*Dissertation On*

# CLINICAL PROFILE OF ACUTE KIDNEY INJURY IN ICU PATIENTS

*Submitted in partial fulfillment of requirements for*

***M. D. DEGREE BRANCH I IN GENERAL MEDICINE***

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*DR. M. G. R. MEDICAL UNIVERSITY, CHENNAI*

***MADRAS MEDICAL COLLEGE &***

***GOVT. GENERAL HOSPITAL***

***CHENNAI – 600 003.***

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## CERTIFICATE

This is to certify that this dissertation entitled **"CLINICAL PROFILE OF ACUTE KIDNEY INJURY IN ICU PATIENTS"** submitted by Dr. C. K. AARTHI, appearing for Part II M.D. Branch I General Medicine Degree examination in April 2011 is a bonafide record of work done by her under my direct audience and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai.I forward this to the Tamil Nadu Dr. M. G. R. Medical University, Chennai, Tamil Nadu, India.

**PROF.C.RAJENDIRAN,M.D.,**
Director,
Institute of Internal Medicine,
Government General Hospital,
Chennai – 600 003.

**PROF.E.DHANDAPANI,M.D.,**
Professor of Medicine
Madras Medical College
Chennai – 600 003.

**PROF.J.MOHANASUNDARAM M.D,D.N.B.,Ph.D**
Dean
Madras Medical College,Chennai-3

# DECLARATION

I solemnly declare that the dissertation titled **"CLINICAL PROFILE OF ACUTE KIDNEY INJURY IN ICU PATIENTS"** is done by me at Madras Medical College & Govt. General Hospital, Chennai during 2008-2011 under the guidance and supervision of the dissertation is submitted to The Tamil Nadu **Dr. M. G. R. Medical University** towards the partial fulfillment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

Place:
Date:

**Dr. C. K. Aarthi**
M.D. General Medicine
Postgraduate Student
Institute of Internal Medicine
Madras Medical College

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# CONTENTS

# Introduction

Acute kidney injury (AKI) is a common clinical problem in intensive care unit (ICU) patients and independently predicts poor outcome.[1-4] Recently, two large multi-centre cohort studies[5,6] reported the occurrence of AKI in an estimated 36% of all patients admitted to the ICU. Moreover, additional observational data indicate that the incidence of AKI is rising.[7,8]

# Aims and objectives of the study

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- Analysis of the clinical spectrum of AKI patients in ICU;
- Identify the cause, risk and prognostic factors for AKI;
- Analysis of the final outcome of the patients with AKI.

# Review of literature

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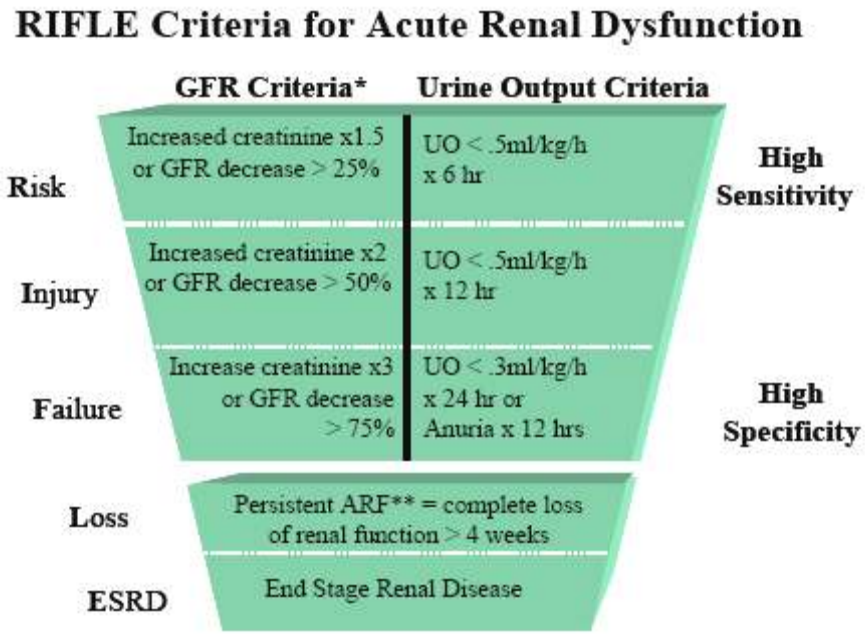
**Definition**

Acute kidney injury is sudden decrease in Glomerular Filtration Rate (GFR) occurring over a period of hours to days resulting in failure of kidney to excrete nitrogenous waste products and maintain fluid and electrolyte homeostasis.

Practically and for clinical trials the definition of AKI is done as per the RIFLE criteria given below:




***(Source : Results of the second Acute Dialysis Quality Initiative consensus conference (May 2002).***

**RIFLE criteria for acute renal dysfunction**

A revision of the criteria was proposed by the Acute Kidney Injury Network (AKIN) - a group representing members of Acute Dialysis Quality Initiative, nephrology and critical care societies. The proposed diagnostic criteria for AKI is an abrupt (within 48 hours) reduction in kidney function defined as an absolute increase in serum creatinine (level of > 26.4 mmol/L (0.3 mg/dl) or a percentage increase in serum creatinine level of > 50% (1.5 fold from baseline) or a reduction in urine output (documented oliguria of < 0.5 ml/kg/hour for > 6 hours. (These criteria should be applied in the context of the clinical presentation and following adequate fluid resuscitation when applicable).

**Epidemiology**

The first case report of fatal AKI is accredited to Hackradh, a German pathologist in 1917 and was based on soldiers who sustained severe traumatic injuries. The concept of AKI in a previously normal kidney was better understood during and after the Second World War. In 1941, Bywaters and Beall described crush injury syndrome in a victim from London[81].Subsequent studies showed acute, potentially reversible failure of renal function with histological features of Acute Tubular Necrosis (ATN),

and also due to other causes such as mismatched blood transfusion, abortion, cardiovascular collapse, sepsis and a variety of nephrotoxic substances.

In recent years, new causes which have been reported included Hantaan virus, ingestion of raw fish, quinine hypersensitivity, ecstacy, HIV infection, inhalation of myotoxin, gelatin infusion and herbal medicine.[12,13]

Nash et al 2002 using same AKI defining criteria at a different institute reported frequency of AKI in hospitalized patients has increased to 7.2%. In-hospital mortality rate was 19.4%. Major causes identified were decreased renal perfusion (39%), nephrotoxin administration (16%), contrast administration (16%),major surgery(9%). Liano et al 1996 Madrid did study in 13 centers covering 2.4 million people .Overall incidence of AKI was 200 cases /million. ATN-45%;Prerenal-21%; Acute on CKD-12.7%; obstructive-10%. Mortality was higher in AKI patients (45%) to other patients admitted (5.4%). Ostermann.M.Chang RW:CCM 2007 showed AKI as an independent risk factor for death . Patients don't just die with AKI they die because of AKI. They detected the following:

RIFLE class F have a mortality of 57%;

RIFLE class I have a mortality of 45%;

RIFLE class R have a mortality of 2%;

Compared to 8.4% of patients with out AKI.

The etiology of AKI varies from place to place . While in our country,Sepsis is the commonest cause. The incidence of insect bite induced AKI is higher in North India.[33]While leptospiral AKI is commonly encountered in kerala and Chennai,Malarial AKI is common in eastern India.[42]About 25 to 35 percent of all medical ARF in African Hospitals develops following ingestion of herbal medicines (Joubert and Sebata, 1982)[36]. In India true incidence of ARF due to chemicals and herbal medicines is not available. Even in case of snake bite, information on the precise incidence of ARF in different geographical regions is lacking. The reported incidence from other countries varies between 1 and 27%.

**Incidence**

AKI complicates approximately 5-7% of hospital admissions and upto 30% of admission to ICU[18]. Retention of nitrogenous waste products, oliguria (urine output- 400ml/d) contributing to extra cellular fluid overload and electrolyte and acid base abnormality are frequent clinical features. AKI is usually asymptomatic and diagnosed when biochemical monitoring of hospitalized patients reveal a new increase in blood urea and serum creatinine concentration.

For the purpose of diagnosis and management,AKI has been divided into three categories:

1. Disease characterized by renal hypoperfusion in which integrity of renal parenchyma is preserved (Prerenal);
2. Diseases involving renal parenchymal tissue (Intrarenal);
3. Diseases involving acute obstruction of urinary tract (postrenal).

AKI is often considered to be reversible, although a return to baseline serum creatinine concentration post injury might not be always possible. To detect clinically significant irreversible damage that may ultimately contribute to chronic kidney disease and AKI has a significant in-hospital morbidity and mortality, the latter in the range of 30-60 % depending on the clinical setting and presence or absence of non renal organ dysfunction.[6]

**Etiology and Pathophysiology**

AKI may be classified into 3 general categories, as follows:

- Prerenal — as an adaptive response to severe volume depletion and hypotension, with structurally intact nephrons;
- Intrinsic — in response to cytotoxic, ischemic, or inflammatory insults to the kidney, with structural and functional damage;
- Postrenal — from obstruction to the passage of urine.

