"A CROSS SECTIONAL STUDY TO KNOW THE PROFILE OF PATIENTS WITH ACUTE INTERSTITIAL NEPHROPATHY ATTENDING KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE"

REG NO. BG0108002

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT BY HOD, PRINCIPAL

This is to certify that the dissertation entitled **"A CROSS SECTIONAL STUDY TO KNOW THE PROFILE OF PATIENTS WITH ACUTE INTERSTITIAL NEPHROPATHY ATTENDING KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE"** is a bonafide research work done by **BY THE CANDIDATE REG NO. BG0108002** in the Department of General Medicine, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum – 590 010.

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LIST OF ABBREVIATIONS USED

AIN	-	Acute interstitial nephropathy
CC	-	Cysteine-cysteine
CCR	-	Chemokine receptor
CD	-	Cluster differentiation
CXC	-	Cysteine – X amino acid cysteine
CYP	-	Cytochrome P
d	-	Deci
DARC	-	Duffy antigen receptors of chemokines
DNA	-	Deoxyribo nucleic acid
dsRNA	-	Double stand ribo nucleic acid
E coli	-	Escherichia coli
ESR	-	Erythrocyte sedimentation rate
gm	-	Gram
GM-CSF	-	Granulocyte monocyte colony stimulating factor
Hb	-	Haemoglobin
HIV	-	Human immunodeficiency virus
HLA	-	Human leukocyte antigen
hpf	-	High power field
IAIN	-	Idiopathic acute interstitial nephropathy
ICAM	-	Inter cellular adhesion molecule
IFN γ	-	Interferon γ
IgE	-	Immunoglobulin E
IgG	-	Immunoglobulin G
IL	-	Interleukin

L	-	Litre
LPS	-	Lipo-polysaccharide
MCP	-	Monocyte chemoattractant protein
mg	-	Milligram
MHC	-	Major histocompatibility complex
MIP	-	Macrophage inflammatory protein
mm	-	Millimeter
mmol	-	Milli mole
NSAIDS	-	Non steroidal antiinflamatory agents
PAF	-	Platelet activating factor
PAMPS	-	Pathogen associated molecular patterns
RANTES	-	Regulated upon activation of normal T cell expressed and secreted
RNA	-	Ribo nucleic acid
TBM	-	Tubular basement membrane
Th1	-	Helper T cell
TINU	-	The interstitial nephritis with uveitis syndrome
TLR	-	Tall like receptors
TNFα	-	Tumor necrosis factor α
VCAM	-	Vascular cell adhesion molecule

ABSTRACT

Background and objectives

Acute interstitial nephropathy is associated with increased morbidity, direct and indirect health care costs. Incidence is increasing and no studies have been done in the present setting. The objectives of the present study were to study the clinical and laboratory profile and leading causes of acute interstitial nephropathy and correlation between histopthology and clinical outcome.

Methodology

The present study was conducted in Department of Medicine and Nephrology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 26 patients suspected to have AIN on clinical grounds and proven by renal biopsy presenting during the period of January 2009 to December 2009. Percutaneous renal biopsy was performed in all the patients. Platelet count, prothrombin time, partial thromboplastin time and blood group were established before the procedure was undertaken.

Results

A total 150 biopsies were done during the study period of which 26 (17.33%) had AIN. Males (69.23%) outnumbered females (30.77%) with male to female ratio of 2.25:1. Majority (50%) had age between 45 to 60 years. The most common clinical presentation was oliguria (84.62%). Out of 26 cases majority (57.69%) patients had serum creatinine levels >5.0 mg/dL. Mild to moderate changes were seen in each of 38.46% patients whereas in 23.08% cases significant tubulointerstitial changes were observed. In this study each of 42.30%

patients had drug induced AIN and idiopathic. Infections were seen in 15.38%. Among the patients with drug induced AIN, NSAIDS was the predominant (72.72%) cause whereas 27.27% were due to antibiotics.

Interpretation and conclusion

This study confirms that AIN remains an important cause of acute renal failure and that it is mainly drug-induced, with non-steroidal drugs being particularly implicated. Patients with diffuse (significant) histopathological tubulointerstitial changes had significantly increased serum creatinine levels causing delayed and incomplete recovery compared to patchy (mild and moderate) changes.

Keywords

Acute interstitial nephropathy (AIN); Acute renal failure; Renal biopsy;

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INTRODUCTION

Acute interstitial nephropathy (AIN) has been reported in one percent of renal biopsies during the evaluation of asymptomatic hematuria or proteinuria.[1] Significant interstitial nephropathy of one percent was observed in 8000 cases which underwent autopsy.[1] 1 to 15% of all renal biopsies in patients with apparent renal disorders will show acute interstitial nephropathy.[1]

Acute interstitial nephropathy, a rather uncommon disease that was occurred at a relatively stable rate over the years. However an increased incidence has been reported from 1 to 4% per annum over a period of time.[2] This increasing trend reflects increased awareness, availability of better facilities for diagnosis or it may be truly increased incidence which is unknown.

A western study of 128 patients reported the causes of AIN as drugs with antibiotics (71%), infection related (15%), idiopathic (8%), tubulointerstitial nephritis and uveitis (5%) and sarcoidosis (1%).[3]

Another retrospective study of 2598 renal biopsies over a 12 years period showed AIN in 2.6% of native biopsies. Among them drug related were 92% and remaining were idiopathic.[2]

A two year retrospective study of non-neoplastic renal diseases in Kerala, India on 1592 cases reported 87 (5.46%) cases of AIN.[4]

Another Indian study of 5415 cases at Vellore, reported 2.5% of AIN cases.[5]

Multiracial study of 394 patients involving Indian race at London underwent renal biopsy for abnormal renal function. The study showed that 30 patients had AIN, out of which 17 were Indians.[6]

Another study on 10 cases of acute allergic interstitial nephropathy with recent onset of renal failure due to use of drugs showed, NSAIDs as the cause in four cases, cimetidine in three cases, antibiotics in two cases and allopurinal in one case. Among them three patients received haemodialysis, two of them received steroids. Renal function improved in nine patients by 35 days but one patient had progressive deterioration of renal function.[7]

Acute interstitial nephropathy is associated with increased morbidity, direct and indirect health care costs. There is a paucity of data regarding AIN hence more data is required from India to study the disease. Incidence is increasing and no studies have been done in the present setting. Hence the present study was undertaken to know the clinical profile and causes of AIN which will help to study the course of the disease, clinical spectrum and its management.

OBJECTIVES

The objectives of the present study were;

1. To study the clinical and laboratory profile of patients with acute interstitial nephropathy.

2. To know the leading causes of acute interstitial nephropathy and correlation between histopthology and clinical outcome.

REVIEW OF LITERATURE

History

Councilman was the first to describe acute non purulent interstitial nephritis (AIN) in 1898. Volhard and Fahr included interstitial lesions in their classification of renal diseases in 1914. In the pre-antibiotic era, AIN was observed in connection with scarlet fever or diphtheria.

In 1946, More et al, described interstitial lesions from pharmaceutical drugs. Between 1971 and 1974, Klassen, Mc Cluskey, Milgrom, Steblay, Andres, Wilson and Rudofsky reported that interstitial nephritis could be mediated by the immune system. At the present time, there is a growing knowledge of interstitial antigens, nephrogenic T-cells and fibrogenic processes.[8]

Definition

Acute -interstitial nephritis (AIN) is a disease characterised by predominant involvement of the renal interstitium and tubules by inflammatory cells, often associated with oedema or fibrosis and tubular atrophy. Interstitial nephritis is commonly accompanied by variable tubular damage, so the term -interstitial nephritis, or -interstitial nephropathy, is preferable and is often used interchangeably with interstitial nephritis. Tubulitis refers to infiltration of the tubular epithelium by leukocytes, usually lymphocytes.

Primary -interstitial nephritis denotes inflammation that is limited to tubules and interstitium: glomeruli and vessels are uninvolved or show minor

changes. Secondary -interstitial nephritis denotes -interstitial inflammation associated with a primary glomerular or vascular disease.[9]

Epidemiology

As the clinical features of AIN are not specific and there is a need for renal biopsy for diagnosis, the precise assessment of incidence and prevalence is complex. In the literature, the only study to look at the prevalence of AIN was reported by Pattersson et al.[10] Examining 314,000 military recruits in the Finnish army who had haematuria and /or proteinuria, 174 underwent a renal biopsy. However, only two were found to have AIN, giving a prevalence of 7 per million in this cohort.[10] In any renal unit, AIN is present in 1% to 3% of all renal biopsies,[11] with drug-related AIN being found in nearly 50% these cases. In groups of patients being biopsed to determine a cause for their acute renal failure, the incidence of AIN was 8% to 14%,[12] and in the majority the diagnosis was not suspected before biopsy**.**

Importance of interstitial changes in renal function

From the literature, it is suggested that changes in the interstitium are a final common pathway in all types of end-stage renal disease and are the most common and pivotal lesion in nephrology, particularly as they can occur as a primary process and also as a secondary process following glomerular or vascular diseases.[8]

Different morphologic observations strongly suggest that changes in tubular function and glomerular filtration correlate significantly with the presence

of progressive deterioration of the interstitial tissues, rather than with changes in glomerular tuft integrity.[13]

Many explanations have been proposed to describe this structure-function correlation: the "clogged drain" theory, capillary bed changes, and the vascular tone hypotheses.

- Filtrate delivered by an intact glomerular tuft cannot pass into a collecting apparatus through tubules that are disrupted by inflammatory infiltrates, thus the name "clogged drain".

- A continuous decline in -vascular capillary surface area, as might occur in interstitial nephropathy, might provoke an increase in resistance in the efferent arterioles. This could lead to outflow restriction from the glomeruli by decreasing circulatory capacity, such that filtration would reduce.[13]

- In the vascular tone hypothesis, with moderate inflammation in the interstitium and some tubular atrophy, a minimum amount of sodium might be actively pumped out of the proximal tubule and thick ascending limb, and so the osmotic gradient in the interstitium may not adequately build-up. Therefore, very little water would be removed from the tubular fluid, polyuria would develop, and the increase in tubular flow rate would reduce the secretion of renin from the juxtaglomerular apparatus. Thus, the content of angiotensin 2 would decrease in the efferent arteriole. The net effect of these events would be that the tone in the efferent arteriole would reduce, with a consequent fall in the glomerular filtration rate.

This outcome is known as a modified Thurau mechanism, whereby glomerular filtration adjusts to insufficient tubular function.[2,]

Aetiology

The commonest cause of AIN in most series is drugs. Infectious agents have sporadically been associated with AIN[14] but whether these are true associations, or related to therapy, is uncertain. Tinu syndrome (the interstitial nephritis and uveitis syndrome) is a well-recognized but uncommon cause of AIN. Systemic diseases such as systemic lupus erythematosus, vasculitis and acute post-infectious glomerulonephritis may be associated with AIN but as these conditions occur with a well-defined glomerular lesion, they have not been included in the present study. Occasionally, there is no overt reason for development of AIN and when a cause cannot be clearly attributed, the term "idiopathic" (that is, unknown aetiology) is used.

Table 1. Causative factors of acute interstitial nephritis[1,15]

Drugs	Antibiotics	Cephalosporins, ciprofloxacin, ethambutol, isoniazid, macrolides, penicillins, rifampin, sulfonamides, tetracycline, vancomycin
	NSAIDs	Almost all agents – Aspirin, Phenoprofen, Ibuprofen, Indomethacin, Naproxen, Piroxicam
	Diuretics	Furosemide, thiazides, triamterene
	Miscellaneous	Acyclovir, allopurinol, amlodipine, azathioprine, captopril, carbamazepine, clofibrate, cocaine, diltiazem, famotidine, indinavir, mesalazine, omeprazole, phenteramine, phenytoin, pranlukast, propylthiouracil, quinine, ranitidine
Infectious agents	Bacteria	*Corynebacterium diphtheriae, Legionella, Staphylococci, Streptococci, Yersinia, Brucella, Escherichia coli, Campylobacter*
	Viruses	Cytomegalovirus, Epstein-Barr virus, hantaviruses, hepatitis C, herpes simplex virus, human immunodeficiency virus, mumps, polyoma virus
	Other agents	*Leptospira, Mycobacterium, Mycoplasma,* rickettsia, syphilis, toxoplasmosis, *Chlamydia*
Idiopathic	Immune	Anti-tubule basement membrane disease, interstitial nephritis and uveitis (TINU) syndrome

Clinical presentation and diagnosis

AIN is a heterogeneous disorder not only in aetiology, but also in presentation, laboratory findings and outcomes. The diagnosis is most commonly considered in hospitalized patients who experience a progressive rise in serum creatinine. The aetiology of acute renal failure in such patients is frequently unclear, especially if they are infected, receiving multiple medications, undergoing diuresis, and/or exhibiting haemodynamic instability. In such complex settings, AIN is frequently placed low in the differential diagnosis of acute renal failure if there is no concomitant fever, skin rash, eosinophilia, or eosinophiluria. Although these accompanying signs suggest AIN when present, their absence is not helpful in excluding the diagnosis.

The triad of fever, rash, and eosinophilia is generally found in less than 30% of patients with AIN.[16] These allergic manifestations are commonest in beta-lactam associated AIN than in other drug-related causes of AIN.[17] The reduced output of urine is an inconstant finding and urinalysis commonly shows mild to moderate proteinuria with an increased number of red and white blood cells. Nephrotic range of proteinuria is rare and is only found in AIN due to non-steroidal anti-inflammatory drugs, when it is usually associated with minimal change glomerulonephropathy.[18]

Eosinophilia and eosinophiluria are variable findings and they tend to support the diagnosis of allergic, drug-induced AIN, when present. The published frequency of eosinophiluria (it is not often tested for) varies according to the criteria used for the definition of eosinophiluria and the method used for staining

of urinary leukocytes, as it ranges from 40% to 100%.[19] Hansels stain is approximately four times more sensitive than Wrights stain.[20] However, it has been suggested that the presence of eosinophiluria is relatively specific and may be diagnostic for AIN.[20] In one study where patients with a confirmed diagnosis of AIN were compared to those with other causes of renal disease, eosinophiluria was found to have a sensitivity of 40%, specificity of 72%, but a positive predictive value of only 30%.[21] In fact eosinophiluria can be found in chronic interstitial nephritis of different aetiologies, in transplant rejection, prostatitis and in eosinophilic cystitis[20] so it is not specific for AIN and its absence does not reject the probability of this type of nephritis. All the evidence considered, eosinophiluria is not a definitive test for the diagnosis of AIN.[21]

Ultrasound imaging of patients with AIN shows a normal to enlarged kidney with increased cortical echogenicity similar to, or higher than, that of the liver[19] and corresponds with the extent of interstitial infiltration in the biopsy.[22] There are no specific characteristics on ultrasonic imaging that differentiate AIN from other causes of acute renal failure. The renal biopsy (preferably done under ultrasound guidance) is the only tool for a firm diagnosis.

IMMUNE SYSTEM

The organized cells and molecules that have a specialized function in defending the body against foreign substances is called the immune system.[23] Two types of responses have been identified. Innate (natural) responses mount the same qualitative and quantitative response each time the infectious agent is encountered; innate immunity comprises phagocytic cells (neutrophils,

monocytes, and macrophages), cells that release inflammatory mediators (basophils, mast cells, and eosinophils), as well as natural killer cells. The molecular components of innate responses include complement, acute-phase proteins, and cytokines such as the interferons. On the other hand, acquired (adaptive) responses "learn" to mount more focused and efficient responses on repeated exposure to a given infection; acquired immunity involves the proliferation of antigen-specific B and T cells, which occurs when the surface receptors of these cells bind to antigen.[23]

There are specialized cells (antigen-presenting cells) (the prototype being the dendritic cell), that present peptides of the protein antigen to lymphocytes and collaborate with them; in response to the antigen B cells secrete immunoglobulins to remove extracellular microorganisms. T cells help B cells to synthesize the antibody and can also kill intracellular pathogens by stimulating macrophages and by eradicating virally infected cells. Innate and acquired responses usually work together to get rid of pathogens.[23]

Acute immune response

Infection with a pathogen stimulates an acute inflammatory (immune) response in which cells and molecules of the immune system are recruited to the affected site.[23]

The complement proteins are important to this process and comprise a cascade of proteolytic substances that aids the recognition and clearance of microorganisms. The stimulation of complement produces C3b, which coats the surface of the pathogen. The neutrophil chemoattractant and activator C5a is also

generated, and together with C3a and C4a leads to the release of histamine by degranulating mast cells. Histamine causes smooth muscle contraction and increases in vascular permeability.[23] Cytokines and other substances released from damaged tissues activate the expression of adhesion molecules on vascular endothelium, alerting passing leukocytes to the presence of infection. The cell-surface molecule L-selectin on neutrophils recognizes carbohydrate structures such as sialyl-Lewis on the activated endothelial surface.[24] These molecules support neutrophil rolling along the vessel wall and, if additional chemokine signals are detected by the neutrophil, it too becomes activated, sheds L-selectin from its surface and expresses cell-surface adhesion molecules, such as the integrins that alter their conformation to be able to recognise their counter-ligands on endothelial cells. One important ligand is ICAM-1, which increases its expression on the blood-vessel wall in response to inflammatory mediators such as bacterial lipopolysaccharide and the cytokines interleukin-1 (IL-1) and tumor necrosis factor α (F. Complement components, prostaglandins, leukotrienes, and other inflammatory mediators all contribute to the recruitment of inflammatory cells, as do chemoattractant cytokines called chemokines, for example the chemokine interleukin-8 is a powerful neutrophil chemoattractant. The activated neutrophils migrate through the endothelium, moving up the chemotactic gradient to accumulate at the site of infection, where they are well placed to phagocytose any C3b-coated microbes.[23]

Mast cells

Mast cells express high-affinity receptors for the Fc portion of IgE, and bind IgE antibodies. When a mast cell, armed with IgE antibodies, is re-exposed to the specific allergen, a series of reactions takes place, leading eventually to the release of mediators that cause immediate hypersensitivity reactions. First, antigen (allergen) binds to the secreted or membrane-bound IgE antibodies. Multivalent antigens bind to more than one IgE molecule and cross-link adjacent IgE antibodies and the underlying mast cell IgE Fc receptors. The cross-linking of IgE Fc receptors (Fc RI) activates signal transduction pathways via the cytoplasmic portion of IgE Fc receptors. These signals activate two independent processes, one leading to mast cell degranulation with discharge of preformed (primary) mediators that are stored in the granules, and the other involving synthesis and release of secondary mediators. These mediators are responsible for the initial symptoms of immediate hypersensitivity and they initiate the events that lead to the late-phase response.[25] In addition to inducing mediator release and production, signals from IgE Fc receptors promote the survival of mast cells and can enhance expression of the Fc receptors, providing an amplification mechanism.[26]

Primary mediators

Primary mediators contained within mast-cell granules can be divided into three categories:

Biogenic amines

The most important vasoactive amine is histamine, which causes intense smooth muscle contraction, increased vascular permeability and increased secretion by nasal, bronchial and gastric glands.

