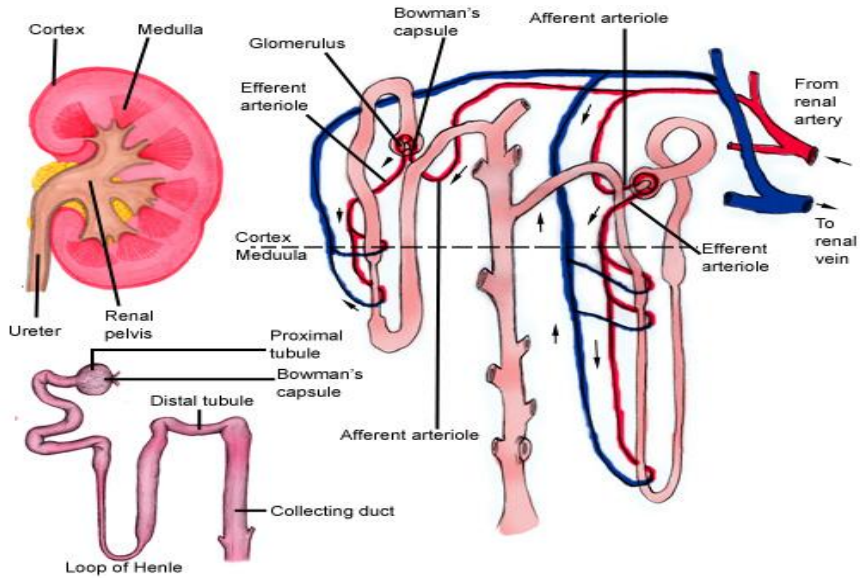
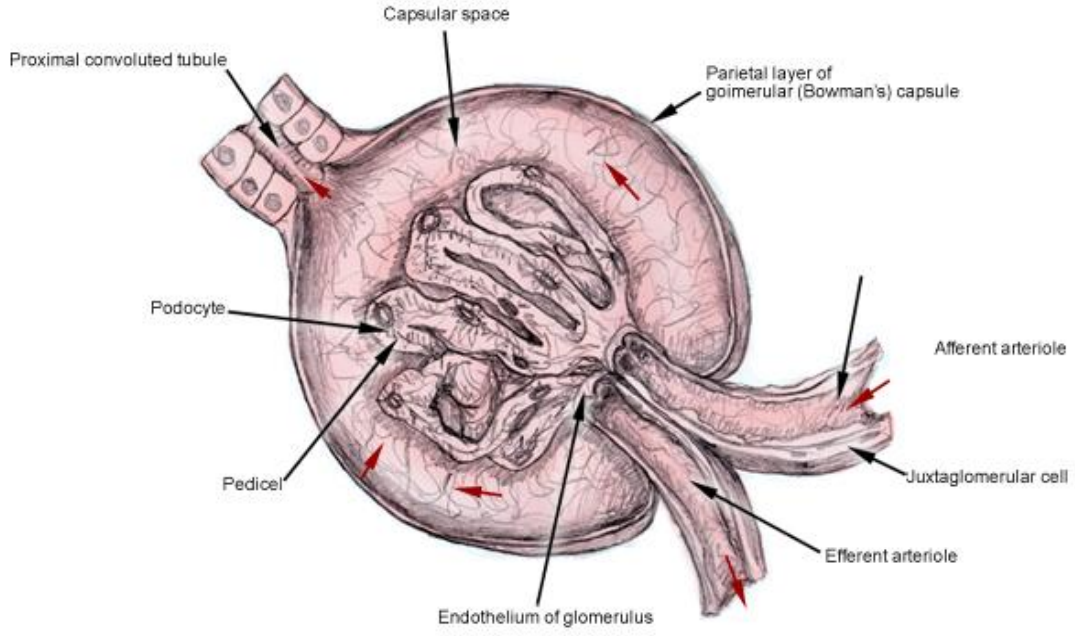


BLOOD SUPPLY OF KIDNEY



NEPHRON



GLOMERULUS

REVIEW OF LITERATURE

HISTORICAL REVIEW OF LITERATURE:

The history of AKI dates back to 17th century. At first the term " ischuria " was used to denote retention of urine or suppression of urine output. Following that in late 17th century, it is classified into types like "ischuria urethralis, ischuria ureterica, ischuria vesicalis, ischuria renalis"[7] depending on the organ involved.This leads to further improvement in understanding of renal diseases. The clinical features and course of ARF was well established by 18th century. Also by the end of 18th century, the microscopic features , structural alterations in acute renal failure was well studied.

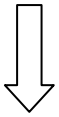
In 1941, Bywaters and Beall reported four cases of renal impairment due to crush injury. In that they also described the pathological changes in kidney and also demonstrated the presence of tubular damage and pigmented casts inside the tubular lumen.

During world war I, 'war nephritis' was the term used to denote the acute renal failure caused by severe trauma. After that, many experimental studies were conducted regarding the volume hemostasis, hemodynamics of shock, kidney function and this leads to better understanding of ARF. By 1951, almost complete pathogenesis of ARF was established. The term acute renal failure was introduced

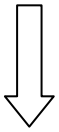
by Homer W.Smith in the book " The kidney ; structure & function in health & disease".

HISTORICAL MILE STONES :-

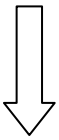
Galen (empty bladder) - (greek, roman)



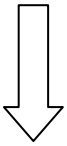
Morgagni, 1760 (Ischuria renalis) - (18^{th} century)



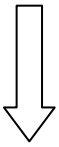
Bright, 1888 (Acute Bright's disease) - (19^{th} century)



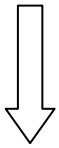
Davies, 1917 (War nephritis) - (20^{th} century, before world war)



Bywaters and Beall, 1941 (crush syndrome)- (20^{th} century, after world war II)



Smith, 1951 (ARF)



ADQI, 2004 (AKI)

Following that in late 20th century, John P Merril described the clinical course of acute renal failure and its management. Also George E Schreiner described the treatment of acute renal failure. Williams J Kolfi contributed to the treatment by inventing artificial kidney After this, studies focuses on the treatment aspects and early diagnosis of ARF. Recently more studies were conducted to identify an ideal marker for kidney function. and also ARF in special clinical conditions like sepsis, AIDS, malignancies, following major cardiac surgery is extensively studied.

ACUTE KIDNEY INJURY

The term acute kidney injury denotes the impairment of kidney function over hours to days, resulting in retention of nitrogenous and other waste products and derangements in volume regulation , electrolyte and acid-base homeostasis. AKI is not a single disease but, rather, a term for a heterogenous group of conditions that have common features like an increase in blood urea nitrogen level, an increase in serum creatinine level, and decrease in urine output.

AKI is synonymous with the older term acute renal failure (ARF) and replacing the ARF in recent literature. The term AKI was introduced in the year2004 by Acute Dialysis Quality Initiative (ADQI)[8].This is because the term failure reflects only part of the spectrum of damage to the kidney that occurs

clinically. The newer term AKI reflects the fact that the rise in serum creatinine does not mean total failure of the kidneys. It is only a dysfunction which may or may not lead to failure. And also the term renal is not well understood by the general population. Replacing it with the term 'kidney' makes communication with the patients and public more easier[9].

EPIDEMIOLOGY

The prevalence of AKI is increasing in both developing and developed countries. In developed countries surgery and trauma are the most common causes of AKI accounting for 60% of cases. In developing countries medical disorders (30% to 35%), drugs and toxins(18% to 33%),obstetric complications(8% to 10%) are the most common causes of AKI[10]. In addition to this, in tropical countries infections like falciparum malaria, leptospirosis, dengue, AIDS and acute diarrheal diseases and snake envenomation also cause AKI. AKI due to the toxicity of herbal and non herbal products is also commonly reported in tropical countries.

ETIOLOGY AND PATHOGENESIS OF AKI

The causes of AKI can be divided in to 3 broad categories,

1.pre renal azotemia

2.parenchymal disease

3.post renal obstruction

PRE RENAL AZOTEMIA

It is the most common form of AKI. It involves rise in SCr or blood urea nitrogen concentration due to inadequate renal blood flow[11] and intraglomerular hydrostatic pressure thereby decreasing glomerular filteration rate. It involves no parenchymal damage to the kidneys and it is rapidly reversible once intraglomerular hemodynamics are restored. Prolonged periods of pre renal azotemia can lead to ischaemic injury of the tubules which is called as acute tubular necrosis(ATN).

Causes of pre renal azotemia

1. Hypovolumia

2. Decreased cardiac output

3. Decreased effective circulating volume

- Congestive cardiac failure
- Liver failure

4.Impaired renal autoregulation

- NSAIDs

- ACE inhibitors, ARB
- Cyclosporin

Pathogenesis of pre renal azotemia:

Normal GFR is maintained by interactions between the renal plasma flow and the transcapillary hydraulic pressure gradient which is determined by the relative resistence of the afferent and efferent arterioles. Decreased renal perfusion is the hallmark of pre renal azotemia. This will result in number of immediate systemic and renal compensatory responses. These responses are mediated by angiotensin II, norepinephrine and vasopressin[(12)].

Decrease in renal perfusion results in sympathetic activation releasing noradrenaline. This increases the cardiac output and helps in restoration of renal perfusion pressure. Peripheral resistence is also increased to maintain blood pressure. This can further decrease renal blood flow but is counteracted by other intrarenal mechanisms.

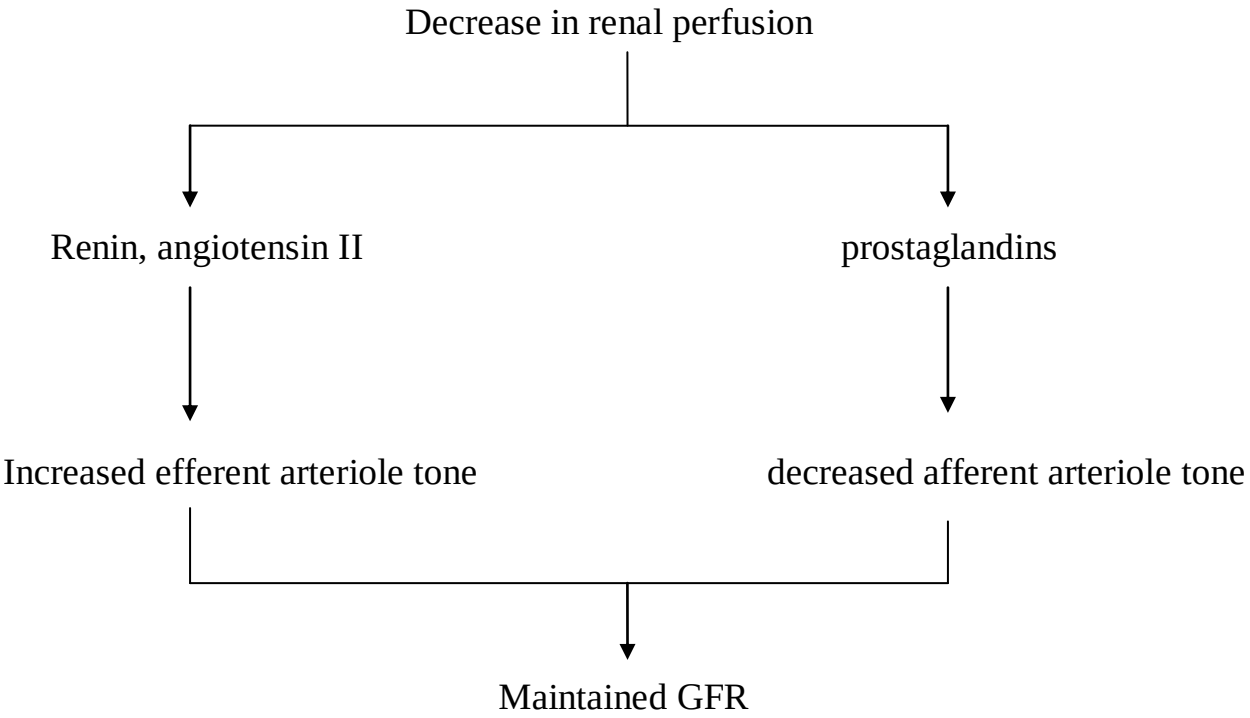
Sympathetic activation also releases renin. Renin activates the renin-angiotensin-aldosterone cascade resulting in formation of angiotensin II. Angiotensin II preserves GFR by its preferential vasoconstrictive action on the efferent arteriole[(13)]. Anti diuretic hormone (ADH) is released from posterior

pituitary in response to hypovolumia. It acts on V1 receptors causing vaso constriction , hence increases the blood pressure.

Autoregulation[14] is the first line defence of kidney against fluctuations of arterial blood pressure. When the renal perfusion decreases, the afferent arteriole senses the degree of stretch and thus relaxes. This is called **MYOGENIC REFLEX**.

