INFECTIONS AND IMMUNOMODULATION ON LIVER TRANSPLANT PATIENTS

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I, Dr.M.MEENA, solemnly declare that this dissertation entitled, **"INFECTIONS AND IMMUNOMODULATION IN LIVER TRANSPLANT PATIENTS"** is the bonafide work done by me during my post graduate course in MD Microbiology at the Department of Microbiology, Govt. Stanley Medical College and Hospital, Chennai, during 2015–2018 under the guidance and supervision of **Dr. ROSY VENNILA, M.D.,** Director of Department of Microbiology, Madras Medical College, Chennai. The dissertation is submitted to **The Tamilnadu Dr. M.G.R. Medical University**, Chennai in partial fulfillment of the University regulations for the award of degree of M.D. Microbiology, Branch IV, examination to be held in April 2018.

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LIST OF ABBREVIATIONS

LT – Liver Transplantation

HSV – Herpes simplex virus

CMV – Cytomegalo virus

EBV – Epstein Barr Virus

PTLD – Post Transplant Lymphoproliferative disease

PCR – Polymerase chain reaction

CNI – Calcineurin Inhibitors

MMF – Mycophenolate Mofetil

HAV – Hepatitis A virus

HBV – Hepatitis B virus

HCV – Hepatitis C virus

PBS – Primary Biliary Cirrhosis

BCS – Budd Chiari Syndrome

ALD – Alcoholic liver disease

DCLD – Decompensated Liver Disease

WD – Wilsons disease

CF – Cystic Fibrosis

TT 1 – Tyrosinemia 1

HCC – Hepatocellular Carcinoma

CCA – Cholangiocarcinoma

ALT – Alanine transaminase

AST – Aspatate transaminase

ALP – Alkaline phosphatase

GGT – Gamma glutamyl transferase

PT – Prothrombin time

MIC – Minimum Inhibitory concentration

DNA – Deoxy Ribonucleic acid

RNA – Ribonucleic acid

SSI – Surgical Site Infections

UTI – Urinary tract Infections

PT – Prothrombin Time

ESBL – Extended Spectrum Beta lactamases

MRSA – Methicillin Resistant Staphylococcus aureus

VRE – Vancomycin Resistant Enterobacteriaceae

CV TIP – Central venous tip

DT Fluid – Drainage tube fluid

E.coli – Escherichia coli

Kleb. Pneumoniae – Klebsiella pneumoniae

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INFECTIONS AND IMMUNOMODULATION IN LIVER TRANSPLANT PATIENTS

INTRODUCTION:

Liver Transplantation is the surgical replacement of diseased liver with the healthy liver from another person (allograft). It is a standard life saving procedure for many end stage liver diseases and acute liver diseases. According to the United Network for Organ Sharing (UNOS) in the United States, a total of 6331 liver transplantations were performed during 2008-2009, with a survival rate of 85% at one year. Survival rate after liver transplantation has improved over the years, due to advances in surgical techniques and a reduction in allograft rejection produced by new potent immunosuppressive agents. Inspite of use of protective barriers, antimicrobial prophylaxis, and vaccination, infections still represent a major cause of morbidity and mortality after liver transplantation. The opportunistic infections are the leading cause of death during the first three years after liver transplantation. The diagnosis of these infections are delayed because of potent immunosuppressive therapy that diminishes inflammatory responses and the clinical signs of infection may be absent or blunted, leading to delayed diagnosis and treatment.[1] The risk of infection is determined by the intensity of exposure to infectious agents and the

overall level of immunosuppression. The infections after liver transplantation may be acquired, reactivation of latent infection in the recipient, donor transmitted diseases and nosocomial.

The incidence of infection is found to be 80% in liver transplant recipients and among them, the most common infection is bacterial (70%), followed by viral (20%) and fungal (8%) infection.[2] The bacterial infection occurs with the highest incidence during the first month after transplantation and most commonly involve the surgical site, the abdominal cavity, blood stream, urinary tract and the respiratory system. The common bacterial infections are Enterococcus, Viridans Streptococci, Staphylococcus aureus and members of the Enterobacteriaceae family and there is an increasing trend towards antimicrobial resistance patterns among bacteria.[2]

