1. INTRODUCTION AND REVIEW OF LITERATURE

1.1 INTRODUCTION

1.1.1 Anatomy and Functions of Kidney

Anatomy of Kidney

The kidneys are part of the urinary system. There are two kidneys in the body, one on either side of the spine under the lower ribs, deep inside the upper part of the abdomen. The adrenal glands are found just above each kidney and are part of the body's endocrine system. Each kidney consists of several hundred thousand functionally independent units called nephrons, and each nephron consists of one glomerulus and one double hairpin-shaped tubule that drain the filtrate into the renal pelvis.

![Figure 1.1. The Nephrons(1)](image)

The glomeruli are present in the kidney cortex and are covered by the Bowman's capsule. They are lined with parietal epithelial cells and contain the mesangium with many capillaries to filter the blood. The glomerular filtration barrier consists of endothelial cells, the glomerular basement membrane and visceral epithelial cells (also known as podocytes). All molecules below the molecular size of albumin (that is, 68 kDa) pass the filter and enter the tubule, which consists of the proximal convoluted tubule, the loop of Henle and the distal convoluted tubule. An intricate counter current system forms a high
osmotic gradient in the renal medulla that concentrates the filtrate. The tubular epithelial cells reabsorb water, small proteins, amino acids, carbohydrates and electrolytes and non-reabsorbed compounds pass from the tubular system into the collecting ducts to form urine(1).

Functions of Kidney

Kidney functions are described as below:

I. The kidneys are the major organs which regulate homeostasis (balance of the various body functions) in the body. They help to control blood pressure.

II. The kidneys help to maintain balance in fluid, acid-base, and electrolytes in the blood.

III. The kidneys remove waste from the body (nitrogenous waste like ammonia, urea, and creatinine) and remain vital substances in the body require functioning.

IV. The kidneys produce erythropoietin which stimulates the production of red blood cells and enzymes(2).

1.1.2 Kidney Diseases

1.1.2.1 Acute Kidney Disease (AKD)(3)

Acute kidney disease develops rapidly, over days or weeks; resulting in fifty percent or more nephrons to lose their function. AKD is developing due to a disorder that directly affects the blood supply to the kidney or urine flow from the kidney. AKD is often reversible. In AKD, most of the patients recover their kidney function while in some patients left with residual damage. This residual damage leads to progressive decline in kidney function after some time. In some cases, irreversible renal failure developed and required dialysis-dependent for survival.

Symptoms of acute kidney disease include fluid and electrolyte abnormalities, anemia, acute pulmonary edema, pruritus secondary to uremic frost, confusion, metabolic acidosis, congestive heart failure, nausea, and vomiting.

Type of Acute Kidney Disease:

AKD is divided into three types, based on the location of the cause.
Prerenal

In this kind of AKD, renal dysfunction occurs due to decrease blood flow to the kidney and due to reducing GFR. Diseases responsible for prerenal AKDs are blood loss, hypotension, dehydration, cardiogenic shock, septic shock, or thrombosis.

Intrarenal

Renal impairment occurs secondary to damage that is sustained at the site of the nephrons. Diseases responsible for intrarenal AKDs are acute cortical necrosis, acute tubular necrosis, acute pyelonephritis, acute glomerulonephritis, acute vasculitis, malignant hypertension, trauma, rhabdomyolysis - drugs, nephrotoxins- IV contrast, or aminoglycosides.

Postrenal

This type of AKD is reported due obstruction in kidney that prevents excretion of urine, which leads to renal failure. Diseases responsible for postrenal AKDs are renal calculi, prostatic hypertrophy, blocked urinary catheter, or tumor.

1.1.2.2 Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) is also called chronic renal insufficiency or chronic renal failure. CKD is a progressive loss in renal function over a period of months or years. Progression of CKD can be managed by using medicines and making some lifestyle changes.

Symptoms

In the initial stage of CKD, there is no any specific symptoms observed, but patients feel unwell and experiencing a reduced appetite. The initial stage of CKD can be detected by the increase in serum creatinine or protein in the urine. However, as the CKD is progress, means kidney function decreases, it results in to increase blood pressure, volume overload, urea and potassium accumulate, decrease erythrocytes synthesis, metabolic acidosis, iron deficiency anemia, sexual dysfunction, and many more.
Causes

The main causes of CKD are diabetes and hypertension. Other diseases that are responsible for CKDs are infections, polycystic kidney disease, glomerulonephritis, lupus and other immune disease, pyelonephritis, and birth defect.

Stages of Chronic kidney disease

CKD is divided into five stages based on glomerular filtration rate (GFR) as below.

Stage 1: In this stage, glomerular filtration rate is normal or relatively high GFR (≥ 90 ml/min/1.73 m²) but kidney is damaged.

Stage 2: In this stage, mild reduction in GFR (60–89 ml/min/1.73 m²) with kidney damage.

Stage 3: In this stage, GFR is moderately reduced to 30–59 ml/min/1.73 m².

Stage 4: In this stage, GFR is severely reduced to 15–29 ml/min/1.73 m².

Stage 5: When GFR reduced to < 15 ml/min/1.73 m² called as established kidney failure, or end-stage kidney disease (ESRD).

1.1.3 End Stage Renal Disease (ESRD)

When the kidneys stop working well enough to live without dialysis or a transplant is called as end stage renal disease (ESRD). This kind of kidney failure is permanent. So, ESRD patients required dialysis or a kidney transplant for survival.

Causes

Major causes of ESRD are glomerulonephritis, diabetes, and high blood pressure. The mechanism for the development of ESRD after these diseases is describing as below.

Glomerulonephritis

In glomerulonephritis, inflammation and damage are reported in glomeruli, and hence affects glomeruli ability to filter excess water and waste products from the blood. Chronic glomerulonephritis can be caused by
conditions that scar the glomeruli, inflammation of the blood vessels, infections, or immune diseases; however often the cause is unknown.

**Diabetes and Diabetic Nephropathy**

Insulin is responsible for the metabolism of the blood glucose level. In diabetic patients, insulin synthesis is decreased or not synthesis in body. Hence blood glucose level is increased in diabetic patients. This increased blood glucose level damages the blood-filtering capillaries in the kidneys and resulting into ESRD.

**High Blood Pressure**

High blood pressure (hypertension) damages the blood vessels that supplying blood to the kidneys. This result into thickening of blood vessels wall and decreasing the internal diameter of vessels; and hence reduction of blood supply to the kidney and decreased kidney function. Factors that play a vital role in high blood pressure are age, obesity, high alcohol consumption and high dietary salt.

Other causes of ESRD are born defect, some reactions to medicines, blood loss, trauma or injuries to kidney, severe anatomical problems of the urinary tract and exposes to toxic drugs, etc.

**Symptoms**

Common symptoms observed in ESRD patients are fatigue, headaches, loss of appetite, itching (pruritus) and dry skin, weight loss, nausea, bone pain, muscle twitching or cramps, drowsiness and confusion, nosebleeds or blood in the stool, problems concentrating or thinking, menstrual periods stop (amenorrhea), problems with sexual function, swelling of the feet and hands (edema), sleep problems, or vomiting.

**Diagnosis**

ESRD may identify by the complete medical history, physical examination and diagnostic procedures includes kidney biopsy, computed tomography scan (CT scan), blood tests which includes kidney function, electrolyte levels, and blood cell counts, urine tests and renal ultrasound (sonography).
Introduction and Review of Literature

**Treatment**

The only two treatments are available for the ESRD patients are dialysis and kidney transplant.

_Dialysis_

Dialysis is a process by which waste products and excess fluids are removed from the body and helps in maintaining blood pressure and red blood cells production. There are two types of dialysis.

1) **Hemodialysis**

In hemodialysis, surgically created path (vascular access) is created in patients and by this path patient is connected to the dialysis machine. Patient’s blood is pumped through a dialysis machine, which removes waste products and excess fluids from the blood. After this process, blood is return to the body.

2) **Peritoneal Dialysis (PD)**

In peritoneal dialysis, excess body fluids and waste products are removing from the body by the exchange mechanism. In PD, abdomen (peritoneum) is filled with the dialysate (dialysis fluid), using catheter. The lining of the abdominal cavity acts as a membrane which diffuses excess fluids and waste products from the blood stream into the dialysate and after few hours, used dialysate in the abdomen is drained out and discarded, and again peritoneal cavity is filled with fresh dialysate.

There are two types of PD:

i. Continuous cycler-assisted peritoneal dialysis (CCPD) uses a machine (called a cycler) to do exchanges.

ii. Continuous ambulatory peritoneal dialysis (CAPD) uses gravity to help manual exchanges.

Hemodialysis has advantages over the peritoneal dialysis regarding survival, while patients who underwent of PD having more uninterrupted time for work, family, and social activities than hemodialysis.

**1.1.4 Kidney Transplantation**

In kidney transplantation, donor [living or died (deceased or cadaver donor)] kidney is transplant to the ESRD patients using surgical procedure.
Based on source of the donor organ, kidney transplantation is classified as living-donor transplantation and deceased-donor (cadaveric) transplantation. One of the risks of a kidney transplant is that body will reject (fight) the new kidney. To help keep body from fighting new kidney, kidney transplant patients require taking a lifelong immunosuppressant drug to prevent rejection of transplanted kidney.

In Kidney transplantation, quality of life and patient survival rate are better than patients who use dialysis. Hence, kidney transplantation is a treatment of choice for many people with ESRD.

1.1.4.1 History of Kidney Transplantation

In 1902, Emerich Ullmann performed first successful experiment for kidney transplantation on dog. The kidney, auto-transplanted in the neck of a dog and it remained functional for five days. Then Alexis Carrel develops the technique of vascular sutures for which he was awarded by the Nobel Prize in Physiology or Medicine in 1912.

The first human kidney transplant was attempted by Dr. Yuri Voronoy in 1933, in the Soviet Union. A kidney was removed from the deceased donor 6 hours before transplant and was replanted into the thigh. This patient died 2 days later(4). Ruth Tucker at Little Company of Mary Hospital in Evergreen Park, Illinois, performed first successful transplant. Because of unavailability of immunosuppressive therapy, transplanted kidney was rejected ten months later.

The first kidney transplantation in living patients was performed by Jean Hamburger in 1952, in France. Transplanted kidney survives only three weeks(5). In 1954, Joseph Murray and team, at the Peter Bent Brigham Hospital, Boston, performed first successful human kidney transplantation between the identical Herrick twins. After the successful transplantations between identical twins, the use of renal transplantation in humans was broadening. Because of this, the development of immune biology and the immunosuppressant drug has stepped into the focus of interest.

In India, Dr. P K Sen and his team were attempted initial experimental kidney and liver transplants in dogs at King Edward VII Memorial (KEM)
Hospital, Mumbai in the 1950s. The first human kidney transplant in India was performed at the KEM Hospital, Mumbai in May 1965, on patient who had hypernephroma, using a cadaver donor. However, this patient was surviving only for 11 days after transplant.

Dr. Johny and Dr. Mohan Rao of CMC Hospital, Vellore, performed first successful live donor renal transplant in January 1971 and it was almost 17 years after the first “identical twin” transplanted by Murray et al., in 1954(6).

In Gujarat, first live related kidney transplantation was performed at Muljibhai Patel Urological Hospital, Nadiad in 1980.

1.1.4.2 Results of Kidney Transplantation

A success rate of kidney transplantation is measured by patient survival rate and graft survival rate. The patient care is divided into early and late post-transplant period. In early transplant period, acute allograft rejection episodes are most common. In this period, relatively a large amount of immunosuppressive medication must be administered while in late post transplant period, immunosuppressive medication load was lower as compared to early transplant period. Patient’s death rate and return to dialysis is key determinant point for identification of success rate of late renal allograft failure(7).