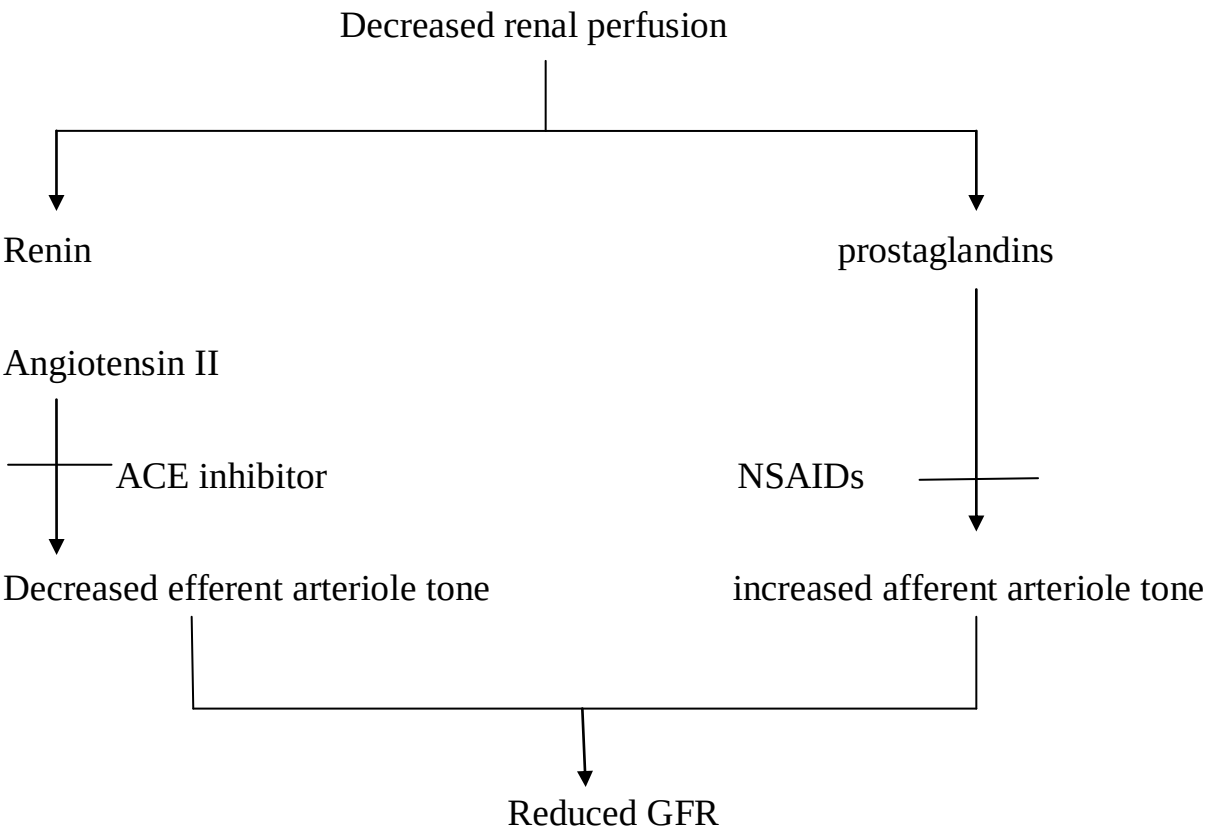
TUBULO-GLOMERULAR FEEDBACK also plays an important role in auto-regulation. Macula densa presenting in the cortical collecting ducts senses the decrease in solute delivery to the distal tubules and leads to afferent arteriole dilatation by releasing nitric oxide.

AUTOREGULATION:-



Autoregulation and other intrinsic compensatory mechanisms fails once the systolic blood pressure falls below 80 mmhg. At this stage, renal blood flow is not maintained even with the afferent arteriolar dilatation. Instead increasing levels of angiotensin II results in renal vaso constriction and further decreases the renal blood flow. There will be decrease in urine output, increase in blood urea nitrogen and plasma creatinine resulting in pre renal azotemia. If this is not reversed soon, it may lead to ischaemic acute tubular necrosis.

FAILURE OF AUTOREGULATION:-



RENAL PARENCHYMAL DISEASE (INTRINSIC AKI)

The most common form of intrinsic AKI is acute tubular necrosis. The common causes of ATN are :

1. Sepsis
2. Ischaemia
3. Nephrotoxins – both exogenous and endogenous.

Sepsis associated AKI:

AKI complicates more than 50 % of cases of severe sepsis and increases the risk of death. Most cases of AKI in sepsis occurs in the presence of hemodynamic collapse but decrease in GFR can occur even without overt hypotension.

Pathogenesis of sepsis associated AKI:

- In the early stages of sepsis, there will be generalized arterial dilatation[15,16] including efferent arteriole dilatation which is mediated by inflammatory cytokines, nitric oxide etc. This results in decrease in GFR.

- In later stages due to the compensatory activation of sympathetic nervous system, renin- angiotensin- aldosterone system, vasopressin, endothelin there will be renal vaso constriction leading to reduction in GFR.
- Cytokines released in sepsis can cause direct damage to endothelial cells resulting in micro thrombi.
- The reactive oxygen species released in sepsis along with the excessive neutrophil activation can cause damage to renal tubular cells.

Ischaemic AKI:

Kidneys receive 20 % of the cardiac output[17]. Renal outer medulla is particularly vulnerable to hypoxia because of the arrangement of blood vessels. S3 segment of the proximal tubule is metabolically very active and also vulnerable to hypoxia. Ischaemic AKI is usually progression of some pre renal condition to a stage where compensatory mechanism fails. Excessive levels of angiotensin II , endothelin I, catecholamines causes renal vaso constriction overcoming the protective effects of nitric oxide and prostaglandins. This results in hypoxia. Inflammatory cytokines are released in response to ischaemia and they result in increased leucocyte- endothelial adhesion and endothelial injury.

The damage to tubular cells manifests as disruption of actin cytoskeleton, loss of brush border, loss of cellular polarity, loss of cell matrix interactions and loss of tight junctions resulting in detachment[18]. With further injury the cells undergo either necrosis or apoptosis.

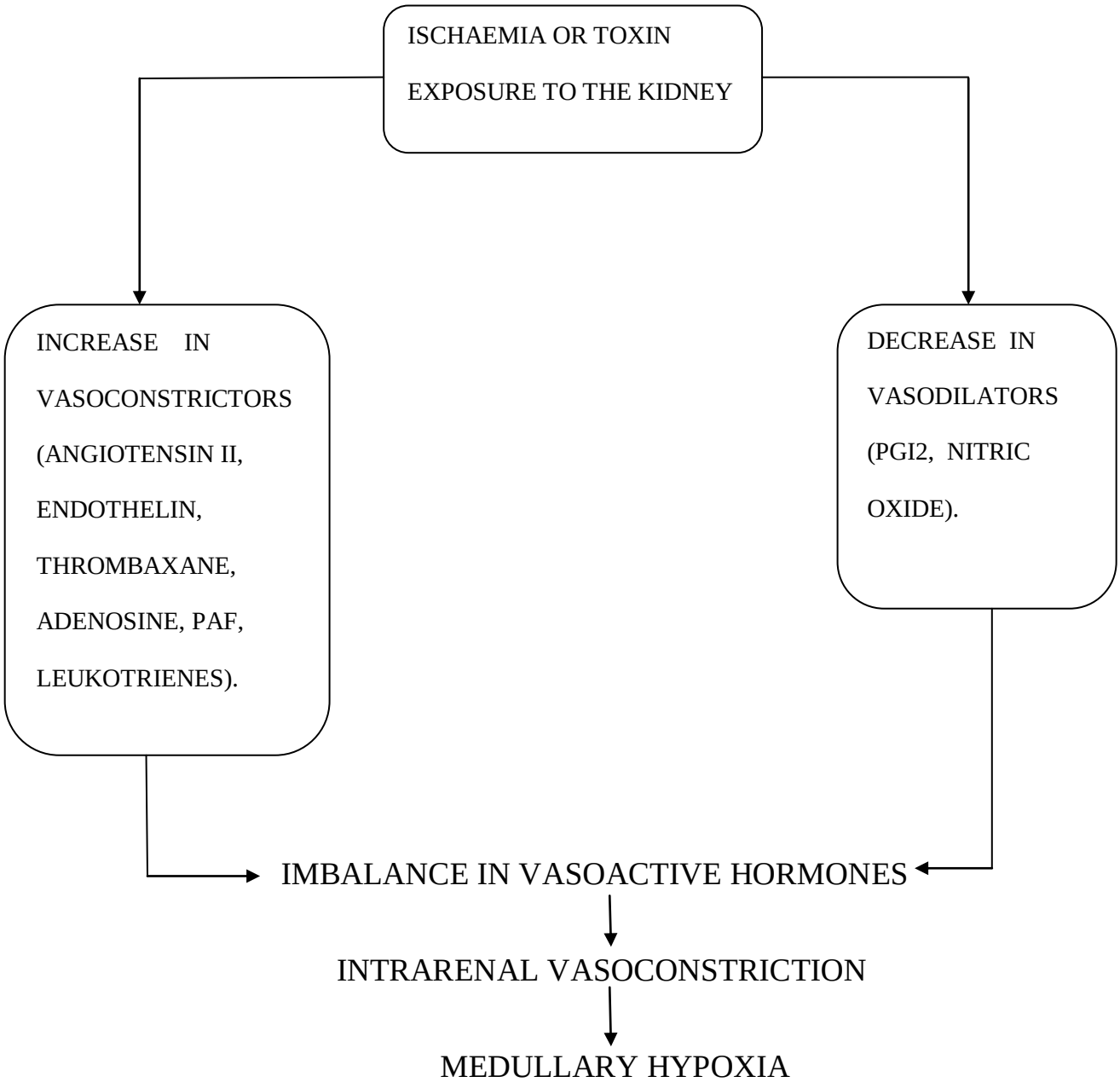
Post-operative AKI:

Ischaemia associated AKI is a common ,serious complication following major operation like cardiac surgery with cardiopulmonary bypass, vascular procedures with aortic cross clamping[19], intra abdominal procedures. Common risk factors for post operative AKI include underlying chronic kidney disease, older age, diabetes mellitus, emergency procedures, congestive cardiac failure.

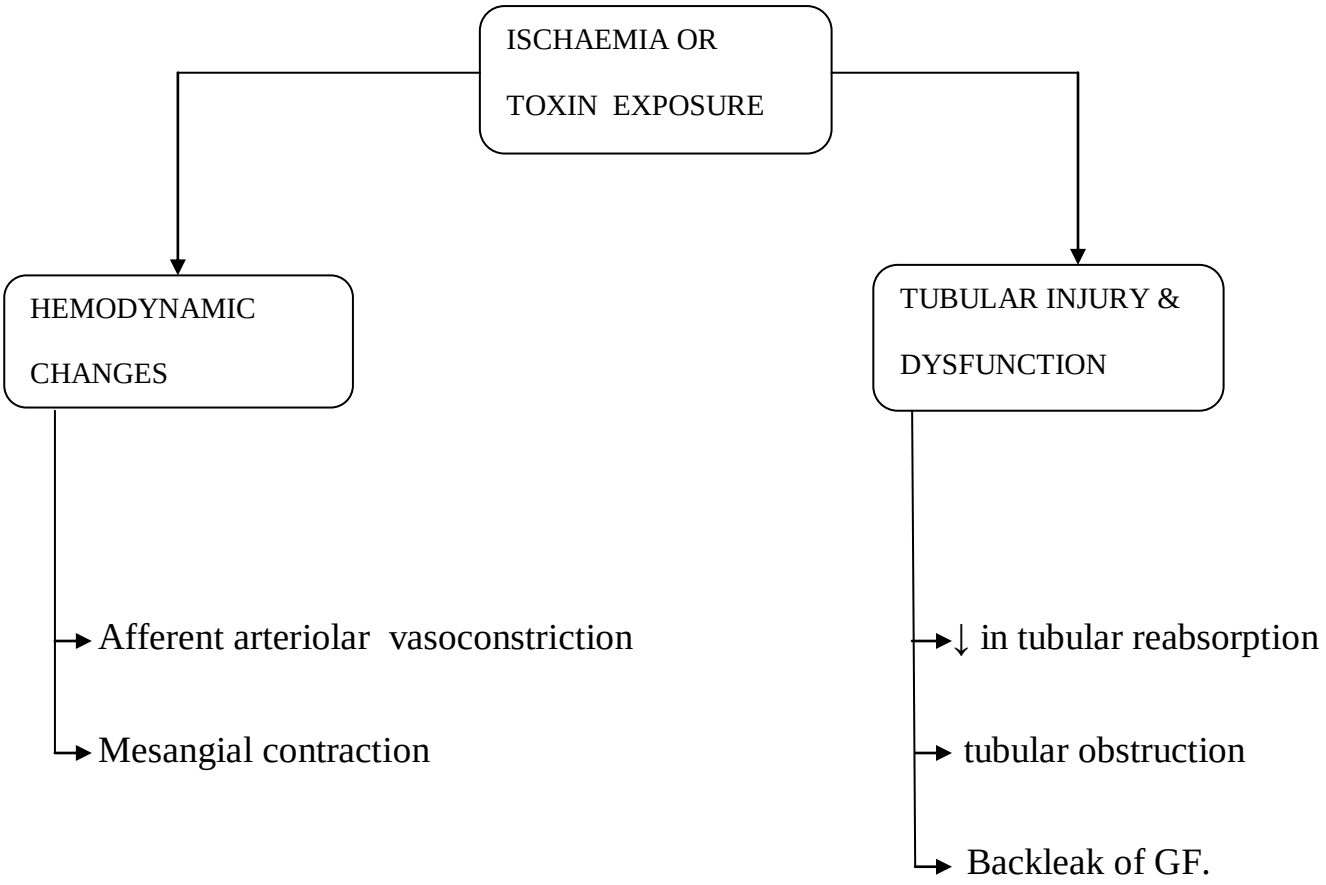
The pathophysiology of post-operative AKI following cardiac surgery is multifactorial. It includes,

- Nephrotoxic contrast agents used for cardiac imaging prior to surgery may increase the risk of AKI.
- Longer duration of cardio pulmonary bypass is also a risk factor for AKI.
- Cardio pulmonary bypass can also results in extra corporeal circuit activation of leucocytes and other inflammatory processes resulting in hemolysis and pigment nephropathy[20].

INTRARENAL HEMODYNAMICS IN ISCHAEMIC AKI:-



PATHOPHYSIOLOGY OF ISCHAEMIC AKI



Other causes of ischaemic ATN:

other causes of ischaemic ATN includes severe burns, acute pancreatitis, extensive trauma. The incidence of AKI in patients with burns more

than 10 % of total body surface area involvement is around 25 %[21]. Hypovolumia is the main contributing factor for AKI in case of severe burns and acute pancreatitis. In addition to that other factors like dysregulated inflammation, secondary sepsis may also increase the risk of development of AKI. Rarely extensive fluid resuscitation in case of burns, acute pancreatitis, severe trauma can result in abdominal compartment syndrome and renal vein compression leading to AKI.

NEPHROTOXINS ASSOCIATED AKI

Various exogenous and endogenous toxins can lead to tubular damage and AKI.

Endogenous toxin associated AKI :

- Myoglobin – rhabdomyolysis
- Hemoglobin – intra vascular hemolysis
- Uric acid and phosphate – tumour lysis
- Paraproteins – multiple myeloma.