While this classification is useful in establishing a differential diagnosis, many pathophysiologic features are shared among the different categories.

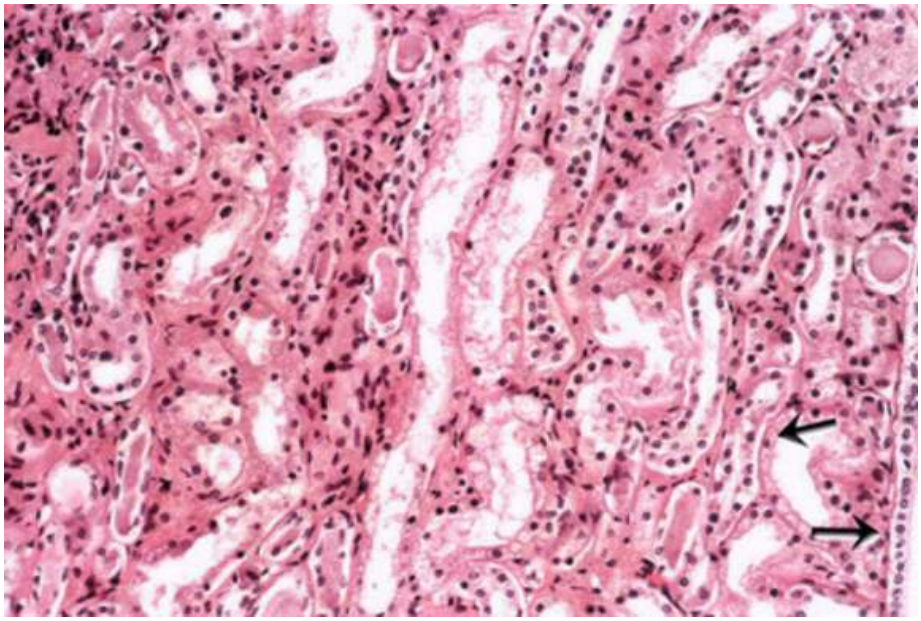
Patients who develop AKI can be oliguric or non oliguric, have a rapid or slow rise in creatinine levels, and may have qualitative differences in urine solute concentrations and cellular content. This lack of a uniform clinical presentation reflects the variable nature of the injury. Classifying AKI as oliguric or non oliguric based on daily urine excretion has prognostic value. Oliguria is defined as a daily urine volume of less than 400 mL/d and has a worse prognosis, except in prerenal failure. Anuria is defined as a urine output of less than 100 mL/d and, if abrupt in onset, suggests bilateral obstruction or catastrophic injury to both kidneys. Stratification of renal failure along these lines helps in decision-making (eg, timing of dialysis) and can be an important criterion for patient response to therapy.

**Pre renal AKI**

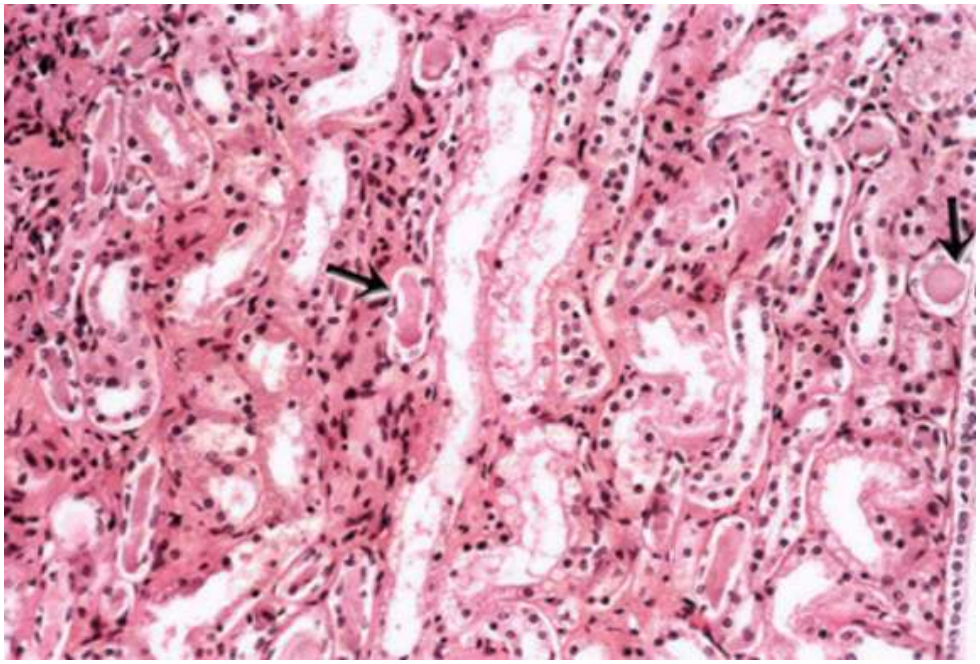
Pre renal AKI represents the most common form of kidney injury and often leads to intrinsic AKI if it is not promptly corrected. Volume loss from Gastrointestinal tract, renal, cutaneous (eg, burns) and internal or external hemorrhage can result in this syndrome. Pre renal AKI can also result from decreased renal perfusion. Liano et al found prerenal AKI responsible for 48% of community acquired AKI and 58% of hospital acquired AKI.[6] Volume depletion and congestive heart failure increased the odds ratio of hospital acquired AKI by 9.4 and 9.2 fold respectively.[6]

**Intrinsic AKI**

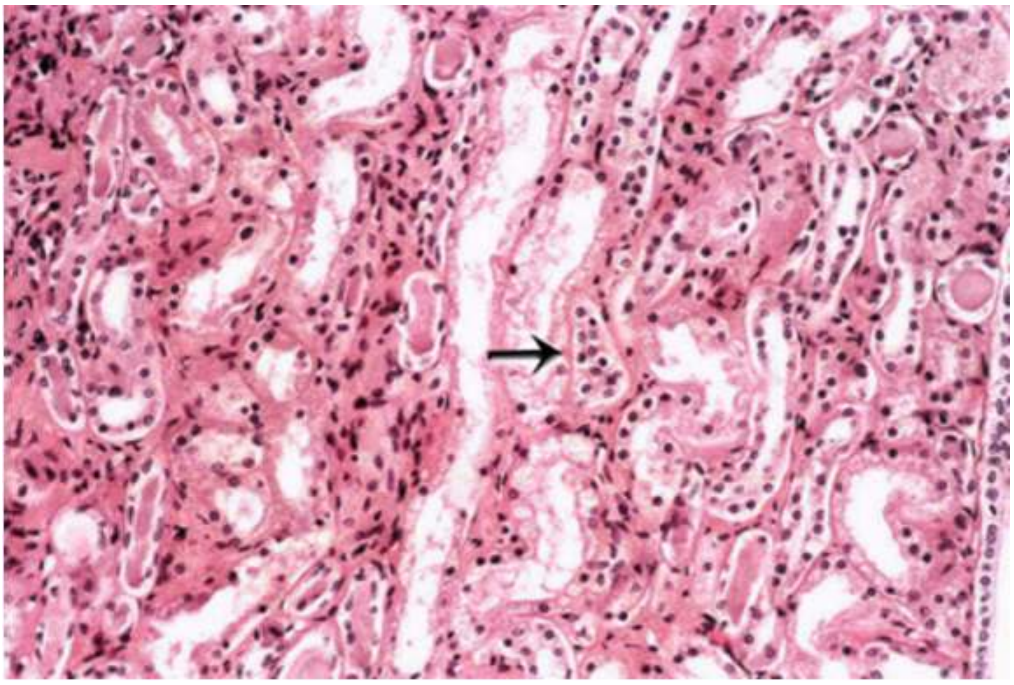
Structural injury in the kidney is the hallmark of intrinsic AKI, and the most common form is acute tubular injury (ATN), either ischemic or cytotoxic. Frank necrosis is not prominent in most human cases of ATN and tends to be patchy. Less obvious injury includes loss of brush borders, flattening of the epithelium, detachment of cells, formation of intratubular casts, and dilatation of the lumen. Although these changes are observed predominantly in proximal tubules, injury to the distal nephron can also be demonstrated. In addition, the distal nephron may become obstructed by desquamated cells and cellular debris.



