A PROSPECTIVE STUDY OF KIDNEY RELEATED DISEASES AND THEIR CLINICAL MANAGEMENT IN PATIENTS FROM SOUTH TAMILNADU

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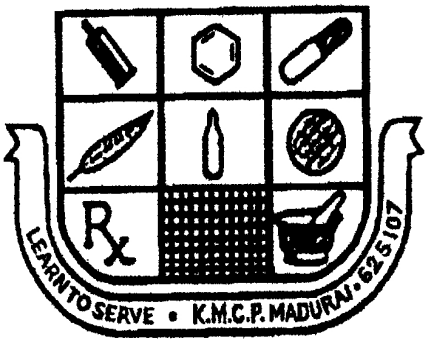

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This is a bonafide dissertation work entitled **"A PROSPECTIVE STUDY OF KIDNY RELEATED DISEASES AND THEIR CLINICAL MANAGEMENT IN PATIENTS FROM SOUTH TAMILNADU "** submitted by **K. NAGOOR GANI,** Register No. **26111783** to The Tamilnadu Dr. M.G.R. Medical University, Chennai , in partial fulfillment of the requirement for the award of Master of Pharmacy in Pharmacy Practice (Branch- VII) at K.M. College of Pharmacy, Madurai, is a work carried out by him under my guidance and super vision during the year 2012-2013.

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CONTENTS

ABBREVIATIONS

CKD	-	CHRONIC KIDNEY DISEASES
ARF	-	ACUTE RENAL FAILURE
CRF	-	CHRONIC RENAL FAILURE
GFR	-	GLOMERULAR FILTRATION RATE
ESRD	-	END STAGE RENAL DISEASES
RRT	-	RENAL REPLACEMENT THERAPY
BUN	-	BLOOD UREA NITROGEN
HB	-	HAEMO DIALYSIS
QOL	-	QUALITY OF LIFE
HRQOL	-	HEALTH RELATED QUALITY OF LIFE
PD	-	PERITONIAL DIALYSIS
MUE	-	MEDICATION USE EVALUTION

INTRODUCTION

RENAL DISEASES [8]

Renal diseases are as complex as its structure, but there is facilitated by dividing them into those that affect the four basic morphologic components: - glomeruli, tubules, interstitium and blood vessels. Some components appear to be more vulnerable to specific forms of renal injury; eg:-most glomerular diseases are immunologically mediated, whereas tubular and interstitial disorders are frequently caused by toxic (or) infectious agents. In addition the anatomic and functional interdependence of the components of the kidney implies that damage to one almost always secondarily affects the others.

Severe glomerular damage impairs the flow through the peritubular vascular system and also delivers potentially toxic products to tubules – tubular destruction by increasing intraglomerular pressure may induce glomerular atrophy. However, there is a tendency for all forms of chronic renal diseases ultimately to destroy all four components of the kidney, culminating in chronic renal failure and what has been called End Stage Renal Disease.

Renal diseases are responsible for a great deal of morbidity. Approximately 70,000 deaths are attributed yearly to renal diseases in united states. Millons of people are affected annually by non- fatal kidney diseases, most notably infections of the kidney or lower urinary tract, kidney stones and urinary obstruction. Similarly dialysis and transplantation keep many patients alive who would formerly have died of renal failure. Adding to the pool of renal morbidity.

Clinical manifestations of renal diseases:- [8]

The clinical manifestations of renal diseases can be grouped into reasonably well-defined syndromes.

Azotemia is a biochemical abnormality that refers to an elevation of the BUN and creatinine levels and is related largely to a decreased GFR. Azotemia is produced by many renal disorders, but it also arises from extra-renal disorders.

Pre-renal azotemia is encountered when there is hypoperfusion of the kidneys (eg: in hemorrhage, shock, volume depletion, CRF) that impairs renal function in the absence of parenchymal damage.

Similarly post-renal azotemia is seen whenever urine flow is obstructed below the level of the kidney. Relief of the obstruction is followed by correction of the azotemia.

When azotemia becomes associated with a constellation of clinical signs and symptoms and biochemical abnormalities, it is termed **uremia.** Uremia is characterized not only by failure of renal excretory function, but also by a host of metabolic and endocrine alterations, secondary involvement of the gastro-intestinal system (eg: uremic gastroenteritis) , peripheral nerves (eg: peripheral neuropathy) and heart (eg: uremic fibrinous pericarditis) , which is usually necessary for the diagnosis of uremia.

The clinical presentations of renal disease include:-

Acute Nephritic Syndrome is a glomerular syndrome dominated by the acute onset of usually grossly visible hematuria, mild to moderate proteinuria and hypertension – classic presentation of acute post streptococcal glomerulonephritis.

Nephrotic Syndrome is characterized by heavy proteinuria (more than 3.5gm/day), hypoalbuminemia, severe edema, hyperlipidemia and lipiduria.

Asymptomatic hematuria (or) Proteinuria (or) a combination of both is usually a manifestation of subtle (or) mild glomerular abnormalities.

Acute Renal Failure is dominated by oliguria (or) anuria, with recent onset of azotemia. It can result from glomerular , interstitial (or) vascular injury (or) acute tubular necrosis.

Chronic Renal Failure is characterized by prolonged symptoms and signs of uremia, is the end result of all chronic renal parenchymal diseases.

Renal Tubular Defects are dominated by polyuria, nocturia and electrolyte disorders (eg: metabolic acidosis). They are the result of either diseases that directly affect tubular structure (eg: medullary cystic diseases) or defects in specific tubular functions. The latter can be inherited (eg: familial nephrogenic diabetes, cystinuria, renal tubular acidosis) or acquired (eg: lead nephropathy).

Urinary Tract Infection is characterized by bacteriuria and pyuria. The infection may be symptomatic (or) asymptomatic and it may affect the kidney (pyelonephritis) or the bladder (cystitis) only.

Nephrolithiasis (renal stones) is manifested by renal colic, hematuria and recurrent stone formation.

Urinary Tract Obstruction and renal tumors represent specific anatomic lesions with often varied clinical manifestations.

Warning signs of Kidney diseases [2]

Kidney disease usually affects both the kidneys. If the kidneys ability to filter the blood is seriously damaged by disease, wastes and excess fluid may build up in the body.

Six warning signs of kidney disease include:-

High blood pressure

- Blood and / or protein in the urine
- A creatinine and BUN test, outside the normal range

Bun and creatinine are waste that builds up in blood when the kidney function is reduced.

- A GFR less than 60
- More frequent urinaton, particularly at night, difficult or painful urination.
- Puffiness around eyes, swelling of hand and feet.

DRUGS INDUCED KIDNEY DISEASES

Drug induced kidney diseases are the major adverse event associated with multiple medication classes. Medications use accounts for 2% of hospital admissions for acute renal failure and upto 15% of admissions into intensive care.

Hospital-acquired renal failure includes any documented incident of renal failure that occurs within the hospital setting. Hospitalized patients are vulnerable to renal failure from a variety of causes, including diagnostic procedures (1V contrast), sudden decrease in blood pressure (gastrointestinal bleed, sepsis, variceal bleed) and the addition of nephrotoxic medications (aminoglycosides, amphotericin, chemotherapy). Upto 16% of patients with baseline normal renal function who experience renal injury within the hospital setting have medication-induced renal failure.

Patients who experience acute-onset renal failure often complain of increased shortness of breath, ankle swelling and weight gain. These symptoms reflect the reduced ability of the kidney to clear extra fluid from the body. If the kidney failure is due to a medication, stopping the medication may allow the kidney to recover .If the kidney has extensive damage; the kidney may reduce or even stop producing urine. Hemodialysis may be necessary for a short-term bridge until the kidney can recover. In some cases, the damage is irreversible and the patient will require life-long dialysis or a kidney transplant.

Drug-induced renal disease can mimic renal disease from other causes, such as autoimmune disease and infection. A thorough physical examination and medical history should be performed. Laboratory tests will show an increase in serum

creatinine and blood urea nitrogen (BUN) when a significant loss of kidney function occurs. Additional urine tests, such as protein excretion, creatinine concentration, osmolality, or sodium excretion may be requested to pinpoint the cause of the renal defect. Finally, in some cases, a renal biopsy may be performed to directly examine he histological changes within the kidney.

Renal failure, whether caused by medications or other processes, can be classified as **acute or chronic.** Chronic renal failure develops over a long-period of time (many months to years) with continued exposure to a nephrotoxin or from the natural ageing process or onset of disease. Chronic renal failure can be further classified into five stages of progressively worsening renal function. A subset of all chronic renal failure patients will eventually progress to stage 5(end-stage renal disease). Most patients who reach stage 5 renal failure require dialysis or a renal transplant to live.

PRE-RENAL INJURY [11]

Pre-renal causes result in decreased blood flow to the kidney resulting in acute renal failure. Patients with congestive heart failure have reduced ability to effectively pump blood to other organs. An exacerbation (worsening) of heart failure may increase the risk of acute renal failure by reducing blood flow into the kidneys. Excessive dehydration due to fluid loss (protracted vomiting, diarrhoea , blood loss, etc.) without fluid replacement will cause acute renal failure. Severe infections can lead to sepsis, a life-threatening condition that results in a drop in blood pressure significant enough to reduce blood flow into the kidneys. Excessive diuretic use may lead to severe dehydration and increase the risk of acute renal failure.

The kidney tries to compensate for decreased renal blood flow by altering the hemodynamics (blood flow) within the kidney, but these changes may not be sufficient to prevent acute renal failure. If the loss of blood flow to the kidney is prolonged, the direct damage to kidney tissue may occur due to loss of adequate perfusion and oxygenation of kidney tissue.

Blood and Urine studies to distinguish pre-renal from intra- renal injury [11]

	BUN to creatinine ratio	**Urine osmolality**	**Fractional excretion of sodium**
Pre-renal injury	>20 :1	>500 m OSm	<1%
Intra- renal injury	<20 :1	250 – 300 m OSm	>3%

Table - 1

The fractional excretion of sodium is equal to 100 [3 (urine sodium/ serum sodium)] [4 (urine creatinine/ serum creatinine)]. This value is less than 1% in most patients with pre-renal injury.

In patients with pre – renal injury, the parenchyma is undamaged and the kidneys respond as if volume depletion has occurred. Thus, kidneys avidly reabsorb sodium in order to reabsorb water. Specific causes of fractional excretion of sodium less than 1% that are not the result of pre – renal injury include contrast nephropathy and pigment nephropathy.

INTRA-RENAL INJURY

Intra-renal failure sometimes called intrinsic kidney damage is due to direct insult to kidney tissues, especially the nephron. It is subdivided into four categories:

- Tubular disease
- Glomerular disease
- Vascular disease
- In intrinsic injury, the renal parenchyma is injured. The damage to tubule cells leads to certain urine microscopic studies. Parenchymal injury causes impaired sodium reabsorption and results in a fractional excretion of sodium greater than 3 % and an isotonic urine osmolality of 250- 300 m OSm.

Tubular disease

Acute tubular necrosis is the most common cause of intra-renal toxicity in hospitalized patients. This condition is usually induced by ischemia (or) toxins. In ischemic acute tubular necrosis, unlike pre-renal injury, the GFR does not improve with the restoration of renal blood flow. Ischemic acute tubular necrosis is frequently reversible, but if the ischemia is severe enough to cause cortical neurosis, irreversible renal failure can occur.

Contrast agents and aminoglycosides are the agents most often associated with acute tubular necrosis. The condition can also be caused by pigment from myoglobiuria (rhabdomyolysis), hemoglobinuria (hemolysis).

Acute tubular necrosis has 3 phases. Renal injury evolves during the initiation phase, which lasts for hours to days. In the maintenance phase, which last for days to weeks, the GFR reaches its maximum and urine output is at its lowest. The recovery phase lasts for days, often beginning with post acute tubular necrosis diuresis. Hypovolemia from excess urine output is a concern during this phase. Despite recovery of urine production, patients can still have difficulty with uremia and homeostasis of electrolytes and acid because of tubular function is not completely recovered. Diligent monitoring is indicated throughout all phases of acute tubular necrosis.

Patients at risk for acute tubular necrosis include those diabetes, congestive heart failure (or) chronic renal insufficiency. Acute tubular necrosis may be prevented by promptly treating patients with reversible causes of ischemia (or) pre-renal injury and by maintaining appropriate hydration in patients who are receiving nephrotoxins.

Glomerular Disease

Glomerulonephritis is characterized by hypertension, proteinuria and hematuria. Most of glomerulonephritis are associated with chronic renal disease. In general two types of glomerulonephritis that cause pre renal injury are rapidly progressive glomerulonephritis and acute proliferative glomerulonephritis .The later type occurs in patients with bacterial endocarditis (or) other post infections conditions.

Rapidly progressive glomerulonephritis can be a primary disorder, or it can occur secondary to systematic disease. Once this condition is suspected, treatable systematic disease must be sought through serologic markers or renal biopsy. Renal function can decline quickly in patients with rapidly progressive glomerulonephritis, end stage renal disease can develop in days to weeks. Patients with rapidly progressive glomerulonephritis are treated with gluco corticoids and cyclophosphamide (cytoxan) .

Vascular Disease

Microvascular (or) macrovascular disease (major renal artery occlusion) (or) severe abdominal aortic disease) can cause renal failure.

The classic microvascular disease often present with microangiopathic hemolysis and renal failure occurring because of capillary thrombosis (or) occlusion, often with accompanying thrombocytopenia. Typical examples of these diseases are :

- Thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome
- HELLP syndrome (hemolysis, elevated liver enzymes)

The classic pentad in thrombotic thrombocytopenic purpura includes;

- Fever
- Neurologic changes
- Renal failure
- Microangiopathic hemolytic anemia
- Thrombocytopenia

Hemolytic uremic syndrome is similar to thrombotic thrombocytopenic purpura but does not present with neurologic changes.

HELLP syndrome is a type of hemolytic uremic syndrome that occurs in pregnant woman with the addition of transaminase elevations.

The microvascular diseases that cause renal failure are often treated with plasmapheresis and sometimes with cortico-steroids. An increasing platelet count is a marker of improvement Atheroembolic disease is another important cause of irreversible acute renal failure. Patients with atherosclerotic disease who undergoes an invasive procedure (eg: vascular surgery (or) interventional vascular studies (or) have an acute arrhythmia are at increased risk for renal failure induced by atheroembolic. Acute renal failure from embolic disease may present one day to seven weeks after the inciting event.

Atheroembolism is relatively common in tertiary care and intensive care units, presenting classically with "purple toes and renal failure".. The diagnosis of atheroembolic disease can be confirmed on skin (or) renal biopsy. Treatment is nonspecific, but avoiding further vascular intervention and anticoagulation is strongly recommended.

Interstitial Disease

Acute interstitial nephritis usually presents with fever, rash and esinophilia. Urine staining that is positive for eosinophils is suggestive of this condition. Acute interstitial nephritis is usually the result of an allergic reaction to a drug, but it may also be caused by autoimmune disease, infection (or) infiltrative disease.

Many drugs can cause interstitial nephritis, but the most common are;

- NSAIDS
- Penicillins
- Cephalosporins
- Sulfonamides
- Diuretics
- Allopurinol

Renal function should improve after the offending agent is withdrawn. Corticosteroids are sometimes helpful in speeding recovery.