Exogenous toxin associated AKI:

- Radiocontrast – contrast nephropathy

- Nephrotoxic drugs (aminoglycosides, cisplatin, tenofovir, zolendronate.) – tubular injury.
- Miscellaneous toxins – snake venom,other animal venoms, paraquat, copper sulphate poisoning, herbal medicines.

Kidneys receives around 20 % of total cardiac output. Due to this high blood flow the toxin exposure to nephrons is also high. Hence the tubular, interstitial, endothelial cells are exposed to high concentration of toxins causing injury to them. All these structures of kidney are vulnerable to toxin mediated injury. Risk factors associated with nephrotoxin mediated AKI are older age, pre renal azotemia, CKD. Hypoalbuminemia increases the free circulating drug concentrations and hence increase the risk of AKI.

Contrast nephropathy:-

The definition of contrast induced nephropathy (CIN)[22] is an elevation of SCr > 0.5 mg/dl above base line or increase of SCr > 25 % within 48 hrs of administration of contrast. The risk of developing CIN is minimal if the renal function is normal. It is markedly increased in the presence of pre existing CKD and diabetic nephropathy. CIN usually resolves within one week. More severe form requiring dialysis occurs in patients with associated risk factors like CKD, CCF, Multiple myeloma. The pathogenesis of CIN[23] includes,

1. Hypoxia in the renal outer medulla.
2. Direct damage or free radical mediated cytotoxic damage to the tubules[24].
3. Precipitation of contrast material in the tubule causing transient obstruction.

Antibiotics and chemo therapeutic agents:

The most common agents associated with AKI are,

- Aminoglycosides[25]
- Amphotericin – B[26]
- Vancomycin
- Acyclovir
- Cisplatin, carboplatin
- Ifosfamide
- Bevacizumab

Toxic ingestions:

Ethylene glycol, an anti freeze agent can cause AKI by direct tubular injury. The metabolite 2- hydroxyethoxyacetic acid is responsible for tubular injury. Melamine, a food adulterant can cause nephrolithiasis and AKI. Chinese

herb nephropathy and BALKAN nephropathy are specific types of toxin mediated nephropathy caused by medicinal herbs. The toxin identified in medicinal herbs is aristolochic acid.

Endogenous toxins:

It includes myoglobin, hemoglobin, uric acid and myeloma light chains. Myoglobin and hemoglobin lead to pigment nephropathy. The pathogenesis of pigment nephropathy includes,

- Vasoconstriction
- Direct proximal tubular toxicity[27]
- Mechanical obstruction of the distal nephron lumen due to precipitation.

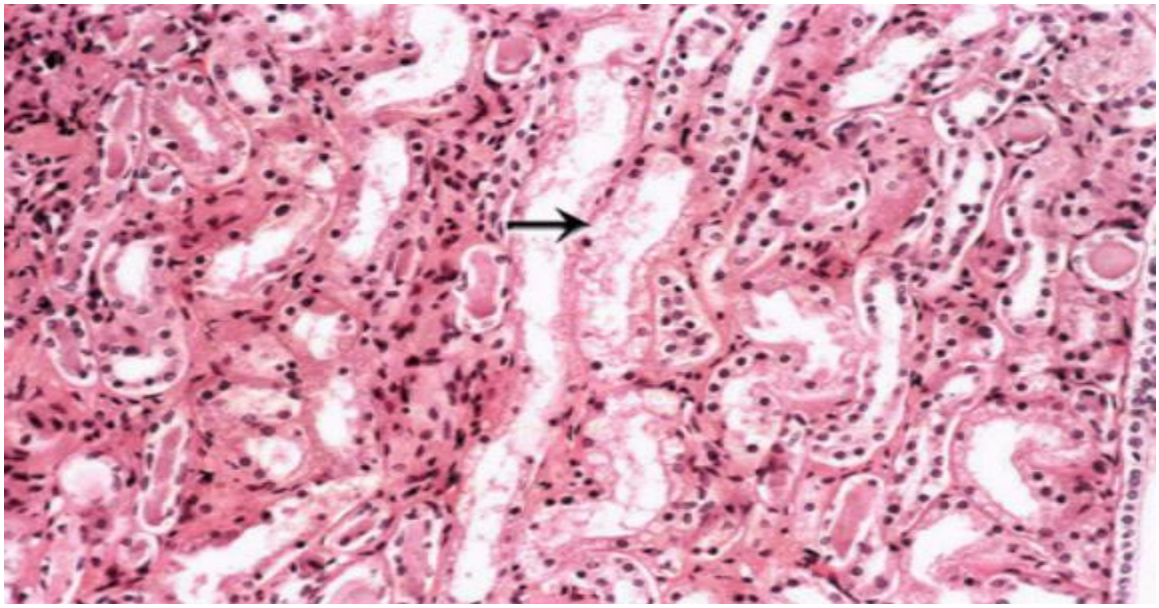
Uric acid is released in excessive amount in case of tumour lysis syndrome[28] and can cause AKI by precipitating in renal tubules. Myeloma light chains can cause AKI either by direct tubular toxicity or by forming obstructive intra tubular casts with Tomm horsfall protein[29].

OTHER CAUSES OF INTRINSIC AKI:

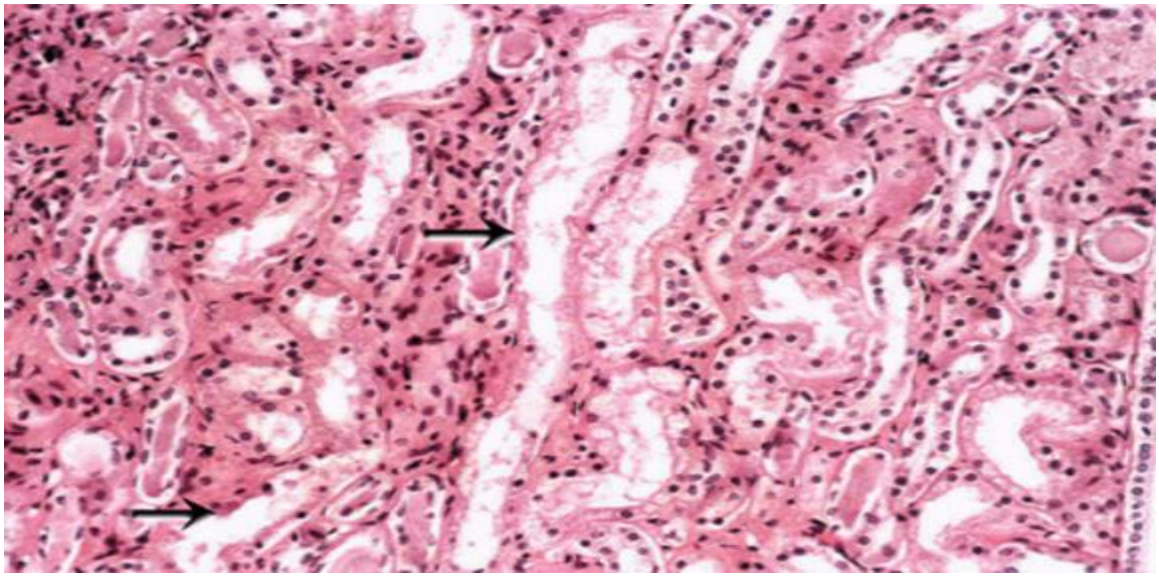
Other rare causes can be categorized according to the anatomical site involved.

- Microvascular causes

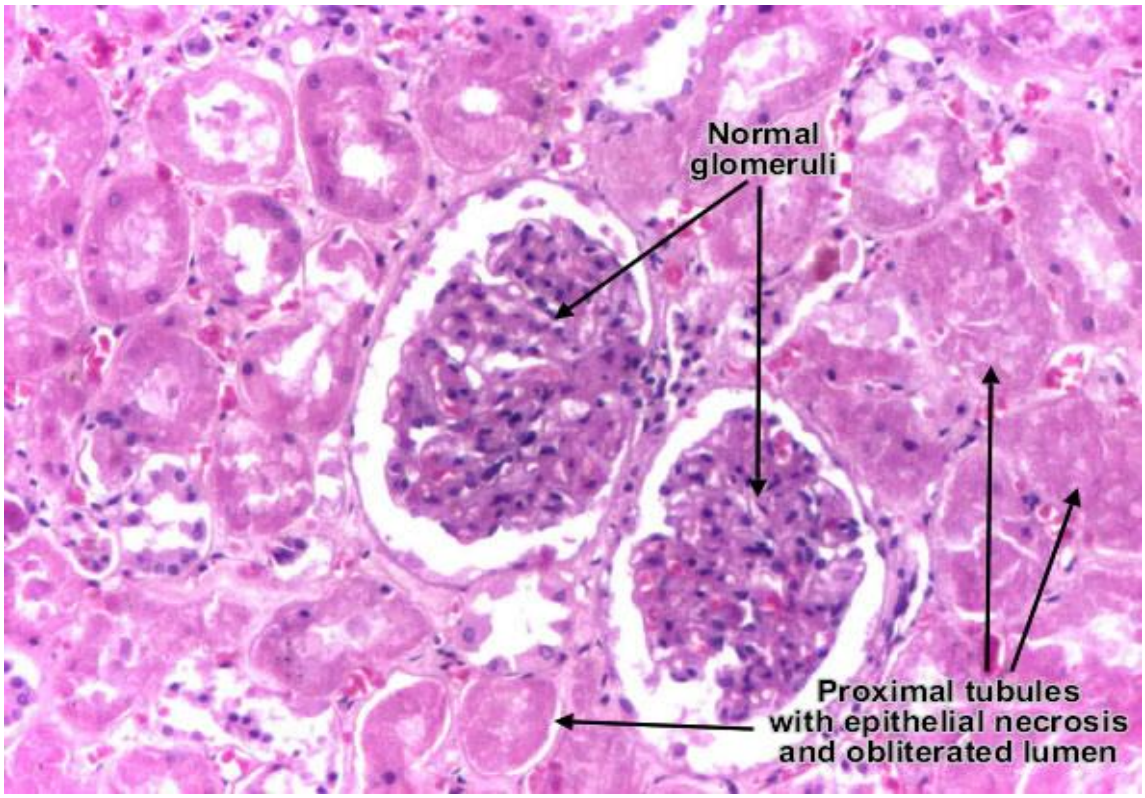
        - Atheroembolic renal disease
        - Malignant hypertension
        - Scleroderma renal crisis
- Glomerular causes
        - RPGN
- Tubular causes
        - Crystalline nephropathy
        - Myeloma kidney
- Interstitial causes
        - Acute interstitial nephritis
        - Infiltrative malignancies
        - Acute pyelonephritis



Sloughing of cells, which is responsible for the formation of granular casts, is a feature of acute tubular necrosis



Photomicrograph of a renal biopsy specimen shows renal medulla, which is composed mainly of renal tubules. Patchy or diffuse denudation of the renal tubular cells with loss of brush border is observed, suggesting acute tubular necrosis as the cause of acute renal failure.



Histopathology of AKI associated with toxins and venoms

AKI IN TROPICS – COMMON CAUSES:-

INFECTIONS	PLANT TOXINS	POISONS	MISCELLANEOUS
Falciparum malaria	Mushroom	Animal poisons	G6PD deficiency
Leptospirosis	Herbal medicine	Snake bites	Heat stroke
Typhoid	Djenkol beans	Wasp sting	Natural disasters
Haemorrhagic fevers	Propolis	Bee sting	HUS
Infective diarrhea	Cleistanthus	Scorpion sting	Trauma
HIV	collinus	Spider bite	Acute cortical
Scrub typhus		Chemicals	necrosis
Chlamydia		Copper sulphate	Surgical AKI
Legionnaires disease		Ethylene glycol	Obstetric AKI
Melioidosis		Paraquat	
Zygomycosis		Formic acid	
Rift valley fever			

AKI FOLLOWING SNAKE BITE:-

Around 2,00,000 cases of snake bites have been reported in India every year. And death due to snake bite is estimated to be around 35,000 to 50,000.

PATHOGENESIS:

Kidney is more prone to snake venom toxicity because of its high blood flow. It is commonly seen in bites by snakes belong to viperidae family. AKI in snake bite is most commonly due to ATN. But any structure in kidney may be affected causing any of the following lesions[30].

1. Interstitial nephritis
2. Vasculitis
3. Mesangiolysis
4. Glomerulonephritis

The pathogenesis of AKI following snake bite is multifactorial. It includes,

1. Direct nephrotoxicity of snake venom
2. Hypotension, circulatory collapse
3. Deposition of hemoglobin, myoglobin in renal tubules
4. Alteration in intrarenal hemodynamics
5. Injury by the inflammatory cytokines and other mediators.

- Snake venom can cause direct injury to proximal tubules[31] resulting in decrease in GFR and hence can result in AKI.
- Snake venom can also directly activate the endothelial cells and resulting in release of inflammatory cytokines. Also, the enzymes present on snake

venom like metalloproteinases initiate inflammation resulting in release of cytokines like IL-1, IL-6, activation of classic and alternate pathways of complement system[32]. This can cause either direct injury or alteration in intra renal hemodynamics causing AKI.

POST RENAL ACUTE KIDNEY INJURY

Obstructive nephropathy describes any functional or pathologic changes in the kidney that result from urinary tract obstruction.

Causes:

The most common cause in young men is nephrolithiasis[33]. In older age group, the most common cause is either benign prostate hypertrophy or carcinoma of the prostate. In women, pregnancy[34,35] and gynecological tumours[36] are the most common causes.

Pathophysiology:

In initial stages of urinary tract obstruction, the intra tubular pressure increases. Hence, the net hydrostatic pressure across the glomerular capillary wall decreases resulting in reduction in GFR. In later stages, the intraglomerular pressure itself decreases due to angiotensin II and thromboxane A2

mediated vasoconstriction. In long standing obstruction, the parenchyma atrophies and fibrosis and scarring of the tubulointerstitium occurs.

COMPLICATIONS OF AKI

The common complications are:

- Uraemia
- Hypervolumia
- Hyponatremia
- Hyperkalemia
- Metabolic acidosis
- Hyperphosphatemia and hypocalcemia
- Bleeding
- Infections
- Cardiac complications – arrhythmias, pericarditis, pericardial effusion.