*Flattening of the renal tubular cells due to tubular dilation*



*Intratubular cast formation*



*Intratubular obstruction due to the denuded epithelium and cellular debris.*

Intrarenal vasoconstriction is the dominant mechanism for the reduced glomerular filtration rate (GFR) in patients with ATN. The mediators of this vasoconstriction are unknown, but tubular injury seems to be an important concomitant finding. Urine backflow and intratubular obstruction (from sloughed cells and debris) are causes of reduced net ultrafiltration. The importance of this mechanism is highlighted by the improvement in renal function that follows relief of such intratubular obstruction. In addition, when obstruction is prolonged, intrarenal vasoconstriction is prominent in part due to the tubuloglomerular feedback mechanism, which is thought to be mediated by adenosine and activated when there is proximal tubular damage and the macula densa is presented with increased chloride load.

Apart from the increase in basal renal vascular tone, the stressed renal microvasculature is more sensitive to potentially vasoconstrictive drugs and otherwise-tolerated changes in systemic blood pressure. The vasculature of the injured kidney has an impaired vasodilatory response and loses its autoregulatory behavior. This latter phenomenon has important clinical relevance because the frequent reduction in systemic pressure during intermittent hemodialysis may provoke additional damage that can delay recovery from ATN. Often, injury results in atubular glomeruli, where the

glomerular function is preserved, but the lack of tubular outflow precludes its function.

A physiologic hallmark of ATN is a failure to maximally dilute or concentrate urine (isosthenuria). This defect is not responsive to pharmacologic doses of vasopressin. The injured kidney fails to generate and maintain a high medullary solute gradient, because the accumulation of solute in the medulla depends on normal distal nephron function. Failure to excrete concentrated urine even in the presence of oliguria is a helpful diagnostic clue in distinguishing prerenal from intrinsic renal disease; in prerenal azotemia, urine osmolality is typically more than 500 mOsm/kg, whereas in intrinsic renal disease, urine osmolality is less than 300 mOsm/kg.

Glomerulonephritis can be a cause of AKI and usually falls into a class referred to as rapidly progressive glomerulonephritis (RPGN). Glomerular crescents (glomerular injury) are found in RPGN on biopsy; if more than 50% of glomeruli contain crescents, this usually results in a significant decline in renal function. Although comparatively rare, acute glomerulonephritides should be part of the diagnostic consideration in cases of AKI.

**Postrenal AKI**

Mechanical obstruction of the urinary collecting system, including the renal pelvis, ureters, bladder, or urethra, results in obstructive uropathy or postrenal AKI.

If the site of obstruction is unilateral, then a rise in the serum creatinine level may not be apparent due to contralateral renal function. Although the serum creatinine level may remain low with unilateral obstruction, a significant loss of GFR occurs, and patients with partial obstruction may develop progressive loss of GFR if the obstruction is not relieved. Causes of obstruction include stone disease; stricture; and intraluminal, extraluminal, or intramural tumors.

Bilateral obstruction is usually a result of prostate enlargement or tumors in men and urologic or gynecologic tumors in women.

Patients who develop anuria typically have obstruction at the level of the bladder or downstream to it.

**Diagnostic Evaluation of an Acutely Azotemic Patient.**

**History**

A detailed and accurate history is crucial to aid in diagnosing the type of AKI and in determining its subsequent treatment. A detailed history and a

physical examination in combination with routine laboratory tests are useful in making a correct diagnosis.

- Distinguishing AKI from chronic renal failure is important, yet making the distinction can be difficult. A history of chronic symptoms — fatigue, weight loss, anorexia, nocturia, and pruritus — suggests chronic renal failure.
- Take note of the following findings during the physical examination:
    - Hypotension
    - Volume contraction
    - Congestive heart failure
    - Nephrotoxic drug ingestion
    - History of trauma or unaccustomed exertion
    - Blood loss or transfusions
    - Evidence of connective tissue disorders or autoimmune diseases
    - Exposure to toxic substances, such as ethyl alcohol or ethylene glycol
    - Exposure to mercury vapors, lead, cadmium, or other heavy metals, which can be encountered in welders and miners
- People with the following comorbid conditions are at a higher risk for developing AKI:

    - Hypertension
    - Congestive cardiac failure
    - Diabetes
    - Multiple myeloma
    - Chronic infection
    - Myeloproliferative disorder
- Urine output history can be useful. Oliguria generally favors AKI. Abrupt anuria suggests acute urinary obstruction, acute and severe glomerulonephritis, or embolic renal artery occlusion. A gradually diminishing urine output may indicate a urethral stricture or bladder outlet obstruction due to prostate enlargement.
- Because of a decrease in functioning nephrons, even a trivial nephrotoxic insult may cause AKI to be superimposed on chronic renal insufficiency.

**Physical examination**

Obtaining a thorough physical examination is extremely important when collecting evidence about the etiology of AKI.

- Skin
    - Petechiae, purpura, ecchymosis, and livedo reticularis provide clues to inflammatory and vascular causes of AKI.

- Infectious diseases,thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), and embolic phenomena can produce typical cutaneous changes.

- Eyes
  - Evidence of uveitis may indicate interstitial nephritis and necrotizing vasculitis.
  - Ocular palsy may indicate ethylene glycol poisoning or necrotizing vasculitis.
  - Findings suggestive of severe hypertension, atheroembolic disease, and endocarditis may be observed on careful examination of the eyes.
- Cardiovascular system
  - The most important part of the physical examination is the assessment of cardiovascular and volume status.
  - The physical examination must include pulse rate and blood pressure recordings measured in both the supine position and the standing position; close inspection of the jugular venous pulse; careful examination of the heart, lungs, skin turgor, and mucous membranes; and assessment for the presence of peripheral edema.

- In hospitalized patients, accurate daily records of fluid intake and urine output and daily measurements of patient weight are important.
- Blood pressure recordings can be important diagnostic tools.
- Hypovolemia leads to hypotension; however, hypotension may not necessarily indicate hypovolemia.
- Severe congestive cardiac failure (CHF) may also cause hypotension. Although patients with CHF may have low blood pressure, volume expansion is present and effective renal perfusion is poor, which can result in AKI.
- Severe hypertension with renal failure suggests renovascular disease, glomerulonephritis, vasculitis, or atheroembolic disease.

- Abdomen
  - Abdominal examination findings can be useful to help detect obstruction at the bladder outlet as the cause of renal failure, which may be due to cancer or an enlarged prostate.
  - The presence of tense ascites can indicate elevated intra-abdominal pressure that can retard renal venous return and result in AKI.
  - The presence of an epigastric bruit suggests renal vascular hypertension, which may predispose to AKI.

**Causes**

The causes of AKI traditionally are divided into 3 main categories – prerenal, intrinsic, and postrenal.

- Prerenal AKI
    - Volume depletion
        - Renal losses (diuretics, polyuria)
        - GI losses (vomiting, diarrhea)
        - Cutaneous losses (burns,Stevens-Johnson syndrome)
        - Hemorrhage
        - Pancreatitis
    - Decreased cardiac output
        - Heart failure
        - Pulmonary embolus
        - Acute myocardial infarction
        - Severe valvular disease
        - Abdominal compartment syndrome (tense ascites)
    - Systemic vasodilation
        - Sepsis
        - Anaphylaxis
        - Anaesthetics

        - Drug overdose
    - Afferent arteriolar vasoconstriction
        - Hypercalcemia
        - Drugs (NSAIDs, amphotericin B, calcineurin inhibitors, norepinephrine, radiocontrast agents)
        - Hepatorenal syndrome
    - Efferent arteriolar vasodilation – ACEIs or ARBs
    - Renal artery occlusion
- Intrinsic AKI
    - Vascular (large and small vessel)
        - Renal artery obstruction (thrombosis, emboli, dissection, vasculitis)
        - Renal vein obstruction (thrombosis)
        - Microangiopathy (TTP, hemolytic uremic syndrome [HUS], DIC, preeclampsia)
        - Malignant hypertension
        - Scleroderma renal crisis
        - Transplant rejection
        - Atheroembolic disease

- Glomerular
  - Anti–glomerular basement membrane (GBM) disease (Goodpasture syndrome)
  - Anti–neutrophil cytoplasmic antibody-associated glomerulonephritis (ANCA-associated GN) (Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis)
  - Immune complex GN (lupus, postinfectious, cryoglobulinemia, primary membranoproliferative glomerulonephritis)
- Tubular
  - Ischemic
  - Cytotoxic
    - Heme pigment (rhabdomyolysis, intravascular hemolysis)
    - Crystals (tumor lysis syndrome, seizures, ethylene glycol poisoning, megadose vitamin C, acyclovir, indinavir, methotrexate)

        - Drugs (aminoglycosides, lithium, amphotericin B, pentamidine, cisplatin, ifosfamide, radiocontrast agents)
    - Interstitial
        - Drugs (penicillins, cephalosporins, NSAIDs, proton-pump inhibitors, allopurinol, rifampin, indinavir, mesalamine, sulfonamides)
        - Infection (pyelonephritis, viral nephritides)
        - Systemic disease (Sjogren syndrome, sarcoid, lupus, lymphoma, leukemia, tubulonephritis, uveitis)
- Postrenal AKI
    - Ureteric obstruction (stone disease, tumor, fibrosis, ligation during pelvic surgery)
    - Bladder neck obstruction (benign prostatic hypertrophy [BPH], cancer of the prostate [Ca prostate], neurogenic bladder, tricyclic antidepressants, ganglion blockers, bladder tumor, stone disease, hemorrhage/clot)
    - Urethral obstruction (strictures, tumor, phimosis)
    - Intra-abdominal hypertension (tense ascites)
    - Renal vein thrombosis

**Laboratory Studies**

Several laboratory tests are useful for assessing the etiology of AKI, and the findings can aid in proper management. These tests include complete blood cell (CBC) count, serum biochemistries, urine analysis with microscopy, and urine electrolytes.