Enzymes

These are contained in the granule matrix and include neutral proteases (chymase, tryptase) and acid hydrolases. The enzymes cause damage to local tissues and lead to production of kinins and activated components of complement (e.g. C3a) by acting on their precursor proteins.

Tryptase is an abundant product of human mast cells. It is a serine protease with a molecular size of 134 kD, it is composed of four monomers of 32 to 34 kD, each with one catalytic site.[27] Its presence is restricted to mast cells, where tryptase exists within secretary granules in a complex with heparin proteoglycan.[27] Biologic activities include lysis of fibrinogen, augmentation of histamine-mediated contractility of air way smooth muscle, and degradation of vasoactive intestinal peptides.[28] It is also mitogenic for fibroblasts, smooth muscle cells, and bronchial epithelial cells.[29] Studies have indicated that tryptase-positive mast cells may be involved in renal interstitial injury.[30]

Proteoglycans

These include heparin, a well-known anticoagulant, and chondroitin sulphate. The Proteoglycans serve to package and store the other mediators in the granules.

Secondary mediators

Secondary mediators include two classes of compounds (1) lipid mediators and (2) cytokines. The lipid mediators are generated by reactions in the mast-cell membranes that lead to activation of phospholipase A2, an enzyme that acts on membrane phospholipids to produce arachidonic acid. This is the parent compound from which leukotrienes and prostaglandins are derived by the 5-lipoxygenase and cyclooxygenase pathways.

Leukotrienes

Leukotrienes C4 and D4 are the most potent vasoactive and spasmogenic agents known. On a molar basis, they are several thousand times more active than histamine in increasing vascular permeability and causing bronchial smooth muscle contraction. Leukotriene B4 is highly chemotactic for neutrophils, eosinophils, and monocytes.

Prostaglandin D2

This is the most abundant mediator derived from the cyclooxygenase pathway in mast cells. It causes intense bronchospasm as well as increased mucus secretion.

Platelet-activating factor (PAF)

PAF is produced by some mast cells. It causes platelet aggregation, release of histamine, bronchospasm, increased vascular permeability, and

vasodilation. It has important pro-inflammatory actions. PAF is chemotactic for neutrophils and eosinophils.

At high concentrations, it activates the newly recruited inflammatory cells, causing them to aggregate and degranulate. Because of its ability to recruit and activate inflammatory cells, it is considered important in the initiation of the late –phase response. Although the production of PAF is also triggered by the activation of phospholipase A2, it is not a product of arachidonic metabolism.

Cytokines

Mast cells secrete many cytokines, which contribute to the late-phase reaction of immediate hypersensitivity because of their ability to recruit and activate inflammatory cells. The cytokines include TNF, IL-1, IL-3, IL-4, IL-5, IL-6, and GM-CSF, as well as chemokines, such as macrophage inflammatory protein (MIP)-1α and MIP-1β.[31] Mast cell-derived TNF and chemokines are important mediators of the inflammatory response seen at the site of allergic inflammation.

Macrophages

Macrophages have critical roles in host response to injury and the mechanisms by which it is repaired.[32] They infiltrate damaged tissues where they adapt to the local microenvironment by developing properties that either cause further injury (such as might be advantageous in defence against infection), or alternatively evolve into cells that promote resolution of inflammation and facilitate tissue repair once the original cause of injury has been eliminated.[32]

Classical activation of macrophages

Macrophages have a range of receptors on the cell surface that enable them to recognise infectious organisms including receptors with pathogen-associated molecular patterns (PAMPs), which include Toll-like receptors (TLR), mannose receptor and scavenger receptor families. TLRs identify a range of microbial products including lipopolysaccharide (LPS) that binds to TLR4, bacterial unmethylated CpG DNA that binds to TLR9 and viral double-stranded (ds) RNA that binds to TLR3.[33] Classical activation comprises activation of macrophages with two signals. The first is the involvement of TLR and the second is yielded by the cytokine IFN-γ that is secreted by T-helper lymphocytes or natural killer cells. This dual activation leads to macrophage to produce nitric oxide, reactive oxygen species and other proinflammatory cytokines particularly TNF-α and IL-12, also the expression of MHC class Π and costimulatory molecules which promote antigen presentation. These responses are designed to intensify microbial killing and stimulate adaptive immunity.[34] TLRs also identify endogenous ligands secreted by damaged tissues such as heat-shock protein 60 and 70 which are ligands for TLR4[35] and ds DNA which interacts with TLR9.[36]

Classically activated macrophages have been found at sites of cell immune-mediated inflammation, including glomerulonephritis,[37] especially during the initial induction of the inflammatory response.

Alternative activation of macrophages

The alternatively activated macrophage developed after the exposure to IL-4 or IL-13.[38] These cells show enhanced expression of mannose receptor and

MHC class Π, increased endocytosis, decreased nitric oxide production (due to both decreased expression of iNOS and increased production of arginase) and enhanced expression of IL-1 decoy receptor and IL-1ra.[39] Thus these cells have a reduction in the killing of intracellular organisms but the enhanced matrix production suggest a role in tissue repair.[40]

Type Π-activated macrophage

Recently Mosser[41] has recognized the "type Π-activated macrophage". They explained that macrophages exposure to activating stimuli such as LPS or CD40L in the presence of IgG immune complexes resulted in enhanced IL-10 expression and reduced IL-12 expression but with preservation of other proinflammatory cytokines such as TNF-α and IL-6.[42,43] These cells in vivo favour the development of Th2 type immune responses with increased T cell IL-4 production and IgG class switching by B cells.[44]

Following adhesion to activated endothelium, macrophages transmigrate to the focus of injury in response to a chemotactic gradient. Renal injury, whether toxic, ischaemic, or immunologic, can lead to chemokine production by endothelium, mesangial cells and tubular cells. The most extensively studied chemokine/receptor partners for macrophage chemotoaxis are MCP-1 and its receptor CCR2, and RANTES, macrophage inflammatory protein-1α and 1β (MIP-1α and MIP-1β) and their receptors CCR1,3, and 5.[45]

Eosinophils

Eosinophils are often present in increased number during AIN and may be detected in the urine. Eosinophils are a type of granulocyte derived from bone marrow, distinguished by their morphologic features, particularly their specific granules, and associations with specific diseases. Specific granules contain lysosomal hydrolases and most of the cationic proteins unique to eosinophils.[46] The core of the granule is composed of major basic protein, and the non core matrix contains eosinophil cationic protein, eosinophil derived neurotoxin, and eosinophil peroxidase.[47,48] Major basic protein, so named because it is one of the most abundant cationic (basic) eosinophil granule proteins, is a 14,000-dalton protein rich in arginine residues.[49] It has no recognized enzymatic activity, but is toxic to helminthic parasites, tumor cells, and host cells.[50]

The effector functions of eosinophils involve acute cellular responses, such as degranulation, oxidative-burst activity, and eicosanoid release. The ability of eosinophils to be involved in other types of cellular responses suggests that eosinophils can collaborate with lymphocytes and other immunologic and mesenchymal cells in various ways that are pertinent to health and disease. In tissues, eosinophils might also initiate antigen-specific lymphocyte responses for antigens specific to certain mucosal sites. Other direct cell-cell interactions between eosinophils and other types of cells are feasible on the basis of their expression of CD4 and the capacity of eosinophils to respond to lymphocyte products.[51] Thus, specific cytokines and lymphokines may promote other activities of mature eosinophils in addition to effector functions. Finally, cytokines elaborated by eosinophils could affect other cells nearby. Transforming

growth factor-α, synthesized by eosinophils,[51] may stimulate endothelial cells and fibroblasts.

Because of their distribution in tissues of the respiratory, gastrointestinal, and lower genitourinary tracts, resident eosinophils may be active cellular participants in mucosal immune responses at these sites.

Chemokines and eosinophil recruitment

Chemokines that are important for eosinophil recruitment are expressed at sites of allergic inflammation following allergen challenge. The chemokine eotaxin has particular specificity for eosinophils. In fact studies with neutralizing antibodies demonstrate that chemokines such as RANTES, MCP-5, and MIP 1α are also important in eosinophil tissue recruitment.[52] In man there are also differences in the timing of expression of different CC chemokines at sites of allergic inflammation.

Chemokines bind to 7 trans-membrane-spanning chemokine receptors expressed by eosinophils. Eosinophils express CCR3 receptors which bind eotaxin as well as RANTES and MCP-3, making the CCR3 receptor an attractive therapeutic target.[53]

Basic concepts of adaptive immune response

The shape of antigen and the peptide-MHC complex are the basis of detection by the antibodies and the combining site on the T cell receptor respectively. Secreted antibodies or membrane-expressed antibodies acting as B cell receptors, usually recognize discontinuous epitopes, composed of amino

acids that are brought together when the protein folds into its native structure. When an epitope on an antigen fits well with a particular combining site on the B cell, the resultant population of antibodies against this epitope tends to dominate the antibody response. In contrast, the epitopes recognized by α/β T cell receptors (where α and β are the two chains that make up the receptor) are linear peptides derived from intracellular breakdown of the antigen. These peptides are transported to the cell surface within the peptide-binding groove of the MHC molecule.[23]

Antibodies and T cell receptors can differentiate between closely related antigens but they sometimes recognise apparently unrelated antigens. This may occur if the two antigens share an identical epitope, or if two different epitopes have similar shapes and charges. Sometimes this leads to molecular mimicry, whereby epitopes on microbial agents stimulate the production of antibodies (or the proliferation of T cells) which react with self antigens. Molecular mimicry may be a cause of autoimmune disease. An example of this is post-streptococcal rheumatic fever, which is caused by antibodies induced by an epitope on streptococcal M protein that also recognise a similar epitope on cardiac myosin.

Some antigens (the T cell-independent antigens) can stimulate B cells without help from T cells. T-independent antigens include the polysaccharides or polymerized flagellin of bacteria. These have many repeating epitopes that bind to the B cell receptors and along with activation signals which a variety of cell types can provide, they activate B cells without help from CD4 T cells. T cell-independent antigens do not induce the formation of germinal centres, memory B cells or the somatic hypermutation which results in the production of high-

affinity antibodies. The extent of class switching from IgM to other classes of antibodies is also limited. For these reasons, T cell-independent antigens generally give rise to low-affinity IgM antibodies.[23]

Most antigens can only stimulate B cells with help from CD4 T cells and are therefore referred to as T cell-dependent antigens. After a B-cell receptor binds such an antigen, it is internalized and processed by the B cell into short peptides, which are carried to the cell surface by MHC class Π molecules. Neighbouring CD4 T cells that are able to recognize these peptide-MHC complexes (since they have been exposed to antigen-presenting dendritic cells) become activated and express costimulatory molecules such as CD40 ligand on their surface. CD40 ligand on the activated T cell binds to its receptor (CD40) on the B cell, and this induces the B cell to begin the processes of somatic hypermutation and immunoglobulin class switching. The cytokines IL-2, IL-4, and IL-5 that are released from the T cells also provide help. Dendritic cells and macrophages, by presenting peptide-MHC class Π complexes, can also activate naive helper CD4 T cells, so that they express costimulatory molecules and release immunostimulatory cytokines. Once the immune system is stimulated by an immunogenic epitope, additional epitopes on the antigen may be drawn into the response. This effect is referred to as epitope spreading. It may involve other antigens (intermolecular spreading). Its clinical relevance is that in some autoimmune diseases, a complex of several molecules, may provoke a broad spectrum of autoantibodies. Other events that lead to autoantibody formation include revealing of cryptic (hidden) epitopes which can occur after a change in the processing of antigen as may happen when proinflammatory cytokines

stimulate antigen-presenting cells. Further, B cells may generate peptides which are not produced by dendritic cells or macrophages, as seen with the model antigen hen-egg lysozyme.

The continual mutation of microorganisms causes a phenomenon called antigenic drift. The mutants may not be recognised by the memory component of the immune system. In addition, the exchange of genetic material between related organisms can lead to antigenic shift. Very few of the memory cells which were generated during exposure to the native organism may be able to recognize the new variant. The influenza pandemics which have killed large numbers of people when the virus has swept relatively unchallenged across the globe has resulted from antigenic shift.[23]

T lymphocytes

Stem cells migrate from the bone marrow to the thymus, where they develop into T cells. This process continues throughout life, although the thymus does degenerate a little in older people. Most T cells in the thymus have α/β T cell receptors and undergo a series of selection procedures. Unlike the antibody molecule, which acts as the antigen receptor on B cells and recognizes antigen in its native (natural) state, the α/ β T cell receptor recognizes short peptides. These are generated by intracellular processing of protein antigens. Peptides are presented to the T cell receptor by MHC molecules on the surface of an antigen presenting cell. The T cell receptor recognizes an individuals own MHC molecules (self) together with peptides derived from foreign antigens. MHC molecules are highly polymorphic and the desirable immature T cells are those

which can recognize self MHC molecules but are not autoreactive. This is achieved by thymic education, a process which involves both positive and negative selection. Cells are positively selected if they express a T cell receptor that can recognize the MHC complexes on a body's own epithelial cells in the thymic cortex. Positive selection stops spontaneous apoptosis (death of the cell). More than 95% of T cells are not selected at this stage and therefore die in the thymus. In contrast, negative selection involves the induction of apoptosis in any T cell expressing a T cell receptor with a high affinity for the complex of a self peptide plus a self MHC molecule on dendritic cells and macrophages in the thymic medulla. During thymic education, some molecules on the surface of T cells increase expression and others reduce their expression. The molecules have been characterised using monoclonal antibodies. This led to a nomenclature in which a given molecule was assigned a "cluster of differentiation", or CD number, for example CD1, CD2, and CD3. The CD4 and CD8 molecules are of particular note with regard to T cell development; together with the CD3 group of molecules, they form part of the T cell-receptor complex. CD4 binds to an invariant part of the MHC class Π molecule, whereas CD8 binds to an invariant part of the MHC class I molecule. CD4 T cells usually act as helper T cells and recognize antigens presented by MHC class Π molecules, while CD8 T cells are usually cytotoxic and recognize antigen presented by MHC class I molecules. Early in T cell development in the thymus, immature T cells express both CD4 and CD8. If they have an appropriate T cell receptor, these double-positive immature T cells have the potential to recognize an antigen-derived peptide presented by either MHC class I or MHC class Π molecules. As T cells mature in

the thymus, the expression of one of these molecules is lost, resulting in a single–positive CD4 or CD8 T cell.

A minority of T cells in the thymus use γ and δ chain genes to produce a T cell receptor. These γ/ δ T cells rapidly leave the thymus, and some may develop outside the thymus, possibly in the gut. They are thought to contribute to mucosal defences.

The antigens they recognise include both proteinaceous and nonproteinaceous antigens from mycobacteria and other infectious organisms. In addition, they have an important immunoregulatory role because they influence antibody production and immunoglobulin class switching by B cells and may modify T cell responses.[23]

Effector functions of T cells

CD4 T cells are mainly cytokine-secreting helper cells, whereas CD8 T cells are mainly cytotoxic killer cells. CD4 T cells can be divided into different subsets; type 1 (Th 1) helper T cells secrete interleukin-2 and interferon-γ. Type 2 (Th 2) helper T cells secrete interleukin-4, 5, 6, and 10. Cytokines influence the type of immune response generated against particular infectious agents. For example, the release of interleukin-12 by antigen-presenting cells stimulates the production of interferon-γ (immune interferon) by Th 1 cells. This cytokine efficiently activates macrophages, enabling them to kill intracellular organisms. In general, the production of cytokine by Th 1 cells facilitates cell-mediated immunity, including the activation of macrophages and T cell-mediated cytotoxicity; while Th 2 cells help B cells produce antibodies.[23]

Elimination of virally infected cells is carried out by CD8 cytotoxic T cells. The infected cell displays peptides derived from the intracellular viral protein within its MHC class I molecules and is recognised by the cytotoxic T cell. Cytotoxic T cells bind to this viral peptide-MHC complex and then kill the infected cell. They can insert perforins into the target-cell membrane, which produce pores through which proteolytic enzymes called granzymes are passed from cytotoxic T cells into the target cell. At least one of these proteolytic enzymes activates the caspase enzymes which induce apoptosis in the target cell. Cytotoxic T cells also can bind the Fas molecule on the target cell using their Fas ligand, and this also activates caspases within the target cell and induces apoptosis.[54]

Any released virus is immediately susceptible to the effect of antibodies. In addition to directly killing infected cells, CD8 T cells also produce a number of cytokines, including TNF-α and lymphotoxin. Interferon-γ, another product of CD8 cells, reinforces antiviral defences by making adjacent cells resistant to infection.[55]

Control of the immune response

A successful immune response will get rid of the inciting antigen and,then return itself to a resting level. In addition to cleansing itself of antigen, the immune system uses several other mechanisms to down-regulate its activity. IgG itself can switch off the response to its corresponding antigen, a type of negative feedback loop. This suppression of IgG production occurs when the FcγR and the B-cell receptor on the same cell are linked by immune complexes containing the

relevant antigen and transmit inhibitory signals into the nucleus of B cell. Cytokines participate at another level of regulatory control, for example, the secretion of interferon-γ by Th 1 cells inhibits Th 2 cells and the secretion of interleukin -10 by Th 2 cells reciprocally inhibits Th 1 cells.[56]

Immunoregulation involves many other interactions of the immune system with both the endocrine and nervous systems, with cross-talk between these systems involving hormones, cytokines, and neurotransmitters. The following sections on Th 2 cells and interleukin-4, as well as the large section on chemokines are presented because of the current perceived role of these cells and mediators in interstitial nephritis.

Th 2 helper cell subset

The theory that T helper cells, in humans and rodents, can be divided into functionally specific types (named Th 1and Th 2) has changed the understanding of adaptive immune reactions. The immune responses associated with Th 1 and Th 2 cells are accompanied by specific forms of cytokine secretion and these cytokine profiles have, in turn, helped to describe the various immune effects of these cytokines.

In 1986, Mosmann et al[57] demonstrated that functionally distinct subsets of CD4+ T cells could be defined by their pattern of cytokine production. Th 2 cells, defined by their propensity to secrete interleukin-4 (IL-4), IL-5, and IL-10, are important in allergy, mast cell/ IgE-mediated immediate type hypersensitivity responses, and helminth infections, in which protective responses are mediated by eosinophils. In addition, cytokines produced by Th 2 cells act as regulators of

the immune response. In addition, cytokines IL-13, and particularly IL-10 regulate Th 1 responses, suppress delayed hypersensitivity responses, and have inhibitory effects on macrophages, especially in the context of the activation by Th 1 cytokines such as IFN-γ. Th 2 responses are associated with high levels of antibody production promoted by cytokines such as IL-4 that stimulate B-cell growth. The profile of immunoglobulin isotypes is heavily influenced by the Th 1/Th 2 balance of the immune response.