Some of these complications can be fatal if left untreated. The average mortality rate in AKI is from 45 % to 60 %.

INDICATIONS OF RENAL REPLACEMENT THERAPY IN AKI

1) BIO-CHEMICAL INDICATIONS

- Refractory hyperkalemia (>6.5 meq/litre)

- Metabolic acidosis (pH ≤ 7.10)
- Electrolyte disturbances (hypercalcemia)
- Tumour lysis syndrome (hyperuricaemia)
- Hyperphosphatemia

2) CLINICAL INDICATIONS

- Urine output < 0.3 ml /kg for 24 hrs)
- Absolute anuria for 12 hrs
- Multiple organ failure
- Volume overload
- Pericarditis
- Uraemic encephalopathy
- Uraemic bleeding

Renal replacement therapy at appropriate time can prevent most of the complications and is life saving. Delay in initiation of dialysis is one of the important causes for mortality in AKI. This delay is in part due to non availability of a single accurate test to diagnose AKI.

DIAGNOSTIC EVALUATION OF AKI:-

In patients presenting with AKI , detailed history, physical examination, urine analysis, review of previous medical records, drug history,

laboratory tests, renal ultrasound and at times, a renal biopsy may be sufficient to find out the cause of AKI.

Special investigations like ANA, ANCA, anti- GBM, complement level, cryoglobins, ASO titre, protein electrophoresis are useful in certain conditions to diagnose the cause of AKI.

Before starting treatment AKI must be distinguished from CKD. This can be done clinically by eliciting antecedent history of renal disease in the past , radiologically using USG abdomen which can assess the renal size. The size of the kidneys will be usually smaller (contracted) in CKD. But in certain chronic conditions like diabetes kidney size may be normal. They can be differentiated from AKI by using history of renal problem in the past. Also certain clinical findings like anaemia, calcium deficiency can point out the cause of renal failure as a chronic condition rather than a acute cause.

It is important to differentiate AKI from CKD because AKI usually needs aggressive treatment and is often reversible with appropriate treatment. Whereas, CKD should be managed in a different way to minimize the complications and to improve the life style of the patient.

But some patients may have acute on chronic kidney disease. In those patients the differentiation is difficult and they should be managed like AKI.

The following table shows some differentiating features between AKI and CKD

FEATURE	AKI	CKD
Antecedent history of renal disease	Absent	Present
Prior sustained elevation of Creatinine for > 3 months	Absent	Present
Anaemia	Usually absent at onset	Present
Elevated serum phosporous, PTH. Decreased serum calcium	Absent (in early phase)	Present
Neuropathy	Absent	Present
Band keratopathy	Absent	Present
Renal bone disease	Absent	Present
Small kidneys on USG	Absent	Present (in some diseases normal/ large size)
Tolerance to azotemia, acidosis	Absent	Present
Stability of azotemia	Absent(daily rise)	Present

Once the diagnosis of AKI is established, then the cause of AKI should be determined. The following table shows some urine diagnostic indices that can differentiate pre renal azotemia from intrinsic AKI.

DIAGNOSTIC INDEX	PRE RENAL AKI	INTRINSIC AKI
Urine Na^+ concentration (meq /litre)	<20	>40
Fractional excretion of Na^+ (%)	<1	>1
Urine urea nitrogen / plasma urea nitrogen ratio	>8	<3
Fractional excretion of urea (%)	<35	>50
Urine osmolality (mOsmol/kg H_2O)	>500	<250
BUN /creatinine ratio	>20	<10 – 15
Renal failure index	<1	>1
Urine sediment	Normal	Granular casts, Epithelial cell casts

HISTORY AND PHYSICAL EXAMINATION:

Careful detailed history is very important to establish the cause of AKI. It should include,

- History regarding urinary symptoms – voiding difficulties, hematuria, dysuria, urine output.
- History of volume overload or volume depletion – peri orbital swelling, weight gain, edema suggests volume overload state, whereas vomiting, hemorrhage, diarrhea, polyuria suggests volume depletion state.
- History of any nephrotoxic drug intake like NSAIDs, ACE inhibitors, aminoglycosides. And also history of intake of any over the counter medications, herbal products should be elicited.
- Any recent exposure to IV contrast is also important.
- History of any antecedent infection should be elicited.
- History of any pre existing illness like hypertension, diabetes, peripheral vascular disease is also important to categorise the risk of AKI.

PHYSICAL EXAMINATION:

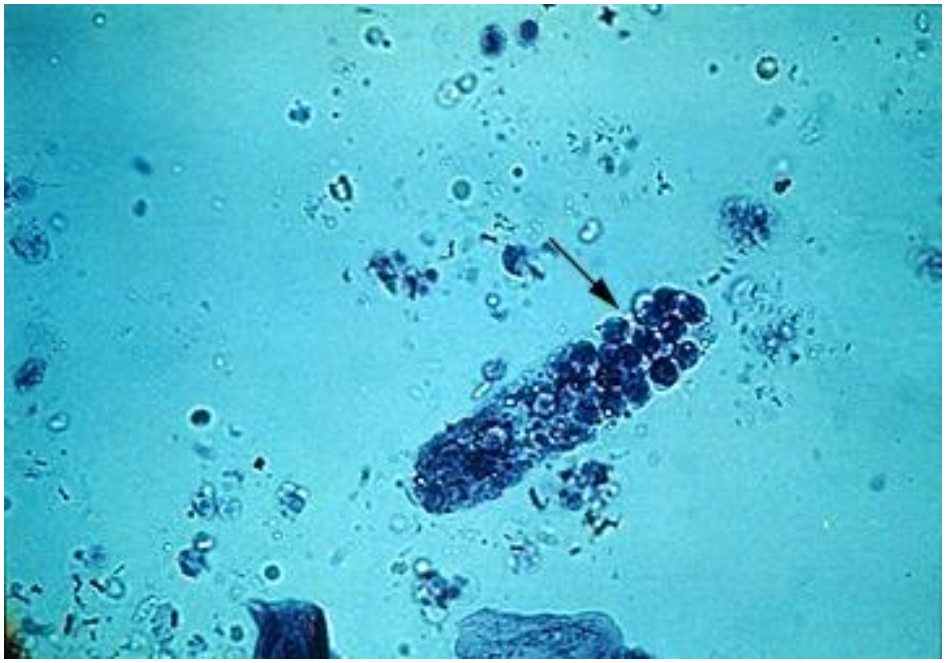
Physical examination is mandatory to assess the volume status of the patient. Physical findings like presence of pedal edema, anasarca, distended neck veins, presence of S3 or S4 gallop, inspiratory crackles at lung bases suggests a volume overload state. Presence of kussumal breathing indicates metabolic acidosis. Other systemic signs like arthritis, rash can provide clues regarding other rare causes of AKI like vasculitis, SLE and other connective tissue disorders.

DIAGNOSTIC TESTS:

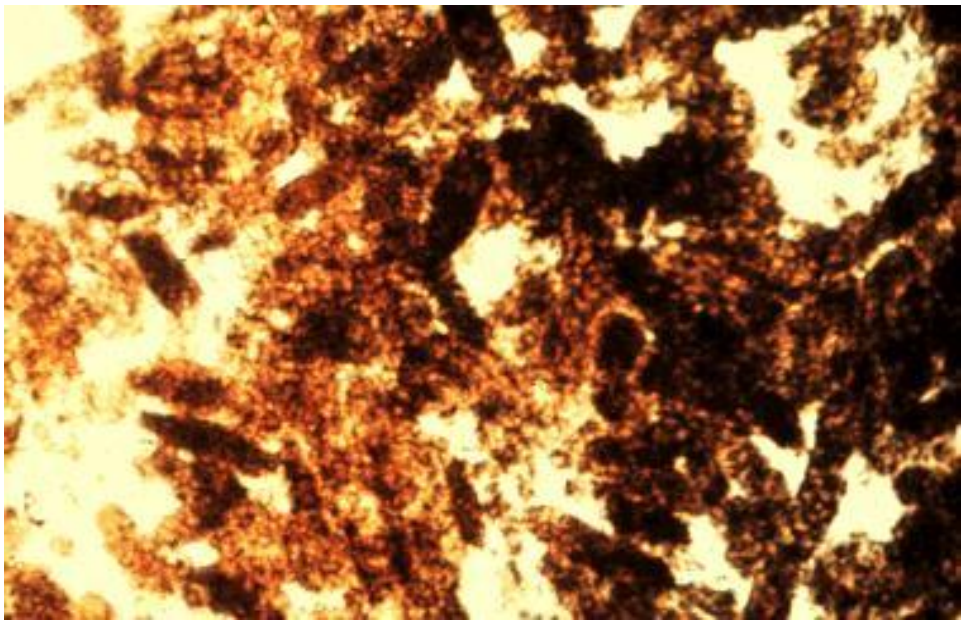
1.URINE ANALYSIS

In the evaluation of AKI, urine analysis and microscopic examination for the presence of any urinary sediment is very important[37]. It not only distinguish pre renal azotemia from post renal causes but also distinguish between tubular, glomerular and interstitial causes.

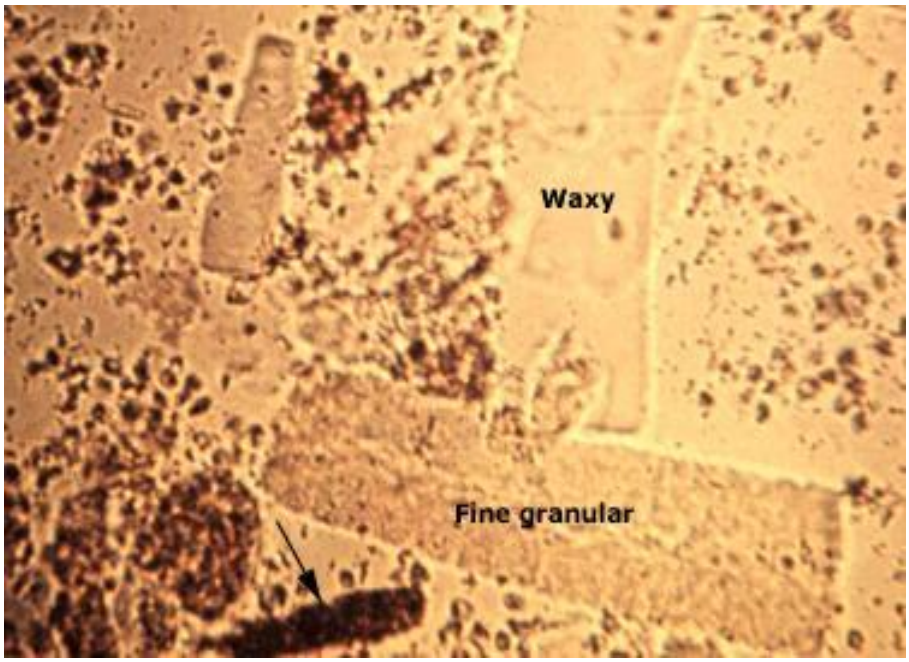
TYPE	SEDIMENT
PRE RENAL	Bland; hyaline cast.
ACUTE TUBULAR NECROSIS	Muddy brown granular cast; epithelial cell cast
GLOMERULO NEPHRITIS	Dysmorphic RBC; RBC cast
ACUTE INTERSTITIAL NEPHRITIS	Eosinophils; WBC and WBC cast.
POST RENAL	Monomorphic RBC and WBC or crystals.



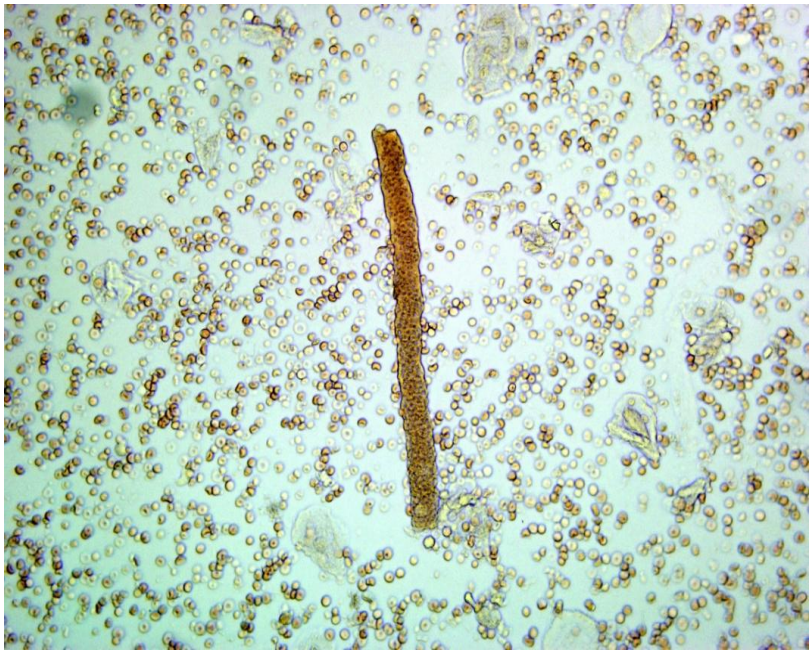
WBC CAST:



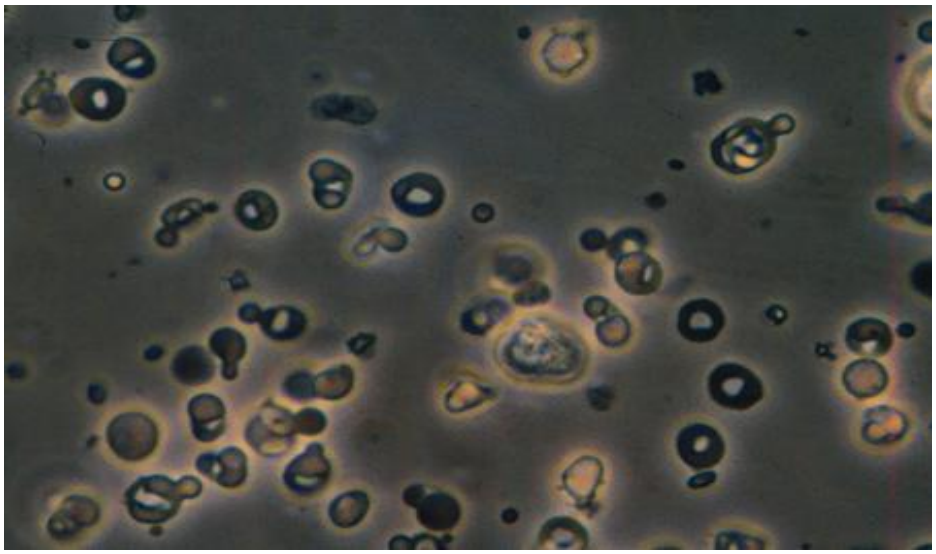
MUDDY BROWN CAST



GRANULAR CAST



RBC CAST



DYSMORPHIC RBC

URIC ACID CRYSTALS

BLOOD INVESTIGATIONS:

Review of blood counts and screening tets for coagulation abnormalities can provide valuable information regarding the cause of AKI. The presence of schistocytes in peripheral smear suggests the presence of DIC, HUS, TTP as a cause of AKI. The investigation should also include serum electrolytes, BUN, creatinine, pH value.