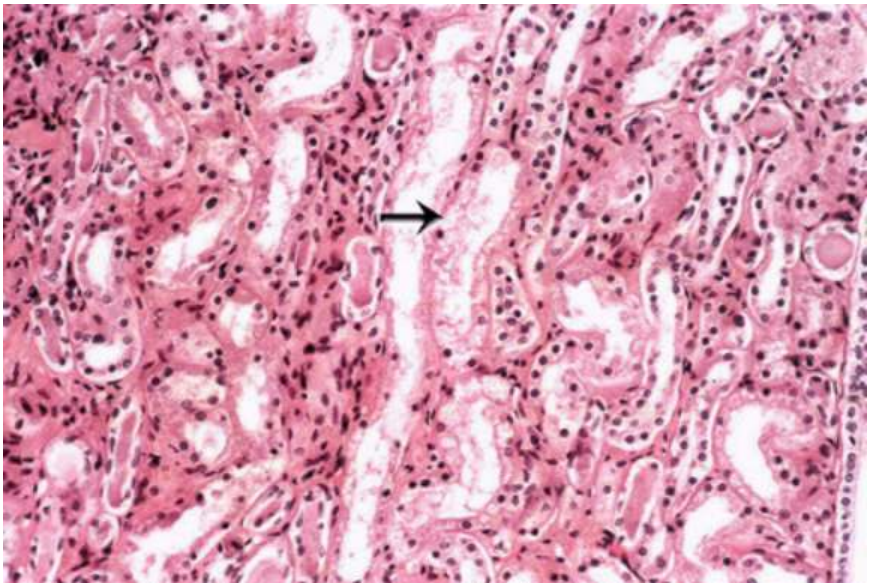
- Blood urea nitrogen (BUN) and serum creatinine
    - Although increased levels of BUN and creatinine are the hallmarks of renal failure, the rate of rise is dependent on the degree of renal insult as well as protein intake with respect to BUN.
    - The ratio of BUN to creatinine is an important finding, because the ratio can exceed 20:1 in conditions in which enhanced reabsorption of urea is favored (eg, in volume contraction); this suggests prerenal AKI.
    - BUN may be elevated in patients with GI or mucosal bleeding, steroid treatment, or protein loading.
    - Assuming no renal function, the rise in BUN over 24 hours can be roughly predicted using the following formula: 24-hour protein intake in milligrams X 0.16 divided by total body water in mg/dL added to the BUN value.

- Assuming no renal function, the rise in creatinine can be predicted using the following formulas:
  - For males: weight in kilograms X [28 – 0.2(age)] divided by total body water in mg/dL added to the creatinine value
  - For females: weight in kilograms X [23.8 – 0.17(age)] divided by total body water added to the creatinine value
- As a general rule, if serum creatinine increases to more than 1.5 mg/dL/d, rhabdomyolysis must be ruled out.

- CBC count, peripheral smear, and serology
  - The peripheral smear may show schistocytes in conditions such as HUS or TTP.
  - A finding of increased rouleaux formation suggests multiple myeloma, and the workup should be directed toward immunoelectrophoresis of serum and urine.
  - The presence of myoglobin or free hemoglobin, increased serum uric acid level, and other related findings may help further define the etiology of AKI.
  - Serologic tests for antinuclear antibody (ANA), ANCA, anti-GBM antibody, hepatitis, and antistreptolysin (ASO) and complement levels may help include and exclude glomerular disease. Although

serologic tests can be informative, the costs can be prohibitive if these tests are not ordered judiciously.

- Urinalysis
    - Findings of granular, muddy-brown casts are suggestive of tubular necrosis.



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

- The presence of tubular cells or tubular cell casts also supports the diagnosis of ATN. Often, oxalate crystals are observed in cases of ATN.

- Reddish brown or cola-colored urine suggests the presence of myoglobin or hemoglobin, especially in the setting of a positive dipstick for heme and no RBCs on the microscopic examination.
- The dipstick assay may reveal significant proteinuria, which would suggest glomerular or interstitial disease.
- The presence of RBCs in the urine is always pathologic. Eumorphic RBCs suggest bleeding along the collecting system. Dysmorphic RBCs or RBC casts indicate glomerular inflammation, suggesting glomerulonephritis is present.
- The presence of WBCs or WBC casts suggests pyelonephritis or acute interstitial nephritis. The presence of urine eosinophils is helpful in establishing a diagnosis but is not necessary for allergic interstitial nephritis to be present.
- The presence of eosinophils, as visualized with Wright stain or Hansel stain, suggests interstitial nephritis but can also be seen in urinary tract infections, glomerulonephritis, and atheroembolic disease.
- The presence of uric acid crystals may represent ATN associated with uric acid nephropathy.
- Calcium oxalate crystals are usually present in cases of ethylene glycol poisoning.

**Urine electrolytes**

- Urine electrolyte findings also can serve as valuable indicators of functioning renal tubules.
- The fractional excretion of sodium (FENa) is the commonly used indicator. However, the interpretation of results from patients in nonoliguric states, those with glomerulonephritis, and those receiving or ingesting diuretics can lead to an erroneous diagnosis. FENa can be a valuable test for helping to detect extreme renal avidity for sodium in conditions such as hepatorenal syndrome. The formula for calculating the FENa is as follows:
    - $FENa = (U_{Na}/P_{Na}) / (U_{Cr}/P_{Cr}) \text{ X } 100$
    - Calculating the FENa is useful in AKI only in the presence of oliguria.
    - In patients with prerenal azotemia, the FENa is usually less than 1%. In ATN, the FENa is greater than 1%. Exceptions to this rule are ATN caused by radiocontrast nephropathy, severe burns, acute glomerulonephritis, and rhabdomyolysis.
    - In the presence of liver disease, FENa can be less than 1% in the presence of ATN. On the other hand, because administration of

diuretics may cause the FENa to be greater than 1%, these findings cannot be used as the sole indicators in AKI.

- In patients who are receiving diuretics, a fractional excretion of urea (FEUrea) can be obtained, since urea transport is not affected by diuretics. The formula for calculating the FEUrea is as follows: $FEUrea = (U_{urea}/P_{urea}) / (U_{Cr}/P_{Cr}) \times 100$
- FEUrea of less than 35% is suggestive of a prerenal state.

- Bladder pressure: Intra-abdominal pressure of <10 mm Hg is considered normal and suggests abdominal compartment syndrome is not the cause of AKI. Patients with an intra-abdominal pressure below 15-25 mm Hg are at risk for abdominal compartment syndrome, and those with bladder pressures above 25 mm Hg should be suspected of having AKI as a result of abdominal compartment syndrome.
- Emerging biomarkers: A number of biomarkers are being investigated to risk stratify and predict AKI in those at risk for the disease. The reason for this is because creatinine is a late marker for renal dysfunction and, once elevated, reflects a severe reduction in GFR. The most promising biomarker to date is urinary neutrophil gelatinase-associated lipocalin (NGAL), which has been shown to predict AKI in children undergoing cardiopulmonary bypass surgery.

**Imaging Studies**

In some cases, renal imaging is useful, especially if renal failure is secondary to obstruction. The American College of Radiology recommends ultrasonography, preferably with Doppler methods, as the most appropriate imaging method in AKI.[5]

- Ultrasonography
    - Renal ultrasonography is useful for evaluating existing renal disease and obstruction of the urinary collecting system. The degree of hydronephrosis does not necessarily correlate with the degree of obstruction. Mild hydronephrosis may be observed with complete obstruction if found early.
    - Obtaining images of the kidneys can be technically difficult in patients who are obese or in those with abdominal distension due to ascites, gas, or retroperitoneal fluid collection.
    - Ultrasonographic scans or other imaging studies showing small kidneys suggest chronic renal failure.
- Doppler ultrasonography
    - Doppler scans are useful for detecting the presence and nature of renal blood flow.