1.1.4.3 Causes of Graft Loss

The early post transplant period is defined as first three post transplant months. In first few transplant days, surgical issues are predominating while medical and immunological issues tend to predominate thereafter. In early post transplant period, causes of the graft dysfunction or graft loss are either non-immunological or immunological. The non-immunological causes include acute tubular necrosis, vascular (obstruction or stenosis), urological or infections. While immunological causes includes, antibody-mediated acute rejection, T-cell-mediated acute rejection, thrombotic micro angiopathy and nephrotoxicity, etc.(7).

The late post transplant period refers as more than one year after transplantation. The major causes of graft loss in late post transplant periods are the chronic graft dysfunction or the death with functioning graft (DWFG).
The causes responsible for graft loss and rates of graft loss, estimated by the US Renal Data Systems report of 2003, are described in the Fig. 1.2.

**Figure 1.2. Kidney Allograft Loss after First Year(7)**

CAN: chronic allograft nephropathy, CAD: chronic allograft dysfunction, CVD: cardiovascular disease, DWFG: death with functioning graft

Due to development of new immunosuppressive medications, the incidence rate of acute rejection and early graft failure has declined dramatically, and because of this, one-year graft survival rate is increased up to 95%, in most of the transplant centers(7).

**1.1.5 Development of Immunosuppressant Drugs**

In 1948, the first patients crippled with rheumatoid arthritis were given the Merck Company’s Crotone (cortisone) at the Mayo Clinic and intense worldwide interest in the pharmacological actions of adrenal cortical hormones followed(8). In 1951, Billingham and Morgan independently showed that cortisone increased the survival of skin grafts in rabbits, setting the stage for the use of steroids to prevent allograft rejection(9).

Induction of tolerance in adult animals (rather than newborns) was accomplished by lethal irradiation and bone marrow infusion. It was followed by attempts at human immunosuppression for organ transplants were with preliminary total-body irradiation and allograft bone marrow rescue. These procedures were carried out in Paris, Boston, and elsewhere in the late 1950s. This regimen was too difficult to control, and graft versus-host disease was inevitable. So sub lethal dose of radiation was used, and it was found sub
lethal irradiation alone in human patients was quite immunosuppressive which was used until 1962, the year of the first general availability of Azathioprine (Imuran). In Boston, 12 patients were treated in this way, but with only one long-term survival in a man receiving his transplant from his non-identical twin. In Paris, similar success was obtained with sibling grafts(8).

In 1960 Schwartz and Dameshek showed that 6-mercaptopurine delays skin graft rejection in rats(10). In 1960, Calne visited Boston for a period of research with Murray and Hitchings and Elion of Burroughs Wellcome, then at Tuckahoe, provided him with new derivatives of 6-MP. Of these, BW57-322 (later known as Azathioprine [Imuran]) proved to be more successful in dog kidney transplants and less toxic than 6-MP(11). After that Azathioprine (AZA) was first used in the clinic at the Peter Bent Brigham Hospital, Boston in 1962. Soon thereafter, AZA was introduced into renal transplantation in a rapidly increasing number of renal transplant units throughout the world. In 1963, Murray et al. and Starzl et al. studies showed that AZA could prevent kidney graft rejection in humans and usage with steroid improved the outcome(12, 13).

The polyclonal antibody preparations, anti-lymphocyte globulin (ALG) and anti-thymocyte globulin (ATG), were developed in mid-1970s. These drugs were prescribed with AZA and prednisolone as the baseline regimen or used for induction or for the treatment of steroid-resistant rejection. The success rate was increased up to 50% at one year, and the mortality rate was typically 10% to 20%.

AZA and steroids were the backbone of immunosuppression in renal transplantation for many years. In the early 1980s, the situation was transformed with the introduction of cyclosporine (CyA). Because the poor results of kidney transplantation before CyA, statistically significant improvement in graft survival rates was observed after CyA. Graft survival rate was increased up to 80% at one year. Mortality rates decreased with more effective immunosuppressant drug, less use of corticosteroids, and overall improvements in surgical and medical care.

After the introduction of CyA, the standard immunosuppressive regimen consisted of CyA and prednisone, often combined with AZA, now
used as an adjunctive agent in so-called triple therapy. Although CyA having significant effect on graft survival and patient survival rate, its effect on acute and chronic Nephrotoxicity was a major detriment.

In 1985, OKT3, the first monoclonal antibody which having capacity to treat first acute rejection episodes. However, this drug had toxicity, so its use was restricting only for the episodes of rejection that were resistant to high-dose steroids while in some programs it was also used as an induction agent. With this limited armamentarium of medications “CyA, AZA, corticosteroids, and the antibody preparations” the transplant community entered the 1990s, achieving, with justifiable pride, success rates of up to 90% in many centers and minimal mortality.

MMF was introduced in 1995, after three randomized controlled trials showed significant reduction in the incidence of acute rejections within first six months with equal graft and patient survival at 12 months(14-16). Over next decade, AZA gradually replaced MMF as an immunosuppressive agent.

In 1997, Neoral (microemulsion preparation of CyA), became available. This microemulsion formulation had more consistent exposure to CyA than the older formulation. This facilitated the individual tailoring and monitoring of CyA therapy, which translated into a reduced incidence of acute rejection episodes and an improved graft survival, without increasing adverse effects related to CyA toxicity in kidney transplantation(17-19). After development of microemulsion of CyA few studies were performed to compare MMF to AZA in combination of microemulsion formulation and steroid as background immunosuppression in renal transplant. But, one study conducted by MYSS and its follow up studies did not show any difference in acute rejection rate or graft survival in two groups(20, 21).

Tacrolimus (TAC) was introduced in 1997, after many clinical trials and having more effective in patients with steroid-resistant rejection episodes and its capacity to produce equivalent patient and graft survival as CyA(22-25). So, within few years CyA was replaced by TAC as an immunosuppressive agent.

After next year’s many new immunosuppressant drugs were introduced like Mycophenolate Sodium (2004), Sirolimus (1999), and also new antibody
preparations like ATG (1999), Daclizumab (1999) and Basiliximab (2000). By the introduction of new drugs and its safety and efficacy, 1 year survival rate of kidney transplant recipients is increased to 95% (7).

1.1.6 Immunosuppressant Drugs

Immune system of the body protects the body against harmful foreign molecules/tissue and also prevents the body against various infections. However, this protection can result in rejection of the transplanted tissue. This is happened as transplanted organ work as a foreign organ of the body, so body own immune system oppose this organ, which results into the rejection of the transplanted organ. So to prevent rejection of transplanted tissue/organ, it is requiring suppressing immune system of the body. In transplant patients, various immunosuppressant drugs are prescribed to suppress immune system and so prevent the rejection. Few commonly used immunosuppressant drugs are described as below.

1.1.6.1 Induction Antibody Preparations

1) Muromonab-CD3 (OKT3)

Muromonab-CD3 is a murine monoclonal antibody and is synthesized by hybridoma technology.

Use

Muromonab-CD3 is used for treatment of corticosteroid-resistant acute allograft rejection in cardiac and hepatic transplant patients, for acute rejection of renal allograft, and to deplete T cells from donor bone marrow prior to transplantation.

Mechanism of action

OKT3 produce its immunosuppressant drug effect by binding the T-cell receptor-associated CD3 glycoprotein, leading to initial activation and cytokine release, followed by blockade of function and T-cell depletion.

Adverse effects

It produces anaphylactic reactions, infections, high fever, cerebral edema, seizures, aseptic meningitis, encephalopathy, and headache.
Because of more adverse effects of OKT3 and development of more tolerable rabbit anti-thymocyte globulin and IL-2 receptor antagonists, OKT3 is rarely used for transplant patients(26).

2) Anti-thymocyte Globulin (ATG)

Based on derived source, ATG is divided into two type; one is derived from horses (ATGAM) and second is rabbits (thymoglobulin) derived.

Use

In combination with other immunosuppressive agents, ATG is used to prevent early allograft rejection at the time of transplantation. ATG is also used to treat corticosteroid-resistant acute rejection and severe rejection episodes. Intraoperative administration of ATG was associated with a lower incidence of delayed graft function (DGF) and shorter hospital stay(27).

Mechanism of action

They produce their immunosuppressant effect by binding to various cell surface markers, leads to complement dependent lysis of lymphocytes.

Adverse effect

Chills, skin rashes, fever, thrombocytopenia, leucopenia, and infections due to CMV or other viruses will be produced after the usage of ATG.

Several studies conducted to compare thyroglubulin with ATGAM shows that thymoglobulin was associated with better graft survival and more effective in preventing rejection, than ATGAM(28).

3) IL-2-receptor antagonists

IL-2 Receptor Antibodies are Daclizumab and Basiliximab. Basiliximab is consists of 75% human protein and 25% murine, and hence it is designated as “chimerized”. While Daclizumab is consist of 90% human protein, and hence it is designated as “humanized.”

Use

IL-2-receptor antagonists are used as a prophylaxis in low-to-moderate risk renal transplantation recipients in combination with CyA and corticosteroids to prevent acute rejection after transplant(29).
Mechanism of action

Daclizumab and Basiliximab are anti-CD25 antibodies. They bind to α chain of the IL-2 receptor on activated T cells and interfere with the proliferation of T cells. Basiliximab is about 10-fold more potent than daclizumab. Blockade of this receptor foils the ability of any antigenic stimulus to activate the T-cell response system.

Adverse effects

Both daclizumab and basiliximab are well tolerated. Commonly observed adverse event with this class of drug is related to GI tract.

4) Alemtuzumab

Alemtuzumab is a humanized anti-CD52 monoclonal antibody.

Use

Alemtuzumab is used for the treatment of refractory B-cell chronic lymphocytic leukemia. Alemtuzumab is also used in corticosteroid-avoidance protocols in combination with sirolimus and low-dose calcineurin inhibitors in transplant patients.

Mechanism of action

It exerts its effects by triggers antibody dependent lysis of lymphocytes (both B and T cells), NK cells, and, to a lesser extent, of monocytes and macrophages.

Adverse effects

It includes thrombocytopenia, neutropenia, autoimmune diseases, and thyroid disease.

5) Rituximab

Use

It is used in the treatment of leukemia, lymphomas and autoimmune diseases. It is also used in kidney transplant patients in combination with plasmapheresis and IVIG to treat antibody mediated rejection and to desensitize patients with preformed antibodies for ABO- and/or HLA-incompatible kidney transplant(30).
Mechanism of action

It produces its effect by binding to CD20 and down regulates the B cell receptor.

Adverse effect

It produces severe infusion reaction, bowel obstruction, cardiac arrest, infections, cytokine release syndrome, tumor lysis syndrome, perforation, and pulmonary toxicity.

1.1.6.2 Maintenance Immunosuppressive Drugs

1) Glucocorticoids

The glucocorticoids are used in transplantation and in various autoimmune disorders as an immunosuppressive agent. They are still one of the mainstays for attenuating rejection episodes.

Use

The steroids are used to suppress acute rejection of solid organ allograft, in chronic graft-versus-host disease and in autoimmune conditions like temporal arthritis, systemic lupus erythematosus, refractory rheumatoid arthritis, and asthma.

Mechanism of action

It produces an immunosuppressive effect by blocking T-cell and antigen presenting cell (APC) derived cytokine expression. Glucocorticoids bind to cytoplasmic receptor to form a complex, which translocate into the nucleus and binds to glucocorticoids response elements (GRE) in the promoter regions of cytokine genes. Glucocorticoids also inhibit the translocation of transcription factor AP-1 and NF-κB into the nucleus. Therefore, production of several cytokines (IL-1, 2, 3, 6, TNF-α, gamma-interferon) are inhibited.\(^{(31)}\)

Adverse effect

It is diabetogenic and can cause weight gain, vascular necrosis hypercholesterolemia, cataracts, osteoporosis, and hypertension.
2) Calcineurin Inhibitors (CNIs)

I) Cyclosporine

Cyclosporine is an 11-amino-acid cyclic peptide from *Tolypocladium inflatum*.