RADIOLOGIC EVALUATION:

Renal ultrasound is very useful in diagnosing urinary tract obstruction and hence a post renal cause for AKI. Also in the initial evaluation of any renal failure ultrasound gives valuable information regarding renal size, echo texture. This is important to distinguish AKI from CKD.

KIDNEY BIOPSY:

Kidney biopsy is not always required in the management of AKI. If the cause of AKI is not apparent then it can help in the diagnosis of certain disease like RPGN. Also it is important in certain conditions like lupus nephritis to correctly classify the disease before starting any immunosuppressive treatment.

MARKERS OF KIDNEY FUNCTION:-

At present there is no single marker available that can predict the kidney function. Serum creatinine and BUN are commonly used to assess the kidney function.

UREA AND UREA CLEARANCE

Urea elimination by kidney is a complex process. Hence BUN is a less useful marker of kidney function plasma level of urea is influenced by many factors other than GFR . Non renal causes for elevated BUN level are GIT bleeding, steroid use, total parenteral nutrition. Also malnutrition, chronic liver disease can cause decrease in BUN level due to reduced production[38].

CREATININE AS A MARKER FOR KIDNEY FUNCTION:-

Creatinine is a metabolic product of creatine and the major sources are skeletal muscles, dietary meat. Daily production of creatinine ranges from 20 to 25 mg / kg / day in males and 15 to 20 mg / kg /day in females.

Creatinine is eliminated by both glomerular filtration and proximal tubular secretion. In healthy individuals, >90% of creatinine elimination is by glomerular filtration and the rest is by tubular secretion. But when renal

function starts declining, the proportion of creatinine which is eliminated by tubular secretion increases upto 50%[39].

Glomerular filtration rate (GFR):

GFR is defined as the sum of the filtration rate of all functional nephrons. The normal value is around 125 ml/min/1.73m^2 for men and 100 ml/min/1.73m^2 for women. GFR is measured by the following formula,

$$GFR = U * V / P.$$

Where, U is the concentration of the substance in urine

P is the concentration of the substance in plasma

V is urine flow rate.

The substrate used should be biologically inert, freely and completely filtered by the glomeruli, neither secreted nor absorbed by tubules, and not degraded by the kidneys.

Inulin was once considered gold standard of exogenously administered markers of GFR. But, a number of factors like scarcity, high cost, problems related to urine collection to determine inulin clearance limits the usefulness of inulin as a marker of GFR. Creatinine is routinely used to calculate GFR.

Estimation of creatinine clearance & GFR by creatinine based equations:

Cock croft- gault formula, modification of diet in renal disease study (MDRD) equation are the two widely used creatinine based equations for the estimation of GFR in adult.

- COCKCROFT – GAULT EQUATION[40]:

$$\text{Est. creatinine clearance} = \frac{(140 - \text{age}) \times \text{body weight} \times 0.85 \text{ (if female)}}{72 \times \text{plasma creatinine}}$$

- MDRD EQUATION :

Est. GFR = $170 \times (PCr)^{-0.999} \times (age)^{-0.175} \times (0.762$ if female) $\times$ (1.180 if African American) $\times (BUN)^{-0.170} \times (albumin)^{+0.318}$.

Cockcroft- gault and MDRD equations are important as they can underestimate GFR with normal renal function and overestimate GFR with severe renal dysfunction.

LIMITATIONS OF CREATINIE AS A MARKER FOR GFR:

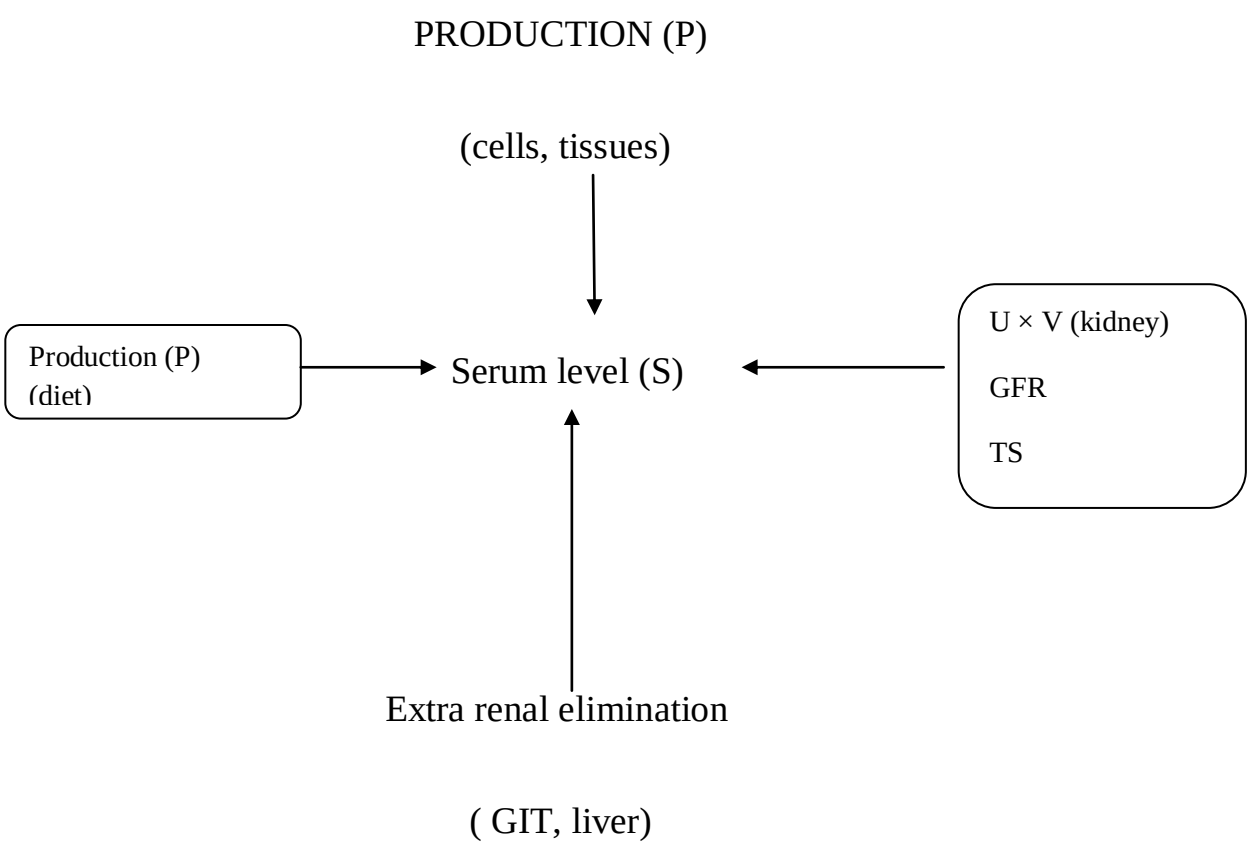
Creatinine based GFR equations tend to over estimate renal function. so,

when using creatinine to assess renal function the following limitations should be considered.

1) Creatinine production depends on certain factors of a patient like body mass, race, age etc…
2) The change in plasma creatinine doesnot correlate with decline in renal function in a linear fashion.
3) The changes in creatinine in an individual should be interpreted based on the baseline creatinine value. For this a base line normal value is essential which is not available in most cases.
4) Creatinine level can also be altered by substances that interfere with the tubular secretion of creatinine. For example, drugs like trimethoprim, cimetidine blocks tubular secretion and hence can increase creatinine level.
5) Creatinine is a useful marker of GFR in the steady state only. In acute kidney injury it does not correlate with the sudden changes in GFR.

So, changes in serum creatinine level lag several days behind actual changes in GFR. Also the alterations in the level of serum creatinine for small changes in GFR are not so sensitive or specific. Hence many other low molecular weight serum proteins have been investigated as suitable endogenous markers of GFR

DETERMINANTS OF SERUM LEVEL OF CREATININE:



Where U × V denotes renal excretion.

(ie) the serum levels are determined by the interaction between production, excretion of creatinine.

NOVEL BIOMARKERS:-

BUN and creatinine are the biomarkers of kidney function. They rise only after a lag period after AKI. Several novel biomarkers are being investigated recently to detect AKI in earlier stage.

MARKER	COMMENT
SSAT	SSAT was able to distinguish ARF with tubular injury from ARF without ATN
CYR61	CYR61 is upregulated in kidneys with IRI—able to distinguish prerenal from intrarenal ARF
IL-18	IL-18 elevated in human kidney ATN (native and transplanted kidneys)
NHE3	NHE3 differentiated prerenal from intrarenal ischemic ATN from other intrarenal causes of ARF
KIM-1	Specific for *ischemic* ARF/ATN when compared with other forms of kidney disease
Gro-α, KC	Gro-α correlates well with renal recovery from AKI/DGF in transplant, early increase in urine and blood well before rise in serum creatinine in ARF models
NGAL	NGAL sensitive, specific and predictive marker of ARF in blood and urine of patients after cardiopulmonary bypass
Actin, IL-6 and IL-8	All three markers predicted prolonged ARF following renal transplantation in humans

CYR61, cysteine-rich protein 61; DGF, delayed graft function; Gro-α, human growth-related oncogene-α; IL-6, interleukin-6; IL-8, interleukin-8; IL-18, interleukin-18; KC, keratinocyte-derived chemokine; NHE3, Na^+/H^+ exchanger isoform 3; SSAT, spermidine/spermine *N*1-acetyltransferase.

- KIM – 1[41] - kidney injury molecule is a transmembrane protein.it is expressed in epithelial cells of proximal convoluted tubules. It is expressed only following ischaemic or toxic injury to the epithelial cells. It is not expressed in significant level in normal state. So, it can be used as a marker for AKI.
- NGAL[42] – neutrophil gelatinase associated lipocalin is also called as lipocalin -2 or siderocalin . it is a protein first detected in granules present in neutrophils. It is found to have some tissue protective effects like binding to iron siderophore complexes. Following an injury and inflammation, its level increases and can be detected both in urine and plasma. The levels of NGAL is found to increase within 24 hours of development of AKI in both urine and plasma. It is particularly useful in cases of AKI following cardio – pulmonary bypass.
- Certain cytokines like IL-6, IL-8 have also been studied as markers of AKI. In cases of AKI following renal transplantation, the levels of these cytokines IL-6, IL-8 are found to be increased in urine.
- Alanine amino peptidase

  It is an enzyme present in brush border of proximal convoluted tubules. It can be measured by using calorimetry.
- Alkaline phosphatase

It is also present in the brush border of proximal convoluted tubules. S1 and S2 segments contains a tissue non specific alkaline phosphatase whereas the S3 segment contains tissue specific (ie) intestinal alkaline phosphatase. It is also measured by calorimetry.

- αglutathione S –transferase

It is present in the cytoplasm of proximal convoluted tubule cells. It is measured by using ELISA and the levels are found to be elevated in AKI and also in renal cell carcinoma.

- Retinol binding protein:

This protein is involved in the transport of vitamin A. it is produced by hepatocytes. In the kidney, it is filtered by the glomerulus and reabsorbed in the proximal tubules. Hence it can be used as a marker of tubular dysfunction. It can be measured by using ELISA or nephelometry.

- Alpha 1 microglobin:

It is also synthesized in liver and filtered by glomerulus. And it is reabsorbed in proximal tubules. so it can be used as a marker of tubular dysfunction. It is measured by using ELISA, nephelometry.

- Beta 2 microglobin:

It is a part of MHC I molecule. So it is expressed by all nucleated cells of the body. Since it is filtered by glomerulus and reabsorbed in

proximal tubules, it can be used as a marker of tubular dysfunction. It is also measured by using ELISA or nephelometry.

- Clusterin:

  It is expressed on dedifferentiated proximal tubular epithelial cells. Its levels are increased in rodent models of AKI, polycystic kidney disease, renal cell carcinoma. But its use in human beings is not yet fully studied. Its levels can be measured by using ELISA.

- N-acetyl – β – (D) glucosaminidase (NGA)

  It is present in lysosomes of proximal tubular cells. It is measured by using calorimetry.

- Cysteine rich protein (CYR-61)

  In cases of ischaemic kidney injury, CYR-61 is induced in proximal tubules of kidney and excreted in urine within a time period of 3-6 hours. It is detected by using WESTERN BLOT method. But there is no quantitative method to estimate CYR-61.

- Osteopontin

  This is found to be increased in rodent models of AKI. Nut its use in human beings is not yet established. It is detected by using ELISA. The levels of osteopontin correlates with the tubulo interstitial fibrosis and inflammation.

- Microalbumin:

  This is very well studied and is an approved marker to monitor progress in patients with chronic kidney disease. Its levels correlate with proximal tubular damage. It is measured by using ELISA and immuno turbidometry. But it is not much specific to diagnose AKI.

- Exosomal fetuin – A:

  It is an acute phase protein and is synthesized in liver and released in to circulation. Its levels in proximal tubule cytoplasm corresponds to the degree of injury. Urinary levels of this acute phase protein is found to be much higher in ICU patients with AKI compared to healthy volunteers and ICU patients without AKI. It is measured by using immunoblotting method.