The cytokine profile of antigen-stimulated CD4+ T cells and the pattern of T-cell immune responses are determined by a number of factors, including the type, dose, and route of antigen presentation, the epitope T cell receptor binding affinity, the nature and degree of co-stimulatory signals, and the genetic background of the animals. One of the most important and widely studied factors is the cytokine milieu at the time of antigen presentation.[56] IL-12 is crucial for the development of Th 1 responses, whereas IL-4 is required for the generation of Th 2 cells. The presence of IL-12, which is not produced by T cells but by antigen-presenting cells such as macrophages and dendritic cells, polarizes uncommitted T cells toward a Th1 profile. In the absence of IL-12 during the initiation of the immune response, T cells may lose future responsiveness to IL-12.[56]

Although the concept of Th 1/Th 2 immune responses provides a useful framework, it is perhaps overly simplistic to consider that each immune response to an antigen will be strictly either Th 1 or Th 2, with one type of response being protective and the other harmful. The complexity of infectious and inflammatory responses implies that some cytokines (or a single cytokine) within a Th 1or Th 2 grouping may have overlapping or, at times, opposing functions.

Interleukin-4 (IL-4)

Interleukin-4 is a 20 kDa immuno-regulatory cytokine that is secreted by T cells, mast cells, basophils, and a subset of natural killer cells. It is a key modulator of allergic reactions, so it is discussed here. It is produced by Th 2 CD4+ T cells and facilitates the development of a Th 2 phenotype. In vitro, it inhibits interferon (IFN)-γ production by activated T cells. IL-4 inhibits many functions of activated macrophages, including the secretion of reactive oxygen intermediates and nitric oxide, and the expression of tissue factor and macrophage colony stimulating factor. It suppresses macrophage TNF-α and IL-1β production and up regulates expression of IL-1 antagonist. It stimulates macrophage 15-lipoxygenase activity, which may reduce synthesis of the pro-inflammatory leukotriene B4. IL-4 also decreases monocyte expression of all three classes of Fc receptor for IgG. IL-4 induces IgE synthesis and promotes immediate-type hypersensitivity reactions. It also induces differentiation of naïve T cells to Th 2 lymphocytes that secrete additional macrophage-inhibiting cytokines such as IL-10 and IL-13. IL-4 is involved in the alternative activation of macrophages.[58]

Chemokines and their receptors

Chemokines have already been introduced and a more detailed resume of their functions is presented here. Chemokines are a family of small proteins defined by four conserved cysteine residues. These proteins trigger G protein-coupled receptors and stimulate cells to migrate through a concentration gradient, so that leukocyte recruitment is promoted. Some chemokines are homeostatic and

are constitutively produced and secreted. These homeostatic proteins help to direct the trafficking of lymphocytes to lymphoid tissues and are involved in immune surveillance. Other chemokines are considered inflammatory and are only produced by cells during infection or a proinflammatory stimulus. Inflammatory chemokines recruit leukocytes to the injured or infected site. In addition, inflammatory chemokines activate the cells to mount an immune response and initiate wound healing.[59]

Chemokines are proteins with a molecular weight of 8-10 Kd with 20% to 70% similarity in amino acid sequences. They have been subdivided into families on the basis of the relative location of their cysteine residues. There are four known families of chemokines. The α- and β-chemokines, which contain four cysteines, are the largest families. In the α-chemokines, the first two cysteine residues are separated by one amino acid (cysteine-x amino acid-cysteine, or CXC), whereas in β-chemokines, the first two cysteine residues are adjacent to each other (cysteine-cysteine, or CC). Two chemokines that do not fit into this classification, lymphotactin has only two cysteines, while fractalkine is a membrane-bound glycoprotein in which the first two cysteine residues are separated by three amino acids (CXXXC) and the chemokine domain sits on a mucin-like stalk.[60]

The α-chemokines can be further subdivided into those that contain the sequence glutamic acid–leucine-arginine near the N terminal (preceding the CXC sequence).

Eotaxin

Human eotaxin has a molecular weight of 8.4 KDa, 74 amino acids residue poly peptide that is produced by number of normal cells and cell lines. Eotaxin-1, a highly potent eosinophil chemoattractant, was originally purified and separated as a CC-chemokine from the bronchoalveolar lavage fluid of allergen-challenged guinea pigs.[61]

Two further genes encoding for CC chemokines with eosinophil-selective activity, called eotaxin-2 and eotaxin-3 have been identified on chromosome 7, although they are only 30% identical in sequence to eotaxin-1. The eotaxins signal exclusively via CCR3, a receptor highly expressed on eosinophils and also on other cells involved in allergic reactions, including basophils, mast calls and a subpopulation of Th 2 cells. Th 2 cells regulate eosinophil recruitment suggesting that Th 2 derived cytokines may regulate eotaxin gene expression. Both cytokines and glucocorticoids can modulate *in vitro* expression of eotaxin-1 and eotaxin-2 mRNA and protein in human lung epithelial and dermal fibroblast cell lines; TNF-α and IL-1β induce eotaxin-1 and eotaxin-2 expression, as do the Th 2 cytokines IL-4 and IL-13. Furthermore, TNF-α in combination with either IL-4 or IL-13 has a synergistic effect on expression. The glucocorticoid dexamethasone decreases cytokine induced eotaxin-1 and eotaxin-2 expression, an effect not altered by pre-treatment with the protein synthesis inhibitor cyclohexamide. In humans, eotaxin-1 has been detected at elevated levels in the bronchial epithelium of patients with asthma, as well as in lesions of skin biopsies of allergic dermatitis sufferers.[62]

RANTES

The C-C chemokine RANTES (regulated upon activation of normal T cell expressed and secreted), is a 68-amino acid protein, that can be expressed by stimulated fibroblasts, mesangial cells, and tubular epithelial cells.[63]

RANTES is inducible in T cell lines and circulating T cells by exposure to mitogens and antigens and is also produced by monocytes/macrophages. RANTES mediates monocyte and activated memory CD4+ and CD8+ T cell chemotaxis.[64]

RANTES can activate T cells via activation of phospholipase D. It induces calcium influx and up-regulates IL-2 receptors on the surface of these cells suggesting a role in T cell proliferation. In vivo, blockade of RANTES activity using the antagonist Met-RANTES produced significant reduction in proteinuria and leukocyte infiltration.[65]

Chemokine Receptors

Chemokines trigger cell migration and stimulation by binding to specific G-protein-coupled cell-surface receptors on target cells. Sixteen human chemokine receptors had been identified (at the time of writing): five human CXC chemokine receptors (CXCR1 through CXCR5), ten human CC chemokine receptors (CCR1 through CCR10), and one human CXXXC chemokine receptor (CX3CR1). Chemokine receptors are expressed on different types of leukocytes. Some receptors are restricted to certain cells (e.g, CXCR1 is mainly expressed by neutrophils), whereas others are more widely expressed (e.g, CCR2 on

monocytes, T cells, natural killer cells, dendritic cells, and basophils). In addition, chemokine receptors are constitutively expressed on some cells, whereas they are inducible on others. CCR1 and CCR2 are constitutively expressed on monocytes but are expressed on lymphocytes after stimulation by interleukin-2.[66]

In addition, some constitutive chemokine receptors can be down-regulated; CCR2 is down-regulated by lipopolysaccharide, making the cells unresponsive to monocyte chemoattractant protein 1 (which activates only this receptor), but it remains responsive to macrophage inflammatory protein 1α (which activates CCR1 and CCR5). In contrast, the expression of other chemokine receptors is restricted to cell states of activation and differentiation. For example, CXCR3 is expressed on activated Th 1 cells, whereas CCR3, in addition to being expressed on eosinophils and basophils, is preferentially expressed on activated Th 2 cells.[67]

In this way, transient up-regulation of chemokine receptors on leukocytes allows for the selective amplification of either a cell-mediated Th 1-type immune response or an allergic Th 2-type response. Some chemokine receptors are expressed on non-hematopoietic cells, suggesting that the chemokines have roles in addition to leukocyte chemotaxis. Most chemokine receptors bind more than one chemokine but CC receptors bind only CC chemokines and CXC receptors bind only CXC chemokines. This probably is due to structural differences between CC and CXC chemokines. Chemokine receptors, like other members of the family of G-protein-coupled receptors are functionally linked to phospholipases through G proteins. Receptor activation leads to a cascade of

cellular activation, including the generation of inositol triphosphate, the release of intracellular calcium and the activation of protein kinase C.[68]

Chemokine-receptor signalling also activates small guanosinetriphosphate-binding proteins of the Ras and Rho families. Rho proteins are involved in cell motility through regulation of actin-dependent processes such as membrane ruffling, pseudopod formation, and assembly of focal adhesion complexes. Thus, chemokine receptors activate multiple intracellular signalling pathways that regulate the intracellular machinery necessary to move the cell in its chosen direction.

Chemokines also interact with two types of non-signalling molecules. The first one is the erythrocyte chemokine receptor, called DARC (Duffy antigen receptor for chemokines). This receptor, known since the 1950s as the determinant of the Duffy blood group, is expressed on erythrocytes and endothelial cells. Although DARC is structurally related to chemokine receptors, it is distinctive in that both CXC and CC chemokines bind to it and chemokine binding does not induce calcium flux. This receptor may bind and clear chemokines from the circulation. The second type is a group of heparin sulfate proteoglycans. Chemokines are basic proteins and they bind avidly to negatively charged heparin and heparan sulfate. Heparan sulfate proteoglycans capture chemokines in the extracellular matrix and on the surface of endothelial cells, a process that may help to establish a local concentration gradient from the point where chemokine secretion begins.[69]

CCR3

CCR3 is the specific receptor for the CC-chemokines, eotaxin -1, 2, 3, and they interact with high affinity. RANTES and MCP-2, MCP-3, and MCP-4 also have CCR3 as a receptor but, unlike eotaxin, they also recognise additional receptors on monocytes, granulocytes, T cells and NK cells. CCR3 is expressed on eosinophils (from which eotaxin mediates histamine release) and basophils but not on neutrophils, monocytes or freshly isolated peripheral blood lymphocytes. CCR3 is also expressed by Th 2 cells but not Th 1 cells. About 1% of peripheral blood T cells have been found to express CCR3, but following expansion with PHA and IL-2 *in vitro*, lines derived from sorted CCR3+ cells have an enriched CCR3+ population (19%) which produces the Th 2-associated cytokines, IL-4 and IL-5. The production of these cytokines correlates with CCR3 expression. In such cell lines, expanded from CCR3+ and CCR3- T cells, both CD4+ and CD8+ cells produce IL-4, but to a greater extent in the CCR3+ lines.[67]

CCR3 expression has been shown on lymphocytes co-localising with eosinophils at sites of allergic inflammation. Thirty-two T cell clones with four different antigenic specificities were analysed for the expression of CCR3. Thirteen out of 24 expressed high levels of CCR3, with nine of these producing IL-4 and/ or IL-5. This is another indication that CCR3 expression predominates in Th 2, rather than Th 1, cells.[67]

CCR5

The chemokine receptor CCR5 is one member of a family of structurally and functionally related seven-transmembrane-spanning, G-protein-coupled

receptors. CCR5 binds to three of the CC-chemokines, namely macrophage inflammatory protein-1 alpha (MIP-1α), macrophage inflammatory protein-1 beta (MIP-1β), and RANTES (regulated upon activation normal T cell expressed and secreted), but it does not bind monocyte chemoattractant protein-1 (MCP-1). Elevated expression of RANTES has been demonstrated in renal and cardiac allograft rejections, and the chemokines MIP-1α and MIP-1β were shown to be elevated in liver allograft rejection and in the early phase of cardiac rejection.[70]

Local expression of these chemokines may be responsible for the interstitial and vascular mononuclear cell infiltrates of T cells and macrophages that characterize renal allograft rejection. The identification of CCR5 as the major co-receptor for macrophage-tropic HIV-1 strains has led to a large increase in knowledge about the physiological and pathophysiological role of CCR5. Approximately 20 to 30% of peripheral T cells and 10% of monocytes are CCR5 positive. In a study on cryosections, Rottman et al, described CCR5 by immunohistochemistry. In one case of interstitial nephritis, CCR5 was found on interstitial infiltrating cells, endothelium and vascular smooth muscle cells.[71]

Adhesion molecules

Leukocyte adhesion and transmigration are regulated largely by the binding of complementary adhesion molecules on the leukocyte and endothelial surfaces, and chemical mediators (chemoattractants and certain cytokines) affect these processes by modulating the surface expression or avidity of such adhesion molecules. The adhesion receptors involved belong to four molecular families

(the selectins, the immunoglobulin superfamily, the integrins and mucin-like glycoproteins).

Vascular cell adhesion molecule (VCAM-1) is important for the adhesion and recruitment of lymphocytes, eosinophils and monocytes (most of the AIN cell infiltrates), and it will be discussed in more detail below.

VCAM-1

VCAM-1 is an important adhesion and recruitment molecule for eosinophils that is expressed by endothelial cells. Human VCAM-1 is a transmembrane glycoprotein characterized by the presence of seven C2-type immunoglobulin domains. Approximately 80 kDa in predicted molecular weight, human VCAM-1 contains a 674 amino acid residue extracellular segment, a 22 amino acid residue transmembrane domain, and a 19 amino acid residue cytoplasmic tail. There are multiple-N-linked glycosylation sites, and each C2 domain is associated with a pair of cysteines that form disulfide linkages, stabilizing the overall domain. Although VCAM-1 with seven domains is considered the predominant form, alternatively spliced forms occur.[72]

The ligands (or co-receptors) for VCAM-1 have been identified and are the α4β1 and α4β7 integrins. Integrins are non-covalently linked heterodimers composed of one large α subunit (120-180 kDa) and one small β subunit (90-120 kDa). The principle ligand or co-receptor for VCAM-1 is α4β1/VLA-4. Normally, VCAM-1 has a low to nominal expression on un-stimulated endothelium but it is inducible by a number of cytokines (IL-1, TNF-α, IL-4 and IL-13). When induced, VCAM-1 plays a significant role in migration for

leukocytes that express VLA-4 (e. g, lymphocytes, monocytes, eosinophils, basophils). If an antigenic challenge is "allergic" in nature and involves IgE antibody, mast cells will release IL-4. Although both TNF-α and IL-4 induce endothelial VCAM-1 expression, IL-4, unlike TNF-α, does not up-regulate E-selectin or ICAM-1. This would remove adhesion molecule support for almost all neutrophil and monocyte extravasation, and result in a predominantly eosinophilic infiltration. VCAM-1 also plays an important role in lymphocyte homing and migration.[73]

PATHOLOGY

In the light of the sections on the immune system, chemokine recruitment of immune cells and adhesion receptors, the current knowledge of the pathology of AIN is now reviewed. Although the -interstitium can only respond in a limited manner to a variety of insults, the pattern of response can help define the acuity of the process, the long term prognosis and in some patients the pathogenesis and/or aetiology of the disorder. The initial division of the histologic pattern of AIN is dependent on the presence or absence of significance inflammatory infiltrate in the interstitium. Where the infiltrate is predominant, the characteristics of the cellular components of the infiltrate may further assist in differentiating the types of AIN with differing pathogenesis.

In acute or active forms of interstitial nephritis the interstitium is oedematous and there is a cellular infiltrate that may contain lymphocytes, plasma cells, or polymorphonuclear leukocytes, including eosinophils. If there is prominent neutrophilic polymorphonuclear leukocytes, people think it is more

likely to be associated with ascending infection. Invasion of the tubules by lymphocytes may be seen to resemble the tubulitis of allograft rejection. In more chronic forms, interstitial fibrosis and tubular atrophy is the most prominent feature that may be accompanied by an infiltrate comprised only of small lymphocytes.[8]

Mechanism of insult

The mechanisms by which various aetiologic agents can mediate renal - interstitial injury can be direct through cytotoxic effects or indirect by the induction of systemic inflammatory or immunologic reactions. Direct cytotoxic mechanisms are dose and exposure duration dependent, such as that which is seen in analgesic and lead nephropathy; such processes are often chronic and do not induce AIN. Indirect reactions are often idiosyncratic as occurs in the AIN associated with non-steroidal anti- inflammatory agents (NSAIDs). The nature of the injury may be determined to some extent by factors unrelated to the agent such as pre-existing renal disease, or extra renal factors that can affect renal dosage such as abnormal liver function.[8]

In addition, the differences in susceptibility of different nephron segments can modify the renal response to these agents, such as with heavy metal exposure.[8]

Detailed pathological features

Grossly, the kidneys are enlarged, and the degree of enlargement is proportionate to the extent of involvement. Infectious processes with suppuration

produce abscesses and, if there is associated obstruction, pyonephrosis. Extension of the infectious process through the renal capsules results in perinephric abscess. Drug reactions and AIN due to immunologic injury result in large, pale, and swollen kidneys. The external surface is smooth.[9]

The most striking histological finding is the presence of numerous cells, mainly mononuclear, in the renal interstitium. Tubular changes, characterized by areas of epithelial injury and interstitial oedema, or fibrosis and oedema, are usually seen. The absence of glomerular lesions and significant glomerular deposits by immunofluorescence is required for differential diagnosis from primary glomerular disease, lupus glomerulonephritis, essential mixed cryoglobulinaemia, and vasculitis, all conditions in which prominent interstitial cell infiltrates may be present.

Microscopic findings

Under light microscopy, the interstitial infiltrates of mononuclear cells and associated areas of oedema are multifocal and vary in intensity. Most of the mononuclear cells are lymphocytes but plasma cells can be seen occasionally. There are also numerous monocyte/macrophages. Polymorphonuclear cells make up a very limited number of the cell infiltrate as compared to lymphocytes and when present in higher number may indicate acute pyelonephritis. Eosinophils constitute only a small proportion of the interstitial cells, even in drug-induced AIN, where their presence is probably indicative of an allergic response.[14]

Epithelioid and non-caseating giant-cell granulomas are demonstrated in some cases, especially in those in which AIN is related to drugs. Interstitial granulomas were found in 27% of patients with drug-induced AIN.[74]

Patients with interstitial granulomas were found to have an oliguric presentation and permanent renal damage more often than those without.[74] Granulomas are not a specific finding of drug-induced AIN as they can be also found in AIN related to infections or in cases of unknown aetiology. Most of the interstitial lymphocytes are of T lineage, with CD4+ cells and CD8+ T cells occuring in roughly equal proportions.[14] Expression of HLA class Π antigen on T lymphocytes has been observed while CD25 expression (interleukin-2 receptor) was rarely found.[14]

Many interstitial cell infiltrates have been shown to express LFA-1 and VLA-4 integrin molecules by immunohistochemical studies.[75] Tubular injury includes tubulitis (T-lymphocytes infiltrate between tubular cells), breaks of the TBM, and necrosis of tubular cells and loss of tubules, depending on the aetiological agent. According to Ivanyi, B, et al.,[76] tubulitis more often involves the distal nephron. Aberrant expression of HLA-class Π molecules by tubular cells was found in AIN, but no significant correlation between HLA-DR in tubular epithelium and intensity or the phenotype of interstitial infiltrates has been determined.