- Because renal blood flow is reduced in prerenal or intrarenal AKI, test findings are of little use in the diagnosis of AKI.
- Doppler scans can be quite useful in the diagnosis of thromboembolic or renovascular disease.
- Increased resistive indices can be observed in patients with hepatorenal syndrome.

- Nuclear scans
  - Radionucleotide imaging with technetium-99m-mercaptoacetyltriglycine ($^{99m}$Tc-MAG3), $^{99m}$Tc-diethylenetriamine pentaacetic acid ($^{99m}$Tc-DTPA), or iodine-131 ($^{131}$I)–hippurate can be used to assess renal blood flow and tubular functions.
  - Because of a marked delay in tubular excretion of radionuclide in prerenal disease and intrarenal disease, the value of these scans is limited.
- Aortorenal angiography can be helpful in establishing the diagnosis of renal vascular diseases, including renal artery stenosis, renal atheroembolic disease, atherosclerosis with aortorenal occlusion, and in certain cases of necrotizing vasculitis (eg, polyarteritis nodosa).

**Procedures**

- Renal biopsy
    - A renal biopsy can be useful in establishing the diagnosis of intrarenal causes of AKI and can be justified if it will change management (eg, initiation of immunosuppressive medications). A renal biopsy may also be indicated when renal function does not return for a prolonged period and a prognosis is required to develop long-term management.
    - In as many as 40% of cases, renal biopsy results reveal an unexpected diagnosis.
    - Acute cellular or humoral rejection in a transplanted kidney can be definitively diagnosed only by performing a renal biopsy.

**Approach to AKI**

Before instituting measures to treat AKI it is important to identify:

- Whether the AKI is really acute or masking a chronic kidney disease, History of diabetes mellitus, hypertension, glomerulonephritis or kidney disease, ultrasonographically small contracted kidneys, urinalysis with broad casts more than 2 to 3 white blood cells in diameter, low carbamylated hemoglobin suggest presence of chronic kidney disease.

- Whether the AKI is prerenal, renal or post renal?
    - The priorities in treating AKI are to optimize fluid balance, treat underlying causes and institute RRT at the appropriate time.

**Non Dialytic Therapy**

Non-dialytic interventions in the management of AKI include restoration of euvolemic status with crystalloid or colloids and correcting the metabolic derangements.

Pharmacological interventions with dopamine, fenoldopam, thyroxine, Insulin like growth factor-1, loop diuretics, atrial natriuretic peptide have been found to be promising in animal studies but have failed to make a statistically significant impact in human studies. The poor results may be linked to the time interval between occurrence of AKI and the intervention. The results of the metaanalysis of the role of loop diuretics show that frusemide has no clinical benefit in the prevention or treatment of established AKI. Its use may increase the risk of ototoxicity.[28]

The use of dopamine is associated with impaired splanchnic perfusion, increased risk of gram negative

bacteremia and an increased incidence of arrhythmias, particularly atrial fibrillation in the post open-heart patients. Hence there is no role for dopamine in the treatment of AKI.[29]

Medical management includes tight control of blood sugars besides close monitoring of the volume status, renal biochemical parameters and electrolytes. Protein kinase C is a useful agent in systemic inflammatory reaction syndrome (SIRS) induced ARF in ICU. The backbone of treatment of ARF remains adequate supportive care, maintenance of renal perfusion pressure (MAP > 80 mm Hg), avoidance of future nephrotoxic insults and provision of renal replacement therapy.

Emerging pharmacological agents for treatment of AKI are antiapototic and antinecrotic agents (caspase inhibitors – nonselective and selective against Caspase 1, 3, and 7, PARP inhibitors, minocycline); anti-inflammatory (IL-10, activated protein Kinase C, iNOS inhibitor), antisepsis agents (insulin, activated protein kinase C), growth factors (recombinant erythropoietin, hepatocyte growth factor) and vasodilators (Endothelin antagonists,ANP)[30]

**Dialytic therapy**

Dialysis is one of the cornerstones of AKI treatment.

Initiation of renal replacement therapy (RRT) is recommended when severe derangements in electrolyte concentration (potassium, sodium),volume overload, acid base imbalance, pronounced azotemia (BUN more than 100 mg/dl), florid symptoms of uremia (pericarditis, encephalopathy, bleeding, nausea-vomiting) are noted. Options available are peritoneal dialysis (PD),

intermittent hemodialysis (IHD) extended daily dialysis (EDD), slow low efficiency dialysis (SLED) and continuous renal replacement therapy (CRRT). PD is less preferred due to poor delivery of dialysis dose and difficulty in managing ultra filtration. However some trials have shown that continuous peritoneal dialysis has given better results in reducing morbidity and mortality in ICU.

IHD has proved to be beneficial in many of the controlled trials inspite of the fact that it may aggravate the renal injury due to fall in blood pressure. Use of more biocompatible membranes such as polysulfones or polyacrilonitrile improves the outcome of AKI by decreasing complement activation and production of leukotrienes and other cytokines.

With AKI better defined, a recognizable at risk group evolving novel biomarkers to identify AKI early, IHD itself proving to be effective dialytic mode, AKI should become a less morbid condition in the near future. However patients in situations of hypovolemia, hypotension and multiorgan failure (MOF) CRRT is preferred.

**Management of AKI**

AKI is a morbid condition- its clinical manifestations are not limited to the kidney. It is an inflammatory state and a systemic disorder. The systemic consequences of AKI are mediated by:[23] *The acutely uremic state*: leading to

metabolic derangements (carbohydrate, lipid, amino acid and protein metabolism), endocrine alterations (insulin resistance, hyperparathyroidism) and metabolic acidosis. *The injured Kidney*: inducing a proinflammatory state with release of and impaired catabolism of cytokines (IL6, IL8, IL10), activation of immunocompetent cells and release of humoral factors promoting distal organ injury. Thus there is activation of coagulation cascade, increased norepinephrine, angiotensin II, endothelin, platelet activating factor, tumor necrosis factor, toll like receptors and apoptosis especially in septic AKI.

. The long-term consequences of AKI are not benign. AKI is emerging as one of the causes of chronic kidney disease leading to End Stage Kidney Disease. Of 245 children treated for AKI, 174 survived. 16.6%

of the survivors had chronic kidney disease over a 3 to 5-year follow up.[24] The morbidity and mortality of AKI is closely linked to the time of its recognition and intervention hence, management strategies should include measures to prevent AKI atleast in identifiable people at risk, early identification of AKI and aggressive correction of the underlying cause besides early RRT when indicated. Early recognition of AKI and institution of corrective measures will ensure reversal to normal.

**Prevention of AKI**

Ideal management of the condition is thus its prevention. At risk for AKI are the older age group, diabetics (especially if uncontrolled), those with hyperuricemia, dyslipidemia, hypertension, renal disease, heart failure, sepsis, multiple myeloma, volume depletion. and on concomitant nephrotoxic medications – aminoglycosides, diuretics, mannitol, vancomycin, amphotericin B, tacrolimus. Risk factors for AKI in the intensive care unit are myocardial dysfunction, liver failure, endothelial dysfunction, coagulation abnormalities, rhabdomyolyis, hemolytic uremic syndrome, ARDS, bacteremia and endotoxemia, sepsis and septic shock.

**Early Recognition of AKI**

Novel biomarkers of Acute kidney injury have been identified. If these are utilized in the at risk situations for AKI, they will assist early institution of corrective measures. As they represent sequentially expressed biomarkers, it is likely that the AKI panels will be useful for timing the initial insult and assessing the duration of AKI. Based on the differential expression of the biomarkers, it is also likely that the AKI panels will distinguish between the various types and etiologies of AKI.

**Novel biomarkers of Kidney Injury**

Cystatin C, Kidney Injury Molecule –1 (KIM-1), Neutrophil Gelatinase Associated Lipocalin (NGAL), Na+ / H+ Exchanger Isoform 3 (NHE 3), N-Acetyl Glycosaminidase (NAG), - Glutamyl transpeptidase, and Glutathione S transferase and Interleukin-18 are some of the biomarkers of AKI.

The biomarkers of promise include a plasma panel (NGAL and cystatin C) and a urine panel (NGAL, IL- 18 and KIM-1).

The amount of NGAL in urine (uNGAL) at 2 hours after cardiopulmonary bypass is the most powerful and independent predictor of AKI. [27] In a prospective study of 140 critically ill children, Urinary NGAL proved to be a good predictor of impending AKI, its levels being 4 to 6 times more than the controls. The rise in uNGAL occurs 48 hours before the rise in serum creatinine levels. uNGAL levels were higher in children with sepsis than those without sepsis. However the relationship with AKI was maintained.