- Liver fatty acid – binding protein (L-FABP)

  It is present in proximal tubular epithelial cells. It is extensively studied as a bio-marker in chronic kidney disease and diabetic nephropathy. Its utility in AKI is under study. It can be measured by using ELISA.

- γ Glutamyl transpeptidase

  It is present in brush border of proximal convoluted tubules. It is detected by using calorimetry.

- Sodium / hydrogen exchanger isoform (NHES)

  This is a sodium transporter found in the renal tubular cells. Urinary levels of this transporter can be used to discriminate between pre renal azotemia and AKI in ICU patients. It is detected by using immunoblotting method.

URINARY BIO-MARKERS:-

There are certain substances in urine which can be used to diagnose kidney injury at an earlier stage.

- Urine NGAL

  It is significantly increased in patients with ischaemic and nephrotoxic AKI. urinary NGAL was the earliest bio-marker to rise in AKI. In cases of severe ischaemia, NGAL level can be detectable within 3 hours in the urine. Hence, urinary NGAL can be used as an early and sensitive marker for AKI.

- IL-18[(43)]

  Urinary IL-18 is found to have >90% sensitivity and specificity in diagnosing established AKI. Its level in urine rises by 4 to 6 hours after AKI and peak levels are attained by 12 hours and the levels remain elevated upto 48 hours.IL-18 can also be used to predict the development of AKI and this is still under study.

- EGF:

  EGF level in urine is found to be decreased in the presence of AKI. This is because the diseased glomeruli is unable to filter EGF in to urine. Once the renal function gets normalized, the levels of EGF in urine begins to rise and attains the normal value. Hence EGF level in urine may be used as a marker to predict the recovery of renal function.

- IGF-1

  In some studies, IGF-1 level in urine is found to be greater in patients with AKI than normal subjects and this elevated levels of IGF-1 in urine can be used as a marker of renal injury.

- In AKI developed after renal transplantation, certain chemokines like interferon – gamma induced protein of 10 KD (IP-10) , interferon inducible T-cell chemoattractant are found to be increased in urine. But these markers were not studied in AKI with causes other than renal transplantation.
- Other markers like, urinary intercellular adhesion molecule-1 (ICAM-1), urinary endothelin-1(ET) were under study.
- Also in patients with septic shock, certain markers can predict the development of AKI. These include soluble tumor necrosis factor receptors like S-TNF-R1, S-TNF-R2 etc. their levels are fonud to be increased in patients who subsequently develop AKI.

- Other markers to predict prognosis in AKI:

In patients requiring dialysis support in AKI, plasma fibrinogen level was found to be a prognostic factor. Decreased level of plasma fibrinogen is associated with increased mortality

Among these novel biomarkers , cystatin-C have been extensively studied.

CYSTATIN- C

HISTORY:

History of cystatin C dates back to 1961. In 1961, in patients with renal failure, cystatin C was first identified as a trace protein (gamma trace) in CSF and urine. The amino acid sequence of cystatin C was first described by Grubb and Lofberg. Initially it was found to be increased in patient with renal failure. Its role in the measurement of GFR was first demonstrated by Grubb and coworkers in 1985[44]. Following this the role of cystatin C in CKD, AKI has been extensively studied.

Cystatin- C is a protein that belongs to cystatin super family. Cystatin super family includes 3 inhibitory families. Cystatin-C belongs to type 2 cystatin family. It is a cysteine proteinase inhibitor. Its molecular weight is 13 kilodaltons. All nucleated cells in the body produces cystatin-C at a constant rate. It is found in all biological fluids with highest level in semen. Breast milk, saliva, tears also

contains high levels of cystatin –C. It is encoded by CST gene which is located in short arm of chromosome 20[45]. It is a house keeping gene constantly expressed.

Structure:

It is a non glycosylated, basic protein. It structure comprises of a short alpha helix and five stranded beta sheet. It also has two disulphide bonds.

CYSTATIN –C , THE IDEAL MARKER FOR GFR

1) It is freely, completely filtered by glomerular filtration and there is no tubular secretion.
    - Cystatin C is a non- glycosylated protein. Since it doesnot binds to plasma proteins it is eliminated only via glomerular filtration.
2) Constant level in circulation.
    - Cystatin C is produced by all nucleated cells in the body at a constant rate[46]. This is because the gene regulating cystatin C production is a house keeping gene and is constantly expressed. And also, the production of cystatin C is not influenced by inflammatory processes[47].
3) Urine cystatin C – as a marker of tubular dysfunction.
    - Cystatin C is rapidly reabsorbed and degraded in renal tubular cells. In cases of tubular dysfunction, this is impaired and

cystatin C is excreted as such in urine. Hence, cystatin C levels in urine can be used as a marker of tubular dysfunction.

4) Cystatin C is only eliminated by kidney through glomerular filtration. There is no extra renal route of excretion.

CYSTATIN C – BETTER MARKER THAN CREATININE AND CREATININE CLEARANCE:-

Cystatin C level is not affected by

i. Sex[48]
ii. Age
iii. Muscle mass[49]
iv. Protein intake
v. Drugs and metabolic factors

- Serum creatinine levels change according to age. Serum creatinine concentration increases steadily with age. Hence the reference value of serum creatinine value should be adjusted according to age. But serum cystatin c level remains constant after the age of one year.

- Serum creatinine level depends on the muscle mass. Persons having more muscle mass may have increased serum creatinine level. But cystatin c level is independent of muscle mass.
- Serum creatinine level can also be affected by a diet rich in protein. But cystatin c levels is independent of protein intake.
- Also substances that block tubular secretion may interfere in the measurement of serum creatinine. For example, trimethoprim, cimetidine can block the tubular secretion of creatinine. This results in false elevation of serum creatinine levels. Also drugs like cefoxitin, flucytosine can interfere with the measurement of serum creatinine and give falsely high values.
- In patients with DKA, the presence of acetoacetate[38] in the plasma can be falsely detected as creatinine in calorimetry assay and can give falsely high creatinine value.
- Also certain endocrine conditions like hypo/ hyperthyroidism can interfere in plasma creatinine value. But cystatin c measurement is devoid of these limitations and hence it is a better marker than serum creatinine level.
- And also in different laboratories there is no standardization for the measurement of serum creatinine. This can cause intralaboratory variation.

LABORATORY MEASUREMENT OF CYSTATIN C:

Cystatin C can be measured by using radio immune assays, fluorescent or enzymatic immune assays. latex immune assays using cystatin C conjugated with latex particle is found to be superior[50]. The two commonly used latex immune assays are PETIA – Particle Enhanced Turbidometric Immuno Assay, PENIA- Particle Enhanced Nephelometric Immuno Assay. Among these, in 2002 meta analysis study, immunonephelometric method is demonstrated to be superior in the measurement of cystatin C[51]. Dade Behring's automated immunoassay has been approved by FDA for cystatin C estimation.

Reference range for cystatin C :-

For adults and children > 1 yr – 0.53 to 0.95 mg / litre.

Estimation of GFR from serum cystatin C:-

GFR is estimated from serum cystatin C level by using following formulas:

HOEK FORMULA: GFR = - 4.32 +80.35 ×1/ CYSTATIN C

LARSSON FORMULA : $77.239 \times \text{CYSTATIN C}^{-1.2623.}$

Since these formulas are difficult to use in routine use, cystatin C calculator had been developed and using that we can get the GFR by simply entering the value of cystatin C. Also some tables with pre calculated values of GFR for corresponding cystatin C value are available .

The following table helps in the calculation of GFR from cystatin C :-

SERUM CYSTATIN C (mg /litre)	GFR estimated (ml/min)
0.6	145
0.7	119
0.8	99
0.9	85
1.0	74
1.1	65
1.2	58
1.3	52
1.4	47
1.5-1.6	41
1.7-1.8	35
1.9-2.0	30
2.1-2.3	26
2.4-2.6	22
2.7-3.7	18

ROLE OF CYSTATIN C IN OTHER CLINICAL CONDITIONS :-

- Cystatin C and risk of cardiovascular disease and death[52].

  Increased levels of cystatin C are found to be associated with increased risk of several cardiovascular diseases like MI, heart failure, peripheral arterial disease and also with increased risk of death.

- Cystatin C and renal transplantation and acute rejection in adults.

  Cystatin C has increased sensitivity compared with creatinine for the detection of acute reduction in GFR in cases of renal transplantation and hence helps in early detection of acute rejection.

- Cystatin C in cancer chemotherapy

  Cystatin C is superior to serum creatinine in estimation of kidney function in patients with cancer independent of the presence of metastases or chemotherapy.

- Cystatin C and cirrhosis

  In cirrhosis, due to decreased protein intake, low muscle mass and lack of conversion of creatine to creatinine, creatinine clearance is not ideal for the measurement of GFR. Hence serum cystatin C can be used to measure GFR in patients with cirrhosis.

- Cystatin C and neurological disorders

Icelandic type of hereditary cerebral amyloid angiopathy is associated with mutations in cystatin 3 gene. This condition predisposes to ICH, stoke, dementia. Also CST3 gene is implicated in the genesis of Alzheimer's disease. Cystatin C levels have been reported to be higher in patients with Alzheimer's disease.

- Decreased levels of cystatin C have been associated with increased incidence of atherosclerosis and aneurysmal lesions of aorta. This is because these lesions are due to imbalance between the proteinases and their inhibitors. Since cystatin C is a proteinase inhibitor, its deficiency can cause increased activity of proteinases leading to damage and atherosclerosis.
- Likewise in malignancy, decreased levels of cystatin C is found to be associated with more invasiveness of the tumor and metastasis.
- Also the role of cystatin C in demyelinating diseases like multiple sclerosis have been studied. But its role still remains controversial. Further studies are needed to clarify its role.
- Other conditions:

  cystatin C is also found to be associated with age related macular degeneration, pre eclampsia etc.

AIMS AND OBJECTIVES:

1. To evaluate the role of cystatin-C as a biomarker for the early detection of AKI.

2. To compare the predictive ability of cystatin-C with serum creatinine level in early prediction of AKI.

3. To assess the correlation of cystatin-C level with the severity of AKI.

4. To assess the correlation of cystatin-C level with the outcome of AKI.

MATERIALS AND METHODS:

Setting : In patients,

Thanjavur medical college hospital,

Thanjavur.

Ethical committee approval : obtained

Design of study : single centre, prospective observational study

Period of study : April 2012 to November 2012

Sample size : 60 patients

SELECTION OF PATIENTS

INCLUSION CRITERIA:

Patients at risk of developing AKI.

EXCLUSION CRITERIA:

- Patients with diabetes mellitus
- Patients with systemic hypertension, CAD
- Patients with CKD
- Patients with chronic NSAID abuse
- Patients with native drug intake
- Chronic smoking, alcoholism.

METHODOLOGY:

Patients at risk of developing AKI (ie) history of preceding snake bite, ADD, febrile illness with symptoms suggestive of AKI were selected. Patients having one or more risk factors for CKD and patients already having CKD are excluded. Also patients with history of alcohol abuse and chronic smoking were excluded since these can interfere with the measurement of cystatin C.

Patients social, demographic, economic and medical details were recorded in the proforma sheet. Also the history regarding the symptoms of AKI like decrease in urine output was recorded and the duration of symptoms (in hours) was also recorded. Base line clinical examination of patient was done. Vitals were recorded. Baseline investigations done. USG abdomen was done for all patients to assess the renal size and texture to rule out CKD.

Serum creatinine level and serum cystatin level were measured on the day of admission. Then all of them were followed for the development of AKI. Serum creatinine was measured daily and development of AKI was assessed with staging system for AKI proposed by AKIN group (ie),

Stage 1 = rise in serum creatinine ≥ 0.3 mg/dl or ≥ 150 to 200% from baseline.

Stage 2 = rise in serum crearrtinine > 200 to 300 % from baseline.

Stage 3= rise in serum creatinine >300% from baseline or serum creatinine

>4mg with an acute rise of atleast 0.5mg/dl.

The day the AKI criteria was fulfilled according to serum creatinine was noted as day -I. We used either the rise in serum creatinine of ≥ 0.3 mg/dl or ≥ 150 to 200 % from baseline to diagnose AKI. patients who did not develop AKI

served as controls. In controls, serum creatinine was measured for a minimum of 5 days starting from the enrollment. Also the duration of stay in hospital is noted for all patients and the number of dialysis needed for those who developed AKI was also recorded.

STATISTICAL ANALYSIS:

The end point was the day AKI was detected by serum creatinine according to the staging system of AKI given by the AKIN group. And this was compared with the day, cystatin C levels were abnormal. Student-t test was applied to find out the difference in mean serum cystatin C values of those who developed AKI and those who did not developed AKI.