In AIN, the glomeruli are often spared. Arterial and arteriolar changes are usually absent. When present in older persons, they are unrelated to the primary - interstitial process and reflect aging-associated-hypertension, or both.[9]

Immunohistological findings

Immunohistochemical techniques are often used to delineate pathogenic mechanisms. Linear deposits of antibody and complement along the TBM may suggest antibody directed against or cross-reactive with TBM antigens (eg., in some patients with Goodpasture's syndrome and in renal allografts); granular deposits of antibody and complement in the TBM or interstitium (or both of these) suggest an immune complex pathogenesis; and -interstitial nephritis with a T cell and other mononuclear cell infiltrate without deposits of antibody and complement associated with the TBM, suggests a cell- mediated reaction associated with delayed-type hypersensitivity (e.g., drug reactions, interstitial nephritis with uveitis) or cytotoxic T cell injury (e,g., first-set allograft rejection).

TYPES OF ACUTE INTERSTITIAL NEPHRITIS

Acute -interstitial nephritis related to drugs, TINU syndrome and idiopathic AIN are now reviewed. AIN associated with systemic diseases is not a focus for this thesis and will not be considered further.

Drug-induced

In the early reports of AIN due to methicillin, onset of renal dysfunction usually appeared after 10 to 20 days of drug therapy. It is now appreciated that the start of AIN can manifest other types of time kinetics. For example, it can happen quickly within 2 to 3 days after re-challenge with a drug to which an individual has been previously sensitized. It can also happen de novo in response to a previously tolerated medication by the individual. With the enormous

increase in the use of different chemotherapeutic agents over the past five decades, drug-induced acute interstitial nephritis has come to dominate this area of medicine. Although, we must not forget that overall, drug-induced AIN is relatively rare.[14]

The exact incidence of drug-induced AIN is uncertain, as many patients with reversible acute renal failure usually do not undergo renal biopsy. Richet et al found that drug-induced AIN comprised 0.8% of all cases with acute renal failure.[68] Furthermore, AIN was found in quarter of renal biopsies done in patients with drug-related acute renal failure. There are different drugs including β-lactam antibiotics, non-steroidal anti-inflammatory drugs, diuretics, anticonvulsants, sulphonamides, rifampicin, phenindione, cimetidine, omeprazole and an even more heterogeneous group of other drugs perhaps cause allergic AIN.[11] The majority of the reports are single case descriptions and most of these patients had received multiple drugs[14] and the evidence is very weak.

Mechanism of drug allergy

Allergic drug reactions continue to be a serious problem as they are unpredictable and diverse in nature. There are also problems of diagnosis and, other than withdrawal of the drug, treatment is limited. A major difficulty in predicting these reactions is that the immunological processes underlying drug allergy are poorly understood. Broadly anaphylactic reactions, for example to betalactam antibiotics, are associated with specific IgE antibody, whereas skin reactions and other inflammatory responses, for example to sulphonamides, phenytoin, carbamazepine and penicillins, are linked to the presence of sensitized

T cells. The primary effector cells of IgE-mediated reactions are mast cells that are activated by antigen within seconds to release histamine and other chemical mediators; this is often followed by eosinophil recruitment to tissue sites. In the case of cell-mediated reactions, T cells are presumed to release pro-inflammatory cytokines upon activation by the drug. Hence, the T cell is central to understanding drug allergy: it is important in the induction phase of the IgE antibody response as a source of interleukin 4 (IL-4) and other cytokines, and in both the induction and effector stages of T-cell mediated reactions.[77]

T-cell recognition of drugs

Drug-specific T cell clones can be grown and isolated from the peripheral blood of patients allergic to many drugs including penicillins, sulphonamides and lidocaine. The majority of drug specific T cell clones express the α β type of T cell receptor, are of CD4+ or CD8+ phenotype, and are MHC class I or Π restricted, although some T cell clones that recognize lidocaine express the γ δ receptor type.[77]

Patterns of cytokine production by drug-specific T-cell clones are variable. Thus, benzylpenicillin-specific clones produce predominantly a Th 1-like pattern with high IL-2 and interferon γ (IFN-γ) production, whereas sulphamethoxazole and lidocaine-specific clones show a mixed Th 0 or Th 2 phenotype.[77]

Some benzylpenicillin-specific human T cell clones proliferate in response to synthetic MHC class Π-binding peptides that have the appropriate

HLA-DR anchor residues and pericilloylated lysine in selected positions along a polyalanyl back bone.

Drug metabolism and antigen generation

An important factor in immune responses to drugs is whether the drug is chemically reactive and capable of covalent conjugation to carrier proteins. If not, it may require oxidative metabolism to a reactive intermediate. Examples of reactive drugs that spontaneously generate haptens are the penicillins that form amide linkages with the side chain of lysine residues, and sulphydryl drugs such as the anti-arthritic agent D-penicillamine that conjugate by disulphide bonding to cysteine residues. Other drugs that cause allergic reactions, such as sulphonamides, carbamazepine and phenytoin, are not reactive: they are either metabolized to reactive species or may associate noncovalently with immune recognition molecules.

T cell clones derived from patients with allergic reactions to drugs such as sulphametoxazole and propyphenazone showed significantly increased proliferation in response to the eliciting drug in the presence of cytochrome P450-active liver microsomes. Although, the liver is the major site for the drug-metabolizing cytochrome P450 enzymes, blood monocytes express high levels of the cytochrome P450 enzyme CYP1B1, and could be responsible for drug oxidation in the blood, skin and other peripheral tissues.[78]

Clinical and pathological features of drug-associated acute -interstitial nephritis

The reaction of acute -interstitial nephritis (AIN) occurs in only a small number of patients taking any drug and appears never to be dose-related, except in some cases involving penicillin G and allopurinol.[11]

It is suggested from the literature that there may be a maculopapular rash, fever is usual and arthralgia common; sometimes the liver is involved and acute renal failure may develop, with dialysis being necessary in about a third of the patients. Microscopic haematuria is reported to be present in the majority of patients, macroscopic haematuria common, and red cell casts may be observed in the urine. Nephrotic range proteinuria is almost exclusively found in AIN when related to non-steroidal anti-inflammatory drugs. The renal failure is often non-oliguric Eosinophilia is variable; it is said to be commoner in methicillin-related cases, but occurs overall in only 50% of the patients; eosinophiluria may be present,[20] but the absence of eosinophilia or eosinophiluria does not appear to be helpful in excluding the possibility of it being diagnosed. Hyperchloraemic acidosis and impaired urinary concentration have been reported and may persist for months after withdrawal of the drug. The value of symptoms and signs of systemic allergy in predicting AIN were evaluated in a collaborative study: the positive predictive value for fever, arthralgia, blood eosinophilia and hepatocellular damage was low (only 0.60) because these symptoms were also found in 24% of patients with drug- induced acute tubular necrosis. Because of this overlap, it appears that the diagnosis of AIN can be established only by renal biopsy.

Many of the laboratory tests used for diagnosing a hypersensitivity reaction lack both sensitivity and specificity.[18] Circulating antibodies to penicillin, rifampicin, or glafenin and their derivatives have been found in some cases of AIN attributed to these drugs. Circulating antibodies against the tubular basement membrane have been described in some case reports of AIN after the use of methicillin, cephalothin and diphenylhydantoin.[14]

Most patients recover fully, provided the drug responsible is removed. The recovery of renal function depends on how long the renal failure had continued before discovery of AIN.[11] The benefits of treatment with steroids are highly controversial.

The evidence to support the use of steroids in drug-induced AIN comes from anecdotal reports as well as from small, uncontrolled, non-randomized studies.[11]

In one study of fourteen patients, those treated with prednisolone (n=8) had an earlier and more complete return to base line serum creatinine than those left untreated (n=6).[79]

The risks of this therapy must be weighed against its benefits in any given patient. Neilson et al[8] believe that a limited course of high dose prednisolone is advisable for biopsy-proven AIN, if renal failure has persisted for more than one week after the removal of any inciting factor and that steroids should be discontinued if no response is obtained after 3 to 4 weeks of treatment. However, if steroids are to be of benefit, it would seem to be more logical to begin treatment immediately the diagnosis is established providing there are no

contraindications and to reduce the dose in accordance with the response, whether this an improvement in renal function or a continuation of the symptoms.

Antibiotics

β-Lactam

Many cases of methicillin and penicillin-induced AIN were reported during the 1970s. The incidence of renal dysfunction ranged between 12% and 20% of patients treated for staphylococcal infections, or receiving prophylactic treatment before cardiac surgery.[21] Methicillin is now no longer used; and other anti-staphylococcal antibiotics such as flucloxacillin are preferred. The sex incidence of penicillin-induced AIN is about 2-3 males: 1 female.[11] Signs and symptoms of AIN are reported to appear between 2 and 60 days after the start of treatment. Macroscopic haematuria, skin rash, blood eosinophilia and eosinophiluria are present in one-third of the patients. Half of the adults with AIN have increased blood urea. Recovery occurs in 90% of cases. Interestingly sodium wasting, hyperkalaemia and distal tubular acidosis are prominent features in some patients.[1]

Allergic reactions are much less frequent with current penicillin derivatives used in practice than in methicillin-related AIN, including ampicillin, amoxicillin, penicillin G and piperacillin.[1]

Re-challenge with the drug or with a chemically related one can quickly lead to recurrence of the renal and extra-renal symptoms and all β-lactam antibiotics are best avoided in patients who have developed penicillin-related

AIN during treatment with a penicillin compound or a cephalosporin.[21] The frequency of cross-allergenicity between the two groups of drugs is not reported with any certainity, but probably is around 5%-10%. However, cephalosporins are rarely responsible for AIN.[18]

Sulphonamides

Many cases of AIN following the use of normal or high doses of co-trimoxazole (trimethoprim and sulphamethoxazole) have been reported.[18] Signs of hypersensitivity are often absent, severe interstitial infiltrates with eosinophils and granulomas are frequently found in renal biopsies, and full renal recovery does not seem to occur in the majority of affected individuals.

Other antibiotics associated with AIN

Since the first report of rifampicin-associated AIN in 1971,[80] it has always been found in association with tuberculosis. The treatment regimen has often been intermittent and only a small number of cases have resulted from continuous daily treatment. A few hours or days after taking the drug, the patients developed chills, myalgia, fever, lumbar pain, nausea or vomiting and dark urine. Skin rash, eosinophilia, thrombocytopenia, haemolysis and even hepatitis are possible but inconsistent features. Most patients with rifampicin-induced AIN have abrupt oliguria and require dialysis but tubular dysfunction with or without progressive renal failure has also been described.[1]

Renal biopsies show a typical AIN with focal tubular necrosis or atrophy in 50% of cases. In the remainder, marked injury of proximal tubules and a little

interstitial infiltration is observed. Interstitial granulomas are sometimes present.[81] High titres of anti-rifampicin antibodies have occasionally been found during the acute phase. These observations argue for an immune-complex pathogenesis and suggest, at least in some cases, that rifampicin has a direct toxic effect.[11] Most patients make a full recovery, but a few suffer permanent interstitial fibrosis.[11] There is no evidence that steroids hasten recovery and renal failure may progress despite continuous prednisolone therapy.

In a small number of cases other antibiotics have been implicated in the development of AIN for example, vancomycin, tetracycline, erythromycin, nitrofurontoin, and also quinolone derivatives, such as piromidic acid, norfloxacin, levofloxacin and ciprofloxacin.

Non-steroidal anti-inflammatory drugs

The first case reports of AIN from these drugs were made in 1979.[82] Almost all the various NSAIDs in clinical use, which vary in their chemical structure, have been implicated. There may be no symptoms or signs of hypersensitivity but the renal insufficiency has a progressive onset, discovered several months or years after the start of treatment, because the affected patients usually remain polyuric rather than becoming oliguric. More than 80% of AIN cases related to NSAIDs develop a nephrotic syndrome compared to less than 1% when it is related to betalactams.[18] Withdrawal of the offending drug usually leads to resolution and there is no evidence that steroids hasten or improve the result.[11]

Other groups of drugs associated with AIN

Analgesics and salicylates

Biopsy-proven AIN has been found in a few patients receiving therapeutic doses of paracetamol. Salicylate derivatives may lead to AIN including 5-aminosalicylic acid, used as primary treatment and maintenance therapy in inflammatory bowel disease.[1,18]

Diuretics

Thiazides and frusemides have been most commonly implicated in diuretic–induced AIN: both are of course both chemically related to sulphonamides. Acute renal failure develops several weeks after the start of treatment with signs and symptoms of systemic allergy. On biopsy, there are interstitial infiltrates and epithelioid granulomas; immunofluorescence is negative. Withdrawal of the drug, with or without steroid treatment, leads to rapid recovery of renal function in all cases.[11] Bendrofluazide, hydrochlorothiazide alone and tierilic acid[76] have also been thought responsible.

Miscellaneous

The potential for drugs to cause AIN is large. However, some additional relevant examples may also include the following. Acute -interstitial nephritis due to allopurinol sensitivity has been described sometimes with granuloma formation, mostly in patients with pre-existing renal impairment and relative over-dosing or on treatment with thiazides, which lead to increased blood

concentrations. A return to base line renal function occurs after allopurinol is stopped.[1]

Cimetidine has been implicated as a cause of AIN in several patients. Several weeks after the start of treatment, fever, myalgia and non-oliguric renal insufficiency develop.[18] Eosinophils are found in serum, urine and within the biopsies of renal interstitium. Most patients regained normal renal function after withdrawal of the drug, but residual renal damage is found in some cases.[83] Ranitidine is responsible for some cases of AIN. Omeprazole is a commonly used proton pump inhibitor that has been implicated in many cases of AIN. Hypercalcaemia has been reported with omeprazole-induced AIN.[1]

There are many other drugs which have been suspected of causing AIN, for example, captopril, diphenylhydantoin, valproate, warfarin, phenobarbital, streptokinase, acyclovir, interferon-α, Chinese herbal medicine, recombinant interleukin 2, clozapine and rofecoxib.[1]

Infections

AIN is associated with primary renal infections such as acute bacterial pyelonephritis, renal tuberculosis, and fungal nephritis. Systemic infections can cause direct injury because of pathologic processes in the kidney or can be associated with indirect injury caused by medications used in the treatment of infections.[1]

TINU syndrome (interstitial nephritis and uveitis syndrome)

Idiopathic interstitial nephrits and uveitis syndrome (TINU Syndrome) is a relatively uncommon syndrome.[9] When the causal agent for AIN cannot be identified, it is termed idiopathic acute interstitial nephritis (I AIN). It may appear alone or associated with uveitis, but the concomitant development of these disorders raises the concept of a renal-ocular syndrome. In 1975, Dorbin et al[84] described a new syndrome consisting of acute renal failure secondary to AIN associated with lymph node and bone marrow granulomas and anterior uveitis. Moreover, sporadic cases of AIN have been described with granulomas in bone marrow without uveitis, with hypocomplementemia, eosinophilia and tubular deposits of IgE and complement C_3 and with deafness. The great majority of the cases have been adolescent females. The uveitis normally follows the onset of renal problems, and often appears as they are resolving. The condition is normally preceded by symptoms such as asthenia, myalgias, loss of weight, vomiting, fever, anorexia, and abdominal pain, headache or nausea.[1] An increase in the ESR, anaemia and hypergammaglobinemia are often found. The kidneys are affected by AIN with a predominant mononuclear infiltrate in the majority of cases. The clinical form of renal disorder at onset is acute renal insufficiency with preserved diuresis and less commonly, polyuria or Fanconi's syndrome.[1]

Although the aetiology is still unknown, the immunochemical findings point to an autoimmune cause, with involvement of cell mediated immunity. These findings consist of an increase in the levels of immunoglobulins and circulating immunocomplexes, decrease in T cells, absence of specific immunofluorescence, and presence of helper T lymphocytes in the renal

interstitium. The suppression of the peripheral immune reactivity in contrast with the increase in immune reactivity in inflammed sites makes this condition similar to sarcoidosis. Systemic corticosteroids usually resolve the uveitis. Azathioprine has not proved effective in the prevention of exacerbations of uveitis, in contrast to the favourable response to cyclosporine A. In almost all cases, the nephropathy responds to steroid treatment. Some cases have resolved spontaneously.[1]

The evolution is generally benign, with complete resolution of symptoms in almost 100% of reported cases. The uveitis follows its course independently from the nephropathy and sometimes tends to relapse.[1]

MANAGEMENT

Withdrawal of medications that are likely to cause AIN is the most significant step in early management of suspected or biopsy-proven AIN.[1] The majority of patients with AIN improve spontaneously after the withdrawal of medications that resulted in renal failure.

Other supportive care interventions include fluid and electrolyte management, maintenance of adequate hydration, symptomatic relief for fever and systemic symptoms, symptomatic relief for rash.

Indications for dialysis in the management of acute renal failure include uncontrolled hyperkalemia, azotemia with mental status changes, and other symptomatic fluid or electrolyte derangements.

The role of steroids in the treatment in AIN remains to be defined. There are those who continue to question the use of or indications for steroid therapy. It

is true that there are no controlled, randomized trials supporting this recommendation.[1]

However, small case reports and studies have demonstrated rapid diuresis, clinical improvement, and return of normal renal function within 72 hours after starting steroid treatment, although some case reports indicate lack of efficacy, especially in cases of NSAID-induced AIN. The decision to use steroids should be guided by the clinical course following withdrawal of offending medications. Convincing clinical evidence for a role for steroid therapy, however, comes from the idiopathic form of AIN, particularly that with coexistent anterior uveitis, the so-called TINU syndrome.[1]

Steroids are not to be used in cases due to infectious agents, in which proper therapy is directed at eliminating infection. If steroid therapy is started, a reasonable dosage is prednisone 1 mg/kg/day orally (or equivalent intravenous dose) for 2 or 3 weeks, followed by a gradually tapering dose over 3 to 4 weeks. Immunosuppressive agents like cyclophosphamide or cyclosporine, should be used in patients who's biopsy reveals immune complex deposits and those with evidence of circulating antitubular basement antibodies or complement consumption. Considerations should be also given to patients who fail to respond to a 2-week course of steroid therapy.[1]

PROGNOSIS

Most patients with AIN in whom offending medications are withdrawn early can be expected to recover normal or near-normal renal function within a few weeks. Patients who discontinue offending medications within 2 weeks of

the onset of AIN (measured by increased serum creatinine) are more likely to recover nearly baseline renal function than those who remain on the precipitating medication for 3 or more weeks.[1]

Reviewing the three modern series of AIN, only 64.1% of patients made a full recovery (serum creatinine < 132 mmol/L), whereas 23.4% gained a partial recovery (serum creatinine > 132 mmol/L) and 12.5% remained on renal replacement therapy.[1] This relatively poor outcome may reflect the different case-mix in recent series, with fewer patients having traditional allergic-type AIN. It would be useful to have prognostic indicators for AIN, and it has been suggested previously that the long-term outcome is worse if renal failure lasts for more than 3 weeks. However, this is not useful prospectively.[1]

Two series have shown worse prognosis with increasing age, but there appears to be no correlation with peak creatinine concentration. Attempts have also been made to gain prognostic information from the renal biopsy. Some authors have reported that patchy cellular infiltration predicts a better outcome than diffuse disease.[1]

However, more recent studies have not supported a correlation between the degree of cellular infiltration or tubulitis and outcome. The degree of interstitial fibrosis has been correlated to outcome, but such relationship was not confirmed in other studies. These conflicting observations may be due to the patchy nature of the disease and random sampling on renal biopsy.[1]

METHODOLOGY

The present study was conducted in the Department of Medicine and Nephrology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients suspected to have AIN on clinical grounds and proven by renal biopsy presenting during the period of January 2009 to December 2009.