**Use**

Cyclosporine is used to prevent rejection of cardiac, liver, and kidney allogeneic transplants. CyA is used for the treatment of rheumatoid arthritis as an alternative to methotrexate. CyA is also used for erophthalmia and for patients with recalcitrant psoriasis that does not respond to other therapies.

**Mechanism of action**

CyA preferentially suppresses cell mediated immune reactions, whereas humoral immunity is affected to a far lesser extent. After diffusing into the T cell, CyA binds to a cyclophilin (immunophilin) to form a complex that binds to calcineurin. The latter is responsible for dephosphorylating NFATc (cytosolic Nuclear Factor of Activated T cells). Because the CyA-calcineurin complex cannot perform this reaction, NFATc cannot enter the nucleus to promote the reactions that are required for the synthesis of a number of cytokines, including IL-2. The end result is a decrease in IL-2, which is the primary chemical stimulus for increasing the number of T lymphocytes.

**Adverse effects**

CyA produces acute and chronic nephrotoxicity, neurotoxicity (tremor, dysesthesias, insomnia, headache), electrolyte disorders (hyperuricemia, hyperkalemia, hypomagnesemia), gingival hyperplasia, Hypertrichosis, thrombotic microangiopathy (TMA), new onset diabetes, hypertension, hirsutism, bone pain syndrome, and hyperlipidemia.

II) Tacrolimus

Tacrolimus (originally called FK506) is a macrolide that is isolated from the soil fungus *Streptomyces tsukubaensis*. 
Use

TAC is used for the prevention of rejection in kidney and liver transplants and in severe atopic dermatitis that does not respond to conventional therapies. TAC is prescribed with corticosteroid and/or with an anti-metabolite.

Mechanism of action

TAC exerts its immunosuppressive effect as same as CyA, except that it binds to a different immunophilin, FKBP-12 (FK binding protein).

Adverse effects

Adverse effect produced by TAC includes nephrotoxicity, neurotoxicity (tremor, seizures, and hallucinations), insulin-dependent diabetes mellitus, hypertension, electrolyte disorders (hyperkalemia, hypomagnesaemia, hyperuricemia), hyperlipidemia, and anaphylactic reactions.

TAC therapy is associated with lesser episodes of rejection as compare to CyA and also with TAC therapy, lower doses of corticosteroids is required to produce similar immunosuppression and hence TAC therapy was associated with reducing the likelihood of steroid-associated adverse effects. Hence in most of the transplant centers, CyA is replaced with TAC.

3) Mammalian Target (mTOR) Inhibitors

I) Sirolimus

Sirolimus (Rapamycin) is a macrolide obtained from fermentations of the soil mold Streptomyces hygroscopicus.

Use

Sirolimus is used in renal transplantation along with CyA and corticosteroids. Sirolimus is also used as Sirolimus-coated stents in cardiac patients to reducing proliferation of the endothelial cells and hence prevent restenosis.

Mechanism of action

Sirolimus bind to the cytoplasmic FK binding protein and forming a complex with mTOR, which leads to suppressing progression of activated T
cells from the G1 to the S phase of the cell cycle and, consequently, the proliferation of these cells. Unlike CyA and TAC, sirolimus does not owe its effect to lowering IL-2 production but, rather, to inhibiting the cellular responses to IL-2.

**Adverse effects**

Hyperlipidemia is a most common side effect of sirolimus. Other side effects include nephrotoxicity, headache, nausea and diarrhea, leucopenia, and thrombocytopenia. Clinical monitoring of plasma concentration of sirolimus must be monitored closely.

**II) Everolimus**

Everolimus is a derivative of sirolimus.

**Use**

It was used in renal transplantation patients and in patients with advanced renal cell carcinoma. Because of anti-neoplastic and antiviral benefits of Everolimus, usage of Everolimus is associated with lower incidence of malignancy and viral diseases (CMV and BKV infection)(32).

**Mechanism of action**

Everolimus has the same mechanism of action as sirolimus. It inhibits activation of T cells by forming a complex with FKBP-12 and subsequently blocking mTOR.

**Adverse effects**

Everolimus produce adverse effects which include hyperlipidemia, impaired or delayed wound healing, nephrotoxicity, angioedema and increased risk of kidney arterial and venous thrombosis.

**4) Anti-metabolites**

**I) Azathioprine**

Azathioprine is a prodrug that converted in to 6-mercaptopurine (6-MP) and then into thioinosinic acid.
Mechanism of Action

It interferes with DNA synthesis by inhibiting metalloproteinase and synthesis of thioguanine nucleotides.

Adverse events

The major toxicity of Azathioprine is bone marrow suppression. Other adverse effects of AZA include pancreatitis, macrocytosis, and liver toxicity.

II) Mycophenolate acid

Mycophenolate acid has replaced AZA because of its safety and efficacy in prolonging graft survival. Mycophenolate acid is available in two different formulations: mycophenolate sodium and mycophenolate mofetil.

Mechanism of action

Both forms are rapidly hydrolyzed in the GI tract to mycophenolic acid. This is a potent, reversible, uncompetitive inhibitor of inosine monophosphate dehydrogenase, which blocks the de novo formation of guanosine phosphate. Thus, like 6-MP, it deprives the rapidly proliferating T and B cells of a key component of nucleic acids.

Adverse event

Common adverse effects include vomiting, diarrhea, abdominal pain, nausea, anemia, CMV infection, and leucopenia.

5) Belatacept

Belatacept is the first co-stimulatory pathway blockage approved as a maintenance immunosuppressive agent for kidney transplant.

Mechanism of action

Belatacept is a fusion protein combining CTLA-4 with the Fc portion of IgG. It blocks the co-stimulatory pathway CD28-CD80/86 (signal 2) by binding to CD80/86 on T-cells, therefore, inhibits T-cell activation.

Adverse event

The significant side effect is the increased risk of post-transplant lympho proliferative disease (PTLD) primarily involving the CNS in patients
without Epstein-Barr virus (EBV) immunity. Other risk factors for PTLD may include CMV infection and over immunosuppression.

Year of introduction, IS type, mechanism of action, site of action and adverse events of Immunosuppressant drug, are summarized in Table 1.1.
<table>
<thead>
<tr>
<th>Year of introduction</th>
<th>IS type</th>
<th>Drugs</th>
<th>Targets</th>
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<td>Anti-metabolites</td>
<td>Azathioprine</td>
<td>Purine analog myelocytes</td>
<td>DNA synthesis [Promyelocytes proliferation]</td>
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<td>IS type</td>
<td>Drugs</td>
<td>Targets</td>
<td>Mode of action (inhibition)</td>
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<td>1999</td>
<td>Polyclonal antibodies</td>
<td>Anti-thymocyte globulin (ATG)</td>
<td>T and/or B cells (activated)</td>
<td>Blocking adhesion of lymphocytes and platelets to the endothelium</td>
<td>Cytokine release syndrome, Pancytopenia, Anaphylaxis, Allergy</td>
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<td>Platelets</td>
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<td>1985 2000 1999</td>
<td>Monoclonal antibodies</td>
<td>OKT3, basiliximab, daclizumab</td>
<td>CD3, CD25</td>
<td>Block α chain of the IL-2 receptor and hence T cell replication</td>
<td>GI toxicity</td>
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1.1.7 Immunosuppressive Drugs and Long-term Graft Outcome (35, 36)

Immunosuppressive drugs are essential for prevention of acute rejection. However, their role in the prevention of late graft loss is not clear. Experimental studies in animals revealed that immunosuppressive drugs could prevent chronic allograft failure in some combinations, but there is no evidence in humans. Before the 1980s, a combination of corticosteroids and AZA used as an immunosuppressant, in some centers they also used anti-lymphocyte antibody as a prophylactic in the first few post-transplant weeks. Various clinical studies for patient and graft survival rate illustrate that many surviving grafts had signs of dysfunction and fibrosclerotic changes. There is a strong correlation of acute rejection episodes with later dysfunction lead to the hypothesis that these late changes may have an immune pathogenesis. We will, therefore, examine the role of immunosuppressant on long-term outcome and chronic allograft nephropathy.

1.1.8 Complication after Kidney Transplant

The main complications which can occur following a kidney transplant are diabetes mellitus, rejection, and infections.

Diabetes Mellitus

Diabetes means the body has difficulty in maintaining normal blood sugar levels. Immunosuppressant drugs which are prescribed to prevent rejection episode such as Prednisone, TAC, CyA can cause diabetes, which called as new onset of diabetic mellitus (NODAT). If treatment for control of blood sugar level is not started then it affect on patients survival rate and also kidney function, so it is required to start taking insulin or antidiabetic drug to control blood sugar when symptoms like increased thirst, increased frequency of urination, blurred vision, and confusion persisted and blood glucose level shows high.

Rejection

For patients who underwent transplantation, transplanted kidney is a foreign organ, so patients own immune system oppose this kidney and patients body’s immune system fights off or destroys (rejects) anything foreign
to keep it running smooth. So, to prevent the rejection episode transplant patients require taking immunosuppressive medications for the rest of life. It is required to proper management of Immunosuppressant drug in transplant patients to prevent rejection.

Rejection episode is divided into three types: Hyper-acute rejection, Acute rejection, and Chronic rejection. In Hyper-acute rejection, body immediately destroys the transplanted kidney and is very rare form of rejection and is reported immediate after transplant. Acute rejection usually occurs in the first few months after transplant, but it can happen at any time after the transplant. Acute rejection is treated with the use of increased doses of immunosuppressant medication to repress the body’s desire to reject the organ. Chronic rejection is occurring months or even years after the transplant, this form of rejection causes transplanted kidney to stop working slowly. Still, we have no any medication that prevents or cure this chronic rejection episode.

**Infections**

Immunosuppressive medications prescribe to transplant patients which help to prevent rejecting of transplanted kidney by patients own body. However, this drugs also reduce body’s own immune system which may lead to increase susceptible to various infections after transplant surgery. Few common infections after transplantation are a bacterial infection, fungal infection, viral infection including CMV and herpes infection. Infection after transplantation may effect on patients survival and graft survival and also increase the hospitalization of transplant patients. So, prevention of Infection requires for long term graft survival and patients survival.

Other complications after transplantation are Delayed function, Drug toxicity, and Urologic problems. Drug prescribe to transplant patients also produce some complications like Cancer (skin, organ), Gastrointestinal problems, Weight gain, Joint problems, Cataracts, Hyperlipidemia, Acne, Tremors, Gum overgrowth, etc.

So, we were performed a retrospective study to find out the major complication after transplantation and effect of these complications on patients and graft survival rate. We also conduct prospective study to identify
the effect of the immunosuppressant drug on infection, the prevalence rate of infection and effect of infection on various parameters.

1.1.9 Study Center

Study center for our study was Muljibhai Patel Urological Hospital which is situated at Nadiad, a middle of Gujarat. This center is certified by ISO 9001:2008 for a quality management system for design, development, and delivery of clinical services for Urology & Nephrology - including Kidney Transplantation to global standards. First, live donor kidney transplant in Gujarat is performed in this center in 1980. Till date, more than 2500 patients were undergone kidney transplanted at this center, and most of these patients were Indian. All patient laboratory reports, their prescription, and other patient's information were well managed in individual patients file. So, it can be easily traceable. Hence, I choose this center for conduction of retrospective study as well as prospective study in Indian transplant patients.

1.2 REVIEW OF LITERATURE

1.2.1 Studies on Drug Utilization in Kidney Transplant Patients

With the development of more effective immunosuppressant drugs for kidney transplant patients, utilization of immunosuppressant drugs is changed than the previous years in all over the world. Few studies were conducted to identify the changes in drug utilization which are described as bellow.