RESULTS

Of 60 patients studied, 41 patients developed AKI according to the AKIN- staging of AKI , detected by an increase in serum creatinine of $\geq$ 0.3 mg/dl or $\geq$ 150 to 200% (table: 1). Among them, for 40 patients the serum cystatin C levels were abnormal in day 1 itself. . Only one patient had normal serum cystatin C level on day 1 and developed AKI subsequently.(table : 5)

But, all 41 patients had normal serum creatinine level on day 1 and the day of development of AKI according to serum creatinine level (day –I) was either day 2 or day 3. (table:6)

Table:1

DEVELOPMENT OF AKI	NUMBER	PERCENTAGE
YES	41	68.3
NO	19	31.7
TOTAL	60	100

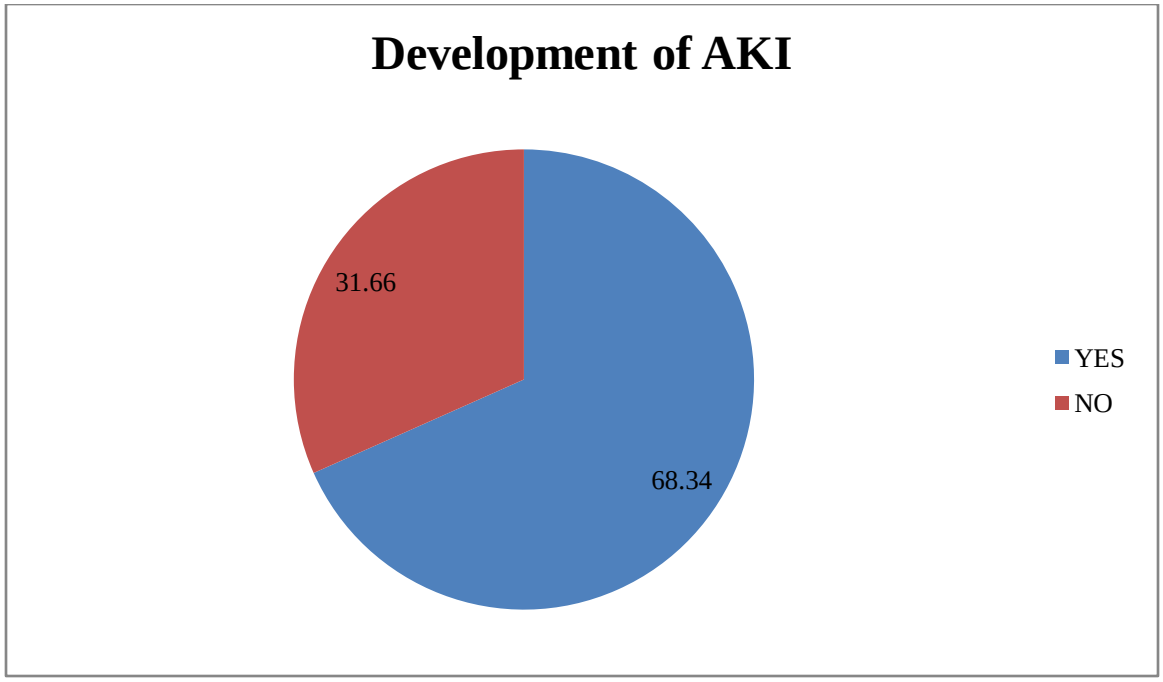


Table:2

	NUMBER	PERCENTAGE
MALE	29	48.3
FEMALE	31	51.7

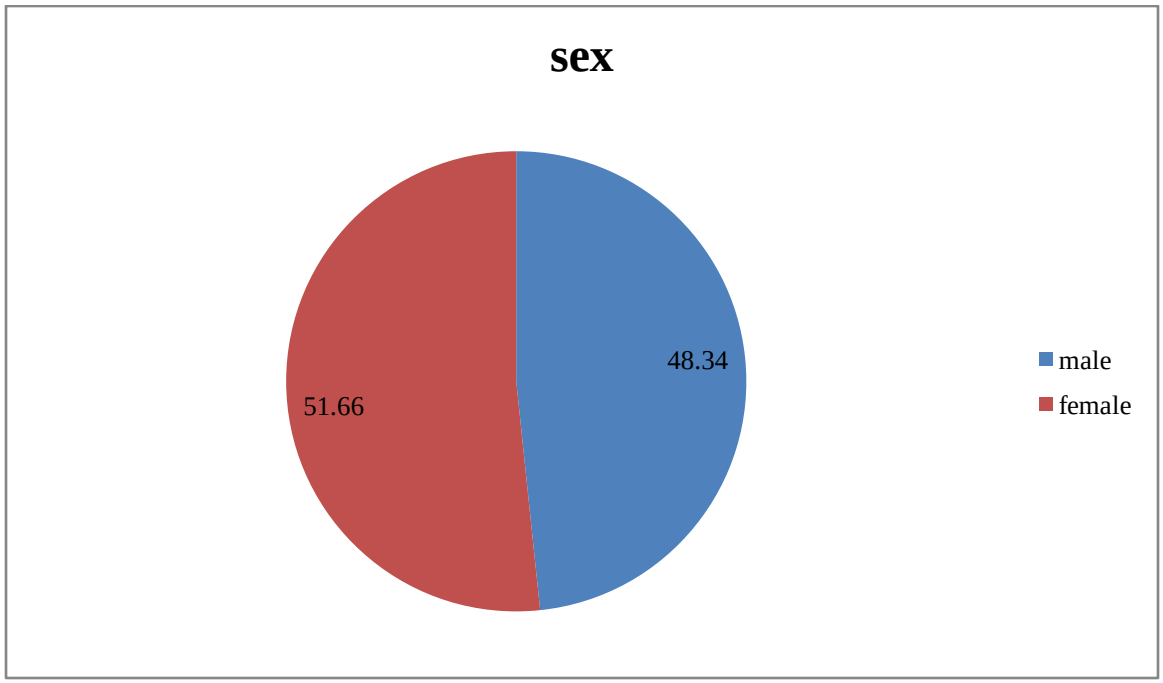


Table:3

DURATION OF SYMPTOMS (IN HOURS)	NUMBER	PERCENTAGE
5 hrs or less	10	16.67
>5 hours	50	83.33
Total	60	100

Table :4

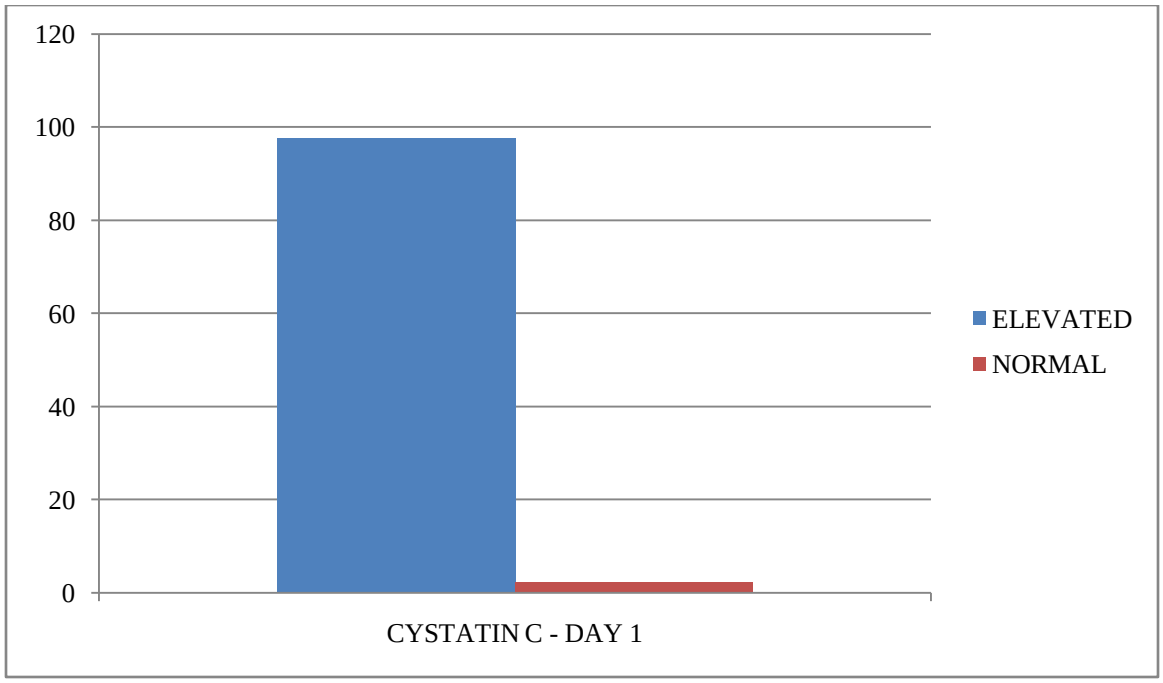
DURATION OF SYMPTOMS (IN HOURS)	NUMBER	PERCENTAGE
3	2	3.3
4	4	6.7
5	4	6.7
6	16	26.7
7	10	16.7
8	12	20.0
9	5	8.3
10	7	11.7
T0TAL	60	100

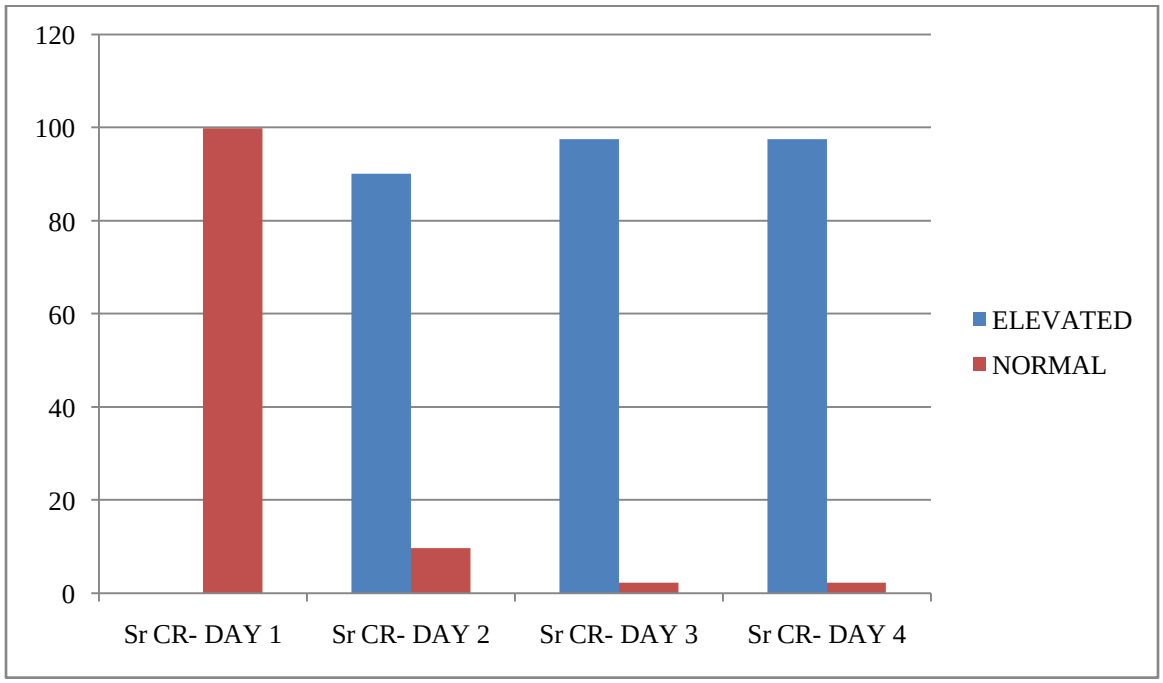
Table :5

	ABNORMAL (ELEVATED)	NORMAL
SERUM CYSTATIN C (DAY 1)	40 (97.6)	1 (2.4)

Table :6

	ABNORMAL (ELEVATED)	NORMAL
SERUM CREATININE DAY-1	0 (0%)	60 (100%)
SERUM CREATININE DAY-2	37 (90.2%)	4 (9.8%)
SERUM CREATININE DAY-3	40 (97.6%)	1 (2.4%)
SERUM CREATININE DAY-4	40 (97.6%)	1 (2.4%)
SERUM CREATININE DAY-5	40 (97.6%)	1 (2.4%)


120
100
80
60
40
20
0
ELEVATED
NORMAL
CYSTATIN C - DAY 1


120
100
80
60
40
20
0
ELEVATED
NORMAL
Sr CR- DAY 1
Sr CR- DAY 2
Sr CR- DAY 3
Sr CR- DAY 4

On applying Student T test for independent samples, there is significant difference (P value<0.001) in mean serum Cystatin values of those who developed AKI and who didn't develop whereas there is no difference in mean serum creatinine values (day one) of those who developed AKI and who didn't develop.

DISCUSSION

Our study shows that serum cystatin C performs as a good marker to detect AKI. And also serum cystatin C permits detection of development of AKI one to two days earlier than the conventional renal function marker serum creatinine. Serum cystatin C was found to be elevated within 6 hours of acute renal insult.

Serum cystatin C >0.95 mg/litre ie , the above the normal range was found to predict the disease course of AKI. Serum cystatin C sensitivity in picking up AKI was found to be more than serum creatinine. These finding is of clinical importance because early detection of AKI provides time to prevent the progression of AKI. It helps to initiate preventive measures earlier and thereby helps to reduce mortality associated with AKI.

Immunonephelometric assay provides rapid, automated measurement of cystatin C within 10 minutes. Serum cystatin C estimation by this method is very accurate and precise. Its reliability is approved by FDA. Pre analytic conditions like clinical storage and freezing and thawing of blood samples and interfering substances like bilirubin and triglyceride can affect measurement of serum creatinine. But serum cystatin C measurement is independent of above disturbances. Serum cystatin C levels reflects even slight change in GFR more rapidly when compared to serum creatinine. This may be due to thefact serum cystatin C is an ideal marker of glomerular filtration than creatinine. Because using serum creatinine as a marker for GFR has certain limitations like tubular secretion, influence by age and body mass. Besides this, in a study by Herget – Rosenthal, Marggraf G, Husing J and et al[53], " early detection of acute renal failure by cystatin C" , they also found out that,

'serum cystatin c is a useful detection marker of ARF, and may detect ARF one to two days earlier than creatinine'.

In our study also among the 41 patients who developed AKI, cystatin C predicts AKI in 40 patients in day 1 itself. The predictive value is 97.6%. In only one patient who developed AKI cystatin C value is normal on day 1.

On the other hand, among the 41 patients who developed AKI, all had normal serum creatinine value on day 1. The predictive value is 0%. On day 2 serum creatinine value is found to be increased in 37 patients with a predictive value of 90.2%. on day 3 40 patients had increased serum creatinine value and the predictivity rises to 97.6% reaching that of cystatin C on day 1.

In a study, " serum cystatin C a superior marker of rapidly reduced glomerular filtration after nephrectomy in kidney donors compared to creatinine" by Hergert Rosenthal S, Pietrick F and et al[(54)], they found that,

'serum cystatin c detects rapid GFR decrease one to two days earlier than creatinine. Cystatin c is an early and accurate marker to detect rapid GFR decreases as in ARF'.

In the study patient with history of snake bite, ADD, febrile illness and at risk of developing AKI were included. During our study the etiology AKI does not seems to have any effect on the predictive value of serum cystatin C in AKI. Also patient with history of chronic alcoholism, smoking were excluded from the study. This was done to ensure that the measurement of serum cystatin C level should be accurate and should not be modified by any other factors besides AKI. This enhances the usefulness of serum cystatin C as an ideal marker to detect AKI.