Study design

The study design was one year cross sectional study.

Study period and duration

The present one year study was conducted during the period of January 2009 to December 2009.

Method of collection of data

Source of Data

All patients admitted in the Department of Nephrology and Medicine of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum who were suspected to have AIN on clinical grounds and proved by renal biopsy were enrolled in the study.

Sample size

Twenty (20) patients suspected to have AIN on clinical grounds and proved by renal biopsy were selected for the study.

Sampling procedure

The sample size was calculated considering 80% of average number of similar cases reported to KLES Dr. Prabhakar Kore Hospital Belgaum, over a period of past three years. The sample size required was calculated to be of 20 patients. However a total of 26 cases were diagnosed with AIN during the study period and hence all the 26 patients were included in the study.

Selection criteria

Inclusion Criteria

- Any patient with acute renal failure, suggestive of AIN with all or more than one or any one of the following clinical features like, hematuria, low grade fever, skin rash, arthralgia, lumbar pain (flank pain).
- Biopsy proven acute interstitial nephropathy, which was not suspected on clinical grounds.

Exclusion Criteria

- Prerenal azotemia.
- Obstructive nephropathy.
- Glomerulo nephritis.
- Acute tubular necrosis.

Procedure

Patients admitted in the wards of Department of Nephrology and Medicine at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre,

Belgaum, were evaluated based on selection criteria and selected by detailed medical history and physical examination. The study was approved by the Ethical and Research Committee of Ethics Committee, Jawaharlal Nehru Medical College, Belgaum. The selected patients were briefed about the nature of the study, the interventions used and a written informed consent was obtained (Annexure–I).

Demographic data like gender and age were collected along with relevant history and recorded on predesigned and pretested proforma (Annexure-II). A thorough clinical examination was conducted and the findings were also recorded.

Routine investigations such as Haemogram (haemoglobin, total count, differential count, erythrocyte sedimentation rate), urine routine and microscopy was done.

Renal functional tests such as blood urea, serum creatinine, serum electrolytes, and liver function tests were conducted and recorded. The culture and sensitivity test for blood and urine was done. Ultrasonographic abdomen finding were also recorded. Renal biopsy was done in all the patients.

Renal biopsy

In all patients in whom a percutaneous renal biopsy was performed platelet count, prothrombin time (or INR), partial thromboplastin time and Blood Group was established before the procedure was undertaken.

Procedure

Biopsies were performed under the guidance of ultrasonography to permit more accurate localization of the kidney. Biopsy of the lower pole of the left kidney was done. Patients lie on their abdomen (prone position). The entry site was marked, area was cleaned with antiseptic agents, and a local anaesthetic agent was injected. The spring-loaded Biopsy Gun (Biopsy, Bard Urological Division, C.R. Bard, Covington, GA, the long-throw device has a depth of 2.2 cm, yielding a specimen with a potential length of up to 1.8 cm) was inserted through the entry site which was marked. After making the entry of the tip of the needle in to the cortex of the kidney, gun was shot and tissue core was collected in media meant for transport.

After completion of the biopsy, patients were instructed to remain at bed rest for 18 to 24 hours. Blood pressure and pulse were monitored frequently. The patient was asked to save an aliquot of each voided urine in a separate clear-plastic specimen jar labeled with the date and time, which was kept at the patient's bedside for inspection. This provides a visual check for evidence of bleeding into the intrarenal collecting system. Hematocrits were determined six to eight hours after the biopsy and again at 18 to 24 hours, or earlier, if hypotension or gross hematuria was observed.

Statistical analysis

The results were tabulated and the data was analysed using rates, ratios and percentages of different clinical manifestations, biochemical parameters and histopathological diagnosis. The Bonterroni multiple comparison test was used for comparison.

RESULTS

The present study was conducted in the Department of Medicine and Nephrology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2009 to December 2009. A total of 26 patients suspected to have AIN on clinical grounds and proved by renal biopsy were enrolled in the study. The data obtained was tabulated and analysed as below.

Table 2. Number of renal biopsies during the study period

Particulars	Number	Percentage
Total number of biopsies	150	100
Acute interstitial nephropathy	26	17.33

A total 150 biopsies were done during the study period of which 26 (17.33%) had AIN.

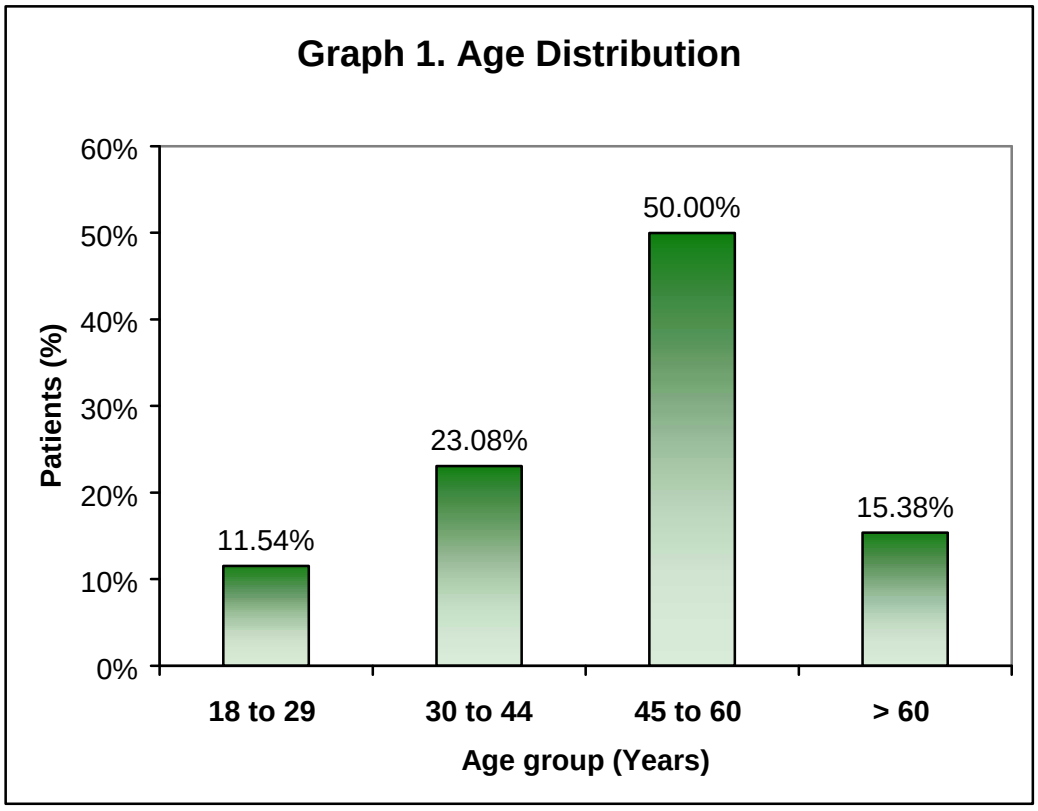
Table 3. Sex distribution

Sex	Number	Percentage
Male	18	69.23
Female	08	30.77

In present study males (69.23%) outnumbered females (30.77%) with male to female ratio of 2.25:1.

Table 4. Age distribution

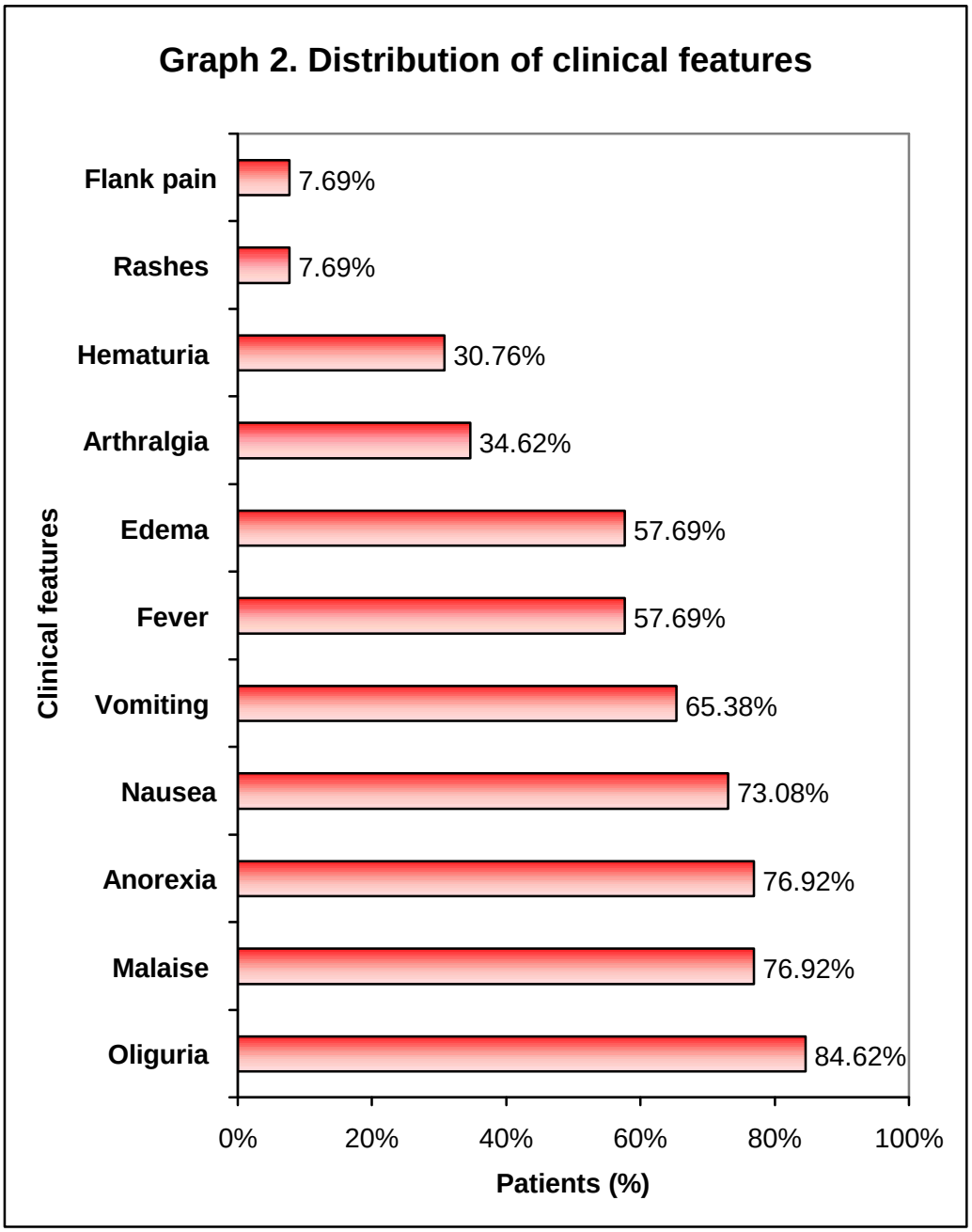
Age group (Years)	Number	Percentage
18 to 29	03	11.54
30 to 44	06	23.08
45 to 60	13	50.00
> 60	04	15.38
Total	26	100



In present study majority (50%) had age between 45 to 60 years followed by 30 to 44 years (23.08%). The mean age of study population was **47.38 ± 12.54** years with range being 24 to 69 years.

Table 5. Distribution of clinical features

Clinical features	Number	Percentage
Oliguria	22	84.62
Malaise	20	76.92
Anorexia	20	76.92
Nausea	19	73.08
Vomiting	17	65.38
Fever	15	57.69
Edema	15	57.69
Arthralgia	09	34.62
Hematuria	08	30.76
Rashes	02	7.69
Flank pain	02	7.69



In present study the most common clinical presentation was oliguria (84.62%) followed by malaise and anorexia (76.92% each), vomiting (65.38%), edema and fever (57.69% each), arthralgia (34.62%), hematuria (30.76%) rashes and flank pain (7.69% each).

Table 6. Drug history (n=26)

Drugs	Number	Percentage
NSAIDS	08	30.77
Antibiotics	03	11.54
Total	11	42.30

In present study out of 26 cases with AIN 11 (42.30%) cases had drug history. Of them eight (30.77%) had history of NSAIDS and three (11.54%) had history of antibiotics.

Table 7. Comorbid conditions (n=26)

Comorbid conditions	Number	Percentage
Hypertension	08	30.77
Diabetes	05	19.23
Chronic kidney disease	05	19.23%
Ischaemic heart disease	02	7.69
Jaundice	00	0.00

In present study eight cases (30.77%) had history of hypertension whereas diabetes was present in five (19.23%) cases. The underlying renal disease (chronic kidney disease) was noted in 19.23% patients

Table 8. Findings of investigations (n=26)

Investigations		Number	Percentage
Haemoglobin (gm%)	Normal*	07	26.92
	< 13 gm%	19	73.08
Total count	Normal (4000 – 11000 /mm^3)	14	53.85
	< 4000 /mm^3	01	3.85
	> 11000 /mm^3	11	42.31
Neutrophils	Normal (40 to 70%)	04	15.38
	< 40%	00	0.00
	> 70%	22	84.62
Lymphocytes	20 to 50%	7	26.90
	< 20%	19	73.08
	> 50%	0	0.00
Eosinophils	Normal (0 to 6%)	25	96.15
	> 6%	1	3.85
Monocytes	Normal (4 to 8%)	19	73.08
	< 4%	4	15.38
	> 8%	3	11.54
ESR (mm/1^{st} hour)	Normal**	7	26.92
	> 20	19	73.08

* Haemoglobin normal values – Males 13 to 16 gm%; females 12 to 15 gm%

** ESR normal values – Males 0 to 15 mm/1^{st} hour; females 0 to 20 mm/1^{st} hour

In present study anaemia was seen in 73.08% and total counts were raised in 42% of patients. The neutrophilia was seen in 84.62% cases whereas eosinophilia in 3.85%.

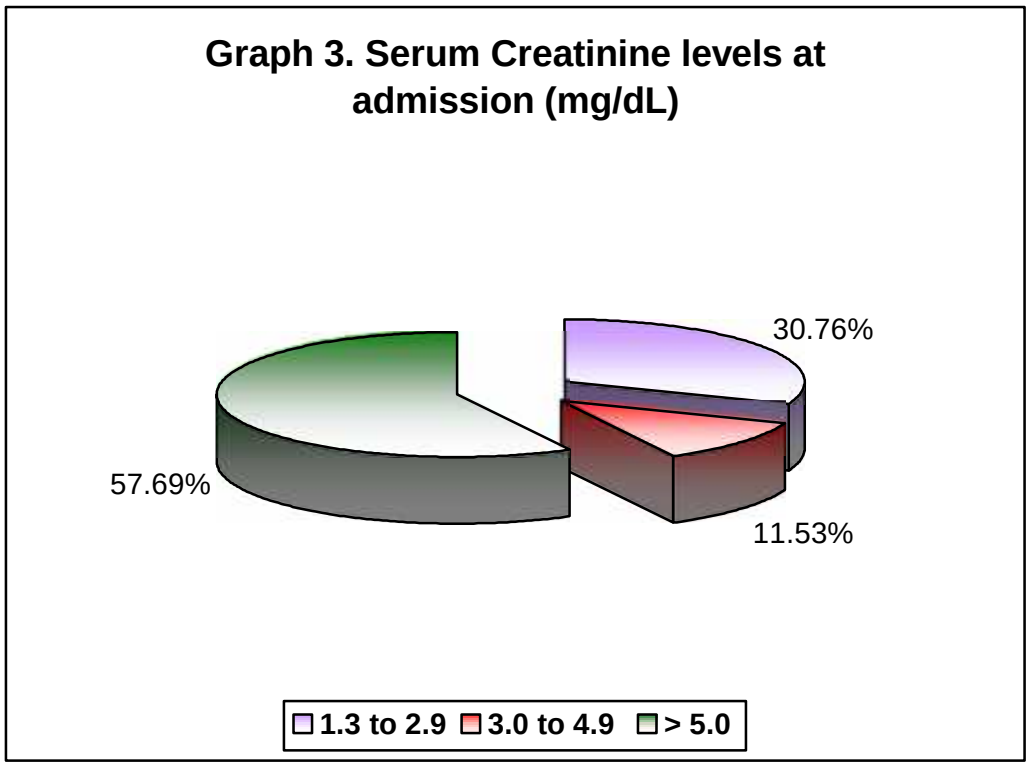
Table 9. Absolute eosinophil count (n=26)

Absolute eosinophil count (cells/mm^3)	Number	Percentage
Normal (150 to 300)	03	11.54
< 150	22	84.62
> 300	1	3.85
Total	26	100

In present study absolute eosinophilic count was raised in one patient (3.85%) out of 26 patients.

Table 10. Serum creatinine levels at admission (n=26)

Serum creatinine levels (mg/dL)	Number	Percentage
1.3 to 2.9	08	30.76
3.0 to 4.9	03	11.53
> 5.0	15	57.69
Total	26	100



In present study out of 26 cases majority (57.69%) patients had serum creatinine levels more than 5.0 mg/dL followed by eight patients (30.76%) between 1.3 to 2.9 mg/dL and three patients between 3.0 to 4.9 mg/dL. All the cases (100%) had serum creatinine levels more than 1.3 mg/dL with mean serum creatinine levels being 6.33 ± 4.76 mg/dL.