Because few measures exist to treat ARF actively, clinicians should try to prevent it. Issues to consider are correcting volume status, avoiding exposure to nephrotoxins, and preparing for high-risk procedures, such as using contrast agents

- Measures to Prevent Acute Renal Failure in Hospitalized Patients
- Prevent hypotension, and correct it rapidly when it does occur.

- Evaluate renal function before any surgery.
- Avoid prescribing nephrotoxic drugs.
- Correct volume deficits or electrolyte imbalances, especially before surgery.
- Replace traditional contrast agents with nonionic contrast, and use contrast sparingly.
- Treat infection quickly.
- Treat oliguria quickly.

**Preventing Contrast Nephropathy**

The incidence of contrast nephropathy can be reduced by adequately hydrating patients before the procedure, replacing traditional agents with nonionic contrast, and limiting the quantity of any contrast agent used.[21]

Using nonionic contrast agents can cut the overall risk of contrast nephropathy by 50%, from about 6% to 3%. In the study by Rudnick and colleagues, risk factors for contrast nephropathy were baseline chronic kidney disease (serum creatinine level higher than 1.5 mg/dL) and diabetes; the use of nonionic contrast agents reduced the incidence in the highest risk patients who had both risk factors from 24% to 12%.

The most effective strategy to hydrate patients is to give IV normal saline, 1 mL/kg/hour, before the procedure. No benefit is gained by adding

mannitol or a loop diuretic. Pretreating with acetylcysteine can reduce the rise of creatinine levels slightly but might have minor clinical impact.

**Outcomes**

The mortality rate in severe AKI is almost 50%, depending on the type of AKI and comorbidities of the patient. In the Madrid study, patients with ATN had a mortality rate of 60%, whereas those with prerenal or postrenal disease had a 35% mortality rate.[6]

Most deaths are not caused by the AKI itself but rather by the underlying disease or complications[6]. In the Madrid data, 60% of deaths were caused by the primary disease and the remaining 40% were caused by cardiopulmonary failure or infection.[6]

AKI is not merely a marker of illness. In a follow-up report[21] of 16,000 patients who were studied by computed tomography with contrast, 183 developed AKI. The mortality rate among those with ARF was 34%, compared with only 7% in a matched cohort from the similarly exposed group.

About 50% of people who survive ATN recover renal function completely and another 40% have an incomplete recovery. Only approximately 5% to 10% require maintenance hemodialysis.

# Materials and Methods

# Materials and Methods

Place

Intensive Medical Care Unit, GGH, Chennai

Design

Observational

Period

May, 2010 to October, 2010

Sample size

50 (Fifty)

Inclusive Criteria

An absolute increase in serum creatinine of more than or equal to 0.3mg/dl (>26.4umol/L). A percentage increase of serum creatinine of more than equal to 50% (1-5 fold from baseline).

Exclusion criteria

Patients with CKD

Patients with abnormal kidney size and abnormal cortico medullary differentiation. A thorough diagnostic evaluation was done by a detailed history, physical examination, urinary analysis, CBC, RFT, Renal USG. In appropriate place, serology of leptospirosis, enteric fever, peripheral smear

for MP/MF, other related investigations were done. The patients were started on appropriate therapy once the diagnosis was made.

Wherever possible the etiological factors were treated. RRT was given according to the clinical and biochemical indications. Ethical committee approval obtained.

# Results

# Results

Observation and Data Analysis

Total no: 50

Males: 28

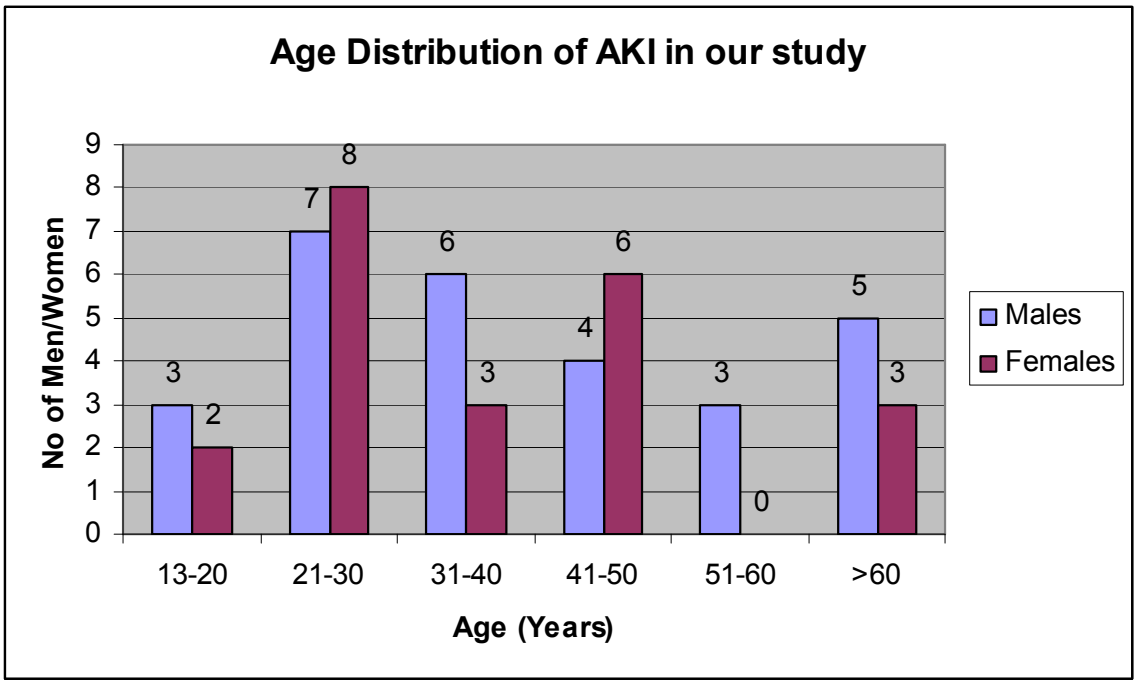
Females: 22

Age: 13-85 yrs

Mean Age: 38.26 yrs

**Age Distribution of AKI in our Study**

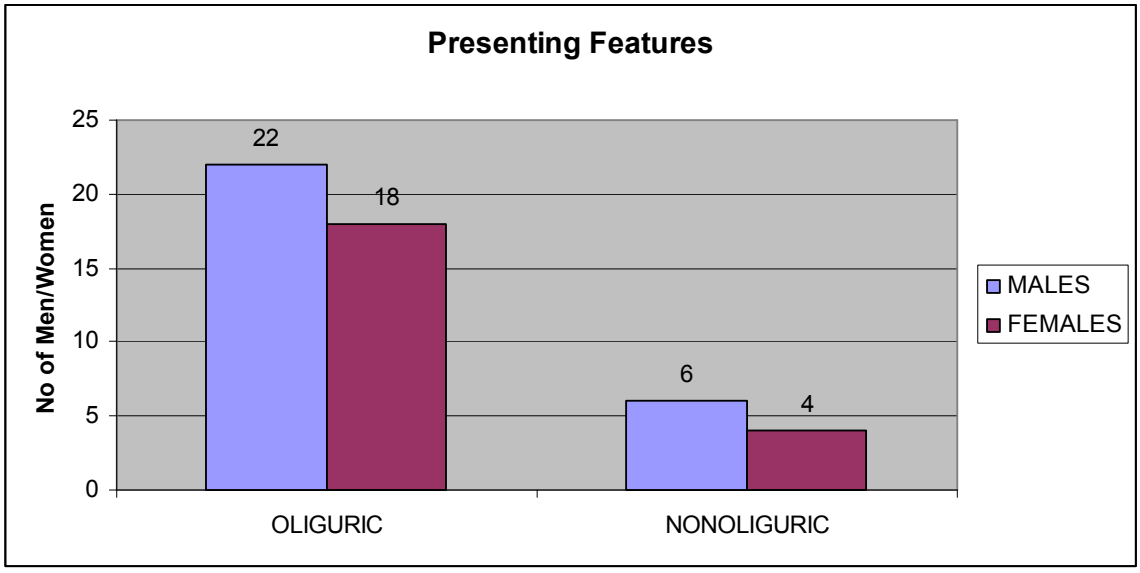
| Age( Years) | Males | Females |
|---|---|---|
| 13-20 | 3 | 2 |
| 21-30 | 7 | 8 |
| 31-40 | 6 | 3 |
| 41-50 | 4 | 6 |
| 51-60 | 3 | 0 |
| >60 | 5 | 3 |
| Total | 28 | 22 |




The peak incidence was in the third decade. There were 8 patients above the age of 60 years. Five of them were at risk , one developed injury and two of them developed failure according to RIFLE criteria.