We selected only patients at risk of developing AKI and also the study group were previously normal persons with out any other risk factors for the development of AKI.

The efficacy of cystatin C has been studied in many special situations. In a study by Carlo Briguari, MD, PhD:, Gabriella Visconti, MD; and et al[55], they concluded that,

'In patients with CKD cystatin c seems to be a reliable marker for the early diagnosis and prognosis of contrast induced acute kidney injury'.

In a study by Qiang Li, Jie-yu Fang, Wei- ping Wang and et al[56], they found out that,

'There is renal injury at early stage of shock. Cystatin C is more sensitive than serum creatinine in assessing renal function at the early stage of shock'.

Also cystatin C level is found to be a better marker of kidnry function than serum creatinine level in ICU patients. In a study by Maryam Nejat, John W.pickering and et al[57], they found out that,

'plasma cystatin c was an effective and earlier surrogate marker of decreased renal function than serum creatinine in a general ICU patients'

Also there is a conflict that the inflammatory process in sepsis can affect cystatin c measurement. But in a study by John Martensson, Max Bell and et al[58],

'the inflammatory response induced by sepsis has no impact on the level of cystatin c in plasma during the first week in the ICU'.

Few other studies have also supported our finding that changes in GFR can be predicted more rapidly, accurately by serum cystatin c than serum creatinine level.

Serum cystatin c values can also be used in patients with chronic kidney disease to predict the prognosis. In a study by Carmen A.Peralta, William Mc clellan MD, MPH, Neil A.Zakasi MD and et al[59], they found out that

'Adding cystatin c to the combination of creatinine and albumin-creatinine ratio measures improved the predictive accuracy for all cause mortality and end stage renal disease'.

LIMITATIONS AND STRENGTH OF THE STUDY:

- Thyroid hormones and glucocorticoid levels can affect the serum cystatin c level. In our study we did not measured serum T3,T4 levels or serum cortisol

level. But neither of our patients had symptoms suggestive of hypothyroidism or glucocorticoid deficiency.

- In our study only patients with normal creatinine level were included. These type of patients with initial normal levels of serum creatinine are generally given less priority and may left unnoticed until they develop AKI. Measuring cystatin C level in these patients may be more beneficial because they can be given special attention and the course of AKI can be altered by early initiation of preventive measures.
- Also these findings may not be suitable for patients with acute on chronic kidney disease.
- Also the serum cystatin c level is measured only on day 1. After that only serum creatinine levels are measured daily.
- Also in our study among the 41 patients who developed AKI , 39 recovered completely with treatment, dialysis support. Only two died. And those who died have been found to have elevated cystatin C level in day 1(>2.2). because of the small number (n=2), we cannot determine the correlation between the cystatin C level and mortality in AKI.

CONCLUSION

- Cystatin C levels predicts AKI better than serum creatinine level.

- Cystatin C levels can predict AKI earlier than serum creatinine value. It can predict AKI atleast 1 or 2 days earlier than serum creatinine.

- The association of cystatin C levels with mortality can not be assessed because of small sample size. Further studies are needed.

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ABBREVIATIONS

1. **ACE** – Angiotensin converting enzyme

2**. ADH** – Anti diuretic hormone

3. **ADD** – Acute diarrheal disease

4. **AKI** – Acute kidney injury

5. **ANCA** – Anti neutrophil cytoplasmic antibody

6. **ANA** – Anti nuclear antibody

7. **ARB** – Angiotensin receptor blocker

8. **ARF-** Acute renal failure

9. **ASO** – Anti strepto lysine – O

10. **ATN** – Acute tubular necrosis

11. **BUN** – Blood urea nitrogen

12. **CAD** – Coronary artery disease

13. **CCF** – Congestive cardiac failure

14. **CIN** – Contrast induced nephropathy

15. **CKD**- Chronic kidney disease

16. **DIC**- Disseminated intravascular coagulation

17. **DKA**- Diabetic ketoacidosis

18**. EGF** – Epidermal growth factor

19. **ELISA**- Enzyme linked immunosorbent assay.

20. **FDA** – Food and drug administration

21. **GFR**- Glomerular filtration rate

22. **HUS**- Hemolytic uremic syndrome

23. **ICU**- Intensive care unit

24. **IGF-1**- Insulin like growth factor -I

25. **KIM-1**- Kidney injury molecule-I

26. **MDRD**- Modification of diet in renal disease.

27. **MI**- Myocardial infarction

28. **NGAL**- Neutrophil gelatinase associated lipocalin

29**. NSAID**- Non steroidal anti inflammatory drug

30. **PAF**- Platelet activating factor

31**. PTH**- Parathyroid hormone

32. **RBC**- Red blood corpuscle

33. **RPGN**- Rapidly progressive glomerulo nephritis

34. **SCr**- Serum creatinine

35. **SLE**- Systemic lupus erythematosus

36. **TTP**- Thrombotic thrombocytopenic purpura

37. **WBC**- White blood corpuscle

PROFORMA

Name: Age: Years Sex: Male/Female

Address: IP No:

Occupation: Date and time of admission:

Date and time of discharge/death:

Duration of inpatient stay:

HD / PD :

HISTORY:

Admitted with c/o:

H/O presenting illness:

Past history: DM/HT/CAHD/CKD/NSAID abuse/COPD/NATIVE DRUG INTAKE/ GLOMERULONEPHRITIS

Personal history: smoker/alcoholic

Family history:

Treatment history/ any surgical procedure:

CLINICAL FEATURES:

Level of consciousness:

G/E: pallor/icterus/clubbing/cyanosis/pedal edema/skin lesions(purpura,echymosis,rash).

Dyspnoeic/ facial puffiness/ anasarca. JVP:

Pulse: / min BP: / mmHg. RR: / min.

CARDIOVASCULAR SYSTEM: S1,S2 , murmur , pericardial rub .

RESPIRATORY SYSTEM: VBS , Crackles

ABDOMEN EXAMINATION:

CENTRAL NERVOUS SYSTEM:

INVESTIGATIONS:

	on admission / /2012	/ / 2012	/ / 2012	/ /2012	/ / 2012
Blood urea mg%					
Serum creatinine mg%					
Serum Cystatin C mg/l (duration of symptoms)					

2. Serum electrolytes sodium- meq/l
Potassium- meq/l

3. USG abdomen:
Right kidney - mm* mm. Echo- , CMD- .
Left kidney - mm* mm.Echo- , CMD- .
IMP:

4.COMPLETE BLOOD COUNT:
Hb: gm%
Tc: cells/cubic mm.
Dc: P % L % E %
RBC: cells/cubic mm.
Platelets: cells/cubic mm.

5. URINE:
Albumin -
Sugar -
Deposits -

6.ECG:

7. Chest X-ray :

TREATMENT GIVEN:

OUTCOME:

MASTER CHART

S.NO	NAME	AGE	SEX	DURATION OF SYMPTOMS	Bl.UREA	Sr.CYSTATIN C	Scr D1	Scr D2	Scr D3	Scr D4	Scr D5	DI	NO. OF DIALYSIS	DURATION OF STAY	OUTCOME
1	RAJAKUMARI	40	2	10	41	1.1	0.6	1.9	3	3.9	5	2	4	15	1
2	PALANI	45	1	6	42	1.3	0.8	2	2.9	5	5.8	2	5	19	1
3	RAJENDRAN	58	1	5	40	0.9	0.8	0.8	0.9	0.8	0.7	-	0	5	1
4	KUPPUSAMY	60	1	6	38	1.2	0.8	1	1.4	2.7	4	3	2	10	1
5	NATARAJAN	60	1	6	40	1.4	0.7	1.9	3	5.3	7	2	5	20	1
6	SIVASANKARAN	19	1	6	42	1.1	0.9	1	1.6	3.8	5.2	3	3	11	1
7	NEELAMEGAM	40	1	4	40	0.7	0.7	0.8	0.9	0.8	0.8	-	0	5	1
8	DHANALAKSHMI	42	2	10	41	1.2	0.7	1.9	4	5.5	6	2	4	14	1
9	SHAHUL HAMED	60	1	4	38	0.89	0.7	0.7	0.8	0.8	0.7	-	0	5	1
10	VALAMBAL	50	2	10	40	1.4	0.9	3.1	4	6.9	7.2	2	7	26	1
11	SHOBANA	13	2	3	40	1.2	0.8	0.9	1.3	3.9	4.6	3	2	11	1
12	MALLIKA	45	2	3	43	1.3	0.7	2.2	4	5.7	6	2	4	11	1
13	GUNASEKARAN	60	1	4	38	0.8	0.8	0.8	0.9	0.7	0.8	-	0	5	1
14	JOHN KENNADY	36	1	4	42	1.3	0.8	3	4.5	6	5.8	2	4	10	1
15	SAVITHRI	58	2	8	42	1.2	0.7	1.6	3.9	6	7	2	4	12	1
16	SIVAPRAKASAM	48	1	5	44	1.2	0.7	1.8	4	5.1	6.8	2	3	13	1
17	MAHALINGAM	30	1	6	40	0.88	0.8	0.7	0.8	0.9	0.7	-	0	6	1

18	ANANDAN	38	1	8	41	1.5	0.9	1.1	1.9	7.2	6.5	3	6	12	1
19	RAJAMMAL	58	2	6	40	1.7	0.8	3.7	6	7.3	8	2	7	21	1
20	POOMANI	50	2	5	40	0.7	0.7	0.8	0.8	0.9	0.7	-	0	5	1
21	BHAKIYAM	40	2	5	42	1.6	0.7	3	4.9	6	11	2	8	19	1
22	MOHAMMED HUSAIN	43	1	6	38	0.8	0.8	0.7	0.9	0.8	0.8	-	0	6	1
23	RENUKA	32	2	6	40	1.4	0.8	1	1.5	4.8	6.2	3	3	13	1
24	MARIMUTHU	50	1	7	36	0.77	0.8	0.8	0.7	0.7	0.8	-	0	5	1
25	KANSUL	24	1	6	40	1.5	0.8	1.9	2.8	4	5.1	2	5	15	1
26	ANJAN	50	1	6	40	0.85	0.7	0.9	0.9	0.8	0.8	-	0	5	1
27	NATESAN	60	1	8	45	2.1	0.8	4	7.9	12	15.6	2	10	27	1
28	YEGAMBAL	50	2	8	41	1.9	0.8	3.2	4.9	7	8.2	2	7	14	1
29	MARIMUTHU	47	1	7	40	2	0.8	4.4	5.8	6.1	9	2	8	15	1
30	LATCHAMPOO	40	2	8	45	1.9	0.9	3.2	5	8.9	7.9	2	9	17	1
31	VADIVEL	32	1	8	38	0.8	0.9	0.8	0.8	0.7	0.8	-	0	5	1
32	VASANTHA	41	2	6	40	1.9	0.7	1.6	5.8	8	6.8	2	6	18	1
33	SHOBANA	11	2	8	41	2.1	0.8	4.6	5.3	6.9	10	2	8	20	1
34	SEETHALA DEVI	4	2	6	40	1.7	0.8	1	4.1	6.2	7	3	6	13	1
35	ANNAKILI	29	2	7	39	0.82	0.8	0.8	0.9	0.9	0.7	-	0	6	1
36	SELVAKUMAR	29	1	8	46	2.1	0.8	3.9	5	8.8	9	2	7	18	1
37	MUTHULAKSHMI	40	2	7	40	0.79	0.7	0.7	0.8	0.9	0.8	-	0	5	1
38	CHITHRA	30	2	6	40	1.7	0.9	1	2.6	3.8	5.2	3	5	14	1
39	INDIRA	23	2	8	40	1.8	0.8	1.1	1.9	4.5	7	3	6	12	1
40	KASINATHAN	40	1	8	42	1.9	0.9	1.1	2.4	5.2	5.4	2	7	10	1
41	ANJAMMAL	40	2	8	40	0.78	0.8	0.9	0.8	0.9	0.7	-	0	6	1
42	VIJAY	14	1	9	46	2.3	0.9	4.1	6	7.9	10	2	9	21	1
43	JAYALAKSHMI	60	2	10	38	2.1	0.8	2.2	3.9	5.1	8	2	7	20	1
44	RAJAKUMARI	40	2	6	36	0.81	0.7	0.6	0.8	0.9	0.8		0	5	1

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45	MURUGANATHAN	18	1	7	45	1.7	0.9	1	1.8	3	4.4	3	5	12	1
46	SELVI	28	2	7	42	1.9	0.8	2.1	4	4.9	5.4	2	6	15	1
47	RADHIKA	35	2	9	34	0.79	0.7	0.6	0.7	0.6	0.7	-	0	7	1
48	SENTHILNATHAN	40	1	7	46	1.7	0.7	1.9	3.8	4.1	5.4	2	6	15	1
49	AYYAMMAL	40	2	6	30	0.69	0.7	0.7	0.7	0.8	0.7	-	0	8	1
50	DEVARAJ	45	1	8	42	1.9	0.7	0.9	2.6	4.9	5	3	8	15	1
51	USHA	50	2	7	45	1.7	0.7	0.8	1	2.2	3.9	3	7	10	1
52	MALAR	30	2	7	33	0.75	0.6	0.7	0.8	0.7	0.7	-	0	6	1
53	SRINIVASAN	42	1	6	45	1.7	0.8	3.9	5.6	5.5	7	2	6	14	1
54	JAYALAKSHMI	46	2	7	36	0.7	0.8	0.8	0.7	0.7	0.7	-	0	5	1
55	KASTHURI	50	2	10	46	2	0.7	2.9	4.8	6.3	6.9	2	8	19	1
56	JOHN PETER	50	1	9	40	2.1	0.8	3.8	6	8	8.8	2	9	25	1
57	GANESAN	55	1	9	38	0.85	0.7	0.7	0.8	0.9	0.9	3	0	5	1
58	THAMBUSAMY	50	1	10	48	2.7	0.8	3.7	5.2	8.8	9.1	2	10	21	2
59	ANJALAI	50	2	10	46	2.4	0.9	4.3	5.6	8.9	7.8	2	8	20	2
60	VEMBU	45	2	9	32	0.77	0.8	0.9	0.8	0.8	0.8	-	0	6	1