Among the opportunistic viral infections, the most common are the members of herpes virus group, of which Cytomegalovirus infection is the most common infection followed by Epstein-barr virus infection, Herpes simplex virus (HSV) 1 & 2 and Varicella Zoster infection. The fungal infections are most commonly caused by the Candida species followed by Aspergillus species. Cryptococcus neoformans occur less commonly in the form of meningitis, lung disease and cellulitis. Endemic mycoses due to Histoplasma capsulatum, Coccidiodes immitis and Blastomyces dermatidis may occur in liver transplant recipients from endemic regions. The infection due to Pneumocystis jirovecii

occurs, primarily as diffuse bilateral pneumonitis and the use of trimethoprim-sulfamethoxazole prophylaxis has remarkably reduced its incidence after liver transplantation.[1]

Immunosuppressive agents are required in solid organ transplantation for induction and maintenance of immunosuppression or for the treatment of organ rejection. Usually, a corticosteroid in combination with a calcineurin inhibitors (CNI), alone or with an antimetabolite, mycophenolate mofetil (MMF) is started early to maintain immunosuppression to prevent transplant rejection. Corticosteroids have been used for induction of immunosuppression since the first successful cases of solid organ transplantation. Intravenous injection of corticosteroid is administered in high doses during the first few days after transplantation (usually 3 days) in combination with at least one immunosuppressant agent. It is then rapidly tapered over the first week to relatively low doses, 10 to 20 mg daily and are usually maintained in immunosuppression for atleast, 3 to 6 months after transplantation.[3] The introduction of the two CNIs, Cyclosporine A (in 1970s and early 1980s) and tacrolimus (in 1990s) as immunosuppressant agents, greatly improved the outcome of Liver transplantation. Tacrolimus is superior to cyclosporine A in increasing patient and graft survival. Acute graft rejection and steroid resistant rejection episodes are less common with tacrolimus use during the first year after transplantation compared with cyclosporine A. The trough level

monitoring of tacrolimus is done for dose adjustments to prevent toxicity. The major advantage in using, Mycophenolate mofetil is their lack of renal toxicity. In patients with pre-existing renal disease, they have been used in conjunction with low dose CNIs with promising results.[4]

More recently, antibody therapies have been combined with corticosteroids or used to facilitate "steroid-free" regimens. The use of antibodies that specifically inhibit or deplete recipient T-cells has been reported to decrease acute rejection episodes in the liver allograft. It also provides an opportunity to decrease the dose of other immunosuppressive agents such as corticosteroids and calcineurin inhibitors. This "steroid-free" protocol may be beneficial for patients with hepatitis C patients and for those with diabetes and hypertension. Antibody induction along with delayed CNI introduction can be used to reduce renal dysfunction in those with impairment. There was no significant increase in adverse side effects in solid organ transplant recipients receiving antibody induction.[3]

AIM & OBJECTIVES:

AIM:

To determine the common organisms that cause infections in liver transplant patients and the role of immunosuppressants in immunomodulation in liver transplant patients.

OBJECTIVES:

1) To compare the incidence of alcoholic cirrhosis with non- alcoholic cirrhosis indicated for liver transplantation.
2) To identify the common organisms that cause infections in liver transplant patients.
3) The antibiotic sensitivity pattern of the pathogen isolated.
4) To evaluate the role of immunosuppressants in immumomodulation in liver transplant patients.

REVIEW OF LITERATURE

HISTORY:

Liver transplantation is the treatment of choice for patients with cirrhosis, decompensated liver disease, acute liver failure and hepatocellular carcinoma. In 1963 March 1st, Thomas Starzl in Denver did the first liver transplantation in the world on a 3yr old boy with biliary atresia and the boy died during the surgery because of coagulation disorder and uncontrolled bleeding. The first successful human liver transplant was performed by Thomas Starzl in Denver in 1967 on an 18 month old child with unresectable hepatoblastoma, at the university of Colorado, who survived more than 1 year.

In 1979, Calne used cyclosporine in two patients who had undergone liver transplantation for the first time, launching a new step in history of liver transplantation. In 1990, Starzl reported the first use of tacrolimus in patients submitted to liver transplantation, who suffered a rejection even after conventional immunosuppressive treatment. Currently, more than 10,00,000 liver transplantations have been performed in the world so far.[7] The first successful deceased liver transplantation in India was done in 1998 followed by first successful living donor transplantation in November 1998 both done by Dr.Rajasekar.[8]

INDICATIONS FOR LIVER TRANSPLANTATION:[9]

(**A) Acute liver failure**:

1) Viral hepatitis A / hepatitis C

2) Intoxication - Paracetamol poisoning,

3) Wilsons disease,

4) Budd chiari syndrome.