Common medications associated with intra – renal injury [4]

Pathoetiology	Medications	Clinical findings	Treatment
Intrinsic renal injury (vascular effects, Thrombotic microangiopathy)	Ciclosporin ,tacrolimus, mitomycinC, quinine, 5-flurouracil, ticlopidine,clopidogrel, gemcitabine, bleomycin.	Fever Microangiopathic Haemolytic anaemia thrombocytopenia	Discontinue medication Supportive care Plasmapherisis if indicated
Intrinsic renal injury (vascular effects, cholesterol emboli)	Heparin, warfarin, Streptokinase	Fever Microangiopathic Haemolytic anaemia thrombocytopenia	Discontinue medication Supportive care Plasmapherisis if indicated
Intrinsic renal injury (tubular toxicity)	Aminoglycosides, radio contrast media, Cisplatin, nedaplatin Methoxyflurane Amphotericin B Cephaloridine Streptozocin, Tacrolimus, carbamazepine, quionolones, cidofovir, mannitol, foscarnet	FeNa>2%, UoSm<350, urinary sediment with granular casts, tubular epithelial cells	Drug discontinuation Supportive care
Intrinsic renal injury (rhabdomyolysis)	Lovastatin, ethanol, codeine, barbiturates, diazepam	Elevated CPK, acute tubular necrosis, Urine sediment	Drug discontinuation Supportive care

Intrinsic renal injury (severe haemolysis)	Quinine, quinindine, sulfonamides, hydralazine, triamterene, nitrofurantoin, mephenytoin	High LDH, Decreased haemoglobin	Drug discontinuation Supportive care
Intrinsic renal injury (immune – mediated interstitial inflammation)	Penicillin, methicillin, ampicillin, rifampicin, sulfonamides, thiazides, cimetidine, phenytoin, cephalosporines, furosemide, ciprofloxacin, clarithromycin, pantoprazole, omeprazole, NSAIDS.	Fever, rash, eosinophilia, Urine sediment showing pyuria, white cell cast eosinophiluria.	Drug discontinuation, Supportive care
Intrinsic renal injury (glomerulopathy)	Gold, penicillamine, Captopril, NSAIDS, Lithium, fenoprofen, mercury, mefenamate, Interferon-alfa, foscarnet	Edema, moderate – servere proteinuria, RBC casts possible	Drug discontinuation, Supportive care
Intra-renal tubular obstruction	Aciclovir, methotrexate, sulphanilamide, triamterene,foscarnet,indinavir,	Benign urine sediment with obstruction, Acute tubular necrosis	Drug discontinuation, Supportive care

Table - 2

POST-RENAL INJURY [11]

Post- renal injury can only occur if both urinary outflow tracts are obstructed (or) the outflow tract of a solitary kidney is obstructed. The condition is most often due to obstruction of the lower urinary tract.

Patients with severe oliguria (or) anuria (output less than 100ml of urine per day) are likely to have post – renal injury. However not all patients with post- renal injury are oliguric. It usually results from a mechanical barrier to moving urine from the collecting tubules into the bladder and through the ureters. Mechanical obstruction may be caused by enlargement of the prostate, kidney stones or drugs that precipitate in the kidney. (Acyclovir, ganciclovir).

The primary causes of post – renal injury include;

- Prostatic hypertrophy
- Prostatic cancer
- Cervical cancer
- Retroperitoneal diseases

Intratubular causes include,

Crystals (eg: urates)

Myeloma light chains

One of the first elevation steps in most patients with renal injury is to determine whether a patient has post –renal failure, because treatment is frequently relatively easy and the potential for recovery of renal function is often inversely related to the duration of obstruction. Bladder catheterization may be diagnostic and therapeutic inpatients with bladder (or) urethral obstruction.

Hydronephrosis detected on renal ultrasound examination is the major signal that obstruction is present.

In patients with post–renal injury, treatment efforts are directed at the underlying disease. Treatments are available for underlying disease include;

- Bladder caterterization
- Percutaneous nephrostomy
- Lithotripsy
- Ureteral stenting
- Urethral stenting

Causes of acute renal injury [9]

Classification	Common Clinical Disorders
Pre- renal injury	**Intravascular volume depletion**
	Hemorrhage (surgery, trauma)
	Dehydration (gastrointestinal losses, aggressive diuretic administration)
	Severe burns, Hypovolemic shock
	Sequestration (peritonitis, pancreatitis)
	Decreased effective circulating volume
	Cirrhosis with ascites
	Congestive heart failure
	Hypotension, shock syndromes
	Antihypertensive vasodilating medications
	Septic shock, Cardiomyopathy
	Increased renal vascular occlusion/ constriction
	Bilateral renal artery stenosis
	Unilateral renal stenosis in solitary kidney
	Renal artery (or) vein thrombosis (embolism, atherosclerosis)
	Vasopressor medications
	Afferent arteriole vasoconstrictors
	Cyclosporine, NSAIDS
	Efferent arteriole vasodilators
	ACEI's
	Angiotensin receptor -2 antagonists
Functional injury	**Glomerular disorders**
	Glomerulonephritis
	SLE (Systemic Lupus Erythematous)
	Malignant hypertension, Vasculitic disorder
	Acute tubular necrosis
	Prolonged pre-renal states

Intrinsic renal injury	Drug induced (contrast media, aminoglycosides, amphotericin B) **Acute interstitial nephritis** Drug induced (quinolones, penicillins sulpha drugs)
Post –renal injury	**Ureter obstruction** [Bilateral (or) unilateral in solitary kidneys] Malignancy (prostate (or) cervical cancer) Prostate hypertrophy, Renal calculi

Table-3

CHRONIC RENAL INJURY [4]

Prolonged exposure of the kidney to analgesics, calcineurin inhibitors or lithium can cause chronic renal damage. Chronic high doses (2-3gm/ day) of phenacetin, acetaminophen, aspirin and NSAIDS are at increased risk of developing end stage renal disease. Chronic use of these drugs can cause patchy necrosis and fibrosis of the renal medullary interstitium with occasional mononuclear cell infiltration, and atrophy of henle's loop. Inhibition of vasodilatory prostaglandins by NSAIDS and salicyclates can induce medullary ischemia. Drug metabolites tend to become concentrated within the medullary gradient; high levels at the papillary tip and generated via lipid peroxidation induce tissue damage.

Staging of chronic renal injury based on GFR [9]

Stage	Description	GFR
1	At increased risk	>90(with CKD risk factors) >90
2	Kidney damage with normal or increased GFR	60-89
3	Kidney damage with mild decreased GFR	30-59
4	Moderate decreased GFR	15-29
5	Severe decreased GFR Kidney failure	<15(need for renal transplant therapy)

Table-4

Chronic fibrosis leads to small kidneys in most patients who present with concentrating defects, sterile pyuria or mild proteinuria; 25 – 50% of patients presents with papillary sloughing which can be accompanied by haematuria and flank pain. Urogenital transitional carcinomas and renal cell cancers have also been linked with prolonged analgesic use.

Chronic fibrosis with an obliterative arteriolopathy and tubular collapse gives rise to a classic biopsy pattern of striped interstitial fibrosis in patients receiving long – term treatment with calcineurin inhibitors.

Chronic use of lithium for bipolar disorders or depression can cause interstitial fibrosis and nephrogenic diabetes insipidus. Examination of renal biopsies reveals prevalent cortical and medullary tubular cysts or dilatations (primarily of distal and collecting tubules), both focal segmental glomerulosclerosis and global sclerosis, and chronic tubulointerstitial nephropathy.

ELECTROLYTE AND ACID – BASE ABNORMALITIES [4]

Common medications associated with electrolyte and acid –base abnormalities

Pathoetiology	Medication	Clinical Findings	Treatment
Hyponatremia (ADH secretion and sensitivity)	Thiazide diuretics, Chlorpropamide, Vincristine, Intravenous cyclophophamide, Cytoxan, clofibrate, narcotics, haloperidol, thioridazine, amitriptyline, fluphenazine, NSAIDS, acetaminophen	UOsm is less than maximally diluted in presence of low serum Na+	Discontinue medication. Consider fluid Restriction.

Hypokalemia / Hypomagnesemia (increased urinary excretion)	Gentamicin, cisplatin, diuretics, carboplatin, nedaplatin	Increased urinary excretion of K+ and Mg2+ despite low serum levels.	Discontinue medication, Replace K+ and Mg2+
Hyperkalemia (antialdosterone or antiadrenergic effect; blocking sodium channels	ACEIs, beta-blockers, NSAIDS, K+sparing diuretics, heparin, trimethoprin, ciclosporin, pentamidine	Hyperchloremic metabolic acidosis with or without hypokalemia	Discontinue medication, Supportive treatment, HCO3 replacement if necessary
Renal tubular acidosis (decreased aldosterone levels and response)	Ciclosporin, tacrolimus	Hyperkalemia hyperchloremic, metabolic acidosis	Treat hyperkalemia, Consider HCO3 therapy, low K+ diet, avoid concurrent medications with hyperkalemia.
Metabolic acidosis (increased K+and H+ secretion in distal nephron)	Loop and thiazide diuretics	Alkalemia, hypokalemia,hyperchloremia	Discontinue medication, volume replacement if necessary
Nephrogenic diabetes insipidus (decreased ADH response in collecting tubule)	Lithium, demeclocycline, cyclophosphamide, ifosfamide, vincristine, cidofovir tenofovir, didanosine, foscarnet	Polyuria, unresponsive to ADH	Discontinue medication, supportive therapy

Table – 5

Renal Vascular Alterations.

Systemic polyarteritis nodosa with involvement of small and medium- sized renal arteries found by methamphetamine abuse. Patients may have hematuria, proteinuria, renal insufficiency and hypertension. Renal and visceral vascular aneurysms can be seen in angiography. The pathogenesis may be a toxic reaction (or) the result of associated hepatitis B infection. Penicillin and sulfonamide therapies also cause polyarteritis nodosa. Thrombotic microangiopathy (hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura) resulting in thrombus formation in the renal vasculature has been seen in drugs such as oral contraceptive agents, cicosporine, mitomycin C, cisplatin and quinine. Nephrotoxicity has occurred in long term- therapy with mitomycin C alone and in combination with cisplatin, 5-flurouracil, bleomycin, and a vinca alkaloid. Microangiopathic hemolytic anemia and thrombocytopenia are usually present.

Cholestrol embolic from large atherosclerotic arteries to small renal arteries and arterioles can induce an inflammatory obliterative vascular lesion with renal failure due to ischemia. This commonly occurs following invasive procedures, may also with thrombolytic (or) anticoagulant therapies, which remove thrombus formation over ulcerative atherscleotic plaques.

Glomerular Alterations:

Nephrotic syndrome and glomerulonephritis:

The nephrotic syndrome, defined as proteinuria greater than 3.5g/d, with (or) without renal insufficiency is the manifestation of glomerular damage. Minimal change nephrotic syndrome is characterized by normal glomeruli by light microscopy. Drug induced minimal change nephropathy is accompanied by interstitial nephritis and is most common during NSAID therapy. Ampicillin, rifampicin, phenytoin, and lithium have also been implicated.

The pathogenesis is unknown, but nephrotic range proteinuria due to NSAID therapy is frequently associated with T- lymphocytic interstitial infiltrate suggesting disordered cell- mediated immunity. These cells may release lymphokines that

increase glomerular capillary permeability to proteins. Proteinuria usually resolves rapidly after discontinuation of the offending drug. Prednisolone therapy may resolve this lesion.

Focal segmental glomerulosclerosis is the predominant renal lesion in acquired immunodeficiency syndrome (AIDS) patients and result from human immunodeficiency virus (HIV) or heroin abuse. Glomerulosclerosis due to HIV infection may be distinguished from heroin nephropathy tubuloreticular structures and poorer prognosis.

Membranous nephropathy, the most common drug – induced glomerular lesion, is a immune – mediated disorder characterized by immune complex deposition along glomerular capillary loops. Parenteral gold is most common cause that too oral gold therapy for rheumatoid arthritis. The pathogenesis may involve damage to proximal tubule epithelium with antigen release, antibody formation and glomerular immune complex deposition. Renal function is preserved and proteinuria resolves within 6- 39 months of discontinuing gold therapy. Mercury in topical skin preparations and industrial vapours as well as penicillamine cause membranous nephropathy and appears to be immune mediated.

Membranoproliferative gomerulonephritis is a rare consequence of drug therapy that is commonly associated with hydralazine- induced systemic lupus erythematosus. Other drug induced glomerular lesions include penicillamine therapy and combined interleukin-2 and interferon – alpha therapy. Glomerular amyloidosis has been associated with heroin abuse particularly inusers who inject subcutaneously. The pathogenesis may be immune stimulation from chronic skin inflammation.

Acute tubular Necrosis:

Acute necrosis of renal tubular epithelium is the most common mechanisms responsible for drug induced renal insufficiency. Subclincal manifestations include tubular proteinuria and enzymuria. Clincal toxicity becomes apparent as a rise in serum creatinine and BUN concentrations, a decline in creatinine clearance and disturbances of renal tubular electrolyte and water handling. Repititve therapy causing

recurrent subclincal toxicity can have cumulative effects resulting in chronic tubulointerstitial disease. The mechanism is unclear. The GFR decrease proportionately more than renal blood flow decreases, suggesting that renal ischemia in not the primary mechanism.

Other mechanisms include,

- a shunt of blood away from the glomerulus
- reduction of glomerular capillary filtration pressure
- decreased permeability of glomerular filtration surface
- obstruction of tubular flow by damaged epithelial cells and cellular debris
- backleak of the glomerular filtrate across damaged tubular epithelia into the systemic circulation.

The mechanism may depend on the specific nephrotoxic drug. The important drugs include aminoglycosides, radiographic contrast media, cisplatin and amphotericin B.

Urinary findings [13] :- The onset of injury may not be readily detected because urine volume may be normal at first, but if the offending drug is continued , oliguria may ensue. Urine microscopy shows dark granular casts and renal epithelial cell casts, while the fractional excretion of sodium is often more than 2% to 3%. (Normal value < 1%).

Tubulointerstitial Disease: [10]

Acute Allergic Interstitial Nephritis

Acute allergic interstitial nephritis is common and the underlying cause for 3 – 14% of all cases of renal failure. Methicillin allergic interstitial nephritis has been best characterized. Clinical signs occurred about 17 days (ranging from 2 – 44 days) after initiation of therapy and includes fever, maculopapular rash, eosinophilia, pyuria and haematuria, low- level proteinuria and oliguria. Eosinophiluria has been considered an important marker of allergic interstitial nephritis. Anaemia, leucocytosis and elevated Ig E levels, as well as tubular dysfunction, including renal tubular acidosis, hyperkalemia, salt wasting and concentrating defects may also occur.

Allergic interstitial nephritis due to NSAID therapy has a different clinical presentation. A concomitant nil lesion nephrotic syndromes are characteristic. Cytokine therapy induces a unique nephropathy usually hemodynamically mediated due to systemic capillary leak syndrome. Acute interstitial nephritis has occurred during leukocyte A interferon therapy for mycosis fungoides and also during adaptive cancer immunotherapy with interleukin – 2 (IL – 2) and lymphokine – activated killer (LAK) cells, causing predominantly T- lymphocytic renal interstitial infiltrate combined therapy with alpha human interferon and human granulocyte colony stimulating factor(rh G – CSF) has also been associated with ARF and consistent with allergic interstitial nephritis.