1.2.1.1 Study Conducted by Meier-Kriesche HU et al. on Drug Utilization(37)

In this study, they found that usage of induction immunosuppressant has increased from 46% in 1995 to 72% in 2004. They also found that anti-thymocyte globulin was most commonly used induction immunosuppressant (37% of transplant recipients). According to report, calcineurin inhibitors (CNIs) were main maintenance immunosuppressant, being prescribed to 93% patients. They observed trend was move towards the TAC among CNI. In 2004, usage of TAC was increased to 72% as compared to only 21% patient received CyA. Same way among antiproliferative agents, the use of MMF was increased (81%) compared to AZA.
There was continues to increase the utilization of the combination of TAC/MMF; it was the most frequently used discharge regimen (60%), followed by CyA/MMF, the use of which has continued to decline, reaching 16% in 2004. In 2004, only 9% Patients received other regimen- TAC/sirolimus (5%), CyA/sirolimus (3%) and sirolimus/ MMF (1%). At 1 year after transplantation in 2003, 51% of patients were receiving TAC/MMF, 17% were receiving CyA/MMF, 8% on TAC/sirolimus and 1% on sirolimus/ MMF.

After the transplantation, during first three years found that low percentage of patients was continued on their original immunosuppressive discharge regimen. Among patients transplanted in 2001, those on TAC/ MMF regimen at discharge time continued same regimen (75% in 1st year and 57% in 3rd year of 2001).

1.2.1.2 Study Conducted by OPTN/SRTR in the United States on Drug Utilization(38)

U.S. Department of Health and Human Services Health Resources and Services Administration published OPTN/SRTR 2012 annual report in June 2014. According to this report, Usage of inducing agent in kidney transplant patients continued increase as compared to previous year and trends was move towards the usage of antibodies as its use was increased to 84% of patients vs. 72 % in 2004. Among various antibodies usage of ATG as an inducing agent in kidney transplant patients continued to be increased while usage of IL-2 RA was decreased.

According to this report, calcineurin inhibitors were still main maintenance immunosuppressant being prescribed to 95% patients. They reported that trend was move towards the usage of TAC among calcineurin inhibitor. In 2012 usage of TAC has increased to 91 % as compared to only 4% patient received CyA. Same way among antiproliferative agents the use of MMF has increased (95%) compared to AZA. In this result, they also find out that usage of steroids in renal transplant patients was continued to be deceased. Only 65% of patients were treated with steroids.

1.2.1.3 Study Conducted by Australia and New Zealand Dialysis and Transplant Registry on Utilization of immunosuppressant drugs(39)

At Australia:
**Maintenance regimen in Australia:**

This report shows that 97% primary disease donor transplant patients in 2011 were started calcineurin inhibitor as a maintenance regimen. Among this, 87% were on TAC while only 10% patients on CyA. This data shows that trends moved towards the usage of TAC, in 2004 only 38% patients were used TAC while in 2011 it's raised to 87% while usage of CyA was decreasing.

In antiproliferative agent usage of MMF as a maintenance regimen was higher as compared to AZA in 2011 (60% vs. 1%) while usage of steroids was used in 97% patients.

After 1 and two year transplant, usage of TAC as a calcineurin inhibitor continues to be higher as compared to CyA. TAC used in 81% and 78% after 1 and two year transplant in 2011 vs 11% and 10% of CyA. If considering antiproliferative agent usage after 1 and 2 year of transplant, usage of antiproliferative agent was increased as compare to initial regimen and among this antiproliferative agent, usage of MMF continued to be more as compare to AZA (73% Vs 5% after 1 year and 75% vs. 6% after 2 years in 2011). Usage of steroids was decreased after 1 and two year after transplant in 2011, but the number of patients remains on steroids after two years of transplantation has been increased since 2004 and is now 94%, for patients transplanted in 2009.

**Antibody usage in Australia:**

All patients were given inducing agent on the day of transplant in 2011, among this usage of Anti CD 25 (Declizumab, Basiliximab) was most commonly used. It was used in 90% of patients while usage of Intravenous immunoglobulin, T cell depleting polyclonal Ab and Rituximab was 5%, 4%, and 1% respectively.

Anti CD 25 (Declizumab, Basiliximab) usage as an antirejection therapy was higher than other antibody in 2011. However, usage of T cell depleting polyclonal Ab was continued to be increase as an antirejection therapy then previous year (5 % in 2011 Vs 2% in 2007).
At New Zealand:

Maintenance regimen in New Zealand:

In this report, it shows that all disease donor transplant patients started calcineurin inhibitor as a maintenance regimen in 2011 and 71% patients on CyA vs. 29% on TAC. However, usage of TAC was continued to be increase in transplant patients (29% in 2011 Vs 6% in 2004). All patients were also administered MMF as an antiproliferative agent and were started on steroids as an initial drug regimen.

In this report, its reflect that in new Zealand usage of TAC is increase after 1 and two year transplant while usage of CyA was decease. Same decline rate in usage of MMF and steroids was also reported after 1 and two years of transplant.

Antibody usage in New Zealand:

In New Zealand, most of the patients were given inducing agent on the day of transplant. Among this usage of Anti CD 25 (Declizumab, Basiliximab) was most commonly used agent. It was used in 93% of patients while usage of T cell depleting polyclonal Ab and Rituximab was 1% and 2.5% respectively.

T cell depleting polyclonal Ab was most commonly used antirejection therapy than other antibody in 2011 and usage of T cell depleting polyclonal Ab was continued to be increased then previous year (9% in 2011 Vs 2% in 2007).

1.2.2 Studies on Comparison of Immunosuppressant Drugs and Their Effect:

With the development of new drug, graft and patient survival rate after the transplant is increasing. Now a day one-year patient survival rate is increased to 95%. Many trials were conducted to compare the drugs, the impact of drugs on patients and graft survival rate, kidney functions and side effect of drugs. Some of them mention below:
1.2.2.1 Randomized Trial done by Vincenti et al. on Comparison between Cyclosporine and Tacrolimus(40)

Vincenti et al. had performed a 6-month, randomized, open-label, multicenter trial on 682 patients to compare CyA micro-emulsion with TAC. At 6-month, they observed the incidence of treated diabetes was significantly higher in TAC group (48/286, 16.8%) as compared to CyA group (25/281, 8.9%; P = 0.005) and incidence of graft loss, BPAR, or death occurred in 34 TAC patients (9.8%) and in 43 CyA patients (12.8%, P = 0.211). In their study, in CyA arm 59% (20/34) rejection episodes were mild graded (Grade IA or IB), 38% (13/34) were moderate graded (Grade IIA) and 3% (1/34) were severe graded (Grade > 2B) as compared to 46% (11/24), 29% (7/24) and 25% (6/24) in the TAC group, respectively.

At 6 months, they did not find any significant difference between both TAC and CyA group for mean GFR (65.9 ± 23.1 vs. 63.6 ± 20.7, P = 0.285) but for mean creatinine they found a significant difference between both groups (133 ± 57 µmol/L vs. 139 ± 58 µmol/L, P = 0.005). Mean blood pressure was similar between both treatment groups at six months while median LDL-cholesterol, triglycerides, and total cholesterol were higher in the CyA arm than in the TAC arm. They observed higher CMV infection in CyA arm as compared to TAC arm (P = 0.003).

1.2.2.2 Prospective Study done by Larson TS et al. on Comparison between Tacrolimus and Sirolimus(41)

Larson TS et al. performed a prospective study on recipients who underwent transplantation between April 2001 and January 2004 at Mayo Clinic, Rochester. In this study, total 165 patients were enrolled, and among them, 84 patients were randomized to TAC therapy and 81 patients to sirolimus therapy.

During the study, 38% (30 patients) of sirolimus group and 16% (13 patients) of TAC group discontinued the assigned study medication. In Kaplan-Meier analysis, one year patient survival rate (96% vs. 98%, P = 0.42) and graft survival rate (92% vs. 94%, P = 0.95) were non-significant between TAC group and sirolimus group. The similar non-significant difference in the rejection rates was also observed between the groups (P = 0.51). For tubular atrophy, interstitial fibrosis, and glomerulopathy difference were also non-
significant between both groups. They observed higher incidence of chronic vascular changes in the TAC group (43% in TAC vs. 26% in Sirolimus, \( P = 0.03 \)).

The incidence of polyomavirus infection was non-significant between both groups (\( P = 0.37 \)) but systemic CMV infection was significantly higher in TAC group (\( TAC = 12\% \) vs. Sirolimus = 3\%, \( P = 0.02 \)). The incidence of NODAT was non-significant between both group (\( TAC = 10\% \) vs. Sirolimus = 7.5\%, \( P = 0.78 \)). Sirolimus was associated with increased incidence of wound healing complications as compared to TAC. By these results, they conclude that sirolimus + MMF + prednisone regimen having similar patient and graft survival as compared to a regimen of TAC + MMF + prednisone but having low acute rejection rates at one year after transplant.

1.2.2.3 Randomized Trial done by Webster AC et al. on Comparison between Tacrolimus and Cyclosporine(25)

Webster AC et al. comprehensively searched Embase (1980-October 2003), Medline (1966-October 2003), conference proceedings, and Cochrane Collaboration resources and included all randomized trials comparing TAC with CyA solution or CyA micro-emulsion as initial immunosuppressive therapy. By this way, they enrolled 4102 randomized participants from 123 reports of 30 trials.

The results of this study shows, at 6 month, TAC was associated with significant reduction of graft censored for death (44\%; CI = 0.36 to 0.86, RR = 0.56, 95\%) and similar result was also observed after three years (29\%; CI = 0.52 to 0.96, RR = 0.71, 95\%). They also observed TAC treated recipients had significantly lower rejection (confirmed by biopsy or diagnosed by clinically) beyond three months as compare to CyA. For steroid resistant rejection, they also find TAC therapy was associated with 55% reduction at six months as compared to CyA therapy (RR = 0.45, 0.33 to 0.60). At six months, mean creatinine was significantly lower in TAC treated patients as compared to CyA treated patients.

For NODAT, they observed TAC was significantly associated with risk of NODAT at 6-month (RR = 2.56, 1.37 to 4.78), 1-year (RR = 1.86, 1.11 to 3.09), and 3-year (RR = 2.01 to 7.41) after transplant.TAC treatment was
more prone to have vomiting, tremor, dyspepsia, headache, hypomagnesemia, and diarrhea than CyA treatment while CyA treatment was more prone to have hirsutism, constipation, and gingival hyperplasia.

By this study, they conclude TAC is superior to CyA in preventing acute rejection and have improved early graft survival, but TAC treatment has more diabetes, neurological, and GI side effects.

1.2.2.4 Randomized Trial done by Kramer BK et al. on Comparison between Combination Therapy of Tacrolimus and Cyclosporine Vs Azathioprine and Steroid(42)

They performed randomized, comparative six month trial to compare TAC and CyA. Both drugs were given in combination with AZA and steroids. In this study, they enrolled 286 patients in the TAC arm and 271 in the CyA arm in aged 16 to 60 year as intent to treat population (ITT). Among these patients, 237 patients (82.9%) in the TAC treatment group and 222 patients (81.9%) in the CyA group were assessed at two-year follow-up.

Calculated on ITT populations, mortality was significantly lower in TAC group as compare to CyA (2.0% vs 3.3%; P < 0.05) while graft loss rate in both group were non-significant after 2 years (9.3% vs 11.2%; P = 0.12). Biopsy-proven acute rejection was significantly lower in TAC as compare to CyA (19.6% vs 37.3%, P < 0.0001) at first 6 month, but was non-significant during 7–12 and 13–24 month follow-up (4.7% and 0.9% with CyA and 1.7% and 0.8% with TAC, respectively). At 24 month after transplant, composite endpoint consisting of biopsy-proven acute rejection, patient death, and graft loss was reported significantly less frequently in TAC patients than in CyA patients.