(B) Chronic liver failure (Non-cholestatic cirrhosis):

1) Hepatitis B / hepatitis C

2) Autoimmune hepatitis,

3) Alcohol induced cirrhosis

(C) Chronic liver failure (Cholestatic cirrhosis):

1) Primary biliary cirrhosis (PBC)

2) Primary sclerosing cholangitis (PSC)

3) Secondary biliary cirrhosis

(D) Chronic liver failure (Metabolic):

1) Wilson’s disease

2) Hemochromatosis

3) α-1 Antitrypsin deficiency

4) Amyloidosis

5) Cystic fibrosis

6) Tyrosinemia

(E) Chronic liver failure (Vascular):

1) Budd–Chiari syndrome

(F) Other Indications:

1) Primary oxalosis

2) Gycogen storage diseases

3) Hyperlipidemia

4) Polycystic liver disease

(G) Malignant diseases:

1) Hepatocellular carcinoma (HCC, within Milan criteria)

2) Fibrolamellar carcinoma (FLC)

3) Hepatoblastoma

4) Epitheloid hemangioendothelioma

5) Cholangiocellular adenocarcinoma

6) Neuroendocrine liver metastases

(H) Benign liver tumors:

1) Adenomatosis

(I) Liver transplantation in pediatric patients:

1) Biliary atresia

2) Byler's disease

3) Alagille's syndrome

4) Neonatal hepatitis/neonatal viral hepatitis

5) Autoimmune hepatitis

6) Hepatoblastoma.

CONTRAINDICATIONS FOR LIVER TRANSPLANTATION:

(A) Absolute contraindications:

1) Active alcohol abuse

2) Uncontrolled systemic infections

3) Uncontrolled extrahepatic malignancy

4) Uncontrolled / limiting medical conditions

(B) Relative contraindications:

1) Psychosocial conditions

2) Advanced age

3) Severe hepato-pulmonary or severe hepato-renal syndrome

4) Severe obesity/malnutrition

INDICATIONS FOR LIVER TRANSPLANTATION:

1) Viral Hepatitis:

Hepatitis viruses A, B and C cause the majority of viral hepatitis.

(A) Hepatitis A Virus (HAV):

HAV belongs to the Picornaviridae family, is an RNA virus of 7.5kb size and a diameter of 27 nm. It has one serotype but multiple genotypes. The virus spreads from person to person most commonly via the faecal-oral route. The incubation period of is 15-45 days (average, 4 weeks). The virus is excreted in stool during the first few weeks of infection, before the onset of symptoms. Young children are usually asymptomatic. Acute hepatitis A is a more severe form and has higher mortality in adults than in children. The symptoms of acute

infection are fever, malaise, anorexia, nausea, vomiting, hepatomegaly and elevated aminotransferase levels. Jaundice develops in more severe cases. The detection of immunoglobulin M (IgM) for hepatitis A, is the standard for diagnosing acute infection. The infection is usually self-limited and provides lifelong immunity. It does not lead to chronic infection and less than 1% of cases result in fulminant hepatic failure (FHF).[10]

(B) Hepatitis B Virus (HBV):

HBV, belong to the Hepadnaviridae family, is a partially doubled-stranded DNA virus and 3.2 kb size. It has 8 genotype (A-H). The virus consists of a nucleocapsid, HBcAg, which surrounds HBV DNA and DNA polymerase. The nucleocapsid is coated with HBsAg and the intact HBV virion is known as the Dane particle. The HBcAg is not detected in the circulation.[10] HBV is transmitted by both parenterally by transfusion of blood or blood products, intravenous drug abuse with shared needles, hemodialysis, and needlestick injury in healthcare workers and also sexually. The incubation period is 30-180 days (average 12 weeks). In acute infection, the symptoms are fever, malaise, nausea, vomiting, jaundice and right upper quadrant pain. About 5% of adult patients, 30-50% of infected children develop chronic infection.[10] In chronic infection, fatigue is the most common symptom. Patient have abnormal liver function test and the detection of Ig M for hepatitis B core antigen (HBcAg) in serum is required for the diagnosis of acute infection. Hepatitis B surface antigen (HBsAg) may be present in acute infection or in patients who are

chronic carriers (> 6 months). At present, the antiviral treatment is given for the inhibition of viral replication and to prevent or delay the progression of chronic hepatitis to cirrhosis or hepatocellular carcinoma. The drugs currently used for chronic infection include pegylated interferon α-2a and the nucleoside analogues, lamivudine and adenofovir. Globally, an estimated 30% of cases of cirrhosis and 45% of cases of HCC are attributed to HBV infection.[11]