**Presenting Features**

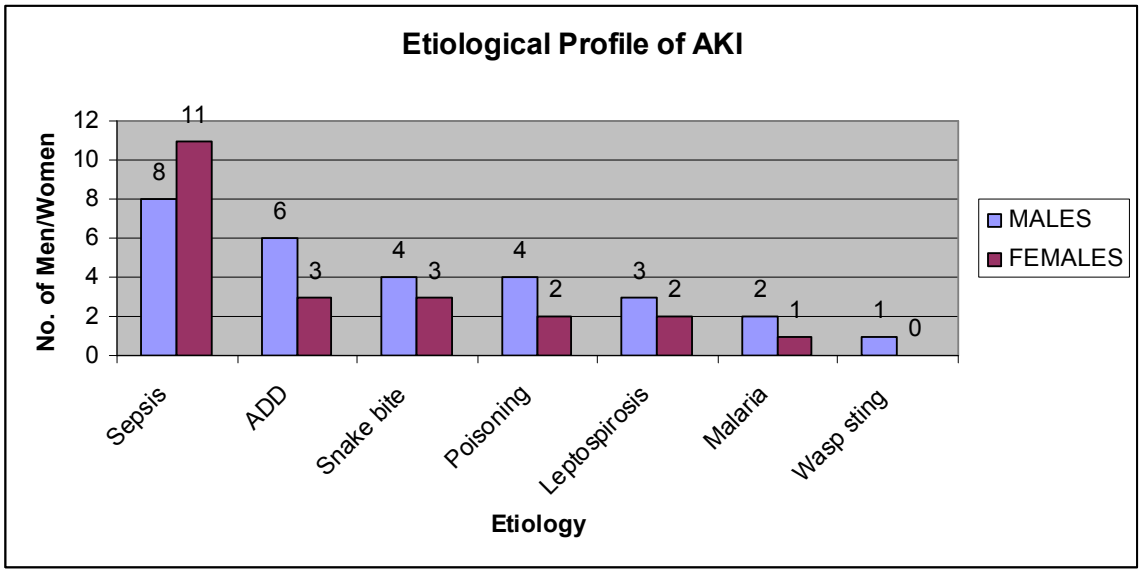
| Urine Output | Males | Females | Total |
|---|---|---|---|
| Oliguric | 22 | 18 | 40 |
| Non oliguric | 6 | 4 | 10 |




The presentation was predominantly oliguric. Out of the ten non oliguric patients 4 patients were a case of poisoning. Two of them were due to insecticide poisoning,one due to OPC poisoning and the other due to organochlorine compound. The other two cases were due to oduvanthalai leaf poisoning and copper sulphate. 3 cases of sepsis presented with non oliguria. One case of snake bite , leptospirosis also presented with non oliguria.

**Etiological Profile of AKI**

| S.no | Etiology | Males | Females | Total |
|---|---|---|---|---|
| 1 | Sepsis | 8 | 11 | 19 |
| 2 | ADD | 6 | 3 | 9 |
| 3 | Snake bite | 4 | 3 | 7 |
| 4 | Poisoning | 4 | 2 | 6 |
| 5 | Leptospirosis | 3 | 2 | 5 |
| 6 | Malaria | 2 | 1 | 3 |
| 7 | Wasp sting | 1 | 0 | 1 |
| | | | | 50 |

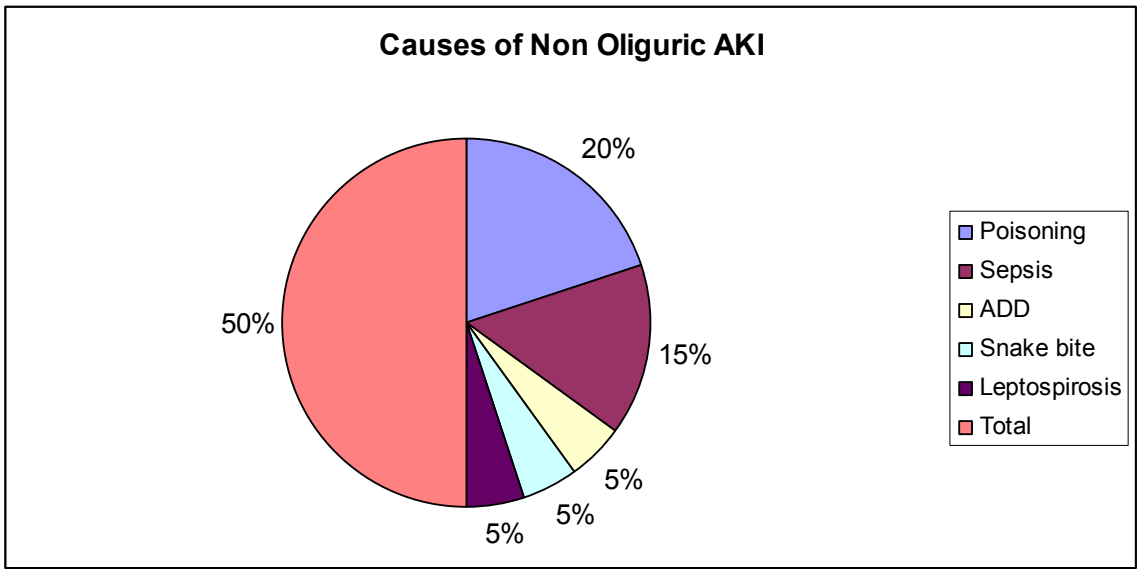



The most common cause of AKI in critically ill patients was sepsis. The second common cause was ADD. Next to it was the snake bite. The Whole Blood Clotting Time was prolonged in all these patients and all were due to

a Russell's viper bite. Among the 6 cases of poisoning three of them had insecticide poisoning. There was 5 and 3 patients of leptospirosis and malaria respectively. Two cases of malaria were falciparum species. There was a case of wasp sting.

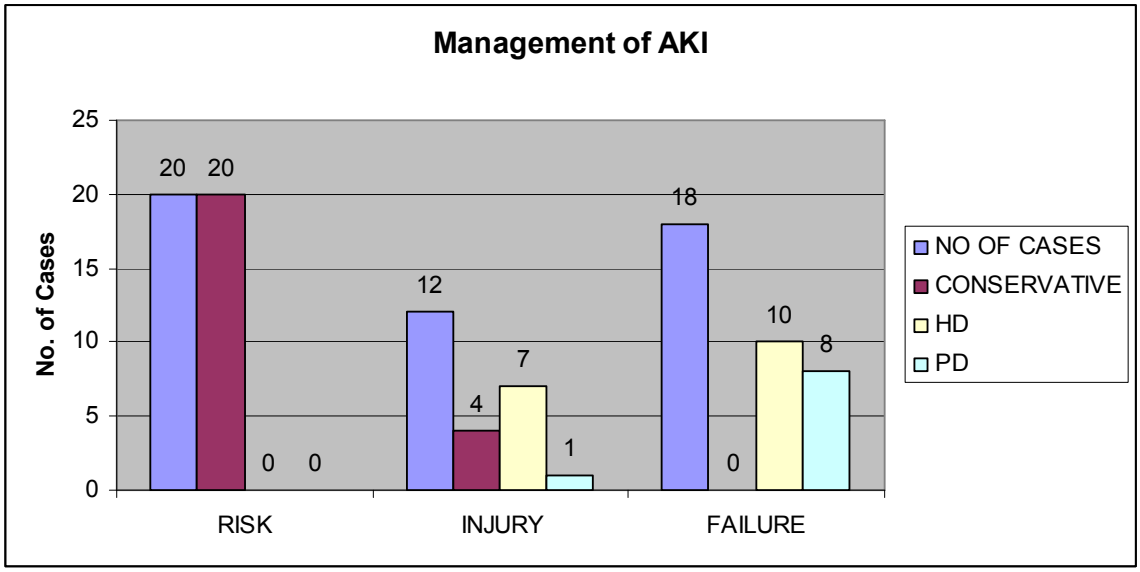
**Causes of Non Oliguric AKI**

| Etiology | No of Cases |
|---|---|
| Poisoning | 4 |
| Sepsis | 3 |
| ADD | 1 |
| Snake bite | 1 |
| Leptospirosis | 1 |
| Total | 10 |