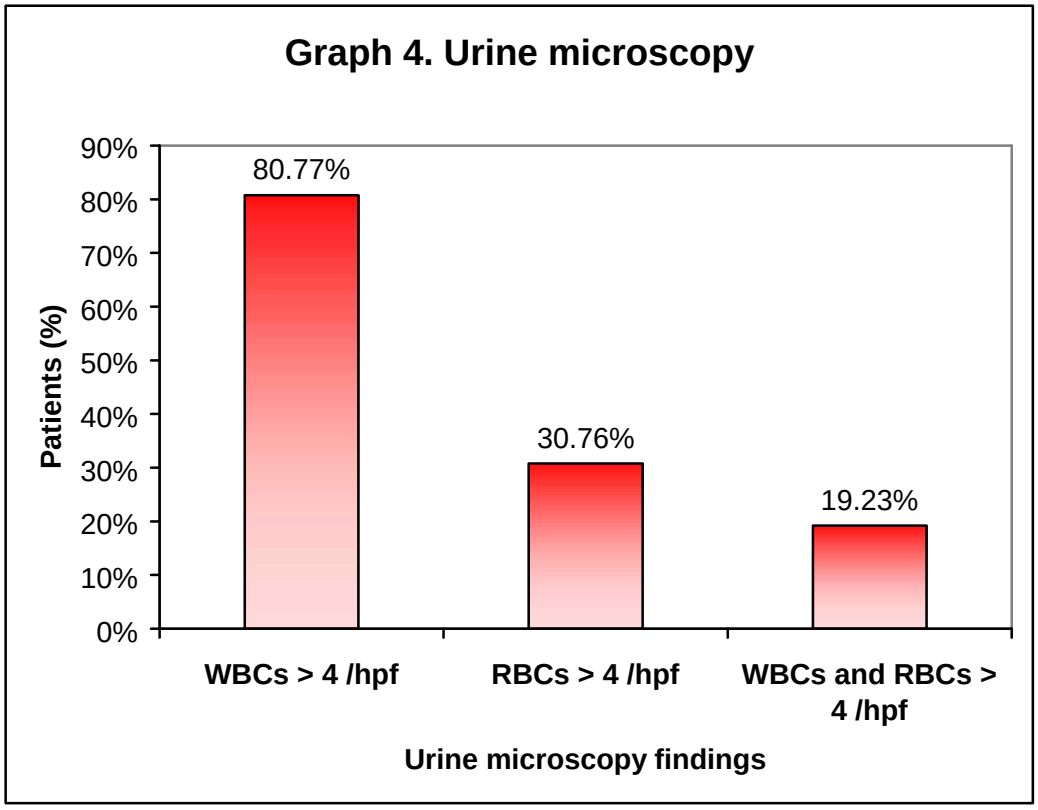
Table 11. Urine albumin levels (n=26)

Urine albumin	Number	Percentage
Normal (Absent)	07	26.92
Traces	07	26.92
+1	06	23.08
+2	06	23.08

In present study the urine albumin findings were normal in 26.92% patients whereas 26.92% patients had traces of proteinuria.

Table 12. Urine microscopy (n=26)

Findings	Number	Percentage
WBCs > 4 (/hpf)	21	80.77
RBCs > 4 (/hpf)	8	30.76
WBC's and RBC's > 4 (/hpf)	5	19.23



In present study urine microscopy findings showed > 4 /hpf WBCs in 80.77% patients whereas 30.76% patients had > 4 /hpf RBCs. Both WBCs and RBCs > 4 /hpf were found in 19.23% patients.

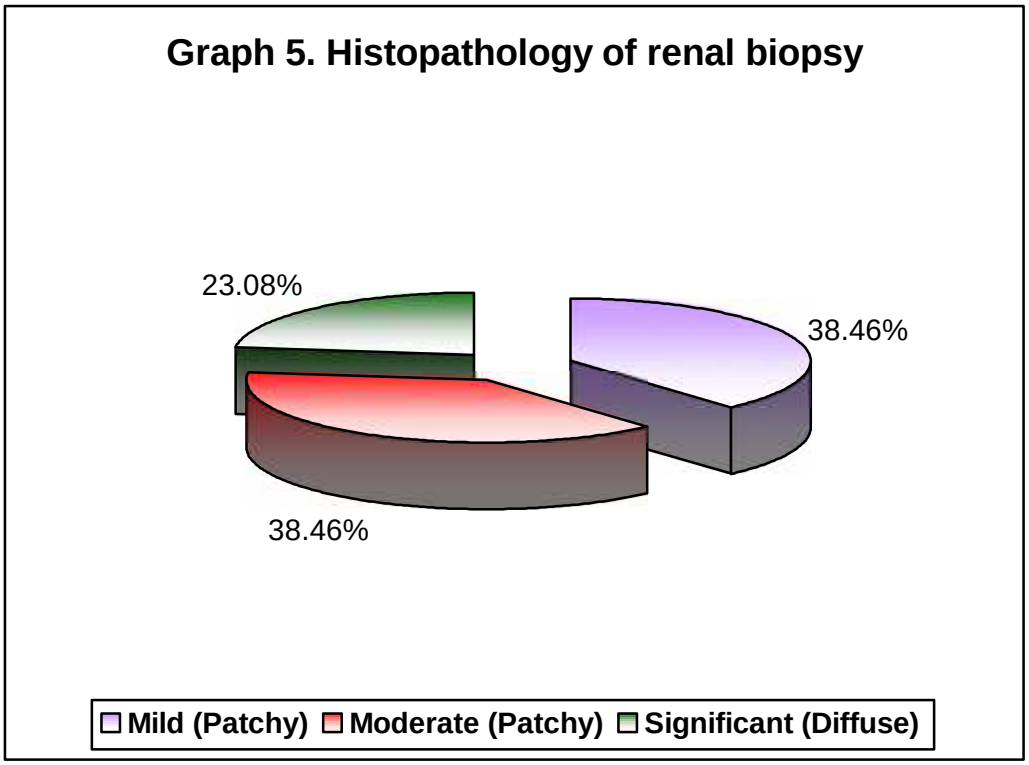
Table 13. Urine culture (n=26)

Organisms	Number	Percentage
Present	04	15.38
Absent	22	84.62

In present study the positive urine culture was seen in four cases (15.38%) and most common organism isolated was Escherechia coli (E. coli). The blood culture examination showed no growth of any organisms.

Table 14. Histopathology of renal biopsy (n=26)

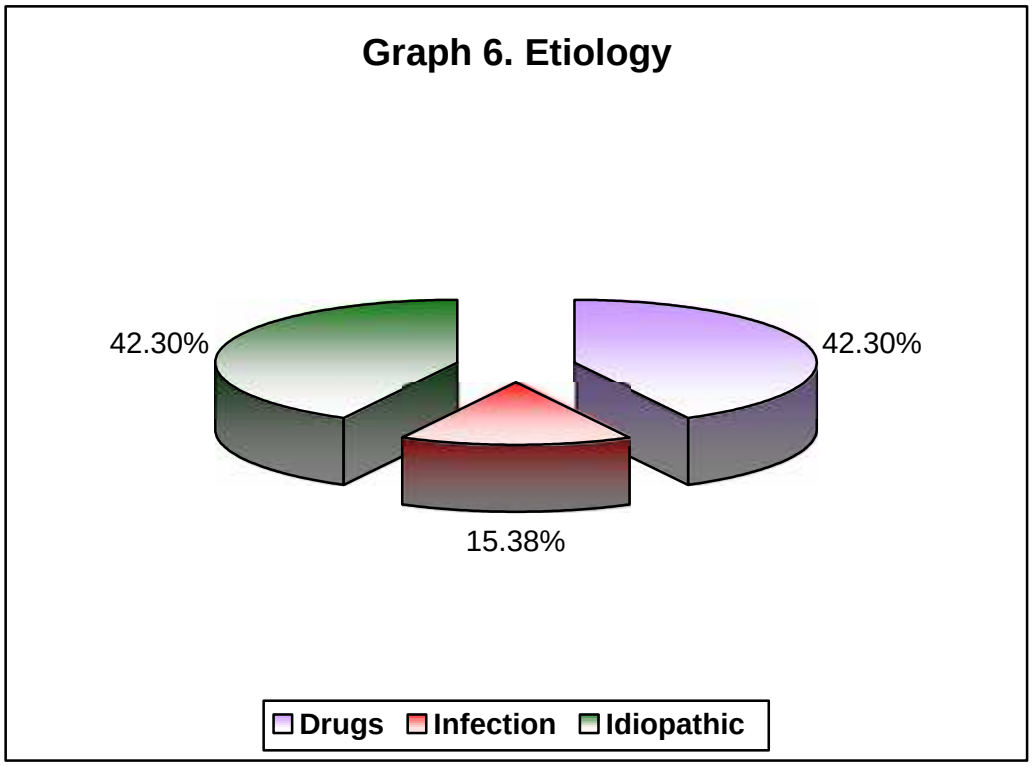
Tubulointerstitial changes	Number	Percentage
Mild (Patchy)	10	38.46
Moderate (Patchy)	10	38.46
Significant (Diffuse)	06	23.08



In present study mild to moderate changes were seen in each of 38.46% patients whereas in 23.08% cases significant tubulointerstitial changes were observed.

Table 15. Etiology (n=26)

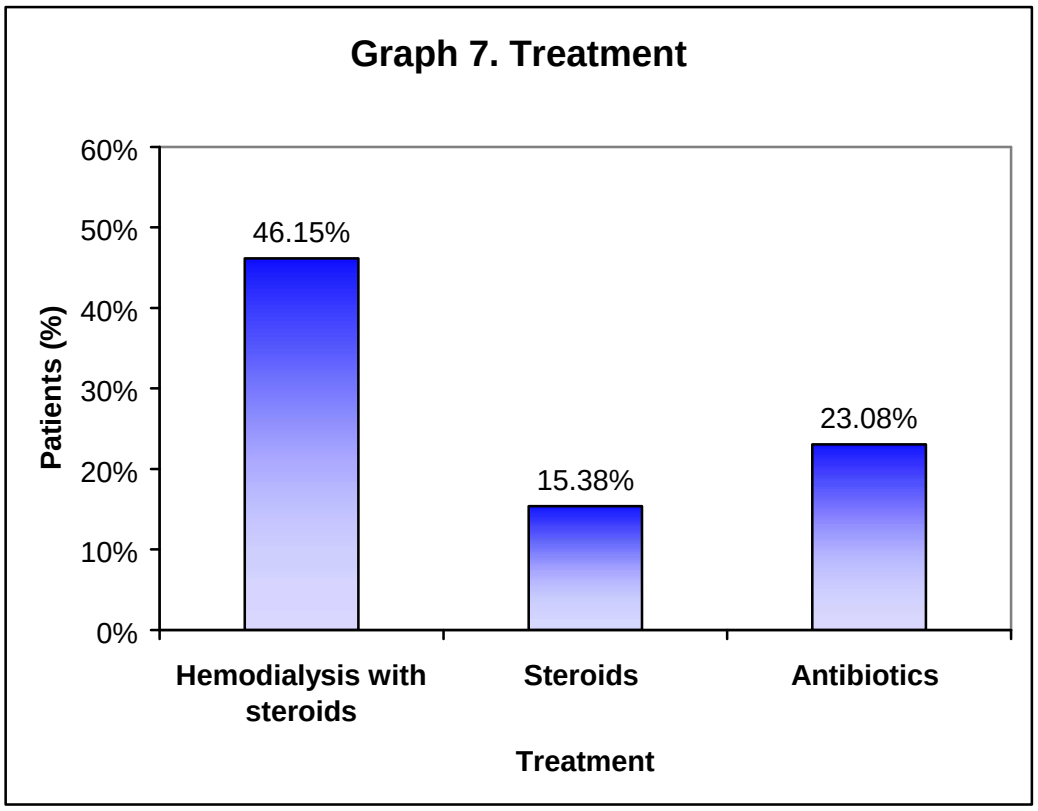
Etiology	Number	Percentage
Drugs	11	42.30
NSAIDS	08	72.72%
Antibiotics	03	27.27%
Infection	04	15.38%
Idiopathic (Without uveitis)	11	42.30



In present study each 42.30% of patients had drug induced AIN and idiopathic (without uveitis). Infections were seen in 15.38%. Among the patients with drug induced AIN, NSAIDS was the predominant (72.72%) cause whereas 27.27% were due to antibiotics.

Table 16. Treatment (n=26)

Treatment	Number	Percentage
Hemodialysis with steroids	12	46.15
Steroids	4	15.38
Antibiotics	06	23.08



In present study out of 26, 46.15% were treated with hemodialysis and steroids, 15.38% required only steroids and 23.08% were treated with antibiotics who had infections.

Table 17. Serum creatinine levels at follow up (n=26)

Serum creatinine levels (mg/dL)	Number	Percentage
Normal (0.5 to 1.3)	11	42.31
1.3 to 2.9	06	23.08
3.0 to 4.9	01	3.85
> 5.0	00	0.00

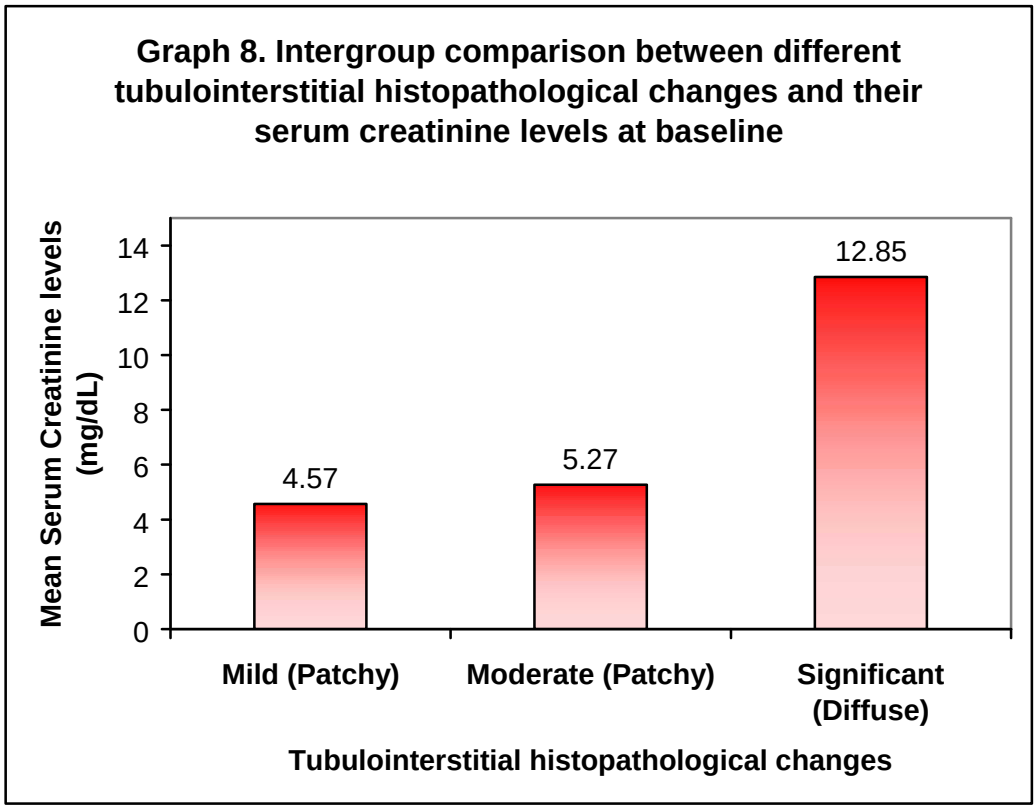
In present study, follow up serum creatinine after treatment at two months were in the normal range among 42.31% patients whereas 23.08% had serum creatinine between 1.3 to 2.9 mg/dL and 3.85% patients had 3.0 to 4.9 (mg/dL).

Table 18. Intergroup comparison between different tubulointerstitial histopathological changes and their serum creatinine levels at baseline (n=26)

Tubulointerstitial changes	Mean Sr. creatinine	
	Mean	**SD**
Mild (Patchy)	4.57	3.03
Moderate (Patchy)	5.27	3.53
Significant (Diffuse)	12.85	6.49

* Comparison between mild and significant group $F_{2,23}$= 8.301; **p=0.002** using Bonterroni multiple comparison test.

** Comparison between moderate and significant group $F_{2,23}$= 8.301; **p=0.006** using Bonterroni multiple comparison test.

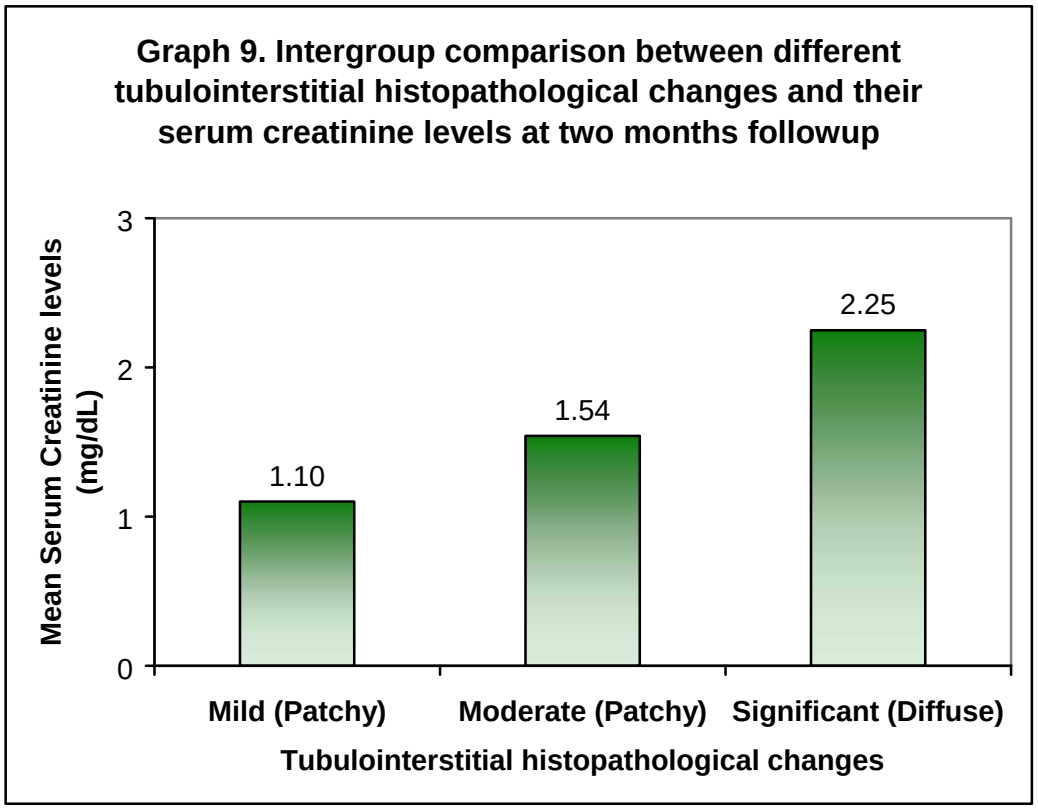


In present study, the mean serum creatinine levels among patients with mild (patchy) tubulouinterstitial histopathological changes were 4.57 ± 3.03, in patients with moderate (patchy) changes 5.27 ± 3.53 and in patients with significant (diffuse) changes mean serum creatinine levels were 12.85 ± 6.49. The comparison between mild and significant group showed significantly increased mean serum creatinine levels (p=0.003) and comparison between moderate and significant group also showed significantly increased mean serum creatinine levels (p=0.006). Comparison of mild to moderate also showed increased mean serum creatinine levels. However this increase was statistically not significant.

Table 19. Intergroup comparison between different tubulointerstitial histopathological changes and their serum creatinine levels at two months followup (n=26)

Tubulointerstitial changes	Mean Sr. creatinine	
	Mean	SD
Mild (Patchy)	1.10	0.37
Moderate (Patchy)	1.54	0.96
Significant (Diffuse)	2.25	0.21

* Comparison between mild and significant group $F_{2,15}$= 2.017; p=0.168 using Bonterroni multiple comparison test.