The renal pathology of allergic interstitial nephritis is a diffuse (or) focal interstitial infiltrate of lymphocytes, plasma cells eosinophils and occasional polymorphonuclear neutrophils. Granulomas may occur. Patchy peritubular inflammation and epithelial cell atrophy with tubular necrosis is also present.

The pathogenesis is an allergic hypersensitivity response. In certain cases a humoral, antibody mediated mechanism may be involved as indicated by the occasional presence of circulating antibody to a drug hapten- tubular basement membrane complex, low serum complement levels and tubular basement deposition of Ig G and component. Moreover, a cell mediated mechanism is absent and the presence of a predominantly T- lymphocyte infiltrate with an increased helper to suppressor cell ratio. The pathogenesis of NSAID interstitial nephritis also involves T –lymphocytes , in response to altered prostaglandin synthesis.

Urinary findings :- [13] include white blood cells, and white cell casts. The fractional excretion of sodium is often above 1% due to tubular damage, though lower values may be seen if there is associated volume depletion. Protein excretion is mild in most cases, although some elderly patients and those with NSAID – induced acute interstitial nephritis may have proteinuria in the nephritic range (>3g / 24hrs).

Some patients may have signs of tubulointerstitial damage such as those with Fanconi syndrome (tubular proteinuria, glucosuria, bicarbonaturia, phosphaturia and aminoaciduria) and renal tubular acidosis.

Prompt and accurate diagnosis of allergic interstitial nephritis is important since failure to stop the offending drug can result in chronic renal insufficiency. The presence of fever, rash, eosinophilia and eosinophiluria are not reliable because one (or) more of them are frequently absent. Alternatively, gallium reveal imaging is a sensitive but nonspecific diagnosis technique. Other interstitial and glomerular lesions including pyelonephritis, nil lesion nephritic syndrome cholesterol embolization can give positive seams limiting the usefulness of this test. Treatment with corticosteroids in a dose of 0.5 – 1mg/kg body weight for 1 – 4 weeks may shorten the duration and improve the extent of renal function recovery.

Drugs causing acute interstitial nephritis [5]

Class	Name of Drug
Penicillins	Methicillin, ampicillin, cabenicillin, Nafcilin, toxacillin amoxicillin.
Other antibiotics	Sulfonamides, polymixin, cephalosporins, rifampicin, erythromycin, cotrimoxazole, lincomycin, quinolones, vancomycin.
NSAIDs	Aspirin, fenoprofen, benoxapofen, Glafenine, lbuprofen, indomethacin Mefenamic acid, phenyl butazone, naproxen, tolmetin.
Diuretics	Thiazides, furosemide, ethacrynic acid, triamterene, indapamide.
Heavy metals	Gold, bismuth
Miscellaneous	Allopurinol, amphetamine azathioprine, captopril, cimetidine, clofibrate, phenytoin

Table-6

Chronic interstitial nephritis [10]

Lithium and cyclosporine cause progressive and irreversible nephropathy. Streptozotoin and other anti- neoplastic nitrosoureas can alsi induce dose dependent chronic tubulointerstitial disease.

Lithium therapy cause renal tubular lesions, including chronic tubulointerstitial nephritis, impaired ability to concentrate urine, incomplete distal renal tubular acidosis and acute renal failure. Impaired ability to concentrate urine is due to dose related decrease in collecting duct response to anti- diuretic hormone. This results from impaired formation of cellular CAMP in response to anti- diuretic hormone and can frequently be reversed by discontinuation of lithium therapy (or) ameliorated with amiloride during continued lithium therapy. Lithium induced ARF occurs during episodes of lithium intoxication. The pathogenesis include dehydration secondary to nephrogenic diabetes insipidus as well as direct proximal and distal tubular cell toxicity. Severe renal insufficiency may occur and can be reversible with supportive care, including dialysis therapy to reduce toxic serum lithium concentrations. The renal lesions include interstitial fibrosis with focal tubular atrophy and glomerular lesions. The duration of lithium therapy has correlated with decline in the GFR suggesting the pathogenesis may involve direct lithium toxicity. Alternative mechanisms include cumulative effects of acute episodes of lithium toxicity, the use of concomitant drugs such as neuroleptics (or) ACEI's and concurrent renal tubulointerstitial disease. Preventive measures include maintenance of lithium serum concentrations in the therapeutic range, avoidance of dehydration and close monitoring of renal function including urinary concentrating ability.

Cyclosporine can also cause interstitial fibrosis and chronic irreversible renal insufficiency after approximately 6 – 12 months of therapy. This is a major limitation as 10% of cardiac transplant patients develop s end stage renal failure with prolonged high doses. The pathogenesis involves sustained renal endothelial cell injury and ischemia(or) direct tubular toxicity. Ciclosporine induced interstitial matrix synthesis and accumulation, apparently due to increased activity of cytokines, peptide growth factors (or) thromborane may also contribute. The risk of chronic interstitial renal disease appears to be lessened with the current lower dose therapy.

Papillary Necrosis

Chronic excessive consumption of combination analgesics containing phenacetin can cause chronic renal tubulointerstitial disease with papillary necrosis and lead to increased hypertension and atherosclerotic cardiovascular disease. In high dose dapsone therapy, used frequently recently for P. carini infections during the HIV epidermic , may also cause papillary necrosis. In addition, the incidence of lower urinary tract transitional cell carcinoma is increased in patients with heavy use of phenacetin. Analgesic nephropathy evolves insidiously over years with clinical expression following a cumulative phenacetin ingestion of 3kg or more.

Renal manifestations include impaired maximal urinary concentration, sterile pyuria , microscopic haematuria, proteinuria and hypertension. Creatinine clearance declines slowly. Upper gastro- intestinal irritation from analgesics with blood loss leading to anaemia has been characteristic. The diagnosis is confirmed by intravenous pyelography with demonstration of papillary necrosis (or) by computed tomography (CT) scan, which shows decreased renal mass and bumpy contours (or) pappilary calcifications. In addition, chronic interstitial disease and papillary nacrosis may occur with the use of NSAIDS alone, particularly in males.

The biochemical mechanism appears to involve metabolism of phenacetin to acetaminophen, when oxidized to toxic free radicals that are concentrated in the pappila during urinary concentration. The ability of the kidney to oxidize acetaminophen may be due to lack of renal cytochrome P-450, co-oxidation of acetaminophen may occur with renal prostaglandin synthesis. Papillary ischemia results from the ability of both salicylate and acetaminophen to inhibit renal medullary synthesis of vasodilatory prostaglandins. Impaired cellular energy production results from ability of salicylate to uncouple mitochondrial oxidative phosphorylation.

Prevention has depended primarily on public health efforts to restrict the sale of phenacetin and combination analgesics; however OTC analgesic use yet causes nephrotoxicity. Individuals requiring chronic analgesic therapy may reduce their risk by limiting the total dose, avoiding the combined use of two (or) more analgesics,

maintaining adequate hydration to prevent renal ischemia and decrease the papillary concentration of toxic substances. Treatment of established nephrotoxicity requires cessation of analgesic consumption, which can prevent progression and improve renal function. Patients should be carefully evaluated tor associated transitional cell carcinoma of the renal pelvis, calyces, ureters and bladder. Carcinoma may present years after analgesic therapy in diagnosed.

Obstructive Nephropathy

Renal tubular obstruction

In drug induced renal injury, renal tubular obstruction can be caused by intra-tubular precipitation of tissue degradation products as drugs (or) their metabolites, acute uric acid nephropathy following chemotherapy, for hemolytic malignancies is the most common cause. Acute oliguric (or) anuric renal injury develops rapidly. The diagnosis is supported by a urine uric acid to creatinine ratio greater than one. Uric acid precipitation can be prevented by pre-treatment hydration, urinary alkalinization and administration of allopurinol. Uric acid nephropathy was also seen at incitation of therapy with uricosuric NSAIDS.

Induced muscle necrosis, non- traumatic rhabdomyolysis, is an important cause of renal injury in part to intratubular precipitation of myoglobin. Drug – induced rhabdomyolysis may result from pressure necrosis following alcohol (or) heroin abuse, extreme neuromuscular stimulation and metabolic demands with abuse of phencyclidine (or) therapy with adrenergic agents including terbutaline and vasoconstriction and muscle ischemia due to abuse of cocaine (or) therapeutic vasopressin infusion . rhabdomyolysis occurred during lovastatin therapy for hypercholesterolemia, also with erythromycin, gemfibrozil, niacin and cyclosporine. Mechanism appears to be accumulation of myotoxic levels of lovastatin due to competitive inhibition by cyclosporine for metabolis through the cytochrome P-450 system.

Precipitation of drugs (or) their metabolites in concentrated acidic urine particularly with previous generations of sulphonamides and this problem is resolved recently with more soluble sulphonamides . It may occur during acetazolamide

therapy and has become more frequent with resurgence with sulphadiazine therapy, toxoplasmosis in AIDS patients. Methotrexate and its metabolite 7-hydroxymethotrexate which is less soluble have also precipitated in urine and cause obligaanuric renal failure during high dose chemotherapy.

It cab be prevented largely by hydration and alkalization of the urine. Acyclovir given intravenously may cause intra- tubular obstruction and ARF. This can be avoided largely and not completely by adminstation dosage slowly with adequate hydration. But ARF is not seen in oral acyclovir.

Massive administration of ascorbic acids, calcium antacids can also result in obstruction of renal tubules. Oxalate, a poorely soluble ascorbic acid metabolite, can also precipitate when administered to patients with ARF (or) congenital nephrotic syndrome. Low molecular weight dextran therapy for volume expansion and sheological effects caused renal injury, possibly by intra- tubular precipitation of filtered dextran. Triamterene may also precipitate in renal tubules and cause renal failure. Renal injury due to intra- tubular precipitation of tissue degradation products (or) metabolites can be largely prevented and treated by maintaining a high urine volume and urinary alkalinazation. Therapeutic agents not intended for systemic administration can cause renal failure in rare cases, apparently by intra- tubular (or) intra-renal precipitation.

Extra- renal Urinary tract Obstruction

Drug therapy may also cause renal insufficiency due to lower urinary tract obstruction. Ureteral obstruction can be caused by calculi (or) retroperitoneal fibrosis due to analgesic, methysergide (or) radiation therapy. Bladder dysfunction with urinary outflow obstruction can result, particularly in males with prostatic hypertrophy, from anti-cholinergic drugs including tricyclic antidepressants. In particular, disopyramide phosphate, an antiarrythmic drug with anticholinergic effects, has caused renal injury due to urinary retention. Bladder outlet and ureteral obstruction may result from bladder fibrosis following hemorrgagic cystitis with cyclophosphamide (or) ifosfamide therapy.

Drug-Induced Nephrotoxicity

Drugs are a common source of acute kidney injury. Compared with 30 years ago, the average patient today is older, has more comorbidities, and is exposed to more diagnostic and therapeutic procedures with the potential to harm kidney function. Drugs shown to cause nephrotoxicity exert their toxic effects by one or more common pathogenic mechanisms. Drug-induced nephrotoxicity tends to be more common among certain patients and in specific clinical situations. Therefore, successful prevention requires knowledge of pathogenic mechanisms of renal injury, patient-related risk factors, drug-related risk factors, and preemptive measures, coupled with vigilance and early intervention. Some patient-related risk factors for drug-induced nephrotoxicity are age older than 60 years, underlying renal insufficiency (e.g., glomerular filtration rate of less than 60 mL per minute per 1.73 m^2), volume depletion, diabetes, heart failure, and sepsis. General preventive measures include using alternative non-nephrotoxic drugs whenever possible; correcting risk factors, if possible; assessing baseline renal function before initiation of therapy, followed by adjusting the dosage; monitoring renal function and vital signs during therapy; and avoiding nephrotoxic drug combinations.

CLINICAL RECOMMENDATION

Patients at highest risk of drug-induced nephrotoxicity are those with one or more of the following: age older than 60 years, baseline renal insufficiency (e.g., GFR < 60 mL per minute per 1.73 m2), and volume depletion, multiple exposures to nephrotoxins, diabetes, heart failure, and sepsis.

Assess baseline renal function using the MDRD or Cockcroft-Gault GFR estimation equation and consider a patient's renal function when prescribing a new drug.

Monitor renal function and vital signs after starting or increasing the dose of drugs associated with nephrotoxicity, especially when used chronically.

Pathogenic Mechanisms

Most drugs found to cause nephrotoxicity exert toxic effects by one or more common pathogenic mechanisms. These include altered intraglomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microan-giopathy.[7–9] Knowledge of offending drugs and their particular pathogenic mechanisms of renal injury is critical to recognizing and preventing drug-induced renal impairment *(Table 1[10–31])*.

Drugs Associated with Nephrotoxicity

DRUGS AND THEIR CLASSIFICATION		***PATHOPHYSIOLOGIC MECHANISM OF RENAL INJURY***
Analgesics		
1	Acetaminophen, aspirin	Chronic interstitial nephritis
2	Nonsteroidal anti-inflammatory drugs	Acute interstitial nephritis, altered intraglomerular hemodynamics, chronic interstitial nephritis, glomerulonephritis
Antidepressants/mood stabilizers		
1	Amitriptyline (Elavil*), doxepin (Zonalon), fluoxetine (Prozac)	Rhabdomyolysis
2	Lithium	Chronic interstitial nephritis, glomerulonephritis, rhabdomyolysis
Antihistamines		
1	Diphenhydramine (Benadryl),	Rhabdomyolysis

DRUGS AND THEIR CLASSIFICATION		***PATHOPHYSIOLOGIC MECHANISM OF RENAL INJURY***
	doxylamine (Unisom)	
Antimicrobials		
1	Acyclovir (Zovirax)	Acute interstitial nephritis, crystal nephropathy
2	Aminoglycosides	Tubular cell toxicity
3	Amphotericin B (Fungizone*; deoxycholic acid formulation more so than the lipid formulation)	Tubular cell toxicity
4	Beta lactams (penicillins, cephalosporins)	Acute interstitial nephritis, glomerulonephritis (ampicillin, penicillin)
5	Foscarnet (Foscavir)	Crystal nephropathy, tubular cell toxicity
6	Ganciclovir (Cytovene)	Crystal nephropathy
7	Pentamidine (Pentam)	Tubular cell toxicity
8	Quinolones	Acute interstitial nephritis, crystal nephropathy (ciprofloxacin [Cipro])

DRUGS AND THEIR CLASSIFICATION		*PATHOPHYSIOLOGIC MECHANISM OF RENAL INJURY*
9	Rifampin (Rifadin)	Acute interstitial nephritis
1o	Sulfonamides	Acute interstitial nephritis, crystal nephropathy
11	Vancomycin (Vancocin)	Acute interstitial nephritis
Antiretrovirals		
1	Adefovir (Hepsera), cidofovir (Vistide), tenofovir (Viread)	Tubular cell toxicity
2	Indinavir (Crixivan)	Acute interstitial nephritis, crystal nephropathy
Benzodiazepines		Rhabdomyolysis
Calcineurin inhibitors		
1	Cyclosporine (Neoral)	Altered intraglomerular hemodynamics, chronic interstitial nephritis, thrombotic microangiopathy
2	Tacrolimus (Prograf)	Altered intraglomerular hemodynamics
1	Angiotensin-converting enzyme	Altered intraglomerular hemodynamics