In their study, a serum creatinine concentration was significantly better in TAC group as compared to CyA group (136.9 vs. 161.6 mmol/L; P < 0.01). If considering unchanged maintenance regimen then more patients of TAC group were unchanged as compared to CyA group (82.5% vs. 66.2%, respectively) at two years while more patients in the TAC group were off steroids and received CNI monotherapy and fewer TAC patients remained on a triple immunosuppressive regimen.
They also compare cardiovascular risk profile and found that TAC having beneficial effect on lowering cholesterol ($5.24 \pm 1.04$ vs $5.49 \pm 1.04$ mmol/L, $P < 0.01$) and triglycerides ($1.59 \pm 0.86$ vs $1.75 \pm 1.03$ mmol/L, $P < 0.05$) at 2 year after transplant. They also measure New-onset diabetes mellitus at 2 year but difference between both drug was statistically non-significant [TAC = 3.6% (08 Patients) vs CyA = 1.9% (04 patients)]. In this study, they did not found any significant difference in blood pressure in both treatment groups at two years. By this study, they conclude that TAC is a highly efficacious as a baseline immunosuppressant and produce long-term beneficial effect on graft function and graft survival.

1.2.2.5 Crossover Study done by Vincenti et al. on Comparison between Tacrolimus and Cyclosporine(43)

Vincenti et al. performed five year crossover study to measure effect of TAC and CyA on graft survival. In Intent-to-treat analysis, they did not find significant difference between both treatment groups for graft survival (64.3% vs. 61.6%; $P = 0.558$) and patient survival (79.1% vs. 81.4%; $P = 0.472$) at 05 year. The rate of crossover and treatment failure was significantly lower in patients randomized to receive TAC-based therapy (9.3% vs. 27.5%; $P < 0.001$ and 43.8% vs. 56.3%; $P = 0.008$, respectively). They found that graft survival was significantly improved in the TAC treatment arm when crossover due to rejection was counted as graft failure (63.8% vs. 53.8%; $P = 0.014$). They also compare both groups for requirement for medications to control hyperlipidemia and hypertension and found that TAC therapy was also associated with a significantly reduced the usage of this concomitant medication. They found that there was a substantial rate of reversal of TAC-associated insulin dependence.

Based on results, they conclude TAC-based therapy was significantly associated with lowering risk of graft failure, without an increase in the incidence of adverse events associated with long-term immunosuppressant.
1.2.2.6 Randomized Trial done by Knoll GA et al. on Comparison between Tacrolimus and Cyclosporine(44)

Knoll GA et al. perform Meta analysis of randomized trials to compare TAC Vs CyA and for that, they reviewing Medline database, Embase database, Cochrane Library, Transplantation and Transplantation Proceedings journal, and in this study, they used eight articles out of 499 articles based on exclusion criteria. Thus final analysis was based on 1037 patients. They found that there was non-significant effect of TAC on graft loss at one year as compared to CyA (OR 0.95; 95% CI 0.65 to 1.40). Similarly, non-significant difference for mortality was also observed between both treatment arms at one year (OR 1.07; 95% CI 0.47 to 2.48). In their study, they found TAC treatment was associated with a significant reduction in episodes of acute rejection as compare to CyA therapy (OR 0.52; 95% CI 0.36 to 0.75) and also the use of anti-lymphocyte antibodies to treat rejection was significantly lower in patients receiving TAC (OR 0.37; 95% CI 0.25 to 0.56). In this study, they reported higher proportion of patients treated with TAC had NODAT as compare to CyA group at one year after transplant (OR 5.03; 95% CI 2.04 to 12.36). They perform sensitive analysis between two groups and found treatment with TAC did not have a significant effect on graft loss (odds ratio 0.68; 95% CI 0.38 to 1.22) or patient mortality (OR 0.80; 95% CI 0.20 to 3.21).

1.2.2.7 Randomized Trial done by Mayer AD et al. on Efficacy and Safety of Tacrolimus and Cyclosporine(45)

Mayer AD et al. perform multicenter, randomized trial to compare the 12-month efficacy and safety of TAC- and CyA-based immunosuppressive regimens in the prevention of renal allograft rejection. This study was conducted at 15 centers. In this study, total of 448 renal transplant recipients was enrolled. Among these patients, 303 patients were on TAC arm and 145 patients on CyA arm. All patients were also receiving AZA and corticosteroids. At the end of study they observed, acute (25.9% vs. 45.7%; P < 0.001) and corticosteroid-resistant rejection (11.3% vs. 21.6%; P = 0.001) were significantly lower in TAC therapy. Actuarial 1-year graft survival rate (82.5%
vs. 86.2%; P = 0.380) and patient survival rate (93.0% vs. 96.5%; P = 0.140) was statistically non-significant between both treatment groups.

In this study, they observed renal impairment, infections, gastrointestinal complaints and neurological complications in both treatment group frequently but mostly reversible. In TAC treated group, they reported higher incidences of diarrhea, elevated serum creatinine, hyperglycemia, tremor, angina pectoris, and diabetes mellitus while in CyA group, they more reported gingival hyperplasia, acne, hirsutism, and arrhythmia. By this study, they conclude that TAC therapy was associated with significant reduction in the incidence of rejection episodes and may have important long-term implications on graft survival.

1.2.2.8 Study done by Sollinger HW on Comparison of Various Doses of MMF and Azathioprine(14)

The U.S. Renal Transplant Mycophenolate Mofetil Study Group compared the two doses of MMF to AZA in patients receiving CyA, steroids, and ATG induction therapy. This double-blind, multicenter, randomized study was conducted to evaluate the efficacy and safety of MMF for the prevention of acute rejection episodes in adult patients. In this study, all patients were followed up for six months.

In this study, total of 499 patients was randomized in three treatment group based on dose and treatment. One group received 2 g MMF (1 g MMF, twice a day), second group received 3 g MMF (1.5 g MMF, twice a day) and third group received AZA (1-2 mg/kg/day). All patients were received CyA, corticosteroids, and ATG.

They reported 47.6% of AZA treated patients had biopsy-proven acute rejection episodes or treatment failure while 31.1% of 2 g MMF treated patients (P = 0.0015) and 31.3% of 3 g MMF treated patients (P = 0.0021) reported with biopsy-proven acute rejection episodes or treatment failure. They also compared time of first biopsy-proven rejection episode or treatment failure and found that 2 g MMF treated patients and 3 g MMF treated patients developed significantly longer time after transplant as compared to AZA treated patients (P = 0.0036, P = 0.0006, respectively).
They also reported, AZA treated patients required more antirejection treatment as compared to patients treated with 2 g MMF and 3 g MMF (AZA = 44.5% vs 2 g MMF = 24.8%, and 3 g MMF = 21.1%). The usage of anti-lymphocyte agents as a part of antirejection therapy was higher in the AZA treated patients (20.1%), while 10.3% in 2 g MMF treated group and 5.4% in 3 g MMF treated patients. At six months after transplant, patient survival and graft survival were similar in all three treatment groups.

1.2.2.9 Study done by European Mycophenolate Mofetil Cooperative Study Group on Comparison of Various Doses of MMF and Placebo (16)

The European Mycophenolate Mofetil Cooperative Study Group compared 2 g MMF treated and 3 g MMF treated patients with placebo treated patients. All patients received CyA and prednisone along with this drug. In this study total 491 patients were enrolled, and among them, 166 patients were randomized in placebo, while 165 patients in 2 g MMF, and 160 patients in 3 g MMF treatment group.

In this study, they observed 2 g MMF treated recipients having significantly lower biopsy-proven rejection as compared to placebo treated recipients (17.0% in 2 g MMF, 13.8% in 3 g MMF and 46.4% in Placebo treated, P < 0.0001). Antirejection therapy requirement for rejection episode was also higher in placebo controlled group (51.8%) as compared to 2 g MMF treated group (28.5%) and 3 g MMF treated group (24.4%).

This study reported 10.2% placebo treated patients were died or lost their graft at 06 months after transplant while 6.7% of 2 g MMF and 8.8% of 3 g MMF treated patients were died or lost their graft at 06 months after transplant. Overall, the frequency of adverse events was similar in all treatment groups, although opportunistic infections, leucopenia, and gastrointestinal problems, were more common in the MMF groups and more in 3 g MMF treated patients as compared to 2 g MMF treated patients. By this study, they conclude that at six months after transplant, MMF treatment was significantly associated with reduction of biopsy-proven rejection rate or other treatment failure. MMF therapy was well tolerated, but 3 g dose was somewhat less well tolerated as compared to 2 g dose.
1.2.2.10 Study done by Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group on Efficacy and Safety of MMF and Azathioprine(15)

This study was prospective, double-blind, multicentre trial in which all patients were followed up for six months after transplant. In this study, efficacy and safety of MMF and AZA were compared. Total 503 patients were enrolled in the study, and among them, 164 patients were randomized to 3 g MMF treated group while 173 patients in 2 g MMF treated group and 166 in AZA treated group. All patients were treated with CyA and corticosteroids along with above drug.

In this study, 15.9% of 3 g MMF treated patients reported with biopsy-proven rejection episode while 19.7% in 2 g MMF treated patients and 35.5% in the AZA group reported with biopsy-proven rejection episode. Among this biopsy proven rejection episode, 6.1% of 3 g MMF, 10.4% of 2 g MMF and 19.9% of AZA treated were grade II or more (histological severity) severe rejection. The requirement of antirejection therapy was 24.4% in 3 g MMF treated patients, 31.2% in 2 g MMF treated patients and 47.5% in AZA treated patients.

Results of this study did not find any significant difference for graft survival between MMF treatment groups and AZA group. Tissue-invasive CMV infection and GI toxicity were more common in the 3 g MMF treatment group as compared to 2 g MMF treated and AZA treated patients.

By this study, it concluded that MMF is associated with a significantly lower rate of treatment failure and reduction in the incidence, severity, and treatment of acute graft rejection as compared with AZA, during the first six months after renal transplantation.

1.2.2.11 Study done by Opelz G on Comparison of MMF and Azathioprine for Graft Survival Rate(46)

Opelz has performed retrospective study to compare MMF with AZA. For this study, they enrolled patients who underwent kidney transplantation between 1998 and 2007 and whose data are reported to the International
Collaborative Transplant Study (CTS). All these patients were followed up for 05 years.

In this study, they did not find any significant difference between both drug for death-censored graft survival and in all-cause graft survival (95% CI 0.89–1.03, HR = 0.96, P = 0.25 and 95% CI 0.91–1.02, HR = 0.96, P = 0.18, respectively) at 5 year after transplant. They also reported requirement of antirejection therapy in MMF treated recipients at 01 years after transplant was significantly lower as compared to AZA treated recipients (95% CI 0.69-0.88, OR 0.78, P < 0.001).

1.2.2.12 Study done by Knight SR et al. on Comparison of MMF and Azathioprine(47)

Knight SR et al. performed systematic literature search using the Transplant Library from the Centre for Evidence of Transplantation. In this review, they analyzed all trails that compare AZA with MMF and published between January 1995 and June 29, 2007. This study was performed to identify whether advantage of MMF over AZA extends in the presence of newer and better CNI like micro emulsion form of CyA and TAC or not.

They reported MMF therapy was associated with reduction of acute rejection (RR = 0.62) and graft loss (RR = 0.76) as compared to AZA therapy. They did not find any difference in malignancy, creatinine level, death, or infection. They concluded that usage of MMF with a calcineurin inhibitor was associated with reducing the risk of acute rejection and hence possibility of graft loss as compared to AZA.

1.2.2.13 Study done by European Trial of MMF in Renal Transplantation on Efficacy of MMF(48)

In this study, two different doses of MMF (2 g and 3 g) treated group was compared with placebo controlled group. Total 491 patients were enrolled and were followed up for three years.

Results of this study, did not find any significant difference between all treatment groups for patients survival at 3 year (Placebo = 88.9%, 2 g MMF = 92.7% and 3 g MMF = 91.8%) and similar non-significant difference for graft survival (Placebo = 78.0%, 2 g MMF = 84.8% and 3 g MMF = 81.2%). But for
death-censored graft loss was significantly higher in placebo controlled group as compared to 2 g MMF group at 3-year after transplant (8.7% vs 16.0%, P = 0.03).