In present study, the mean serum creatinine levels at two months follow up among patients with mild (patchy) tubulouinterstitial histopathological changes were 1.10 ± 0.37, in patients with moderate (patchy) changes 1.54 ± 0.96 and in patients with significant (diffuse) changes mean serum creatinine levels were 2.25 ± 0.21. Comparison of all the three groups showed decrease in mean serum creatinine levels. However this decrease was statistically not significant.

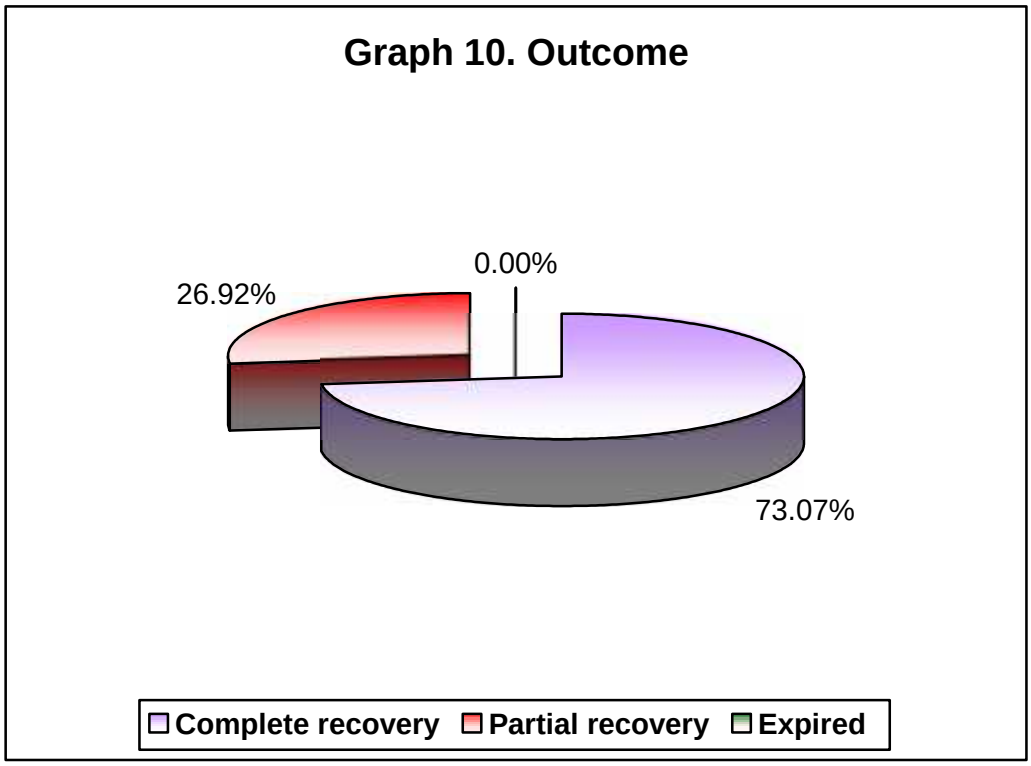
Table 20. Intergroup comparison between different tubulointerstitial histopathological changes and mean reduction in serum creatinine levels from baseline to 2 months follow up (n=26)

Tubulointerstitial changes	Reduction in Mean Sr. creatinine	
	Mean	SD
Mild (Patchy)	3.21	1.21
Moderate (Patchy)	3.23	1.08
Significant (Diffuse)	9.10	0.14

In present study, the mean reduction in serum creatinine levels from baseline to two months follow up among patients with mild (patchy) tubulouinterstitial histopathological changes was 3.21 ± 1.21, in patients with moderate (patchy) changes it was 3.23 ± 1.08 and in patients with significant (diffuse) changes mean serum creatinine levels were 9.10 ± 0.14. Comparison of all the three groups showed decrease in mean serum creatinine levels from baseline to two months followup.

Table 21. Outcome (n=26)

Outcome	Number	Percentage
Complete recovery	19	73.07
Partial recovery	07	26.92
Expired	00	0.00



In present study, all the 26 patients (100%) improved. 73.07% had complete recovery and 26.92% of patients had partial recovery considering on normal serum creatinine levels at two months follow up.

DISCUSSION

Acute tubulointerstitial nephropathy is a preferred term to acute interstitial nephropathy or nephritis because it emphasizes that tubular and interstitial changes are always associated features, whatever the primary process may be.[85]

The incidence of AIN in the biopsy material available for this study was 17.33%, which is higher than the range of generally reported figures (1%-11%, mean 1.8%).[11]

All patients with acute renal failure including those with AIN are not biopsied, since the causative event is often transient and undiagnosed or diagnosed retrospectively. Thus, the true incidence of AIN is underestimated. However increasing trend of incidence reflects increased awareness, availability of better facilities for diagnosis or it may be truly increased incidence which is unknown.

Acute interstitial nephropathy was originally thought to be exclusively infection-induced but it is now recognized to be mainly drug-induced. In the series of biopsy–proven acute tubulointerstitial nephritis described here, 42.30% of the cases were drug-induced, compared to 35% of those reported by Cameron et al.[11] and to a mean of 49% reported in studies from 1974 to 1990 in the study by Schwarz, A et al.[86]

In idiopathic AIN, there was no history of drug usage or other known factors that are likely to cause AIN prior to presentation. In present study among patients with infection and drug induced AIN, 7.69% patients each had partial

recovery whereas 11.53% patients with idiopathic AIN had partial recovery after two months follow up, which was less than the outcome of AIN reported in the literature (26%).[86] This could be due to the smaller sample of the study.

The patient's mean age was 47 years (24-69 years), and 69.23% were men compared to 46.6 years and 56.3% in Bakers study[87] and to 44 years and 56% in Schwarz's Series,[86] thus the patients in the present study were of similar age as that of other studies. The percentage of male patients was higher than that for females and this findings was consistent with the other studies.[86,87]

Uremic symptoms were noted in 50% of the cases reported here, compared to 40% in Schwarz series[86] and some patients had several symptoms like rash in 7.69%, fever in 57.60% and eosinophilia in 3.85% in this study, compared to 50%, 75% and 80% respectively in the study reported by Neilson et al.[8] Recently Baker in his series[87] showed that the symptoms of rash, fever and eosinophilia were present in 14.8%, 35% and 23.3% of patients at presentation, respectively. The findings of this study were in contrast to an earlier series where allergic-type features dominated the clinical picture, which may be explained either by type of drugs (in earlier studies antibiotics were the main causative agents, for example methicillin-induced AIN, while now a wide range of drugs is associated with AIN), or may be due to increased recognition of the disease and earlier discontinuation of the drug. The other reason for this could be patients in present study with AIN were on NSAIDS.

In present study the triad of fever, arthralgia and rash was present in 7.69%, which is slightly less compared to the Bakers series (10%).[87]

The history of hypertension in present study was 30.77% whereas diabetes was present in five (19.23%) cases.

In present study mild anaemia was seen in 73.08% and total counts were raised in 42% of patients. The neutrophilia was seen in 84.62% cases. Similar pattern of haemoglobin (10.5 ± IQR 9.6 to 11.5) was seen in a study conducted by Clarkson et al.[2]

Present study showed positive urine culture in four cases (15.38%) and most common organism isolated was Escherechia coli (E. coli). The blood culture examination showed no growth of any organisms.

In present study 42.30% of patients had drug induced AIN and idiopathic in 42.30%. Infections were seen in 15.38%. Among the patients with drug induced AIN, NSAIDS was the predominant (72.72%) cause whereas 27.27% were due to antibiotics. Whereas a study done by Clarkson et al[2] reported 84% of patients with drug induced AIN, 8% with idiopathic and 15% with other causes. Among the patients with drug induced AIN, 44% had due to NSAIDS and 33% had due to antibiotics. Another study reported drug induced AIN in 71%, infection in 15%, idiopathic in 8%.

In present study mild to moderate (Patchy) changes were seen in each of 38.46% patients whereas in 23.08% cases significant (Diffuse) tubulointerstitial changes were observed.

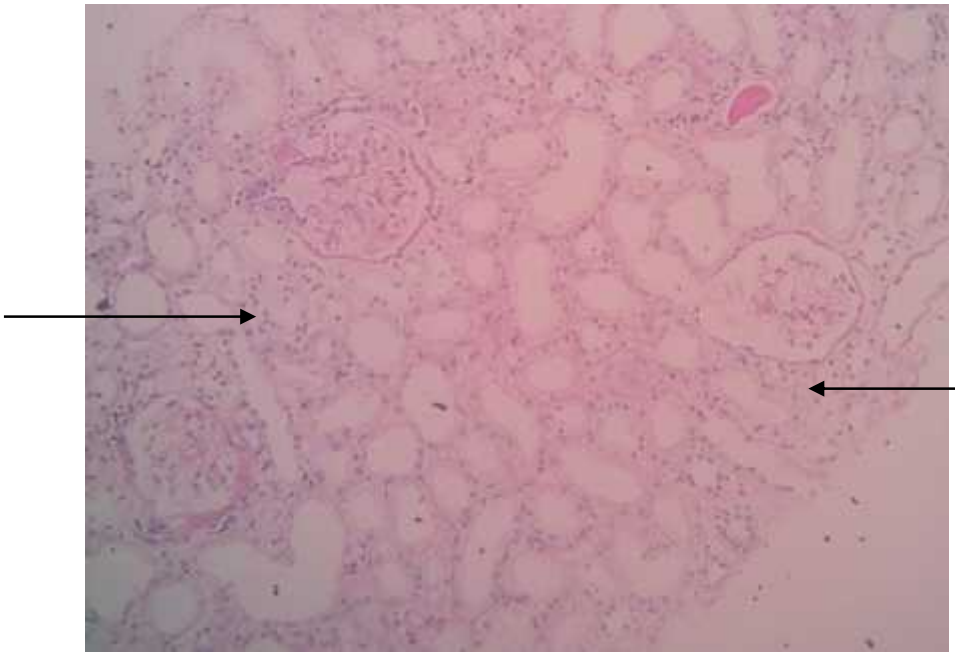


Figure 1. Renal biopsy showing histopathological changes - PAS stain suggestive of patchy (Mild to moderate) changes of AIN

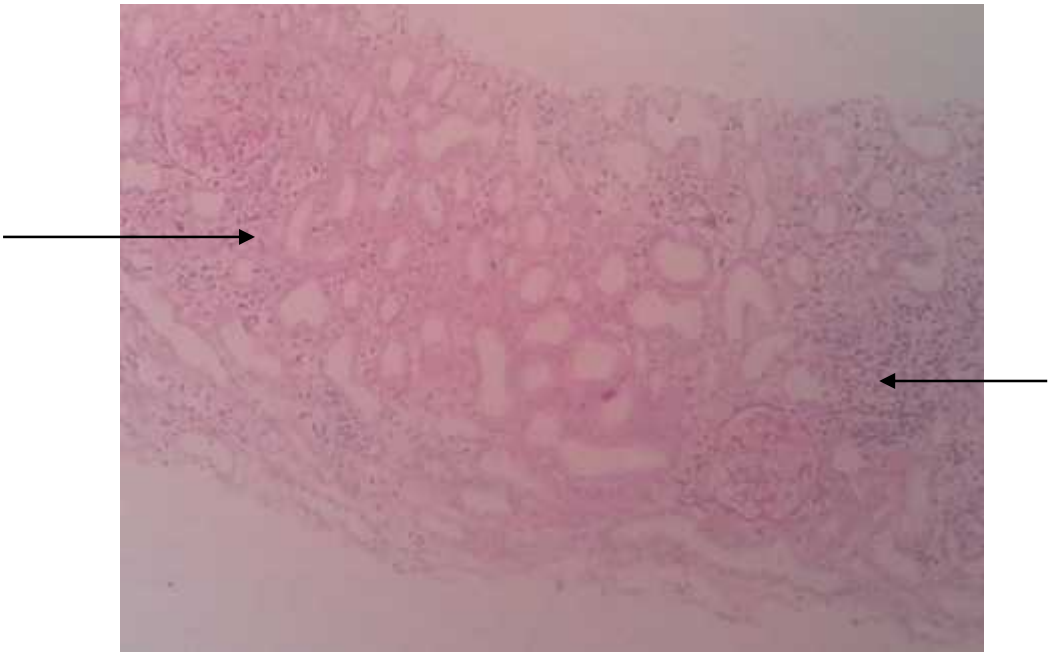


Figure 2. Renal biopsy showing histopathological changes - PAS stain suggestive of diffuse (significant) changes of AIN

The hallmark of AIN is the presence of inflammatory infiltrates within the interstitium on histopathology. These infiltrative lesions may be patchy or diffuse, predominating in the deep cortex and in the outer medulla. They are composed mostly of T lymphocytes, as well as monocytes/macrophages, plasma cells, eosinophils and mast cells. Among T cells present within the interstitium, the relative number of CD4+ cells and CD8+ cells varies from one patient to another.[88] The relative representation of T cells is probably influenced by the type of noxious drug, and the genetic background of the patient.[89]

Present study showed a variable number of infiltrating cells within the renal biopsies and showed no difference between them across the different types of AIN.

In present study, the mean serum creatinine levels among patients with mild (patchy) tubulouinterstitial histopathological changes were 4.57 ± 3.03, in patients with moderate (patchy) changes 5.27 ± 3.53 and in patients with significant (diffuse) changes mean serum creatinine levels were 12.85 ± 6.49. The comparison between mild and significant group showed significantly increased mean serum creatinine levels (p=0.003) and comparison between moderate and significant group also showed significantly increased mean serum creatinine levels (p=0.006).

The mean serum creatinine levels at two months follow up among patients with mild (patchy) tubulouinterstitial histopathological changes were 1.10 ± 0.37, in patients with moderate (patchy) changes 1.54 ± 0.96 and in patients with significant (diffuse) changes mean serum creatinine levels were 2.25 ± 0.21.

Comparison of all the three groups showed decrease in mean serum creatinine levels. However this decrease was statistically not significant but it indicates the recovery depends on histopathological changes.

The mean reduction in serum creatinine levels from baseline to two months follow up among patients with mild (patchy) tubulouinterstitial histopathological changes was 3.21 ± 1.21, in patients with moderate (patchy) changes it was 3.23 ± 1.08 and in patients with significant (diffuse) changes mean serum creatinine levels were 9.10 ± 0.14. Comparison of all the three groups showed decrease in mean serum creatinine levels from baseline to two months follow up.

A study conducted by Clarkson et al[2] reported similar reduction of serum creatinine levels after one month follow-up.

The mainstay of treatment in AIN is supportive therapy. After a presumptive (or biopsy-proven) diagnosis of AIN has been made, any potentially offending drugs should be discontinued, or underlying infections treated. Treatment of AIN would be much more straightforward if it could be diagnosed with a sensitive and specific non invasive test, and if one could reliably determine which agent, in the case of drug-induced AIN, is responsible.

In some patients, the degree of renal insufficiency may be quite significant, and dialytic therapy may be required as a supportive measure. In patients in whom drug discontinuation is not followed by a rapid improvement in renal function one must consider pharmacologic therapy for AIN. In addition, many nephrologists favour early pharmacologic therapy in patients who have a

particularly severe interstitial nephritis, as manifested by either a rapidly rising serum creatinine or diffuse cellular infiltration on renal biopsy, or both. In forms of interstitial nephritis associated with systemic autoimmune disease and glomerulonephritis, pharmacologic therapy is usually appropriate.

Although corticosteroids are the most commonly used immunosuppressive drugs for AIN, there have been no prospective, randomized trials performed to assess the efficacy of this treatment. Evidence for efficacy has come from anecdotal case reports and small, uncontrolled, nonrandomized studies.[8] In a retrospective analysis of 14 patients with methicillin-induced AIN, eight of 14 patients received prednisolone therapy, with an average daily dose of 60 mg for a total mean duration of 9.6 days. Prednisolone therapy was associated with a higher percentage of patients returning to their previous serum creatinine level, a lower average serum creatinine at follow-up, and a shorter time between the peak serum creatinine and its return to a new base line (9.3 versus 54 days).[79] Pusey et al,[90] retrospectively examined seven patients with biopsy-proven AIN treated with high-dose IV methylprednisolone. All responded with onset of diuresis or a spontaneous fall in serum creatinine within 72 hours. In all treated patients, renal function returned to near normal, with creatinine clearances 60 to 90 ml/min. Of the two patients not treated, one recovered renal function slowly, and one progressed to chronic renal insufficiency. There were no detectable adverse effects from the short courses of steroids used in either study.[91] There have been no trials that establish the optimum dosing or duration of corticosteroid therapy. Neilson et al,[8] have recommended a therapy with Prednisolone in an oral dose of approximately 1mg/kg daily, and treatment should be maintained for a

period of approximately 4 weeks. If there has been no significant response by that time, there probably will not be and the drugs should be discontinued.

In this study, 42.30% of the patients were on drugs (causative agents) and same was stopped. 15.38% of the patients received steroid therapy in a dose of 45-60 mg/day for a period of 4-12 weeks, and 46.15% of them received steroids and dialysis together. Overall, 61.53% of this study patients received steroids.

Some have recommended adjunctive therapy with cyclophosphamide at 1 to 2 mg/kg per day, if there is no improvement in serum creatinine after a trial of steroid therapy.[8] Usage of both cyclophosphamide and cyclosporine A to treat AIN is supported by investigations in experimental models of interstitial nephritis,[92] but there are no clinical trails in man.

Plasmapheresis may be considered as adjunctive therapy along with prednisolone or cyclophosphamide in those in whom anti-TBM antibodies are demonstrable in the renal biopsy.

Because AIN is associated with diverse aetiologies, it is difficult to establish a general prognosis for all causes of AIN. Most of the available information on outcomes is derived from patients with probable drug-induced AIN. In general, if drug-associated AIN is detected early (within 1 week of the rise in serum creatinine), and the drug is promptly discontinued, the long-term outcome is favourable for a return to baseline serum creatinine.

The inflammatory lesion of AIN can become a lesion characterized by fibrosis and tubular atrophy, hallmarks of chronic interstitial nephritis, if the

inciting factors persist. Laberke and Bohle compared clinical and morphological findings in 30 cases of AIN, all of which had been confirmed by renal biopsy, to determine whether histological findings could provide conclusive information regarding the course and prognosis of AIN.[93] This was a retrospective study and serum creatinine values were used as clinical criteria for evaluating course and prognosis of disease. The findings suggested that it is important to differentiate histologically between AIN cases with diffuse infiltration and those with patchy and/or incompletely diffuse infiltration. Prognosis is significantly better for the latter. The presence of 1 to 6% neutrophils in the infiltrate also correlated with an adverse prognosis. Patients with AIN accompanied by acute renal failure of more than three weeks duration had a poorer prognosis for complete recovery of renal function.