**Management of AKI**

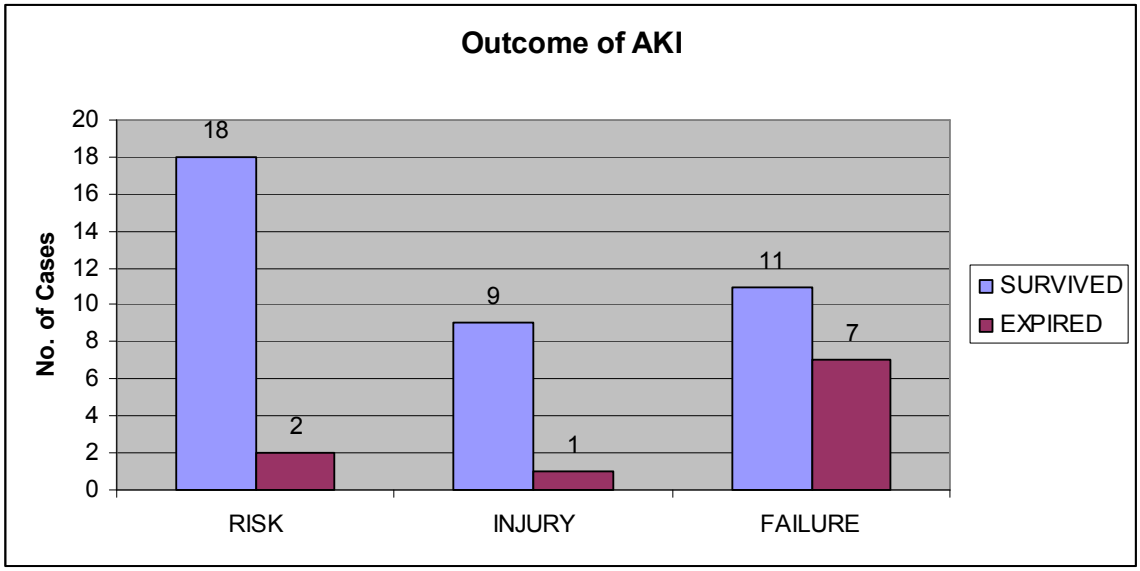
| | No of cases | Conservative | HD | PD |
|---|---|---|---|---|
| Risk | 20 | 20 | 0 | 0 |
| Injury | 12 | 4 | 7 | 1 |
| Failure | 18 | 0 | 10 | 8 |




According to RIFLE criteria, 20 cases classified under class R. All the patients under this class were treated conservatively. While the patients who came under class I were 12 of whom 8 were treated with dialysis. The FAILURE class constituted 18 patients who were all treated with dialysis. Between HD and PD, the former is the preferred mode. Due to the easy availability of HD and better efficacy 57% of the cases who required RRT(60%) were treated with HD.

**Outcome of AKI**

| Outcome | Survived | Expired |
|---|---|---|
| Risk | 18 | 2 |
| Injury | 9 | 1 |
| Failure | 11 | 7 |




Two patients who were at risk expired. Both were case of sepsis that were on ionotropic and ventilatory support managed conservatively for the AKI. The only patient who died of Injury was also a case of sepsis with multiorgan dysfunction.

**Co morbid Conditions Associated**

| Co morbid conditions | Survived | Expired |
|---|---|---|
| DM | 5 | 3 |
| SHT | 1 | 4 |
| CAD | 1 | 1 |
| MOD | 1 | 6 |
| Ionotropics | 1 | 6 |
| Ventilation | 3 | 7 |
| CLD | 0 | 1 |

There were 3 cases of isolated diabetes alone. 4 patients had diabetes and systemic hypertension in combination. There were each one isolated cases of SHT, CAD and CLD. Multi Organ Dysfunction was present in 7 cases of which only one survived. Totally 10 patients had ionotropic or a ventilatory support of which 7 of them expired. 85% morality was observed among patients with MOD and ionotropic support.

# Discussion

# Discussion

AKI is a potentially fatal, but reversible renal disease. The etiology, course, outcome differ in various parts of the world and also within India due to its climatic and geographic diversity and the variable standards of medical care. In our study 50 patients were analysed. There were 28 males and 22 females. Mean age of occurrence was 38.26 years. Maximum number of cases occurred in third to fifth decade. In our study oliguric AKI was predominant (80%). This is in concordance with a previous study by M.A. Muthusethupathi et al in 1999[70]. Sepsis is the leading cause in our study. This is in concordance with most of the multicenter trials. In the study conducted by M. A. Muthusethupathi et al the leading cause of AKI was leptospirosis then in Chennai. Sepsis accounts for 19 cases (38%) of the cases[70]. Of them, 42% were treated with dialysis and 58% treated conservatively. Six patients died. Mortality observed due to sepsis was 32%. Out of the 9 cases of ADD only one died due to arrhythmia which is very less when compared with the report from M.A.Muthusethupathi et al[70] (34.7%). S. K. Agarwal et al studied to find 11% of the AKI was due to ADD in North India. Awareness due to early dehydration therapy and early

referral contribute to the decline in mortality. There were 7 cases (14%) of snake bite all of which were russel's viper with hematotoxicity. There was one death due to snake bite which was complicated by hyperkalemia on presentation. There were 3 cases (6%) of Malarial AKI. There was no death from malarial AKI as against the 42.5% mortality in the study by Zinna et al[80]. A study by Prakash et al from eastern India reported 4.2% of Malarial AKI[24]. Mortality is decreased mainly due to early diagnosis of malaria and early use of HD. We had 4 patients (8%) with Leptospirosis in contrast to 41% cases in M.A.Muthusethupathi et al study[70]. We confirmed the cases based on Modified Faines criteria. Out of the 4 patients, 2 were treated with dialysis and the other 2 conservatively. There was no mortality in our study. In the study of M.A. Muthusethupathi et al 20.8% mortality was present[70]. Low mortality in our study was due to awareness of leptospirosis, its standard diagnostic criteria, therapy, and early referral.

Ostermann M Chang RW 2007 detected the following RIFLE class F has a mortality of 57%, RIFLE class I has 45%, RIFLE class has 21%.[61]

There was an association between AKI and hospital outcome but associated organ failure had a greater impact on the prognosis than the severity of AKI.

# Conclusion

# Conclusion

The presentation of AKI is predominantly oliguric. But non-oliguric AKI should be borne in mind.

Sepsis is the most common cause of AKI in critically ill patients. It has the highest mortality rate too. It is highly essential to prevent the emergence of multi organ failure in any case of sepsis. Similarly, Multi organ failure in the setting of sepsis should be treated aggressively to decrease the high mortality associated with sepsis.

Our patients were managed equally with dialysis whenever indicated and conservatively. Hemodialysis is the preferred mode of dialysis. Peritoneal dialysis is begun only when HD is not available or when it is contraindicated. The frequency of PD is decreased so drastically because of availability of HD and higher efficacy of HD.

Delayed diagnosis and treatment, pulmonary and other infections, the frequent presence of complications and multi organ dysfunction is the chief reason of high mortality.

There was an association between AKI and hospital outcome but, an organ failure has a greater impact on the prognosis of severity of AKI.

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# LIST OF ABBREVIATIONS

AKI- Acute Kidney Injury

RIFLE - Risk, Injury Failure Loss End stage renal disease

CKD- Chronic Kidney Disease

ATN-Acute Tubular Necrosis

HIV-Human Immunodefiency Virus

GFR-Glomerular Filtration Rate

BUN-Blood Urea Nitrogen

USG- Ultrasound

MOD-Multi Organ Dysfunction

CRRT- Continuous Renal Replacement Therapy

RRT- Renal Replacement Therapy

NGAL-Neutrophil Gelatinase Associated Lipocalin

PD-Peritoneal Dialysis

HD-Hemodialysis

ADD- Acute Diarrhoeal Disease

# Proforma

NAME

AGE

SEX

IP NO

COMORBID ILLNESS

DM

SHT

CAD

CLD

PRESENTED/DEVELOPED KIDNEY INJURY

OLIGURIA

ETILOGY OF AKI

IONOTROPIC SUPPORT

VENTILATORY SUPPORT

MULTIORGAN DYSFUNCTION

USG ABDOMEN

LAB INVESTIGATIONS

RENAL FUNCTION TEST

RISK

INJURY

FAILURE

URINE ALBUMIN ,SUGAR,DEPOSITS

QBC MP/MF

MSAT

OTHER RELEVANT INVESTIGATIONS ACCORDING TO THE ETIOLOGY

REQUIREMENT OF RENAL REPLACEMENT THERAPY

OUTCOME

# PATIENT CONSENT FORM

Study detail.

"***Acute Kidney Injury in ICU Patients***"

Study centre : Institute of internal medicine, Madras Medical College

Patients Name :

Patients Age :

Identification number :

Patient may check ( ✓ ) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect of current study and any further research that may be conduction in relation to it, even I ☐

withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological .biochemical, radiological tests. ☐

Signature/thumb impression: place date

Patients Name and Address:

Signature of investigator : place date

Study investigator's Name :

## KEY TO MASTER CHART

U – Blood Urea.

Cr – Creatinine.

A – Albuminuria.

RBC – Red Blood Cells.

PC – Pus Cells.

Cons – Conservative.

PD – Peritoneal dialysis.

HD – Hemodialysis.

DM – Diabetes mellitus.

SHT – Systemic Hypertension.

CAD – Coronary artery disease.

MOD – Multi organ dysfunction.