This study results reported, early (during first six months) biopsy-proven acute rejection was associated graft loss at 3-year. During course of the study, 10.8% of placebo, 4.6% of 2 g MMF and 6.3% of 3 g MMF treated patients were report with acute allograft rejection episode.

Adverse events like CMV infections, Diarrhea, leucopenia, and anemia were more common in MMF treated patients, and mainly in 3 g, MMF treated patients. However, incidence of malignancies was similar across all treatment groups.

It was concluded that MMF was associated with 7.6% reduction in the incidence of graft loss (excluding death) at three years post transplantation. MMF was also associated with reduction of the incidence of acute rejections and hence reduction of late allograft loss.

1.2.2.14 Retrospective Study done by Goldfarb-Rumyantzev AS et al. on Graft and Patient Survival Rate(49)

In this retrospective study, patients who underwent renal transplantation between 01 January 1995 and 31 December 2000 and registered in US Renal Data System were selected and by this way, data of 31,012 patients were collected. All patients were followed up till 31 December 2000. Among these patients, 17,108 patients were treated with PCM, 7225 with PTM and 6679 with PCA.

Survival Analysis:

In Cox model, PTM and PCA therapy was associated with increased risk of allograft failure using PCM as a reference (HR = 1.08; P< 0.05 and HR = 1.14; P < 0.001, respectively). For recipients mortality, they did not find significant difference between PTM and PCM treated recipients (HR = 0.99; P = 0.9), but PCA treated recipients had higher rate of mortality as compared to PCM treated recipients (HR = 1.15; P < 0.005).
Living versus Deceased Donor:

In deceased-donor recipients, author did not find significant difference for graft outcome between PTM and PCM treated patients (HR = 1.04; P = 0.284), but PCA therapy was associated increased risk of graft failure by 18% (95% CI 1.1 to 1.27; HR = 1.18; P < 0.001). In living-donor recipients, PTM therapy was associated with higher graft loss as compared to PCM therapy (95% CI 1.06 to 1.41, HR = 1.22; P < 0.01) but not PCA (HR = 1.05; P = 0.51).

Adult versus Pediatric Recipients:

In this study, recipients were divided in pediatric (Age < 18 years) and adult (Age > 18 years) group. In pediatric patients, graft or recipient outcomes were similar between all treatment groups. However, in adults, PTM therapy was associated with higher graft failure (HR = 1.08; P < 0.05) as compared to PCM therapy but not for recipients survival. While PCA therapy was associated with increased risk for patients death (HR = 1.14; P < 0.01) and graft failure (HR = 1.14; P < 0.001), as compared to PCM therapy.

Effect of Induction Therapy:

In this study, recipients were divided in with and without induction therapy treatment. In Cox model, considering PCM as a reference, PCA and PTM therapy was associated with higher graft failure (HR = 1.15; P < 0.001 and HR = 1.07; P < 0.05, respectively). However, for recipient survival, only PCA regimen was associated with significant risk (HR = 1.14; P < 0.01).

Serum Creatinine Levels:

They compared average creatinine values at six months, one year, three years, five years and seven years in the three study groups. Creatinine value in the PTM group seems to be consistently lower than in PCM or PCA groups, except for the 7-year follow-up.

Acute Rejection Episodes:

For acute rejection, they did not find significant difference between all treatment groups. They conclude that the PCM regimen is associated with lower risk for graft failure as compared with PTM and lower risk for graft failure and recipient death compared with PCA.
1.2.2.15 Study done by Kunz R et al. on Comparison of Triple Drugs Therapy Vs Double Drugs Therapy(50)

Kunz R et al. perform study to compare the effect of triple immunosuppressive maintenance therapy (CyA, AZA, and prednisolone) with double therapy (CyA and prednisolone) in renal transplant patients for identifying effect on graft failure, acute rejection episodes, and mortality. They performed this study by reviewing MEDLINE, reference lists, Science Citation Index, and expert files which were published between 1984 and 1995. They review total 449 originally identified studies. After excluding studies on the bases of exclusion criteria, data of five controlled trials were used for this study. Results of this study, did not find statistically significant difference for graft failure (OR = 0.82; 95% CI = 0.61-1.16), graft survival (OR = 0.83; 95% CI = 0.57-1.21), or acute rejection (OR = 1.02; 95% CI = 0.76-1.36) between triple-drug therapy and double-drug therapy. In this study, they found that patient’s withdrawal rate is low in triple therapy, so it shows more stable immunosuppressive effect on triple therapy. By this study, they conclude that there is no statistically significant difference in the long-term management of renal transplant recipients between the two treatment regimens.

Studies that compare the different treatment regimen and their outcome describe in below Table 1.2.
### Table 1.2. Studies Compare Different Drugs/Drug Regimens and its Outcome

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of Author</th>
<th>Type of study</th>
<th>No. of patient</th>
<th>Comparison</th>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trompeter R et al. (2002)(51)</td>
<td>Prospective</td>
<td>196</td>
<td>TAC vs. CyA</td>
<td>Rejection</td>
<td>36.9% vs. 59.1%, P = 0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient survival</td>
<td>Non significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Graft survival</td>
<td>Non significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypertension</td>
<td>5.1% vs. 8.7%, P = 0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NODAT</td>
<td>68.9% vs. 61.3%, P = 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3% vs. 2.2%</td>
</tr>
<tr>
<td>2</td>
<td>Meier-kriesche HU et al. (2004)(52)</td>
<td>Analysis of OPTN data</td>
<td>5069</td>
<td>MMF vs. AZA</td>
<td>Rejection</td>
<td>24% vs. 28.2%, P = 0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Graft survival</td>
<td>68.9% vs. 63.2%, P &lt;0.001</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient survival</td>
<td>73.2% vs. 69.2%, P = 0.0003</td>
</tr>
<tr>
<td>3</td>
<td>Mysore SA et al. (2008)(53)</td>
<td>Prospective</td>
<td>50</td>
<td>CyA/MMF vs. CyA/Sir vs. TAC/MMF vs. TAC/Sir</td>
<td>Rejection</td>
<td>18% vs. 8% vs. 14% vs. 4% (CyA/MMF vs. TAC/Sir, P = 0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypertension</td>
<td>48% vs. 36% vs. 24% vs. 25% (CyA/MMF vs. TAC/MMF and TAC/Sir, P = 0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CNI toxicity</td>
<td>8% vs. 12% vs. 6% vs. 12% (TAC/Sir and CyA/Sir vs. TAC/MMF, P = 0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient survival</td>
<td>Non significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Graft Survival</td>
<td>Non significant</td>
</tr>
<tr>
<td>Sr. No.</td>
<td>Name of Author</td>
<td>Type of study</td>
<td>No. of patient</td>
<td>Comparison</td>
<td>Parameter</td>
<td>Result</td>
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<tr>
<td>4</td>
<td>Christopher J et al. (2000)(54)</td>
<td>Prospective</td>
<td>15</td>
<td>TAC/AZA vs. CyA/MMF vs. TAC/MMF</td>
<td>Rejection, Patient survival, Graft survival, NODAT</td>
<td>17% vs. 20% vs. 15% Non significant, Non significant, 14% vs. 7% vs. 7%</td>
</tr>
<tr>
<td>5</td>
<td>Ciancio G et al. (2006)(32)</td>
<td>Prospective</td>
<td>150</td>
<td>TAC/Sir vs. TAC/MMF vs. CyA/Sir</td>
<td>Patient survival, Graft survival, Rejection, Creatinine level, NODAT</td>
<td>Non significant, Non significant, 26% vs. 10% vs. 20%, P = 0.07, TAC/MMF vs. CyA/Sir, P = 0.04, TAC/MMF vs. TAC/sir and CyA/Sir, P &lt;0.04</td>
</tr>
<tr>
<td>6</td>
<td>Meier-kriesche HU et al. (2003)(33)</td>
<td>Analysis of USRD data</td>
<td>47693</td>
<td>MMF vs AZA</td>
<td>Rejection</td>
<td>0.9% vs 6.1%, P &lt;0.001</td>
</tr>
</tbody>
</table>
1.2.3 Studies on Side Effects of Immunosuppressant Drugs after Kidney Transplantation

1.2.3.1 Studies on New Onset of Diabetes (NODAT) after Kidney Transplantation

New onset of diabetes is one of the major complications or side effects of the immunosuppressant drug which impact on graft functioning and patients survival.

1.2.3.1.1 Retrospective Study Conducted by Lv C et al.(55)

Lv C et al. has performed retrospective study on patients who underwent renal transplant between January 1993 and December 2008 and who were non diabetic before surgery. By this way, data of 428 patients were used in this study. In this study, fasting plasma glucose (FPG) levels was used to identify the prevalence of NODAT.

The mean follow-up of patients was 5.65 ± 3.68 years. In their study, they found that 20.3% (87 patients) were reported with NODAT during the course of the study and out of these 57 patients reported with NODAT within one year of transplant. The results shows cadaveric donor (OR = 1.18), age of recipients (OR = 1.10), HCV infection (OR = 2.72), body mass index (OR = 1.05), and preoperative FPG level (OR = 1.48) are risk factor for NODAT after transplantation. They also observed patients who were shifted from CyA to TAC, had higher prevalence rate of NODAT (P < 0.05). They also compare patients with and without NODAT and observed that patients with NODAT higher prevalence rates of hypertension, infection, and dyslipidemia (P < 0.05) but in their results they do not find any significant difference between the survival rate and survival time off in both groups.

1.2.3.1.2 Study Conducted by Luan FL et al.(56)

Luan FL et al. study on new onset diabetes mellitus in kidney transplant recipients discharged on steroids free immunosuppressant by reviewing OPTN report. In this study, they enrolled total 25,837 adult kidney transplant recipients who underwent renal transplant between 2004 and 2006 and were non diabetic before transplant. They found that 16% of recipients developed NODAT in first three years of transplant and among this 70% NODAT were reported within one year of transplant. They also noted that
incidence of NODAT was significantly different by use of steroids: 18% of those discharged on steroids compared with 12% of those without steroids. In the use of CNI agent, they reported recipients with TAC as part of their maintenance regimen had higher rate of incidence of NODAT then CyA (17 % Vs 14 %) regardless of steroid use.

In the use of induction agent, they found recipient who given ATG has higher rate of NODAT then Anti IL-2 receptor antibody, alemtuzumab, and other. The incidence of NODAT in ATG treated Patients was 17% while 15.5% and 10% for Anti IL-2 receptor antibody and alemtuzumab, respectively. They reported that incidence of NODAT is lesser in younger recipients. The author also found patients having HCV positive at the time of transplant having a higher incidence of NODAT then without HCV (24% Vs 16%). They also reported that incidence of NODAT was higher in patients having hypertension as an ESRD (21%) while 13%, 17% and 14% in patients having glomerulonephritis, polycystic kidney disease and other as an ESRD.

In this study, it is observed that patients on TAC/sirolimus and TAC/MMF regimen having higher rate of incidence of NODAT, 20%, and 17% respectively while CyA/MMF and CyA/Sirolimus regimen have 14 and 15% NODAT respectively as a maintenance regimen.

1.2.3.1.3 Study Conducted by Kamar Net et al.(57)

This observational study was performed at 17 centers, and total 527 patients were enrolled. Among this, 266 patients were treated with TAC, and 261 patients were treated with CyA. NODAT was reported in total 37 (7%) patients. The incidence rate of NODAT in TAC treated recipients was 10.2% while in CyA treated recipients was 3.8 (P = 0.006).They also reported that onset time of NODAT in TAC treated patients was earlier than CyA treated patients (80% vs. 30% in first three months).