DRUGS AND THEIR CLASSIFICATION		*PATHOPHYSIOLOGIC MECHANISM OF RENAL INJURY*
	inhibitors, angiotensin receptor blockers	
Cardiovascular agents		
1	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers	Altered intraglomerular hemodynamics
2	Clopidogrel (Plavix), ticlopidine (Ticlid)	Thrombotic microangiopathy
3	Statins	Rhabdomyolysis
Chemotherapeutics		
1	Carmustine (Gliadel), semustine (investigational)	Chronic interstitial nephritis
2	Cisplatin (Platinol)	Chronic interstitial nephritis, tubular cell toxicity
3	Interferon-alfa (Intron A)	Glomerulonephritis
4	Methotrexate	Crystal nephropathy
5	Mitomycin-C (Mutamycin)	Thrombotic microangiopathy

DRUGS AND THEIR CLASSIFICATION		***PATHOPHYSIOLOGIC MECHANISM OF RENAL INJURY***
Contrast dye		Tubular cell toxicity
Diuretics		
1	Loops, thiazides	Acute interstitial nephritis
2	Triamterene (Dyrenium)	Crystal nephropathy
Drugs of abuse		
1	Cocaine, heroin, ketamine (Ketalar), methadone, methamphetamine	Rhabdomyolysis
Herbals		
1	Chinese herbals with aristocholic acid	Chronic interstitial nephritis
Proton pump inhibitors		
1	Lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix)	Acute interstitial nephritis
Others		

DRUGS AND THEIR CLASSIFICATION		*PATHOPHYSIOLOGIC MECHANISM OF RENAL INJURY*
1	Allopurinol (Zyloprim)	Acute interstitial nephritis
2	Gold therapy	Glomerulonephritis
3	Haloperidol (Haldol)	Rhabdomyolysis
4	Pamidronate (Aredia)	Glomerulonephritis
5	Phenytoin (Dilantin)	Acute interstitial nephritis
6	Quinine (Qualaquin)	Thrombotic microangiopathy
7	Ranitidine (Zantac)	Acute interstitial nephritis
8	Zoledronate (Zometa)	Tubular cell toxicity

Table-7

ALTERED INTRAGLOMERULAR HEMODYNAMICS

In an otherwise healthy young adult, approximately 120 mL of plasma is filtered under pressure through the glomerulus per minute, which corresponds to the glomerular filtration rate (GFR). The kidney maintains or autoregulates intraglomerular pressure by modulating the afferent and efferent arterial tone to

preserve GFR and urine output. For instance, in patients with volume depletion, renal perfusion depends on circulating prostaglandins to vasodilate the afferent arterioles, allowing more blood flow through the glomerulus.

At the same time, intraglomerular pressure is sustained by the action of angiotensin-II–mediated vasoconstriction of the efferent arteriole. Drugs with antiprostaglandin activity (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]) or those with antiangiotensin-II activity (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]) can interfere with the kidneys' ability to autoregulate glomerular pressure and decrease GFR.[10,32] Other drugs, such as calcineurin inhibitors (e.g., cyclosporine [Neoral], tacrolimus [Prograf]), cause dose-dependent vasoconstriction of the afferent arterioles, leading to renal impairment in at-risk patients.[11]

TUBULAR CELL TOXICITY

Renal tubular cells, in particular proximal tubule cells, are vulnerable to the toxic effects of drugs because their role in concentrating and reabsorbing glomerular filtrate exposes them to high levels of circulating toxins.[12] Drugs that cause tubular cell toxicity do so by impairing mitochondrial function, interfering with tubular transport, increasing oxidative stress, or forming free radicals.[8,13] Drugs associated with this pathogenic mechanism of injury include aminoglycosides, amphotericin B (Fungizone; brand not available in the United States), antiretrovirals (adefovir [Hepsera], cidofovir [Vistide], tenofovir [Viread]), cisplatin (Platinol), contrast dye, foscarnet (Foscavir), and zoledronate (Zometa).[12–14]

INFLAMMATION

Drugs can cause inflammatory changes in the glomerulus, renal tubular cells, and the surrounding interstitium, leading to fibrosis and renal scarring. Glomerulonephritis is an inflammatory condition caused primarily by immune mechanisms and is often associated with proteinuria in the nephrotic range.[12] Medications such as gold therapy, hydralazine (Apresoline; brand not available in the United States), interferon-alfa (Intron A), lithium, NSAIDs, propylthiouracil, and

pamidronate (Aredia; in high doses or prolonged courses) have been reported as causative agents.[12,13,15]

Acute interstitial nephritis, which can result from an allergic response to a suspected drug, develops in an idiosyncratic, non–dose-dependent fashion.[16] Medications that cause acute interstitial nephritis are thought to bind to antigens in the kidney or act as antigens that are then deposited into the interstitium, inducing an immune reaction.[16] However, classic symptoms of a hypersensitivity reaction (i.e., fever, rash, and eosinophilia) are not always observed.[13,16] Numerous drugs have been implicated, including allopurinol (Zyloprim); antibiotics (especially beta lactams, quinolones, rifampin [Rifadin], sulfonamides, and vancomycin [Vancocin]); antivirals (especially acyclovir [Zovirax] and indinavir [Crixivan]); diuretics (loops, thiazides); NSAIDs; phenytoin (Dilantin); proton pump inhibitors (especially omeprazole [Prilosec], pantoprazole [Protonix], and lansoprazole [Prevacid]); and ranitidine (Zantac).[13,16–19]

Chronic interstitial nephritis is less likely than acute interstitial nephritis to be drug induced; it is also insidious in onset, and signs of hypersensitivity are often lacking.[20] Drugs associated with this mechanism of nephrotoxicity include calcineurin inhibitors (e.g., cyclosporine, tacrolimus), certain chemotherapy agents, Chinese herbals containing aristocholic acid, and lithium.[11,20,21] Chronic interstitial nephritis has been reported with analgesics such as acetaminophen, aspirin, and NSAIDs when used chronically in high dosages (i.e., more than 1 gram daily for more than two years) or in patients with preexisting kidney disease.[22,23] Early recognition is important because chronic interstitial nephritis has been known to progress to end-stage renal disease.[20] Diagnosis may be difficult because most patients do not consider over-the-counter preparations to be medications and tend to underreport frequency of use.

CRYSTAL NEPHROPATHY

Renal impairment may result from the use of drugs that produce crystals that are insoluble in human urine. The crystals precipitate, usually within the distal tubular lumen, obstructing urine flow and eliciting an interstitial reaction.[13] Commonly

prescribed drugs associated with production of crystals include antibiotics (e.g., ampicillin, ciprofloxacin [Cipro], sulfonamides); antivirals (e.g., acyclovir, foscarnet, ganciclovir [Cytovene]); indinavir; methotrexate; and triamterene (Dyrenium).[12,13,24] The likelihood of crystal precipitation depends on the concentration of the drug in the urine and the urinary pH.[24] Patients most at risk of crystal nephropathy are those with volume depletion and underlying renal insufficiency.[24]

Chemotherapy for lymphoproliferative disease, leading to tumor lysis syndrome with uric acid and calcium phosphate crystal deposition, has also been associated with renal failure.[25]

RHABDOMYOLYSIS

Rhabdomyolysis is a syndrome in which skeletal muscle injury leads to lysis of the myocyte, releasing intracellular contents including myoglobin and creatine kinase into the plasma. Myoglobin induces renal injury secondary to direct toxicity, tubular obstruction, and alterations in GFR.[26] Drugs may induce rhabdomyolysis directly secondary to a toxic effect on myocyte function, or indirectly by predisposing the myocyte to injury.[26,27] Clinical manifestations of rhabdomyolysis include weakness, myalgia, and tea-colored urine.[27]

Statins are the most recognizable agents associated with rhabdomyolysis, but more than 150 medications and toxins have been implicated.[26] Rhabdomyolysis with statin monotherapy is rare, with an average reported incidence of 0.44 per 10,000 person-years of therapy.[28] Many drugs of abuse, such as cocaine, heroin, ketamine (Ketalar), methadone, and methamphetamine, have been reported to cause rhabdomyolysis.[26,27] Drugs and alcohol are causative factors in up to 81 percent of cases of rhabdomyolysis, and up to 50 percent of patients subsequently develop acute renal failure.[29]

THROMBOTIC MICROANGIOPATHY

In thrombotic microangiopathy, organ damage is caused by platelet thrombi in the microcirculation, as in thrombotic thrombocytopenic purpura.[30] Mechanisms of renal injury secondary to drug-induced thrombotic microangiopathy include an

immune-mediated reaction or direct endothelial toxicity.[30] Drugs most often associated with this pathogenic mechanism of nephrotoxicity include antiplatelet agents (e.g., clopidogrel [Plavix], ticlopidine [Ticlid]), cyclosporine, mitomycin-C (Mutamycin), and quinine (Qualaquin).[30,31]

Preventing Drug-Induced Renal Impairment

Drug-induced nephrotoxicity tends to occur more frequently in certain patients and in specific clinical situations. Therefore, successful prevention requires knowledge of patient-related risk factors, drug-related risk factors, and preemptive measures, coupled with vigilance and early intervention.[7,33] Prevention strategies should target the prescribing and monitoring of potential nephrotoxins in at-risk patients. Whenever possible, risk factors should be corrected before drugs associated with nephrotoxicity are prescribed.

PATIENT-RELATED RISK FACTORS

Patient-related risk factors vary somewhat depending on the offending drug. However, some risk factors are common to all nephrotoxins and include age older than 60 years, underlying renal insufficiency (e.g., GFR of less than 60 mL per minute per 1.73 m^2), intravascular volume depletion, exposure to multiple nephrotoxins, diabetes, heart failure, and sepsis *(Table 2)*.[1–3,7,34,35] There are conflicting reports about the influence of race and genetic variation, as well as whether men are at greater risk of developing acute renal failure compared with women.[34] The risk of acute renal failure increases with the presence of each additional risk factor. Patients with any of these risk factors, especially those who have more than one risk factor (e.g., a patient with diabetes and heart failure), should be closely monitored for changes in renal function when a medication is added or a dosage is increased.

Patient-Related Risk Factors for Drug-Induced Nephrotoxicity

- "Absolute" or "effective" intravascular volume depletion
- Age older than 60 years
- Diabetes

- Exposure to multiple nephrotoxins
- Heart failure
- Sepsis
- Underlying renal insufficiency (glomerular filtration rate < 60 mL per minute per 1.73 m2)

Both "absolute" and "effective" intravascular volume depletion are risk factors for drug-induced renal impairment. Absolute intravascular volume depletion may occur in patients who have gastroenteritis, chronic diarrhea, aggressive diuresis, or poor oral intake.[10] Effective intravascular volume is the volume of blood perceived by baroreceptors located in the right atrium and the kidney. Decreased effective circulating blood volume results from sequestration of fluid into thirdspace compartments and is associated with sepsis, heart failure, ascites, or pancreatitis.[7,36]

DRUG-RELATED RISK FACTORS

Certain drugs are inherently nephrotoxic and include aminoglycosides, amphotericin B, cisplatin, contrast dye, and cyclosporine.[7,34] For others, such as those associated with chronic interstitial nephritis and crystal deposition, nephrotoxicity is dose dependant or related to prolonged duration of treatment.[24] Combination therapy with multiple nephrotoxins can result in synergistic nephrotoxicity, thus increasing the risk of renal injury.[7] Specific preventive measures unique to some of these drugs are highlighted in *Table 3*.[7,10–13,20–24,32,37,38]

Patient-Related Risk Factors and Specific Prevention Strategies for Selected Agents

MEDICATIONS	RISK FACTORS	PREVENTION STRATEGIES
Drugs altering intraglomerular hemodynamics		
ACE inhibitors, ARBs, NSAIDs	Underlying renal insufficiency; intravascular volume depletion; age older than 60 years; concomitant use of ACE inhibitors, ARBs, NSAIDs, cyclosporine (Neoral), or tacrolimus (Prograf)	Use analgesics with less prostaglandin activity (acetaminophen, aspirin, sulindac [Clinoril], nabumetone [Relafen; brand not available in the United States])
		Correct volume depletion before initiation of drug, especially if used on a chronic basis
		Monitor renal function and vital signs following initiation or dose escalation, especially if used in at-risk patients
Cyclosporine, tacrolimus	As above, plus: excessive dose, concomitant use with other nephrotoxic drugs or drugs that inhibit cyclosporine or tacrolimus metabolism	Monitor serum drug concentrations and renal function
		Use lowest effective dose
Drugs associated with tubular cell toxicity		
Aminoglycosides	Underlying renal insufficiency,	Use extended-interval dosing

	duration of therapy > 10 days, trough concentrations > 2 mcg per mL, concomitant liver disease, hypoalbuminemia	Administer during active period of day
		Limit duration of therapy
		Monitor serum drug levels and renal function two to three times per week
		Maintain trough levels ≤ 1 mcg per mL
Amphotericin B	Underlying renal insufficiency, rapid infusion, large daily dosage, deoxycholate formulations more so than lipid formulations, prolonged duration of therapy	Saline hydration before and after dose administration
ACE inhibitors, ARBs, NSAIDs	Underlying renal insufficiency; intravascular volume depletion; age older than 60 years; concomitant use of ACE inhibitors, ARBs, NSAIDs, cyclosporine (Neoral), or tacrolimus (Prograf)	Use analgesics with less prostaglandin activity (acetaminophen, aspirin, sulindac [Clinoril], nabumetone [Relafen; brand not available in the United States])
		Correct volume depletion before initiation of drug, especially if used on a chronic basis
		Monitor renal function and vital signs following initiation or

		dose escalation, especially if used in at-risk patients
Cyclosporine, tacrolimus	As above, plus: excessive dose, concomitant use with other nephrotoxic drugs or drugs that inhibit cyclosporine or tacrolimus metabolism	Monitor serum drug concentrations and renal function
		Use lowest effective dose
Drugs associated with tubular cell toxicity		
Aminoglycosides	Underlying renal insufficiency, duration of therapy > 10 days, trough concentrations > 2 mcg per mL, concomitant liver disease, hypoalbuminemia	Use extended-interval dosing
		Administer during active period of day
		Limit duration of therapy
		Monitor serum drug levels and renal function two to three times per week
		Maintain trough levels ≤ 1 mcg per mL
Amphotericin B (Fungizone; brand not available in the United States)	Underlying renal insufficiency, rapid infusion, large daily dosage, deoxycholate formulations more so than lipid formulations, prolonged duration of therapy	Saline hydration before and after dose administration
		Consider administering as a continuous infusion over 24 hours

		Use liposomal formulation
		Limit duration of therapy
Contrast dye	Underlying renal insufficiency, age older than 70 years, diabetes, heart failure, volume depletion, repeated exposures	Use low-osmolar contrast in the lowest dose possible and avoid multiple procedures in 24 to 48 hours
		0.9% saline or sodium bicarbonate (154 mEq per L) infusion before and after procedure
		Withhold NSAIDs and diuretics at least 24 hours before and after procedure
		Monitor renal function 24 to 48 hours postprocedure
		Consider acetylcysteine preprocedure
Drugs associated with chronic interstitial nephropathy		
Acetaminophen, aspirin, NSAIDs	History of chronic pain, age older than 60 years, female sex, cumulative consumption of analgesic > 1 gram per day for more than two years	Avoid long-term use, particularly of more than one analgesic
		Use alternate agents in patients

		with chronic pain
Lithium	Elevated drug levels	Maintain drug levels within the therapeutic range
		Avoid volume depletion
Drugs associated with crystal nephropathy		
Acyclovir (Zovirax), methotrexate, sulfa antibiotics, triamterene (Dyrenium)	Volume depletion, underlying renal insufficiency, excessive dose, intravenous administration	Discontinue or reduce dose
		Ensure adequate hydration
		Establish high urine flow
		Administer orally

Table-8

Contrast-induced nephropathy is reported to be the third most common cause of acute renal failure in hospitalized patients.[2] The exact incidence, however, varies depending on study design, type and dose of contrast used, and presence of acute renal failure risk factors and other comorbidities.[37] The risk of contrast-induced nephropathy is highest in patients with chronic kidney disease (i.e., a GFR of less than 60 mL per minute per 1.73 m^2), especially in the presence of diabetes.[39] Other risk factors include dehydration, heart failure, age older than 70 years, and concurrent use of nephrotoxic drugs.[37] Patients with risk factors for contrast-induced nephropathy, especially those who have multiple risk factors, require prophylactic interventions before imaging. Prophylactic interventions studied have included normal saline or sodium bicarbonate infusions and acetylcysteine before and after imaging.[38,40] However, the role of acetylcysteine has yet to be defined because clinical trial results have been inconsistent.[37]

PREVENTIVE MEASURES

General preventive measures include using equally effective but non-nephrotoxic drugs whenever possible, correcting risk factors for nephrotoxicity, assessing baseline renal function before initiating therapy, adjusting the dose of medications for renal function, and avoiding nephrotoxic drug combinations *(*Baseline renal function can be estimated at the bedside using the Modification of Diet in Renal Disease (MDRD) formula or the Cockcroft-Gault formula in adults and the Schwartz formula for children The National Kidney Foundation advocates using the MDRD formula for the detection and staging of chronic kidney disease.