(C) Hepatitis C Virus (HCV):

HCV, belong to the Flaviviridae family, is a RNA virus with 9.4 kb size and 55 nm diameter. It has one serotype, but six major genotypes and more than 80 subtypes. The virus is transmitted through transfusion of infected blood or blood products, transplantation of organs from infected donors and sharing of contaminated needles among IV drug users.[11,13] The incubation period is 15- 45 days (8 weeks). Acute infections are usually asymptomatic and donot develop jaundice. About 55-85% of infected patients, remain viremic and may develop chronic liver disease.[13] In chronic hepatitis C, patients may or may not be symptomatic with fatigue being the predominant symptom and aminotransferases may be elevated. The infection can be confirmed by serologic assays to detect antibody to HCV (anti-HCV) or with molecular tests (Qualitative PCR) for the presence of viral particles. For patients with chronic HCV infection, combination therapy with pegylated interferon and the antiviral drug, ribavirin are given for patients with moderate or severe inflammation or fibrosis. About 15-30% of patients with chronic hepatitis C progress to

cirrhosis[13] and this may take decades. Patients with HCV induced cirrhosis are also at increased risk for the development of hepatocellular carcinoma especially with HBV co-infection.

2) Alcoholic liver disease: (ALD)

It is caused by of increased alcohol consumption, leading to fatty liver, alcoholic hepatitis leading to fibrosis and cirrhosis. Alcohol is metabolized by alcohol dehydrogenase into acetaldehyde, then further metabolized by aldehyde dehydrogenase into acetic acid, which is finally oxidized into carbon dioxide and water. This process generates increased NADH that induces fatty acid synthesis and a decreased NAD level that results in decreased fatty acid oxidation. Subsequently, the increased fatty acids combine with glycerol to form triglycerides and accumulate, resulting in fatty liver. Alcoholic hepatitis is characterized by the inflammation of hepatocytes called as alcoholic steato-hepatitis and predispose to liver fibrosis. Cirrhosis is a late stage of liver disease characterised by inflammation, fibrosis and ending in scarring and necrosis.[14] About 10% to 20% of heavy alcohol drinkers will develop cirrhosis of the liver. Symptoms include jaundice, hepatomegaly and right upper quadrant pain. Late complications of cirrhosis include portal hypertension, coagulation disorders, ascites, encephalopathy and the hepato-renal syndrome. Fatty change and alcoholic hepatitis are reversible by abstinence and the later stages of fibrosis and cirrhosis are irreversible. Liver transplantation is the only definitive therapy

for cirrhosis and the patient should be abstinent from alcohol consumption for 6 months prior to transplantation.[15]

3) Primary Biliary Cirrhosis: (PBS)

It is a chronic cholestatic liver disease. It is characterised by destruction of small intrahepatic bile ducts, which results in fibrosis and cirrhosis .The serological marker of primary biliary cirrhosis is the anti-mitochondrial antibody (AMA) and is identified in 95% of patients with primary biliary cirrhosis. These patients usually have fatigue and pruritus. Other auto-antibodies such as antinuclear antibody are also identified. Anti-Sp100 and anti-gp210 have a high specificity for primary biliary cirrhosis and is helpful, when AMA is negative and its presence is associated with clinically more aggressive disease. Liver biopsy is helpful, when AMA is absent and the biochemical profile shows a mixed cholestatic and hepatocellular pattern. Ursodeoxycholic acid (UDCA) plays a major role in the treatment. The Liver transplantation is a life-saving surgery for those with decompensated cirrhosis with excellent outcome.[17]

4) Budd-Chiari Syndrome: (BCS)