In Univariate analysis, they observed IFG before transplantation, recipient age (> 45 years), the presence of at least two CVRFs, maximum lifetime BMI > 25 kg/m², TAC therapy, and positive hepatitis C serology were main discrete factors associated with the development of NODAT. While in a multivariate analysis, they observed evidence of abnormal glucose
metabolism prior to transplantation (OR = 4.7, P = 0.01), lifetime BMI of over 25 kg/m² (OR = 5.1, P = 0.0005), TAC treatment (OR = 3.0, P = 0.007), and positive hepatitis C serology (OR = 4.7, P = 0.02) were risk factors for development of NODAT.

1.2.3.1.4 Study Conducted by Gourishankar S et al.(58)

They studied on patients, who underwent kidney transplant at University of Alberta, Canada between 1 January 1995 and 31 August 2001. In this study, total 386 adult kidney transplant recipients were enrolled. The incidence rate of NODAT in this study was 9.8%. Among them, 6.7% were reported within first six months of transplant while 7.0% were reported in first 12 months and 8.0% in first three years post transplant. Patients who developed NODAT, among them 63% required oral agents for treatment and 14% require insulin therapy.

They perform univariate analysis and found that Incidence rate of NODAT was higher in TAC group as compared to CyA group. Similar higher NODAT in MMF group as compared to AZA group was also observed (HR = 0.4, P = 0.03). They also reported delayed graft function and induction therapy was associated with NODAT (2.1 (1.1– 4.1); P = 0.03) while Hepatitis C antibody status was associated with borderline significance (P = 0.053). However, variables such as polycystic kidney disease, pre-transplant dialysis, hypertension, recipient gender, and CMV mismatch were not associated with the development of NODAT.

In multivariate analysis, they observed incidence rate of NODAT was increased 1.5 fold as increase recipient’s age by every ten years. Similarly, NODAT developed more commonly in patients receiving TAC (HR = 2.6, P < 0.01), deceased donor transplantation (HR = 3.6, P < 0.01), having a rejection episode (HR 2.0, P = 0.02) and positive hepatitis C antibody status at time of transplant (HR 3.4, P = 0.05). They found that prednisone therapy, calcineurin inhibitor dose, and trough levels at any time point following transplantation and BMI (> 30 kg/m²) at transplantation were not associated NODAT. NODAT after transplant was not affected on graft survival rate, patient survival rate and on renal function (creatinine clearance or serum creatinine).
1.2.1.3.5 Study Conducted by Bertram L et al.(59)

In this study, author reviewing the United States Renal Data System and included total 11659 patients who were non diabetic before transplant and underwent renal transplantation between 1996 and 2000 (first kidney transplant). In this study, they found that the cumulative incidence of NODAT was 9.1% at three months (95% CI 8.6–9.7), 16.0% at 12 months (95% CI 15.3–16.7), and 24.0% at 36 months post-transplant (95% CI 23.1–24.9). In Cox’s proportional hazards analysis, they observed recipients age, Hispanic ethnicity (RR = 1.35, P < 0.0001), increasing HLA mismatches, African American race (RR = 1.68, P < 0.0001), hepatitis C infection (RR = 1.33, P < 0.0001), TAC therapy (RR = 1.53, P < 0.0001), body mass index ≥30 kg/m² (RR = 1.73, P < 0.0001), and male donor (RR = 1.12, P = 0.0090) are the main risk factor for NODAT. In this study, they find out the factor that reduced the risk for NODAT are use of MMF, AZA, younger recipient age, a college education, and glomerulonephritis. In this results, they also observed in NODAT patients infection rate is higher than patients without NODAT. In Cox analyses, they observed NODAT was associated with increased graft failure (RR = 1.63, P < 0.0001), death censored graft failure (RR = 1.46, P < 0.0001), and mortality (RR = 1.87, P < 0.0001).

1.2.3.1.6 Study Conducted by Cosio FG et al.(60)

Cosio FG et al. analyzed total 1811 adult, renal allograft recipients, transplanted at Ohio state university between 1983 and 1997. During the study period, 20% recipients (293 recipients) developed NODAT. They observed incidence rate of NODAT was significantly higher in aged (P < 0.001), heavier (P < 0.001), and in African Americans (P = 0.001) recipients.

The results show, in NODAT patients total serum cholesterol and triglycerides (TG), pulse pressure and systolic blood pressure was significantly higher as compared to patients without NODAT. The usage of lipid lowering agents was also significantly higher (53%) than in recipients who had diabetes before transplant (31%) or in patients without NODAT (28%) (P < 0.001).
They also study on Blood pressure level and compare three groups. The difference between NODAT and PDM for systolic BP was non-significant, but systolic BP was significantly higher in NODAT and PDM patients as compared to without NODAT (P < 0.0001). While diastolic pressure was significantly lower in PDM patients as compared to other two groups (P < 0.0001). Similar to systolic BP, pulse pressure was also found to be higher in NODAT and PDM patients compared to without NODAT (P < 0.0001).

The results show, mortality rate in transplant patients was significantly higher in PDM (31% patients) and in NODAT (22% patients) as compared to without NODAT (16% patients) (P < 0.001 and P = 0.005, respectively).

Other studies conducted for identification of incidence rate of NODAT are described in Table 1.3.
### Table 1.3. Studies on Different Drug Regimen and Incidence of NODAT

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Study done by</th>
<th>Year</th>
<th>No. of patient</th>
<th>Definition</th>
<th>Follow up period (Month)</th>
<th>Incidence of NODAT</th>
<th>Population</th>
<th>Drug used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cosio FG et al.(61)</td>
<td>2001</td>
<td>2078</td>
<td>Treated for 30 days</td>
<td>12, 36, 60, 120, 180</td>
<td>7, 10, 13, 21, 30</td>
<td>White/African American</td>
<td>Pre, CyA, AZA/MMF</td>
</tr>
<tr>
<td>2</td>
<td>Vincenti F et al.(40)</td>
<td>2008</td>
<td>567</td>
<td>Treated for 30 days</td>
<td>6, 13</td>
<td></td>
<td>59 centers, 16 countries</td>
<td>Pre, CyA/TAC, MMF</td>
</tr>
<tr>
<td>3</td>
<td>Hagen M et al.(62)</td>
<td>2003</td>
<td>63</td>
<td>Oral glucose tolerance test</td>
<td>2, 48</td>
<td>19, 22</td>
<td>White</td>
<td>Pre, CyA, AZA</td>
</tr>
<tr>
<td>4</td>
<td>David-neto E et al.(63)</td>
<td>2007</td>
<td>84</td>
<td>Oral glucose tolerance test</td>
<td>1, 2, 6</td>
<td>14, 18, 19</td>
<td>Brazilian</td>
<td>Pre, TAC, MMF</td>
</tr>
<tr>
<td>5</td>
<td>Hur KY et al.(64)</td>
<td>2008</td>
<td>77</td>
<td>Oral glucose tolerance test</td>
<td>12, 39</td>
<td></td>
<td>Korean</td>
<td>Pre, CyA, MMF</td>
</tr>
<tr>
<td>6</td>
<td>Porrini E et al.(65)</td>
<td>2008</td>
<td>154</td>
<td>Oral glucose tolerance test</td>
<td>3, 12, 20</td>
<td>31, 20</td>
<td>Spanish</td>
<td>Pre, TAC, MMF</td>
</tr>
</tbody>
</table>
1.2.3.2 Studies Conducted on Infections after Kidney Transplantation

Infections are a common cause of morbidity and mortality after transplantation and are a second most common cause of death in patients with allograft function (66). According to traditional paradigm, early infections (within the first month) are noted mostly due to donor-derived infections, surgical issues, and nosocomially acquired pathogens. Opportunistic pathogens are common in next five months, and it is mainly due to impact of immunosuppressive therapies or who have specific environmental exposures. Late infections may be secondary to conventional or opportunistic pathogens. Time line for various infections after transplantation is mention in Fig. 1.3.

Vaccination is a potentially effective mechanism for preventing common infections in kidney transplants recipients, but limited data are available for the effect of vaccination on safety and efficacy in kidney transplant recipients, but available evidence suggests that inactivated vaccines are safe for transplant patients and also no evidence shows that vaccinations lead to an increased risk of rejection. So KDIGO recommended the usage of inactivated vaccines according to recommended schedules but avoid live vaccines in kidney transplant recipients (67).

![Figure 1.3 Timeline of Common Infections in Transplant Recipients](image-url)

Infection after transplantation increases the hospitalization of patients as well as also affect on graft and patients survival rate. Various studies conducted after transplantation that shows prevalence rate of infection and effect of infection on graft and patient survival which are described as below.

1.2.3.2.1 Study Conducted by Ram R *et al.*

Ram R *et al.* performed a retrospective study on 169 transplant patients who underwent renal transplantation between 1989 to December 2003 at Nizam’s Institute of medical science, Hyderabad. In this study, 146 (86%) patients developed total 410 infections and among this 118 were reported in first four weeks of transplant. In this study, 136 (80.4%) male recipients developed 372 (83.4%) infection while 33 (19.5%) female recipients developed 68 (16.5%) infection. For the prevalence of infection in different age recipients, they found that most of the infection was reported in 20–39 years age patients while less infection is reported in patients with age >60 years.

They found UTI was a most common infection and prevalence rate was 23.6% while *Escherichia coli* were the most common infectious agent. HBV and HCV appeared between 6 months and three year period of transplant and prevalence rate was 9.5% and 7.7% respectively. CMV infection was reported in 28 (21.8%) patients and was mainly reported between four weeks and three months of transplant. Tuberculosis was reported in 18 (10.6%) patients and was associated with renal dysfunction in 38.5% of patients. Total 39 episode of fungal infection was reported in 31 patients and was associated with death in 20% and allograft dysfunction in 42.5%.

They found that patients who have received OKT3 had proportionally greater prevalence of infection episode (9.2%) as compared to IL-2 receptor
blocker (6.8 %). The prevalence of CMV infection was also high in OKT3 treated patients. They did not find any significant difference for the prevalence of infection, severity of infection and number of death due to infection in diabetic and non-diabetic patients.

1.2.3.2.2 Prospective Study Conducted by Maraha B *et al.*(70)

They perform prospective study on patients who underwent renal transplantation between January 1992 and January 1997, at the University Hospital Maastricht, The Netherlands. Total 192 recipients were enrolled and were followed up for one year. Among them, 156 patients received prednisone, AZA, and CyA while 36 patients received AZA, prednisone and TAC as an immunosuppressant drug. During the study period, 284 infectious episodes were reported, and among them, 51% (146) were reported during hospital stay after transplantation.

**Bacterial Infection:**

In this study, they reported total 249 (88% of total) bacterial infection, and among them, 146 (59%) were observed during hospital stay after transplantation. *Enterococcus faecalis* and *Escherichia coli* were most common infectious agent. Out of 249 bacterial infections, UTI was 173, URTI was 23, intra-abdominal infections were 21, wound infections were 6, and unlabeled infection episodes was 26. UTI has reported in 103 transplant recipients, and among them, 56 patients reported with single episode while 47 patients reported recurrent UTI. 45% UTI was reported during hospital stay while 54% UTI were reported during 1-year follow-up after transplantation. They found that UTI was significantly higher in females (70%) than in males (42%) (*P* < 0.0001). They did not find a significant effect of variables such as cadaver kidney, seropositivity to CMV, age, diabetes mellitus and recurrent transplantation on UTI. UTI was not associated with prolonged hospital stay after transplantation (*P* = 0.5).

**Fungal Infection:**

In this study, eight patients have reported with fungal infection, and among them, five patients had Candida infection while three patients developed Pneumocystis carinii pneumonia.
**Viral Infection:**

CMV infection was reported in 24 patients (13%), two patients were reported with *Herpes zoster* infection, and one with herpes *simplex stomatitis*.

**Effect of infection on graft and patients survival:**

In study duration, 79 (41%) patients were reported with acute rejection episode. CMV infection was associated with rejection (OR = 2.9, 95% CI 1.3–6.4) but UTI was not associated with allograft survival (P = 0.3) or allograft rejection (P = 0.9). Eight patients died during study period, and all reported with at least one episode of infection. Five patients were died due to infection among them three due to sepsis and multi-organ failure, one due to intra-abdominal abscess and one due to peritonitis.