General Measures to Prevent Drug-Induced Nephrotoxicity

- Medication dosages using the Cockcroft-Gault formula (in adults) or Schwartz formula (in children).
- Assess baseline renal function using the MDRD equation, and consider patient's renal function when prescribing a new drug.
- Avoid nephrotoxic combinations
- Correct risk factors for nephrotoxicity before initiation of drug therapy.
- Ensure adequate hydration before and during therapy with potential nephrotoxins. Use equally effective non-nephrotoxic drugs whenever possible.

Formulae to Assess Renal Function and Adjust Medication Dosages

AUTHOR	*ESTIMATION FORMULA*	*PURPOSE*
MDRD[41]	eGFR = 186 × serum creatinine (mg per dL) $^{-1.154}$ × age (years) $^{-0.203}$ × (0.742 if patient is female) × (1.210 if patient is	To assess renal function and stage chronic kidney

AUTHOR	*ESTIMATION FORMULA*	*PURPOSE*
	black)	disease[44]
Cockcroft and Gault[42]	Male: eCrCl = ([140 – age (years)] × ideal body weight [kg]) ÷ (serum creatinine [mg per dL] × 72)	To adjust drug dosing for renal function in adults[45]
	Female: male eCrCl × 0.85	
Schwartz[43]	eCrCl = (length [cm] × k) ÷ serum creatinine (mg per dL)	To adjust drug dosing for renal function in children
	k = 0.45 (infants one to 52 weeks of age)	
	0.55 (children one to 13 years of age)	
	0.70 (males 14 to 17 years of age)	
	0.55 (females 14 to 17 years of age)	

Table 9

eCrCl = estimated creatinine clearance; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.

Most drugs that are eliminated renally do not require dosage adjustment until the creatinine clearance falls below 50 mL per minute.46 The preferred formula advocated by the U.S. Food and Drug Administration to guide drug dosing in adults is the Cockcroft-Gault formula because it has been used in nearly all pharmacokinetic studies to generate drug-dosing guidelines.45,47 Compared with the MDRD, the Cockcroft-Gault equation tends to overestimate the GFR and may yield different results depending on the patient.41 For example, the estimated GFR of a 64-year-old, 190-lb (86-kg) woman with a serum creatinine level of 1.3 mg per dL (110 μmol per

L; normal: 0.8 to 1.4 mg per dL [70 to 120 μmol per L]) is 59 mL per minute using the Cockcroft-Gault formula and 44 mL per minute per 1.73 m2 according to the MDRD. In this example, both formulas indicate renal insufficiency, but the patient's medications most likely would not require a dose adjustment.

Adequate hydration is important to maintain renal perfusion and avoid drug-induced renal impairment. Whenever possible, volume status should be assessed and corrected, if necessary, before initiation of nephrotoxic agents. This is particularly true when prescribing medications such as ACE inhibitors, ARBs, and NSAIDs, which induce alterations in renal hemodynamics in patients who are significantly volume depleted.10,32 Signs of significant intravascular volume depletion include orthostatic hypotension, blood pressure of less than 90/60 mm Hg, and decreased skin turgor accompanied by a loss of more than 5 percent of baseline body weight.1–4 Currently, there is no consensus on the optimal solution, volume, or timing of fluids to restore renal perfusion.7

A systems approach involving computerized physician order entry and clinical decision support may reduce the danger of exposing at-risk patients to nephrotoxins, but such systems are greatly underused in the ambulatory setting.48 Forming collaborations between those who prescribe drugs and clinical pharmacists is a good option and should be pursued and developed, although funding such efforts may be a challenge.48 Two reports from the Institute of Medicine recognized that pharmacists are an essential resource in safe medication use and that pharmacist-physician-patient collaboration is important.49,50 The clinical and economic impact of clinical pharmacists in other settings has been extensively reviewed and summarized in the literature.51

VIGILANCE

In one large cohort study of Medicare enrollees in the ambulatory setting, inadequate laboratory monitoring played a role in 36 percent of all preventable adverse drug events.48 In addition, when assessing baseline renal function, physicians should consider monitoring serum creatinine levels after starting or increasing the dosage of drugs associated with nephrotoxicity, especially those used chronically in

patients with multiple risk factors for renal impairment. A systems approach toward adopting an electronic medical record may provide a practical method for automated monitoring of all patients in general, and patients at risk of nephrotoxicity in particular.

RECOGNITION AND EARLY INTERVENTION

Most episodes of drug-induced renal impairment are reversible. Renal function generally returns to baseline provided the impairment is recognized early and the offending medication is discontinued.52 Failure to act on available information relating to clinical findings or laboratory results was the most common monitoring error, occurring in 37 percent of preventable adverse drug events, including those affecting the kidney, in older ambulatory patients.48A decrease in renal function as evidenced by a rise in serum creatinine levels following the initiation of a drug signals the possibility of drug-induced renal injury. An exception to this is an increase in serum creatinine following the initiation of cimetidine (Tagamet) or tri-methoprim (Proloprim), because they compete with creatinine for tubular secretion and are not associated with kidney damage or urine abnormalities.52 Although there are no standard guidelines used to interpret changes in serum creatinine, a 50 percent rise from baseline, an increase of 0.5 mg per dL (40 μmol per L) or more when baseline serum creatinine is less than 2 mg per dL (180 μmol per L), or an increase of 1 mg per dL (90 μmol per L) or more if baseline creatinine is greater than 2 mg per dL have been used as biochemical criteria of acute renal failure. At the first sign of renal dysfunction, the patient's medication list should be reviewed to identify offending agents. If multiple medications are present and the patient is clinically stable, physicians should start by discontinuing the drug most recently added to the patient's medication regimen. Attention should then be directed at avoiding further renal insults by supporting blood pressure, maintaining adequate hydration, and temporarily discontinuing all other possible nephrotoxins.

Manage the renal injury as needed by replacing fluid volume, starting dialysis, adjusting drug doses, trying steroids in cases of acute interstitial nephritis, and avoiding repeated exposure. When in doubt about the cause of renal injury, hold all potentially offending drugs.

First Line Treatment for drug induced renal injuries [13]

Mechanisms and principles for prevention of drug nephropathy [10]

	Mechanisms of renal susceptibility	**Principles for prevention**	**Examples**
A	Large drug exposure due to high renal blood flow	1. Avoid systemic drug administration 2. Limit total drug use	1.Intraperitoneal administration of cisplatin for localized intraperitoneal tumor. 2.Monitor aminoglycoside levels to maintain in therapeutic range, substitute nontoxic antibiotic based on microbial sensitivities.
B	Specialized renal hemodynamics regulated by vasoactive substances	Avoid drugs that inhibit prostaglandin synthesis	Substitute acetaminophen or nonacetylated salicylates ans sulindac for other NSAIDS
C	Tubulaar epithelial cell drug accumulation due to luminal and contraluminal transport	1. Inhibit drug administration from the luminal membrane 2.Inhibit drug absorption	1. Hydration with chloride anions during cisplatin therapy, calcium supplementation during

		from the contraluminal membrane	aminoglycoside therapy. 2. Cilastatin inhibition of imipenem toxicity
D	Renal metabolism of drugs to toxic species	Use drugs with nontoxic renal metabolites	Renal metabolism of active sulindac to inactive sulindac sulfoxide
E	Cellular dysfunction due to drug induced increased energy requirements	Decrease cell energy needs by reducing cell memebrane transport activity	Furosemide use during amphotericin therapy to reduce ischemia and toxicity to the medullary thick ascending loop of henle
F	Water reabsorption and concentration of toxins within the tubular lumen promoting increased epithelial cell membrane contact and transport into cells	1. Prevent dehydration 2. Use of osmotic diuresis to increase luminal water concentration and tubular flow rate.	1. NaCl repletion to prevent amphotericin toxicity. 2. Possible reduction of contrast nephropathy by mannitol diuresis.

Table 10

LITERATURE REVIEW

- **Marie-Laure Cittanova, Anne Zubicki et al.,**[14] conducted a prospective study that included 249 patients admitted for aortic surgery with ACEI's. Preoperative & post operative glomerular filtration rates were assessed with pre-operative & post operative creatinine clearance measurements. Postoperative renal impairment was defined as a 20% decrease in GFR between day 0 (before surgery) and day 7+-1 day (after surgery).Chronic preoperative ACEI's treatment is significantly associated with postoperative renal impairment. Inhibition of compensatory mechanisms caused by rennin angiotensin system blockade might be responsible for the observed decrease in renal function in patients chronically treated with ACEI's undergoin aortic surgery.

- **Gary.C.Curhan, Eric.L.Knight et al.,**[15] studied on 1697 women participating in the nurses health study about the lifetime use of acetaminophen, aspirin & NSAIDS. The main outcome was change in estimated glomerular filtration rate in 11 years. The mean +- SD estimated GFR decreased from 88+-17 to 79+-17ml/min per $1.73m^2$. Acetaminophen use was associated with an increased risk of a GFR decline of atleast 30ml/min per $1.73m^2$ & a GFR decline of 30% or greater. Hence high acetaminophen use may increase the risk of loss of renal function.

- **Thomas.V.Perneger, Paul.K.Whelton & Michael.J.Klag.,**[16] studied that people who take analgesic drugs frequently may be at increased risk of ESRD.They studied on 716 pt's treated for ESRD & 361 control subjects. Participants were interviewed about their past use of medications containing acetaminophen ,aspirin, NSAIDS. Heavier acetaminophen use was associated with an increased risk of ESRD in a dose-dependent fashion. Approximately 8 to 10 percent of the overall incidence of ESRD was attributable to acetaminophen use. .

- **Perneger et al.,**[17] reported the results of a case-control of the use of over-the counter analgesic drugs as a risk for ESRD. Heavy average use of acetaminophen intake (more than 1 pill per day) and medium-to-high cumulative acetaminophen intake (more than 1000 pills in a lifetime) each doubled the odds of ESRD. The results also suggested an association between ESRD & high lifetime intake (5000 or more pills) of NSAIDS other aspirin.

- **Hemsreet B.A.,**[18] documented the association of various antimicrobial medications with the development of RTA. Anti microbial- associated RTA is a relatively uncommon adverse effect, with most reports involving amphotericin B, trimethoprim/ sulfamethoxazole & outdated tetracycline. These agents may induce RTA either through direct tubular toxicity or as fuction of their pharmacologic action.

- **Aranyl , Safirstein RL**.,[19] Reported on cisplatin nephrotoxicity. The kidney accumulates cisplatin to a higher degree than other organs perhaps via mediated transport. Functionally, reduced renal perfusion & a concentrating defect characterize its nephrotoxicity, whereas morphologically necrosis of the terminal portion of the proximal tubule and apoptosis predominantly in the distal nephron characterize its effect on cellfate. Metabolic responses, cell cycle events and the inflammatory cascade seem to be important determinants of the degree of renal failure induced by cisplatin.

- **Cheng HF, Harris RC.,**[20] reported on renal effect of NSAIDS and selective cyclo-oxygenase-2-inhibitors. Similar to conventional NSAIDS, inhibition of cox-2 may cause edema and modest elevations in blood pressure in a minority of subjects. Cox-2 inhibitors may also exacerbate pre-existing hypertension (or) interfere with otyer anti-hypertensive drugs. Occassional acute renal failure has also been reported.

- **Roling J, Schmid H, et al.,**[21] Studied on HIV- associated renal diseases and highly active ART_ induced nephropathy. HIV- related renal impairment can present as acute (or) chronic kidney disease- leads to changes in renal function

by inducing metabolic vasculopathy and renal damage. Chronic renal disease can be caused by multiple pathophysiological mechanisms leading to HIV associated nephropathy.

- **Quershi Iz. et al.,**[22] investigated the effects of ACEI's on recombinant human erythropoietin in CRF patients. The study was conducted in 100 patients (55 males, 45 females) divided into 2 groups. Group 1 patients received rHuEPo and ACI's while group 2 received rHuEPo with other anti-hypertensives. Datas showed that ACI's interfered with rHuEPo therapy for treatment of anaemia in CRF.

- **Weisbord SD et al.,**[23] Studied that the intravascular administration of iodinated radio-contrast media can lead to acute renal dysfunction. Risk factors include pre-existent kidney disease, diabetic mellitus, dose of radio-contrast used, advanced congestive heart failure and intravascular volume depletion.

- **Aleksa.K, et al**.,[24] Studied on ifosfamide induced nephrotoxicity in children with cancer. Nephrotoxicity induced by ifosfamide with younger children less than 3 years is more vilnerable. The underlying hypothesis is that renal ontogeny is involved in the expression and activity of the cytochrome P450 enzymes responsible for metabolism to the nephrotoxic chloroacetaldehyde.

- **Zimmermann AE, et al.,**[25] diagnosed tenofovir-associated acute and chronic renal disease in patients with HIV infection.They studied tenofovir associated therapy had classic findings of acute tubular necrosis, compared the findings with 22 patients. The mean serum creatinine levelincreased from 0.9 to 3.9 mg/dl, and decreased to 1.2 mg/dl during recovery. Tenofovir-associated ARF manifests as acute tubular necrosis thay may not resolve with tenofovir withdrawal. It is associated with multiple drug interactions leading to an increased risk ofARF.

- **Goldman RD, Koren G**[26] studied Amphotericin B nephrotoxicity in children. Neprotoxicity includes decreased glomerular filtration rate and distal tubulopathy with urinary loss of potassium and magnesium, renal tubular acidosis, loss of urine concentrating ability, and sometimes fanconi's syndrome.