In present study, all the 26 patients (100%) improved. 73.07% had complete recovery and 26.92% of patients had partial recovery considering on normal serum creatinine levels at two months follow up.

CONCLUSION

This study confirms that AIN remains an important cause of acute renal failure and that it is mainly drug-induced, with non-steroidal drugs being particularly implicated.

The clinical spectrum has changed since the time when methicillin was the commonest culprit with less overt hypersensitivity responses occurring.

The most common clinical presentations were oliguria, malaise, anorexia, fever and arthralgia. Rashes and flank were only in few cases.

Continuing vigilance is required to identify the emergence of new toxic compounds that cause AIN.

Renal biopsy remains an essential tool in diagnosis. Patients with diffuse (significant) histopathological tubulointerstitial changes had significantly increased serum creatinine levels causing delayed and incomplete recovery compared to patchy (mild and moderate) changes.

Renal outcome will usually be good, if recognized early and treated adequately.

SUMMARY

Acute interstitial nephropathy, a rather uncommon disease that was occurred at a relatively stable rate over the years and associated with increased morbidity, direct and indirect health care costs. Incidence is increasing and no studies have been done in the present setting. Hence the present study was undertaken to know the clinical profile and causes of AIN which will help to study the course of the disease, clinical spectrum and its management.

The present study was conducted in the Department of Medicine and Nephrology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 26 patients suspected to have AIN on clinical grounds and proven by renal biopsy presenting during the period of January 2009 to December 2009. Renal functional tests such as blood urea, serum creatinine, serum electrolytes, and liver function tests were conducted and recorded. In all patients in whom a percutaneous renal biopsy was performed platelet count, prothrombin time (or INR), partial thromboplastin time and Blood Group was established before the procedure was undertaken.

A total 150 biopsies were done during the study period of which 26 (17.33%) had AIN. Males (69.23%) outnumbered females (30.77%) with male to female ratio of 2.25:1. Majority (50%) had age between 45 to 60 years. The most common clinical presentation was oliguria (84.62%) followed by malaise and anorexia (76.92% each). Out of 26 cases with AIN 11 (42.30%) cases had drug history. Out of 26 cases majority (57.69%) patients had serum creatinine levels more than 5.0 mg/dL. Mild to moderate changes were seen in each of 38.46%

patients whereas in 23.08% cases significant tubulointerstitial changes were observed. In this study each 42.30% of patients had drug induced AIN and idiopathic. Infections were seen in 15.38%. Among the patients with drug induced AIN, NSAIDS was the predominant (72.72%) cause whereas 27.27% were due to antibiotics. All the 26 patients (100%) improved and 73.07% had complete recovery.

This study confirms that AIN remains an important cause of acute renal failure and that it is mainly drug-induced, with non-steroidal drugs being particularly implicated. Patients with diffuse (significant) histopathological tubulointerstitial changes had significantly increased serum creatinine levels causing delayed and incomplete recovery compared to patchy (mild and moderate) changes.

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ANNEXURE I – CONSENT FORM

"A CROSS SECTIONAL STUDY TO KNOW THE PROFILE OF PATIENTS WITH ACUTE INTERSTITIAL NEPHROPATHY ATTENDING KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE"

Objective and purpose of the study

This research is intended to study clinical, laboratory and histopathological features in acute interstitial nephropathy and to correlate clinical and laboratory profile with histopathological diagnosis. The principal investigator of the study is Dr. ******* ******** under the guidance of Dr. ****** **********. My co-operation will be of great help to patients with acute interstitial nephropathy in future.

Procedure

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood, urine samples and undergo renal biopsy.

Risk and Benefits

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations which may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn and other complications during renal biopsy like hematuria, perirenal haematoma.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop my participation in this study any time. If you choose not to take part in the study you will receive the standard treatment.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about your rights as a participant you may call Principal and Chairman, J.N.M.C Ethical Committee for Human Research phone number 0831-2471350.

In case of the queries during study or in future you may contact following person

Principal investigator : Dr. ****** *******

Guide : Dr. ****** *******

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant: _____ Signature _____ / Thumb print

Name of the Witness _____ Signature _____

Investigator Name _____ Signature _____

Date: Place:

ANNEXURE II – PROFOMA

Name :

Age / Sex / IP No :

Occupation :

Marital Status :

Socio economic status :

Address :

Provisional Diagnosis :

Final diagnosis :

Presenting complaints

Sl. No.	Symptoms	Yes	No	Remarks
1	Fever / Malaise / Anorexia			
2	Oliguria			
3	Hematuria			
4	Nausea / vomiting			
5	Rash			
6	Arthralgia			
7	Flank pain			

Past History **:** Diabetes Mellitus/Hypertension/Jaundice/

Ischaemic Heart Disease / renal disease

Drug History **:** Ayurvedic, Homoeopathic, Alophathic (NSAIDS, Antibiotics, others)

Family history **:** History of renal disease in the family

Personal history

Diet :

Appetite :

Sleep :

Habits :

GENERAL PHYSICAL EXAMINATION

Pulse : Respiratory Rate :

Blood pressure: Temperature :

Pallor, Icterus, clubbing, cyanosis, lymphadenopathy, edema, rashes

SYSTEMIC EXAMINATION

Per Abdomen

Inspection

Palpation

Percussion

Auscultation

Respiratory system

Inspection

Palpation

Percussion

Auscultation

Cardiovascular system

Inspection

Palpation

Percussion

Auscultation

Central nervous system

INVESTIGATIONS

Haemogram

Hb% :

TC :

DC :

ESR :

Absolute eosinophil count

Urine Routine

Routine:

Microscopy:

Urine for eosinophils

Renal function tests

Blood urea:

Sr. creatinine:

Sr. electrolytes:

Liver function tests

USG abdomen

`

Culture and sensitivity test for blood and urine:

Renal Biopsy:

Any other:

Treatment given:

Follow up:

MASTER CHART

Sl. No.	IP No.	Demography		Presenting complaints											History																General Physical examination										Systemic examination			
															Past History					Drug				Personal																						
		Gender	Age (Years)	Fever	Malaise	Anorexia	Oliguria	Hematuria	Nausea	Vomiting	Rashes	Arthralgia	Flank pain	Diabetes mellitus	Hypertension	Jaundice	Ischaemic heart disease	Renal disease	NSAIDS	Antibiotics	Others	Family	Diet	Appetite	Sleep	Habits	Pulse rate (/min)	Respiratory Rate (/min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Temperature	Edema	Rashes	Pallor	Cyanosis	Per abdomen	Respiratory system	Cardiovascular system	Central nervous system
1	256038	M	26	+	+	+	+	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	Mx	D	D	-	78	20	150	90	N	-	-	-	-	N	N	N	N
2	255241	M	45	+	+	+	+	-	+	+	-	+	-	-	-	-	-	-	+	-	-	-	Mx	D	D	-	86	20	110	80	N	-	-	-	-	N	N	N	N
3	263894	F	58	+	+	+	+	+	+	+	-	-	-	+	+	-	-	+	-	-	-	-	V	D	N	-	80	20	110	70	N	-	-	-	-	N	N	N	N
4	270162	F	25	-	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	V	D	N	-	90	20	130	80	N	+	-	-	-	N	N	N	N
5	268558	M	68	-	+	+	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	V	D	D	-	88	22	110	70	N	-	-	-	-	N	N	N	N
6	278537	F	55	-	-	-	+	-	+	+	-	-	-	-	-	-	-	+	-	-	-	-	V	D	N	-	90	24	130	80	N	+	-	-	-	N	N	N	N
7	264529	M	39	-	-	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	Mx	N	N	-	86	12	130	80	N	+	-	-	-	N	N	N	N
8	285847	M	62	+	+	+	+	+	+	+	-	+	+	+	-	-	-	+	+	-	-	-	V	D	N	-	110	24	130	80	F	+	-	-	-	T	N	N	N
9	293190	M	53	+	+	+	+	-	+	+	-	-	+	-	+	-	-	-	+	-	-	-	Mx	D	N	-	88	20	170	100	N	+	-	-	-	N	N	N	N
10	295921	M	40	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	Mx	D	N	-	80	18	110	70	N	-	-	-	-	N	N	N	N
11	293135	M	69	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	+	-	-	-	Mx	N	N	-	90	18	150	80	N	+	-	-	-	N	N	N	N
12	302425	M	50	+	+	+	+	-	+	+	-	-	-	-	-	-	-	-	-	+	-	-	N	N	N	-	86	18	140	90	N	-	-	-	-	N	N	N	N
13	318490	M	45	-	-	-	-	-	+	+	-	-	-	-	+	-	-	-	-	-	-	-	Mx	D	N	-	84	18	130	70	N	-	-	-	-	N	N	N	N
14	301656	M	37	+	+	+	+	-	+	+	-	-	-	+	-	-	-	-	-	+	-	-	Mx	D	N	-	42	22	110	70	N	-	-	-	-	N	N	N	N
15	313099	M	32	-	-	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	N	N	N	-	90	20	130	80	N	+	-	-	-	N	N	N	N
16	341441	F	47	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	V	N	N	-	90	22	120	80	N	+	-	-	-	N	N	N	N
17	339338	M	64	+	+	+	+	+	-	-	-	+	-	-	-	-	-	-	+	-	-	-	Mx	D	N	-	84	18	150	90	N	-	-	-	-	N	N	N	N
18	303802	M	53	+	+	+	+	+	-	-	-	-	-	-	+	-	-	-	-	+	-	-	Mx	D	N	-	84	20	180	90	N	-	-	-	-	N	N	N	N
19	360994	M	43	+	+	+	+	+	+	+	-	-	-	+	+	-	-	+	-	-	-	-	V	D	D	-	130	26	150	90	F	+	-	-	-	N	N	N	N
20	348110	M	51	+	+	+	+	-	+	+	-	+		+	+	-	-	-	+	-	-	-	V	N	N	-	84	24	110	70	N	-	-	-	-	N	N	N	N
21	297181	M	38	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Mx	D	N	-	74	24	140	90	N	+	-	-	-	N	N	N	N
22	268579	F	53	-	+	+	+	-	+	+	-	-	-	-	+	-	-	+	-	-	-	-	V	D	N	-	80	20	180	100	N	+	-	-	-	N	N	N	N
23	257591	F	45	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	V	D	D	-	70	18	117	80	N	+	-	-	-	T	N	N	N
24	250063	F	60	+	+	+	+	-	+	+	-	+	-	-	-	-	-	-	+	-	-	-	V	D	D	-	84	18	160	90	N	+	-	-	-	T	N	N	N
25	251014	M	24	-	+	+	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	Mx	D	N	-	76	18	150	90	N	+	-	-	-	N	N	N	N
26	227341	F	50	+	+	+	+	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	V	D	N	-	80	20	130	90	N	+	-	-	-	T	N	N	N

MASTER CHART

Sl. No.	IP No.	Investigations																							Diagnosis		Treatment				Outcome		
				Differential						Urine			Renal function tests									Renal Biopsy											
											Microscopy				Sr. Electrolytes							TIC										
		Haemoglobin (gm%)	Total count (/mm^3)	Neutrophils (%)	Lymphocytes (%)	Eosinophils (%)	Monocytes (%)	ESR (mm/1st hour)	AEC (/mm^3)	Routine	WBCs (/hpf)	RBCs (/hpf)	Blood urea (mg/dL)	Sr. Creatinine (mg/dL)	Sr. Sodium (mg/dL)	Sr. Potassium (mg/dL)	Sr. Bicarb (mg/dL)	Sr. Chloride (mg/dL)	Liver function test	USG Abdomen (RPC)	Blood culture	Urine culture	Mild	moderate	Significant	Provisional	Final	Fluid restriction	steroids	Haemodialysis	Antibiotics	Time interval for recovery (Mo	Follow-up Sr Creatinine (mg/dL	Outcome
1	256038	13	10000	75	13	3	9	20	##	A2+	5-6	-	99	10.5	134	4.4	20	110	N	GI	N	N	+	-	-	RPRF-AIN	AIN	+	+	+	-	2	1	I
2	255241	9.9	11300	81	10	1	8	22	##	AT	5-6	-	224	6.6	131	4.3	23	93	N	GI	N	N	-	+	-	RPRF-AIN	AIN	+	+	+	-	2	1	I
3	263894	11	11400	71	21	3	5	20	##	AT	5-8	5 - 8	156	2.5	120	4.2	16	87	N	N	N	N	-	+	-	DM, HTN, UTI, ARF	AIN	+	-	-	-	1	2	I
4	270162	9.5	8300	80	14	1	5	24	80	A1+	5-6	8 - 10	130	1.4	124	4.6	16	98	N	N	N	N	+	-	-	ARF-AIN	AIN	+	-	-	-	2	1	I
5	268558	11	24600	69	22	3	6	22	##	AT	5-6	-	124	5.7	116	5.1	16	90	N	GI	N	N	-	-	+	ARF, SEP	AIN	+	-	-	+	2	-	I
6	278537	8.2	11300	79	12	2	7	68	##	A1+	10-15	-	137	7.9	126	4.7	17	99	N	GI	N	E.c	-	+	-	ARF, CRF	AIN	+	+	+	+	2	2	I
7	264529	15	9400	72	20	1	4	10	44	AT	5-6	-	54	1.6	144	5.8	21	104	N	N	N	N	-	+	-	ARF	AIN	+	-	-	-	1	1	I
8	285847	14	14200	86	12	1	2	18	##	N	10-15	PL	98	5.0	130	3.9	16	100	N	GI	N	E.c	-	-	+	ARF, PYNPH, NSAID-AIN, DM2	AIN	+	-	+	+	2	-	I
9	293190	13	10000	78	14	0	8	18	##	AT	5-6	-	84	7	128	4	18	86	N	GI	N	N	+	-	-	ARF-AIN	AIN	+	+	-	+	1	1	I
10	295921	12	5800	70	22	2	6	18	##	AT	5-6	8 - 10	68	2.2	134	2.5	18	12	N	N	N	N	+	-	-	AIN	AIN	+	+	-	-	1	1	I
11	293135	11	10000	76	14	1	5	18	##	A2+	PL	-	128	4.8	132	5	16	98	N	N	N	N	+	-	-	HTN, ARF-NSAIDS-AIN	AIN	+	+	+	-	1	-	I
12	302425	13	11000	88	10	7	1	18	##	AT	10-12	-	133	5.6	140	6.6	17	109	N	GI	N	N	+	-	-	UTI-ARF-AIN	AIN	+	+	+	-	2	1	I
13	318490	13	8400	74	20	1	5	16	##	N	5-6	-	96	2.0	134	3.8	16	102	N	N	N	N	+	-	-	HTN, ARF	AIN	+	-	-	-	1	2	I
14	301656	11	29800	92	4	0	4	38	##	A2+	20-30	-	338	18.3	130	4.8	7	100	N	GI	N	E.c	-	-	+	UTI-ARF-AIN	AIN	+	+	+	-	2	2	I
15	313099	9.8	11800	82	12	1	4	14	##	N	5-6	-	125	2.1	137	4.6	11	103	N	N	N	N	-	+	-	RPRF-AIN	AIN	+	+	+	-	2	1	I
16	341441	11	6400	80	15	1	4	10	##	N	5-6	-	130	2.2	132	4.5	18	101	N	N	N	N	-	+	-	DM2, ARF-NSAID-AIN	AIN	+	+	-	-	1	1	I
17	339338	9.6	15500	84	12	1	3	14	##	A1+	PL	12 - 15	196	11.4	141	5.9	12	109	N	GI	N	N	-	+	-	UTI, ARF-AIN	AIN	+	+	+	-	2	2	I
18	303802	13	1500	80	14	1	4	20	##	A2+	5-6	8 - 10	239	18.7	130	6.4	13	98	N	GI	N	N	-	-	+	ARF-AIN	AIN	+	-	+	-	2	-	I
19	360994	8	8400	80	16	1	3	20	98	A1+	10-15	12 - 14	90	11	130	5.6	12	102	N	GI	N	N	-	-	+	ARF, CRF, HTN, DM, IHD, UTI	AIN	+	-	+	-	2	-	I
20	348110	8.5	10400	80	10	1	9	22	80	A1+	10-15	-	188	8.7	130	5.4	16	98	N	GI	N	N	-	+	-	UTI, DM, HTN, ARF	AIN	+	-	+	+	2	4	I
21	297181	15	9400	##	22	2	6	28	70	A2+	10-12	-	40	3.0	127	4.7	18	90	N	N	N	N	+	-	-	ARF, AIN	AIN	+	+	-	-	2	1	I
22	268579	11	11900	90	6	0	4	70	24	N	5-6	-	364	18.4	117	4.7	12	85	N	GII	N	N	-	-	+	ARF, HTN, IHD	AIN	+	-	+	-	2	2	I
23	257591	11	5000	67	23	2	8	20	60	A2+	20-25	10 - 12	74	7.4	127	6.3	18	102	N	N	N	E.c	-	+	-	ARF-AIN, UTI	AIN	+	+	+	-	2	1	I
24	250063	9.7	20400	77	12	1	10	18	##	N	5-6	-	104	7.4	123	4.8	22	88	N	N	N	N	+	-	-	RPRF-AIN	AIN	+	+	+	-	2	-	I
25	251014	14	8400	72	18	2	8	18	80	N	5-6	-	50	1.8	130	4	18	98	N	N	N	N	+	-	-	ARF	AIN	+	+	+	-	1	-	I
26	227341	12	12400	83	9	2	6	18	##	A1+	5-6	-	45	2.3	120	4.2	16	80	N	GI	N	N	-	+	-	ARF	AIN	+	+	+	+	2	-	I

ANNEXURE III - KEY TO MASTER CHART

-	-	Absent
+	-	Present
A	-	Albumin
AEC	-	Absolute eosinophil count
AIN	-	Acute interstitial nephropathy
ARF	-	Acute renal failure
AT	-	Albumin traces
BP	-	Blood pressure
CRF	-	Chronic renal failure
d	-	Deci
D	-	Decreased
DM	-	Diabetes mellitus
E. Coli	-	Escherachia coli
ESR	-	Erythrocyte sedimentation rate
F	-	Female
GI	-	Grade I
GII	-	Grade II
gm	-	Gram
Hg	-	Mercury
hpf	-	High power field
HTN	-	Hypertension
IHD	-	Ischaemic heart disease
IP. No.	-	In patient number

L	-	Litre
M	-	Male
mg	-	Milli gram
min	-	Minute
mm	-	Millimeter
Mx	-	Mixed
N	-	Normal
NSAIDS	-	Non steroidal anti inflammatory agents
PYNPH	-	Pyelonephritis
RBC	-	Red blood cell
RPC	-	Renal parenchymal changes
RPRF	-	Rapidly progressive renal failure
SEP	-	Sepsis
Sl. No.	-	Serial number
Sr.	-	Serum
T	-	Tenderness
TIC	-	Tubulo interstitial changes
UTI	-	Urinary tract infection
V	-	Vegetarian
WBC	-	White blood cell