They conclude that Infectious complications, especially UTI, remain a major cause of morbidity in renal transplant recipients and lead to extensive use of antibiotics. By this study, they recommended early removal of urethral catheters and efforts to optimize antimicrobial use in transplant recipients.

**1.2.3.2.3 Study Conducted by Peterson PK et al.(71)**

Peterson PK *et al.* perform prospective study on 518 renal transplant recipients who underwent renal transplantation between 1 October 1977 to September 1981 at the University of Minnesota Hospital. In this study, total 164 patients developed infection and total 205 infection episode were reported. Out of 205 separate infection, 103 (50%) was caused by viral agents, 62 (30%) by bacteria and 7 (3%) were due to fungal infection. In 33 instances (16%), a polymicrobial infection was diagnosed. Total 37 patients died during the study period and among this 32 patients were died due to infection.

Out of 103 viral infections 82 patients developed CMV infection, and 11 patients developed varicella zoster infection. For bacterial infection, they reported that Bacteremias infection was reported in 14 patients while 48 were non-bacteremic infection. UTI was reported in 13 patients, and respiratory tract infection was reported in seven patients. They observed that CMV, bacteremia and fungus infection was reported mainly within the first three
month of transplant and also death due to infection was also high in first three month of transplant.

They also compare various risk factors, and they found patients with HLA identical donor and who receive CyA had a lower incidence of CMV disease. Patients who receive multiple allografts having a lower incidence rate of CMV but higher incidence rate of bacteremia infection. They did not find sex of recipients; pancreas transplantation and splenectomy were associated with the increase the risk of infections.

1.2.3.2.4 Prospective Study Conducted by Rivera-Sanchez R et al.(72)

Rivera-Sanchez R et al. had performed a prospective study on patients who underwent kidney transplantation between November 1999 and October 2001 at Hospital Juárez of México. They enrolled 52 patients and all patients were treated with an immunosuppressive treatment such as prednisone, CyA, and AZA after surgery.

In this study, they evaluate UTI from 3 to 75 days after surgery. They found 19 (37%) patients develop UTI and among them, 7 (13.4%) patients developed re-infection. UTI was less frequent in patients who received kidney from live donor as compared to who received kidney from deceased (28% vs. 70%, P < 0.007). Female are more susceptible to UTI than male (50% vs. 22%, P = 0.045). In this study, they did not observe UTI was associated with graft rejection (P = 0.2518). Escherichia coli (31.5%) was the most common bacterial agent reported in UTI followed by Candida albicans (21.0%) and Enterococcus spp. (10.5%). Other bacterial agents reported in UTI were Klebsiella pneumoniae, Pseudomonas aeruginosa, Micrococcus spp. Enterobacter cloacae and Morganella morganii. In these results, they found that secondary infections produce mainly by Enterococcus spp. (57%) and Escherichia coli (28%).

1.2.3.2.5 Study Conducted by Alangaden GJ et al.(73)

Alangaden GJ et al. conducted an observational study on 127 adult recipients who transplanted between 2001 and 2004 to identify epidemiology and associated risk factor for infection in kidney transplant recipient. All patients were receiving either thymoglobulin or basiliximab as an Induction
immunosuppressant and were maintained on MMF, either TAC or sirolimus and prednisolone. Out of this 127 patient's, 73% patients received TAC, and 27% recipients had received sirolimus. All patients were administered few antimicrobial drug as a prophylaxis.

In this study, 65 patients developed an infection and among this 47% patients developed urinary tract infection while the viral infection was reported in 17% patients, and pneumonia and surgical wound infection were reported 8% and 7%, respectively. Enterococcus spp and Escherichia coli were the most common infectious agent observed in UTI, and they were reported in 33% and 21% patients with UTI. Cytomegalovirus infection was reported in 6 patients, and six patients developed a fungal infection while they did not find infection due to Pneumocystis pneumonia and BK virus. Two patients died due to infection during this study.

1.2.3.2.6 Retrospective Study Conducted by Nafar M et al.(74)

Nafar M et al. perform a retrospective study to identify prevalence and risk factors for CMV infection after transplantation. For this purpose, they enrolled total 427 kidney transplant recipients (258 men and 169 women) with stable kidney function who underwent kidney transplantation at Shahid Labafi inejad Medical Center, Tehran, Iran between January 2010 and May 2012. All patients were treated with triple-drug therapy with TAC or CyA, MMF, and prednisolone. All patients were also administered anti-thymocyte globulin as an induction therapy. 71 patients (16%) were reported with CMV infection, and 19 Patients (4.4%) were reported with recurrent CMV infection. The duration of dialysis, recipients’ age and sex of recipients were not associated with CMV infection. Usage of TAC as a maintenance therapy was associated with CMV infection as compared to CyA therapy (OR = 3.8; 95% CI, 1.3 to 6.2; P = 0.01), but it was not as an independent risk factor for recurrent CMV disease (26.3% vs. 25%, P = 0.70). ATG after transplantation was not associated with CMV infection (38% vs. 28.5%, P = 0.07) nor with recurrent CMV infection (31.8% vs. 38.5%, P = 0.09). By this study, they conclude that intensive immunosuppressant regimen and TAC treated patients were a higher risk of CMV infection.
1.2.3.2.7 Study Conducted by Mathurin P et al. (75)

They perform retrospective study from 1972 to 1990 and prospective study from 1991 to 1996 at Hospitalier Pitie-Salpetriere, Paris, France to compare patients and graft survival rate in HBsAg, HCV infected patients with noninfectious patients. By this way, they enrolled 834 transplant patients in this study. They divided patients according to their virological status as group I (HBsAg– positive), group II (anti-HCV–positive), and group III (patients without HBsAg and anti-HCV antibodies). At five-year after transplant, patient survival was not significant between all group (Group I: 78 ± 5%; group II: 85 ± 3%, group III: 87 ± 2%) but after ten-year of transplant, patient survival was significantly higher in the group III (80 ± 3%) as compared to group I (55 ± 6%) and group II (65 ± 5%) (P < 0.001). Graft survival was significantly higher in Group III patients as compared to Group I and group II at five years (P < 0.001) and ten-year (P = 0.01) after transplant.

They assess the effect of HCV infection on renal transplant patients and observed that at ten year after transplant, variables such as biopsy-proven cirrhosis (P = 0.03), age at transplantation (P < 0.0001), presence of HCV antibodies (P = 0.02) and year of transplantation (P = 0.02), were independent risk factor for patients survival while variables such as age (P = 0.01), year of transplantation (P = 0.003), and presence of HCV antibodies (P = 0.02) were independently associated with graft survival.

They also identify the effect of post transplant HBV on patient survival and graft survival. At ten year, patient survival and graft survival was significantly lower in patients infected with HBV as compared to without. At ten year after transplant, variables such as presence of HBsAg (P = 0.005) and age at transplantation (P = 0.05) were an independent risk factor for patient survival while presence of HBsAg was independent risk factor for graft survival (P < 0.001).

1.2.4 Effect of Recipients Age

Recipient’s age at the time of transplant is one of the risk factors for the rejection episode, graft survival, and patient’s survival. Many studies were
conducted to identify the effect of recipient’s age on above parameter which is described as below mention Table 1.4.

**1.2.5 Usage of Induction Agents**

Induction agents are used to decreasing the immune system of the body immediately at the time of transplant and help to prevent rejection and injury of the transplanted kidney. Few studies were conducted to identify the effect of induction agent on rejection episode, graft survival and patient survival after transplant describe as bellow in Table 1.5.
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of Author</th>
<th>Type of study</th>
<th>No. of patient</th>
<th>Comparison of recipients age</th>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Parada B et al. (2005)</td>
<td>Retrospective</td>
<td>1227</td>
<td>Age ≤ 18 year vs. &gt;18 year</td>
<td>Graft survival</td>
<td>70.6% vs. 78.8%, P = 0.4325</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient survival</td>
<td>98.6% vs. 87.9%, P &lt; 0.02 Non significant</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Creatinine level</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Abou-Jaode MM et al. (2009)</td>
<td>Prospective</td>
<td>107</td>
<td>Age &lt; 50 year vs. 50–60 year vs. &gt; 60 year</td>
<td>Acute rejection</td>
<td>Non significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infection rate</td>
<td>Non significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Creatinine level</td>
<td>Non significant</td>
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<td></td>
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<td></td>
<td>Hypertension</td>
<td>Non significant</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Graft survival</td>
<td>Non significant</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient survival</td>
<td>Non significant</td>
</tr>
<tr>
<td>3</td>
<td>Palomar R et al. (2001)</td>
<td>Retrospective</td>
<td>439</td>
<td>Age ≥ 60 year vs. &lt; 60 year</td>
<td>Acute rejection</td>
<td>31.6% vs. 29.8%, Non significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Graft survival</td>
<td>81% vs. 78%, Non significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient survival</td>
<td>96% vs. 91%, P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tubular necrosis</td>
<td>31% vs. 22.8%, Non significant</td>
</tr>
<tr>
<td>4</td>
<td>Meier-Kriesche HU et al. (2000)</td>
<td>Analysis ofUSRDS data</td>
<td>59,509</td>
<td>Age 18–49 year vs. 50–64 year vs. &gt; 65 year</td>
<td>Graft survival</td>
<td>67% vs. 61.8% vs. 50.7%, P &lt; 0.001</td>
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<tr>
<td>Sr. No.</td>
<td>Name of Author</td>
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<td>No. of patient</td>
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<td>Parameter</td>
<td>Result</td>
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<tr>
<td>5</td>
<td>Kappes U et al. (2001)(80)</td>
<td>Retrospective</td>
<td>123</td>
<td>Age &lt; 60 year vs ≥ 60 year</td>
<td>Graft survival</td>
<td>95% vs 80%, P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient survival</td>
<td>90% vs 82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute rejection</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>
Table 1.5. Studies on Usage of Induction Agents

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of Author</th>
<th>Type of study</th>
<th>No. of patient</th>
<th>Comparison</th>
<th>Parameters</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mourad G et al. (2001)(81)</td>
<td>Prospective</td>
<td>309</td>
<td>Induction vs. non-induction</td>
<td>Acute rejection, Patient survival, Graft survival, CMV infection, NODAT, Leucopenia</td>
<td>15.2% vs. 30.4%, P = 0.001 97.4% vs. 92.1%, Non significant 96.8% vs. 91.1%, Non significant 32.5% vs. 19%, P = 0.009 3.4% vs. 4.5%, Non significant 37.3% vs. 9.5%, P &lt; 0.001</td>
</tr>
<tr>
<td>2</td>
<td>Ciancio G et al. (2002)(82)</td>
<td>Prospective</td>
<td>233</td>
<td>Daclizumab vs. OKT3</td>
<td>Patients survival, Graft survival, Acute rejection, Infection, CMV infection</td>
<td>98% vs. 96%, Non significant 96% vs. 94%, Non significant 2.1% vs. 7.1%, P = 0.011 7.3% vs. 16%, P &lt;0.0036 1.6% vs. 4%, P = 0.14</td>
</tr>
<tr>
<td>3</td>
<td>Yvon Lebranchu et al. (2002)(83)</td>
<td>Prospective</td>
<td>100</td>
<td>Basiliximab vs. ATG</td>
<td>Patients survival, Graft survival, Acute rejection, CMV infection</td>
<td>98% vs. 100%, Non significant 94% vs. 96%, Non significant 8% vs. 8%, Non significant 6% vs. 12%, Non significant</td>
</tr>
<tr>
<td>4</td>
<td>Szczech LA et al. (1998)(84)</td>
<td>MEDLINE analysis</td>
<td>628</td>
<td>Induction vs Non-induction</td>
<td>Graft failure</td>
<td>0.62 (95% CI, 0.43 to 0.90), P = 0.12</td>
</tr>
</tbody>
</table>