- **Dovas.S, et al.,**[27] reported 2 cases that have implicated aminoglycoside-impregnated cement in acute renal failure after surgery for an infected total knee arthroplasty. 2 more cases of post operative ARF after use of combined tobramycin- plus vancomycin impregnated cement in total hip arthroplasty have also been reported.

- **Widemann BC,et al.,**[28] estimated the current incidence of high dose methotruxate (HDMTX) induced renal dysfunction in patients with osteosarcoma and compared the efficacy and recovery of renal function for dialysis – based methods of MTX removal with treatment using CPDG2 (carboxypeptidase G2). Approximately 1.8% of patients with osteosarcoma (68 of 3887 patients) who received HDMTX developed nephrotoxicity.

- **Fred G. Silva.,**[29] studied that renal changes induced by chemicals can effect the tubules, interstitium or both. This review of chemical induced nephropathy in human considers acute tubular necrosis, interstitial nephritis and tubulo interstitial nephritis or nephropathy because the tubules and interstitium are so intimately related injury to one of these 2 components may eventually lead to injury of the other , resulting in tubulo interstitial disease.

- **Busauschina A, et al.,**[30] discussed on cyclosporine neprotoxicity- primary immunosupresant for the prevention of allograft rejection in solid organ transplantation. The underlying pathomechanisms of this toxicity reflect an altered release of vasoactive substances such as angiotensin2, endothelin, prostaglandins and nitric oxide as well as the stimulation of proliferative genes such as transforming growth factor- beta, osteopontin and collagen1 & 1V.

- **Kintzel, Polly E.,**[31] discussed on anticancer drug induced kidney disorders, its incidence, prevention and management. Toxicity can be catagorised as pre-renal uraemia, intrinsic damage or post –renal uraemia. Mechanisms of chemotherapy induced renal dysfunction generally include damage to vasculature or structures of the kidney,haemolytic uraemic syndrome and pre renal perfusion deficits. Dose related nephrotoxicity subsequent to administration of certain chloroethlylnitrosourea compounds is commonly heralded by increased serum creatinine levels, uraemia and protienuria. Cisplatin and carboplatin cause dose related renal dysfunction. High dose azacitidine causes renal dysfunction manifested by tubular acidosis, polyuria and increased urinary excretion of electrolytes, glucose and aminoacids. Haemolytic uraemia is a rare adverse effect of gemicitabine. Methotruxate can cause increased serum creatinie levels, uraemia and haematuria.

- **Ahmad, Syed R, et al.,**[32] conducted a study in order to understand the association between acute renal failure and the two cox-2 inhibitors-celecoxib and rofecoxib. The literature search identified 19 cases of acute renal impairment in association with celecoxib and rofecoxib. Data from AERS (Adverse Event Reporting System) and published case reports suggest that use of both these drugs is associated with renal effects similar to that of conventional non-selective NSAIDS. Patients at greatest risk for renal injury are those with pre-existing renal impairment, heart failure, liver dysfunction those taking diuretics or ACIs and the elderly.

AIM AND OBJECTIVE OF THE STUDY

Drug toxicity in hospitalized patients is a frequent adverse event with nephrotoxicity accounting for nearly 20% of all drug toxicity. Hospitalized patients are vulnerable to renal failure from a variety of causes, including diagnostic procedures (1V contrast), sudden decrease in blood pressure (gastrointestinal bleed, sepsis, variceal bleed) and the addition of nephrotoxic medications (aminoglycosides, amphotericin, chemotherapy). Upto 16% of patients with baseline normal renal function who experience renal injury within the hospital setting have medication-induced renal failure.

The present study has made an attempt to reveal the following details:-

- To study on various renal diseases reported in the nephrology department of the hospital.
- Study on patients with drug induced renal diseases.
- Etiology of drug induced renal diseases.
- Study on corresponding elevations in laboratory parameters in drug induced renal diseased patients.
- Clinical management of patients with drug induced renal disease.

PLAN OF THE WORK

The present dissertation was undertaken to study the incidence of drug induced renal disease and its clinical management.

- Collection of patients admitted with drug induced renal disease in the nephrology unit of the hospital.
- Collection of case history to point out the etiology of drug induced renal disease
- Corresponding elevations in the clinical parameters are observed.
- Clinical management of drug induced renal disease undertaken is studied.
- Consultation with the Nephrologist
- Submission of reports obtained.

BACKGROUND OF THE STUDY

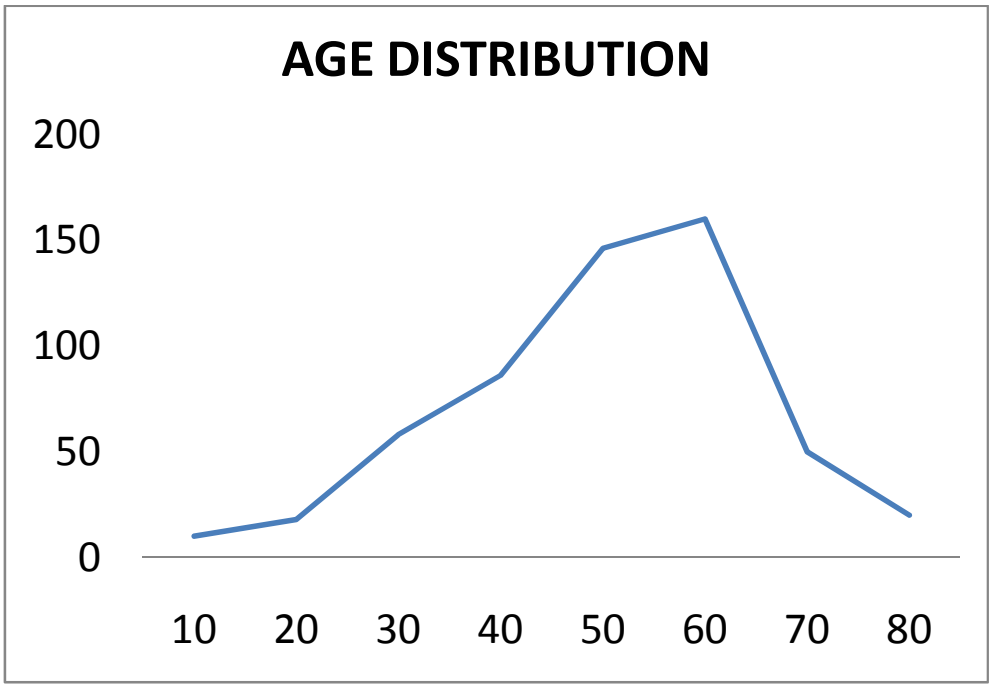
This prospective study was conducted at Nephrology department in **"MEENAKSHI MISSION HOSPITAL AND RESEARCH CENTRE" MMHRC) MMHRC:** This hospital was located in lake area at Madurai. This is a 750 plus bedded hospital built in late 20^{th} century by Dr. SETHURAMAN (FOUNDER). The hospital was especially built for lower realms of humanity in our country and it provides multispecialty medical and surgical treatment at very high levels. The quality control service for each department has been done and their presentation also has been done in every year. This hospital is a deemed autonomous teaching hospital which have academic programs for paramedical disciplines.

This study was conducted between DECEMBER 2012 – JULY 2013.

OBSERVATION AND RESULTS

1. AGE DISTRIBUTION

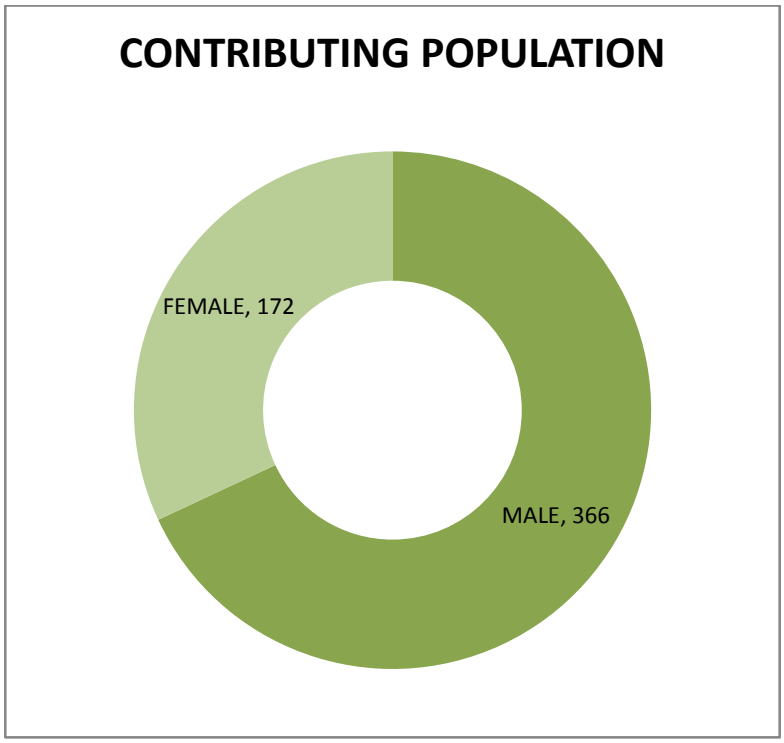
AGE(In years)	No. of patient
1 -10	10
11-20	18
21-30	58
31-40	86
41-50	146
51-60	160
61-70	50
71-80	20



2. SEX DISTRIBUTION

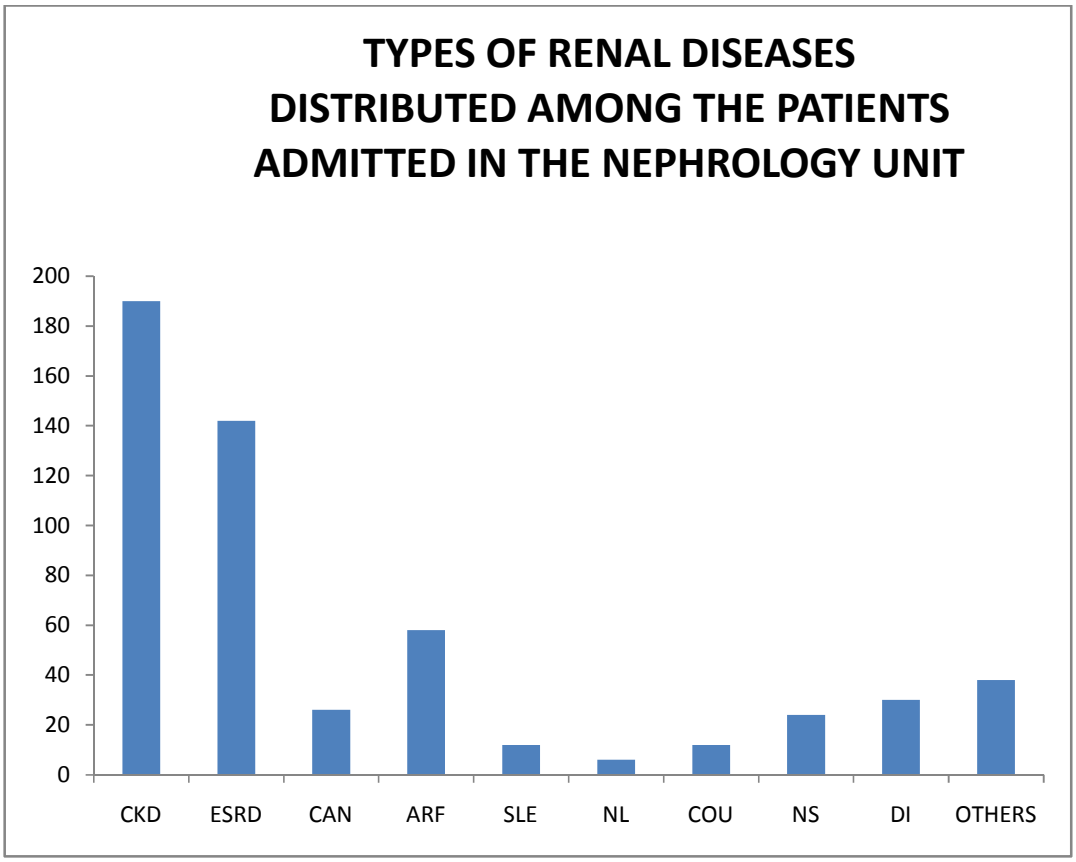
538 patients were admitted in the nephrology department of MMHRC due to various types of renal diseases during the period of Dec 2012– Jul 2013. The sex distributions of the patients with renal diseases studied were 366 (72%) males and 172 (28%) females.

MALE	**68%**
FEMALE	**32%**



3. TYPE OF RENAL DISEASES DISTRIBUTED AMONG THE PATIENTS.

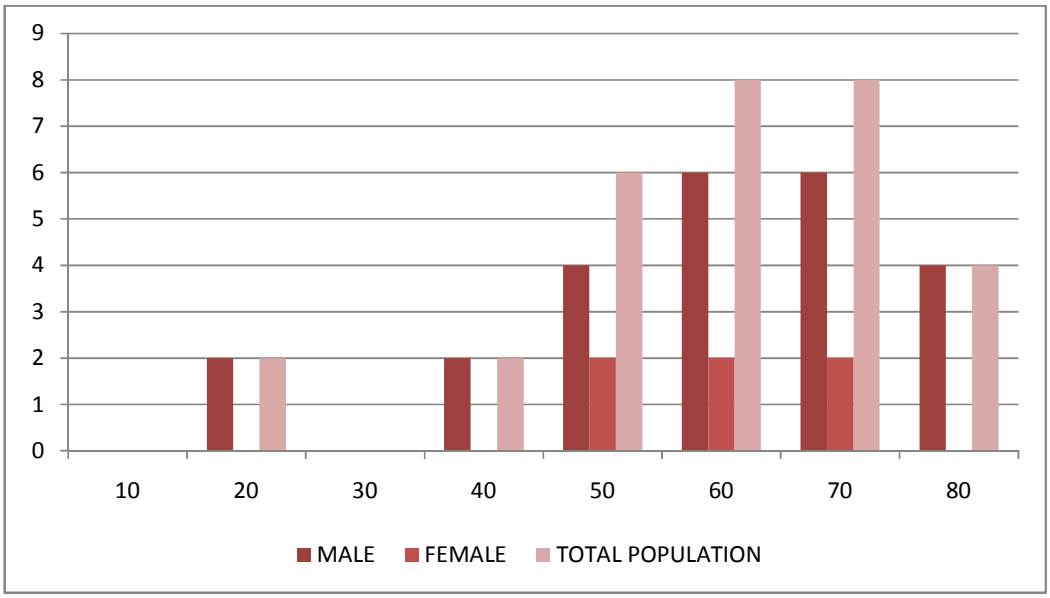
TYPE OF RENAL DISEASES	**NO. OF PATIENT** (%)
CHRONIC KIDNEY DISEASE	190 (35.31%)
END STAGE RENAL DISEASE	142 (26.39%)
CHRONIC ALLOGRAFT NEPHROPATHY	26 (4.83%)
ACUTE RENAL FAILURE	58 (10.78%)
SYSTEMIC LUPUS ERYTHEMATOUS	12 (2.23%)
NEPHROLITHIASIS	6 (1.12%)
CHRONIC OBSTRUCTIVE UROPATHY	12 (2.23%)
NEPHROTIC SYNDROME	24 (4.46%)
DRUG – INDUCED KIDNEY DISEASES	30 (5.57%)
OTHERS	38 (7.06%)



ESRD	– END STAGE RENAL DISEASE
CKD	– CHRONIC KIDNEY DISEASE
CAN	– CHRONIC ALLOGRAFT NEPHROPATHY
ARF	– ACUTE RENAL FAILURE
SLE	– SYSTEMIC LUPUS ERYTHEMATOUS
NL	– NEPHROLITHIAIS
COU	– CHRONIC OBSTRUCTIVE UROPATHY
NS	– NEPHROTIC SYNDROME
DI	– DRUG INDUCED KIDNEY DISEASE

4. AGE DISTRIBUTION

AGE(In years)	MALES	FEMALES	TOTAL
1 -10	0	0	0
11-20	2	0	2
21-30	0	0	0
31-40	2	0	2
41-50	4	2	6
51-60	6	2	8
61-70	6	2	8
71-80	4	0	4

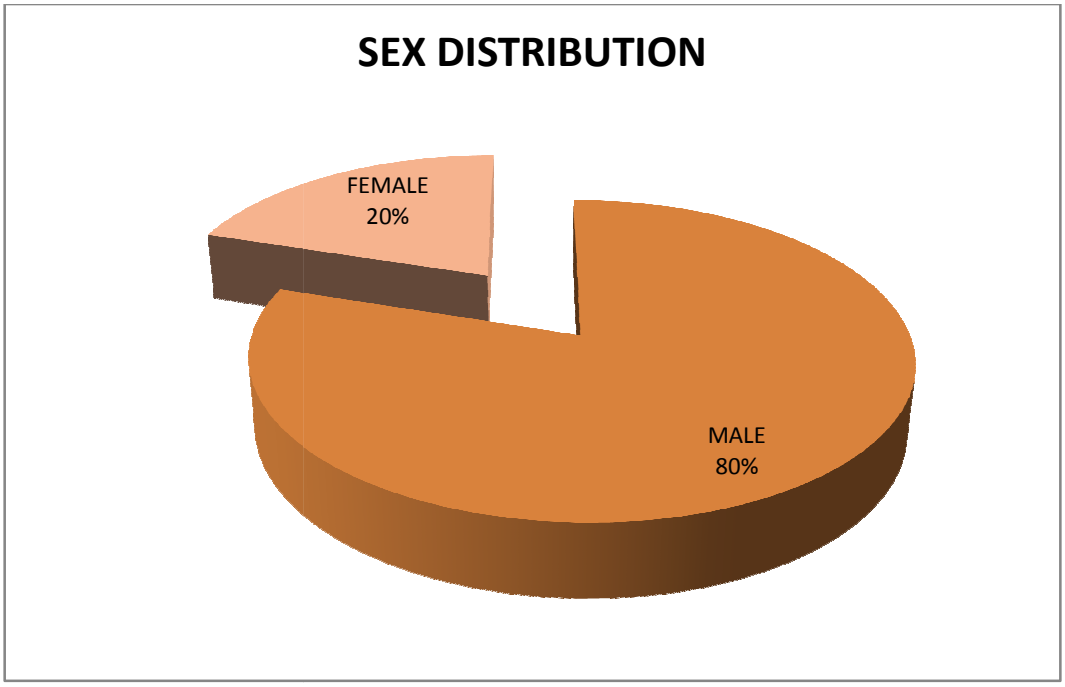


DISTRIBUTION OF DRUG INDUCED RENAL DISEASES

5. SEX DISTRIBUTION

The Study included 30 patients with Drug Induced Renal Diseases from the Nephrology Unit. Among these 30 patients 24 males (80%) and 6 females (20%) were identified.

MALES	80%
FEMALES	20%

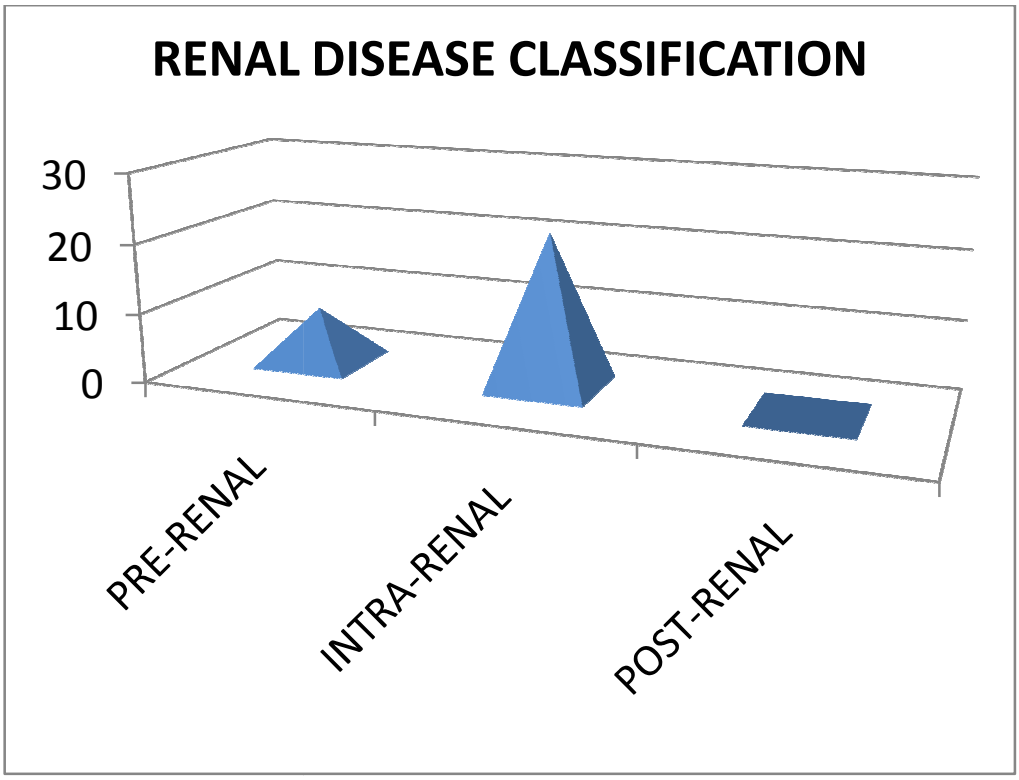


6. CLASSIFICATION OF RENAL DISEASE

The patients were characterized according to the classification of Drug Induced Renal disease.

Most of the medications have caused direct injury to the kidney.

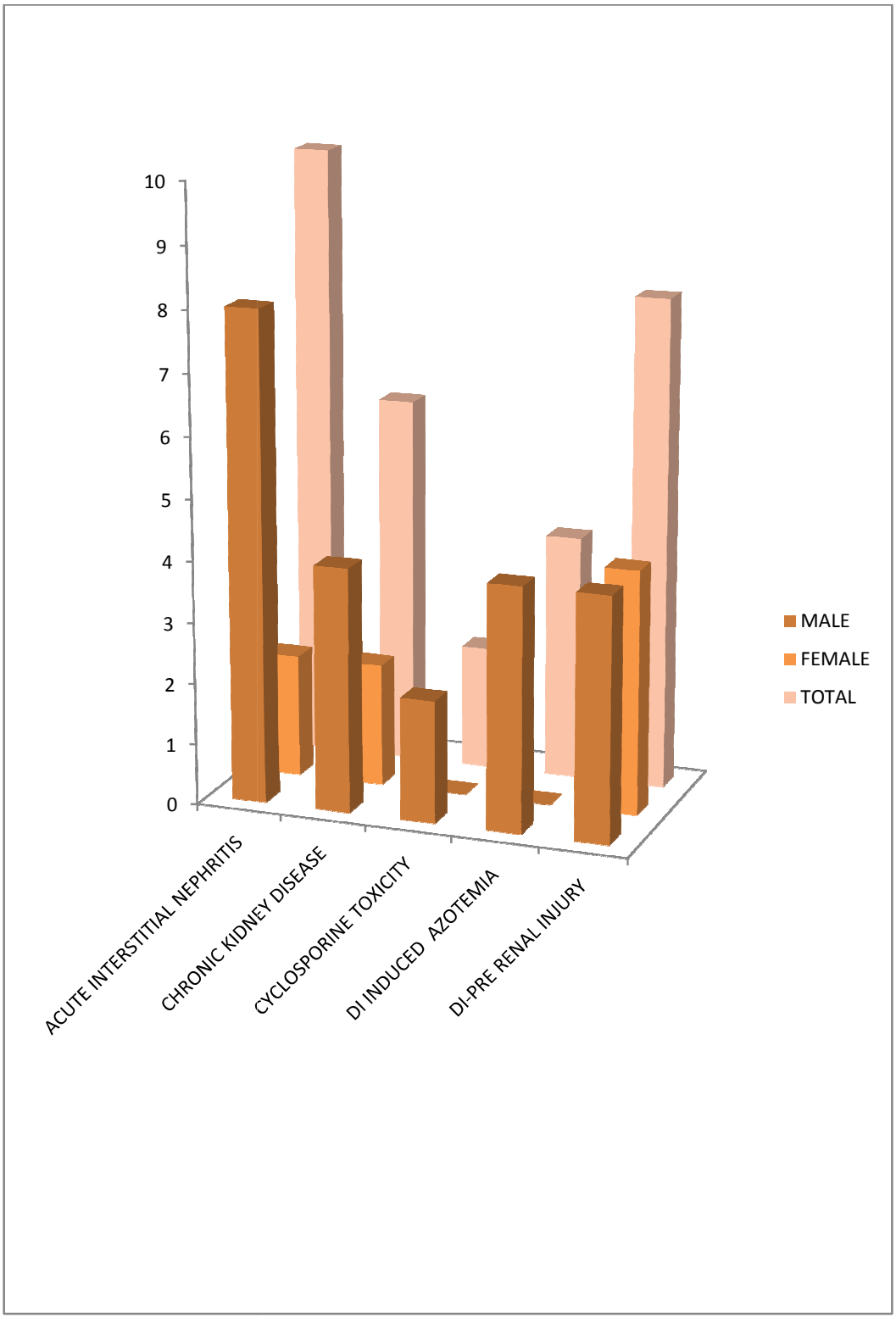
PRE – RENAL	**8**
INTRA – RENAL	**22**
POST - RENAL	**0**



7. TYPE OF DRUG INDUCED RENAL DISEASE DISTRIBUTED AMONG PATIENTS.

Patients were characterized according to the type of Drug induced renal disease.

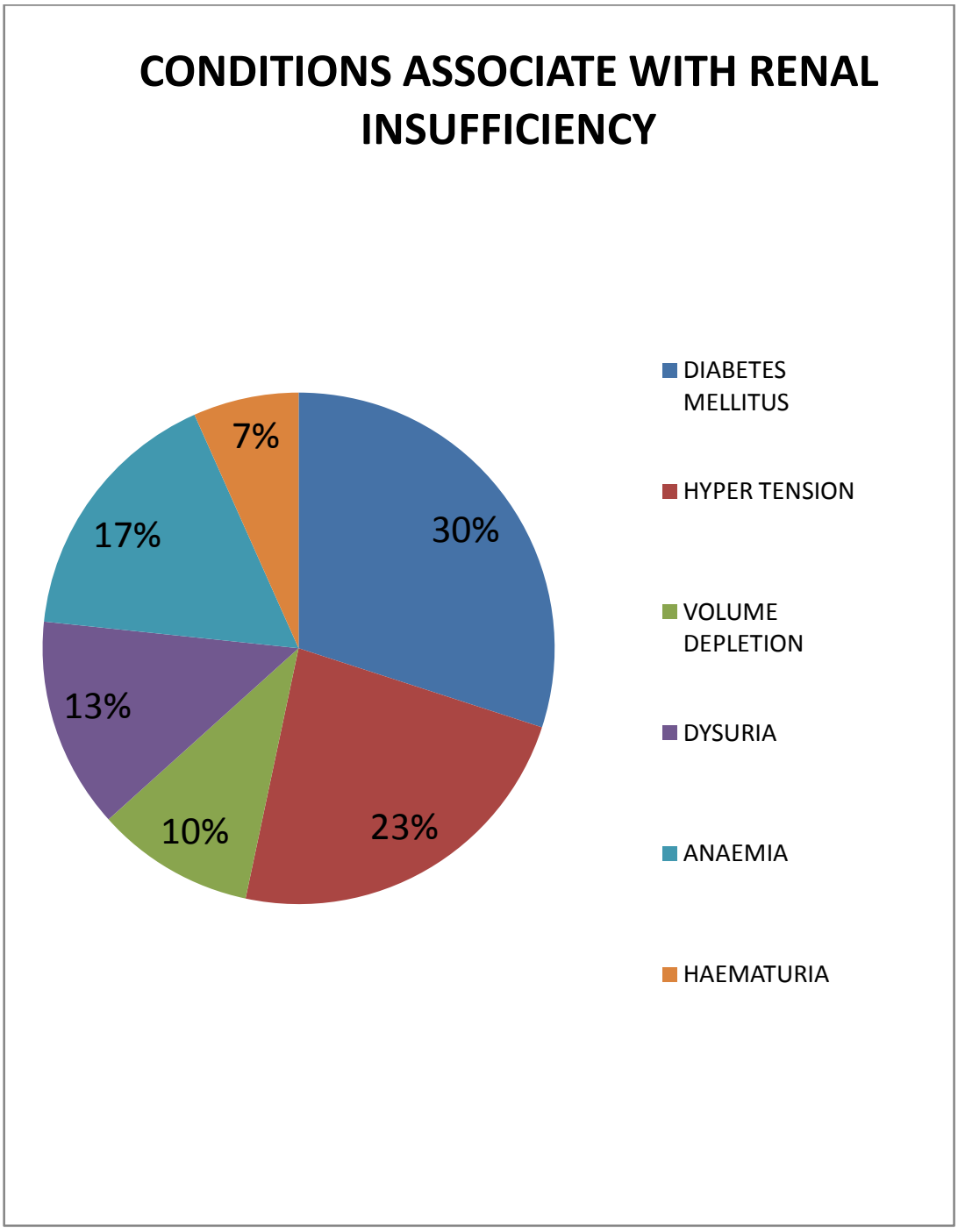
NAME OF THE DISEASE	MALES	FEMALES	TOTAL
ACUTE INTERSTITIAL NEPHRITIS	**8**	**2**	**10**
CHRONIC KIDNEY DISEASE	**4**	**2**	**6**
CYCLOSPORINE TOXICITY	**2**	**0**	**2**
DRUG INDUCED AZOTEMIA	**4**	**0**	**4**
DRUG INDUCED PRE RENAL INJURY	**4**	**4**	8


10
9
8
7
6
5
4
3
2
1
0
ACUTE INTERSTITIAL NEPHRITIS
CHRONIC KIDNEY DISEASE
CYCLOSPORINE TOXICITY
DI INDUCED AZOTEMIA
DI-PRE RENAL INJURY
MALE
FEMALE
TOTAL

8. CONDITIONS ASSOCIATED WITH RENAL INSUFFICIENCY

The various conditions associated with renal injury were analyzed among the patients as follows:-

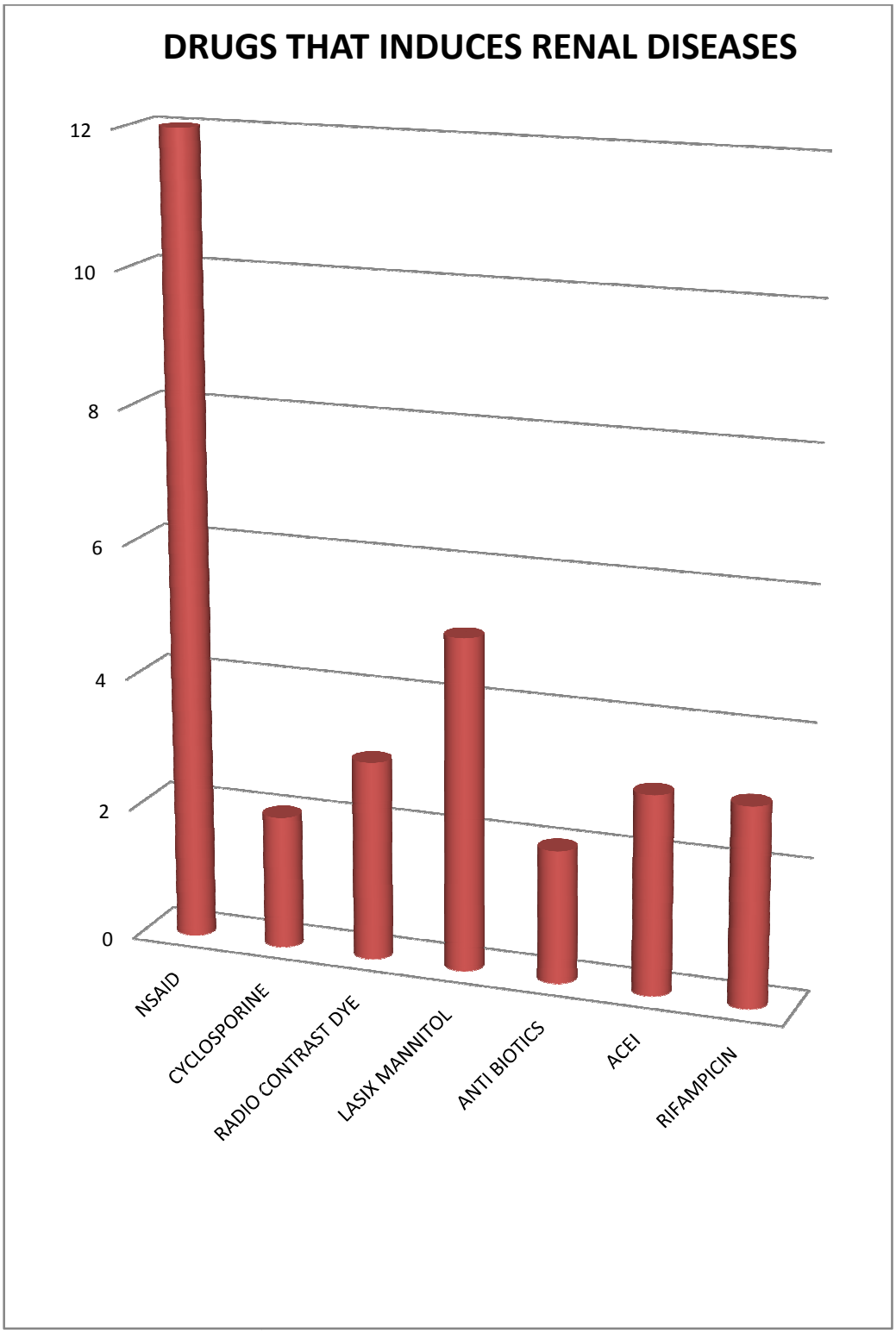
NAME OF DISEASE	NUMBER OF PATIENT
DIABETES MELLITUS	9
HYPERTENSION	7
VOLUME DEPLETION	3
DYSURIA	4
ANAEMIA	5
HAEMATURIA	2


CONDITIONS ASSOCIATE WITH RENAL INSUFFICIENCY
30%
23%
10%
13%
17%
7%
DIABETES MELLITUS
HYPER TENSION
VOLUME DEPLETION
DYSURIA
ANAEMIA
HAEMATURIA

9. DRUGS THAT INDUCES RENAL DISEASES

Drugs / toxins responsible for nephrotoxicity were analyzed among the patients as follows:-

Class of Drug	No. of patient
NSAIDs	**12**
LASIX / MANNITOL	**5**
ANTIBIOTICS	**2**
CYCLOSPORINE	**2**
RADIO – CONTRAST DYE	**3**
ACEI's	**3**
RIFAMPICIN	**3**


DRUGS THAT INDUCES RENAL DISEASES
12
10
8
6
4
2
0
NSAID
CYCLOSPORINE
RADIO CONTRAST DYE
LASIX MANNITOL
ANTI BIOTICS
ACEI
RIFAMPICIN

10. ELEVATIONS IN CLINICAL PARAMETERS STUDIED INCLUDES:-

By monitoring the patient's laboratory data, it is possible to detect a drug – related decline in renal function. The laboratory data that provide information about the functional capacity of the kidneys include the SERUM UREA and SERUM CREATININE concentration.

Normal values:-

Serum urea: - 20 – 40 mg / dl

Serum Creatinine: - 0.5 – 1.5 mg / dl

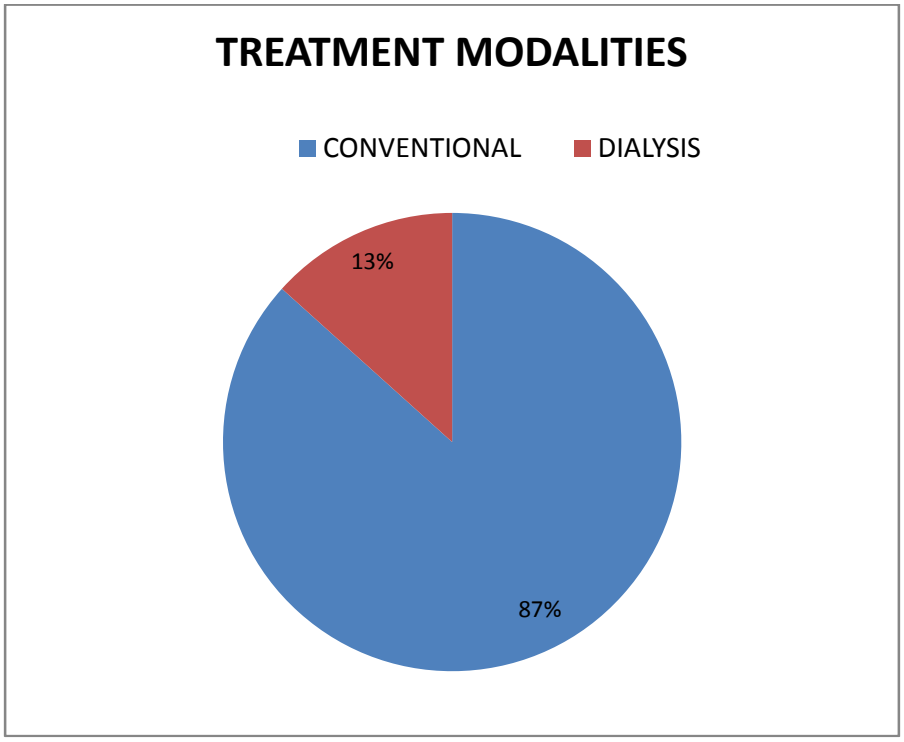
S.NO	ABNORMAL VALUE(in mg/dl)		CORRECTED VALUE(in mg/dl)	
	SERUM UREA	SERUM CREATINE	SERUM UREA	SERUM CREATININE
1	41	2.4	15	0.4
2	72	1.8	54	1.5
3	50	3.3	45	2.5
4	65	5.4	55	2.3
5	120	1.6	78	1
6	72	1.2	50	0.8
7	72	2.5	15	0.7
8	140	2.9	95	1.5
9	116	5.4	95	6.5
10	63	1.9	52	1.2
11	91	1.3	52	0.8
12	77	1	37	1
13	47	2	28	1.8
14	191	8.5	120	6.2
15	176	7.8	104	6.8

SERIAL NO.	ABNORMAL VALUE(in mg/dl)		CORRECTED VALUE(in mg/dl)	
	SERUM UREA	SERUM CREATINE	SERUM UREA	SERUM CREATININE
16	67	4.5	20	0.9
17	54	3.6	42	1.8
18	68	5.3	35	1.3
19	56	2.4	45	1.2
20	94	3.6	38	2
21	72	2.2	39	0.8
22	86	2.5	15	0.7
23	140	2.9	39	1.6
24	161	3.4	31	2.6
25	70	1.9	98	5.6
26	93	1.3	52	0.8
27	78	1.3	37	1.7
28	49	2	28	1.8
29	187	8.5	120	8.2
30	57	1.8	55	1.4

11. TREATMENT MODALITIES

Distribution of therapeutic modalities among the patients :-

CONVENTIONAL	**25 (87%)**
DIALYSIS	**5 (13%)**



DISCUSSION AND CONCLUSION

In this prospective study 538 patients were having various kidney diseases. Prevalence of kidney disease is very high between age group 51to 60 and 41 to 50 were 160 and 146 respectively, and it is due to metabolic rate, food habits, environment etc…

Sex distribution among the sample population

It was observed that male (68%) predominance exists in this study compared to females (32%).

Drug induced renal disease:-

Drug induced renal disease has occurred in 5.57% of the hospitalized patients coming with various renal diseases during the study period. In this study, 30 patients with drug induced nephrotoxicity have been observed out of this noted 20% female (6) and 80% male (24) patients, it is mainly due to sedentary life style.

Out of these 30subjcts 22 subjects having intra renal disease,8 subject having pre renal disease due to insufficient in take of water, quality of water, calcium rich diet like cow milk, dry fish, variety of pickles etc..

Population having metabolic disorder like Diabetes mellitus and hypertension were more prone to get drug induced kidney disease because of food habits and life style.

Age distribution

In this study, patients with an age group between 10 – 80 were exposed to drug induced renal disease.

This study showed that most of the patients with an age group between 51 to 70 were more prone to develop drug induced renal disease. In age group between 51to60, 8 patients were developed drug induced renal injury. Among these 8 patients,2 patient- a case of road traffic accident – on treatment with diuretics developed toxicity, another 1 patient developed antibiotic induced renal injury and

other r 4 patient developed with intake of NSAIDS for complaints of back pain, and 1 patient developed rena ltoxiicity due radiocontrast dye.

8 patients of an age group between 61 – 70 developed drug induced renal toxicity. Among these 8, 2 patient developed radio contrast dye toxicity on post coronary angiogram, 3 patients developed diuretic induced renal injury and 3 patient developed anti hypertensive induced toxicity.

6 patients of an age group between 41 – 50 developed drug induced renal toxicity.Among these 6, 4 patients developed NSAID induced renal toxicity, and 1 patient developed renal toxiccity with antibiotic.

4 patients of an age group between 71 – 80 developed drugs induced renal toxicity. All 4 patients with NSAID.

2 patients with an age group between 11 – 20 developed drug induced renal disease.1patient on treatment with Rifamycin toxicity and another one patient developed cyclosporin induced renal toxicity. 2 patients of an age group between 31 – 40 developed drug induced renal disease, due to Rifamycin induced toxicity for complaints of tuberculosis.

Drugs that induces nephrotoxicity

On conducting this study, it was possible to find out that a wide variety of drugs induced nephrotoxicity in patients who were hospitalized.

It was observed that 6 patients were admitted for Non- steroidal Anti-inflammatory Drug (NSAID) induced renal injury and 3 patients with lasix (or) mannitol induced renal injury.

Similarly other drugs such as cyclosporine, radio- contrast dye, antibiotics [ciprofloxacin, levofloxacin], Angiotensin Converting Enzyme inhibitors (ACEI) and rifampicin induced renal injury was also observed in patients.

NSAIDS (Non Steroidal Anti- inflammatory Drugs) inhibit the formation of prostaglandins through the inhibition of cyclo- oxygenase enzymes, thus reduces the overall blood flow to the kidneyand induces renal injury.Long term use of NSAIDs can cause chronic renal insufficiency. Patients at risk for kidney damage with NSAIDS include those with decreased effective arterial blood volume. It was found that 6 patients tooh treatment for NSAID induced renal injury.

Diuretics stimulate renal vasoconstriction with marked uptake of sodium chloride and thus decreases urine output. Prolonged vasoconstriction can lead to tubular dysfunction and tubular necrosis. It is frequently associated with pre- renal azotemia. It was observed that 3 patients were treated for diuretic induced renal injury.

Antibiotics cause intra-renal injury such as Acute Interstitial Nephritis – a hypersensitivity or allergic reaction to the drug. 2 patients were found with antibiotic induced renal injury.

Radio- contrast dye induces acute vasoconstriction, increases medullary oxygen consumption and eventually leads to tubular ischemia. Severe toxicity is more frequent in diabetic patients with pre- existent renal insufficiency. Prevention can be aimed by vigorous hydration using low doses of contrast media and avoiding multiple contrast procedures. 1 patient was exposed to radio- contrast dye induced renal injury.

Cyclosporine induces vasoconstriction of afferent and efferent arteriole, leading to a drop in Glomerular Filtration Rate. Cyclosporine is dose- dependent and so the dose should be monitored to avoid larger drop in Glomerular Filtration Rate. 1 patient was exposed to cyclosporine toxicity.

Patients whose renal function depends on angiotensin 2 for maximum renal function, may experience a decline in function with the addition of Angiotensin Converting Enzyme Inhibitors. ACEI's reduces the renal blood flow to the kidney and induces injury. 1 patient was treated for ACEI induced renal injury.

Conditions associated with renal insufficiency

On analyzing the laboratory parameters, it was observed that conditions such as diabetes, hypertension, dysuria, anaemia and haematuria were associated with renal insufficiency in patients admitted with drug induced renal disease. Diabetes was observed in majority of the patients.

Drug induced intra – renal injury (directly causing injury to the tubular, vascular, glomerular and interstitial tissues) is predominantly observed rather than pre- renal injury (causing decreased blood flow to the kidneys). On analyzing the type of drug induced renal disease, **Acute Interstitial Nephritis** was found to be pre- dominant.

Treatment Modalities

The treatment involves conventional (or) dialysis.

The basic principle for prevention of drug induced renal disease is to avoid the use of potentially nephrotoxic drugs.

Conventional treatment involves:-

- Withdrawing the nephrotoxic drug
- Correcting the dose
- Following the trough levels
- Hydrating using saline infusion.

These approaches are made to provide careful and adequate hydration to establish high renal tubular flow rate and to maximize the efficacy of drug with minimum toxicity.

Hemodialysis is usually carried out for 4 – 6 hours 3 times weekly in acute renal injury. Most patients notice a gradual reduction of their uraemic symptoms during first 6 weeks of treatment.

Preventive measures such as using alternative non- nephrotoxic drugs, correcting the risk factors, assessing the baseline renal function before initiation of therapy, correcting the dose, monitoring renal function and vital signs during therapy,

avoiding nephrotoxic drug combinations should be undertaken in order to prevent further injury to the kidney. Adequate hydration is important to maintain renal perfusion and to avoid drug induced renal impairment.

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