It is a very rare condition caused by thrombotic occlusion of the hepatic vein. It may be primary or secondary depending on the origin of the obstructive lesion. It is caused by blockage of two or more major hepatic veins that increase the sinusoidal pressure and reduces sinusoidal blood flow leading to sinusoidal dilatation and filtration of interstitial fluid. Non-inflammatory centrilobular cell

necrosis of liver is found in nearly 70% of cases and reperfusion injury may lead to hepatocyte damage. Progressive fibrosis, nodular regenerative hyperplasia and cirrhosis develop during the course of disease. The acute form presents with jaundice, hepatomegaly, and upper abdominal pain with elevated liver enzymes. Portal hypertension and ascites are usually seen in chronic form. Liver biopsy shows congestion, liver cell loss and fibrosis predominantly in the centrilobular area. It is diagnosed by doppler ultrasonography showing ″spider web″ appearance of collateral hepatic venous circulation.[18] Milder forms may be treated with surgical shunts and liver transplantation is the treatment of choice for patients with fulminant liver failure, failure of shunts or progression to cirrhosis.[19]

5) METABOLIC DISORDERS OF LIVER:[20]

(a)Wilsons Disease (WD):

It is also known as 'Hepato-lenticular degeneration', is an autosomal recessive disease caused by mutation of the WD gene (on the long arm of chromosome 13). It causes an abnormal copper deposition in multiple organs including liver, brain, kidney and cornea. Clinical features are usually asymptomatic leading to chronic hepatitis, cirrhosis and fulminant hepatic failure. Neurological symptoms like dysarthria, dysphagia, apraxia and tremor predominantly seen in adults. The diagnosis is by the presence of Kayser-Fleischer ring around the cornea, low serum ceruloplasmin level, increased urinary excretion of copper and elevated liver copper on biopsy. Chelation

therapy with d- penicillamine, trientine, or ammonium tetrathiomolybdate has been shown to be effective in preventing progression of Wilson's disease. When medical treatment fails or patients present with fulminant failure, liver transplantation is the treatment of choice.

(b) Hereditary Haemochromatosis:

It is an autosomal recessive disorder characterised by deposition of iron in tissues and organs. It is caused by homozygous C282Y mutation of the HFE gene, located on chromosome 6 and it is assosciated with changes in hepcidin which is the key regulator of iron homeostasis. Infants present acutely with liver failure in the perinatal period and demonstrate massively elevated ferritin levels, elevated iron saturation (98%), hyperbilirubinemia, hypoalbuminemia, hypoglycemia, and coagulopathy. Treatment of choice is phlebotomy with concomitant follow up of haematocrit. Liver transplantation is indicated for end stage liver disease.

(c) α1-antitrypsin deficiency:

It is an autosomal recessive disease due to defective production of α1 antitrypsin leading to decreased activity of α-1 antitrypsin in the blood and lungs. Severe deficiency causes, chronic obstructive pulmonary disease or panacinar emphysema and liver injury in adults. In children, it may present as neonatal jaundice, hepatomegaly or acute liver failure. Diagnosis is by measurement of α1 antitrypsin in serum and liver biopsy (periodic acid Schiff positive after diastase digestion). Treatment is parenteral therapy using a plasma

preparation of α1 antitrypsin with α1 antitrypsin < 11μmol/L and COPD. Liver transplantation is the treatment of choice in children and adults for end stage liver disease.

(d) Cystic Fibrosis (CF):

It is a multisystem disease caused by mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The lack of CFTR alters ductular chloride secretion which causes viscous biliary secretions with subsequent biliary obstruction that leads to focal biliary fibrosis and ultimately cirrhosis. Depending on the report, 20%-50% of CF patients develop liver disease, which ranges from asymptomatic derangement of liver function tests to focal biliary fibrosis to cirrhosis with portal hypertension and chronic liver failure. Treatment with ursodeoxycholic acid (UCDA) has demonstrated improved bile flow and aminotransferases but does not stop the progression of fibrosis. Liver transplantation is indicated for end stage liver disease.

(e) Tyrosinemia:

TT 1 is an autosomal recessive disorder due to a defect in fumaryl acetoacetate hydrolase enzyme in the tyrosine catabolism pathway, which results in accumulation of metabolites such as fumaryl acetoacetate and malelyl acetoacetate. It causes apoptosis of hepatocytes and renal tubular epithelial cells. Clinical features include acute liver failure, renal tubular dysfunction, chronic liver disease and hepatocellular carcinoma. Fumaryl acetoacetate and maleyl acetoacetate are alkylating agents that cause damage to DNA, which

results in a predisposition to hepatocellular carcinoma. Treatment with Cyclohexendiome blocks tyrosine degradation and preventing formation of the alkylating metabolites. Liver transplantation is indicated for failure of medical treatment.

6) Hepatocellular Carcinoma (HCC):

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and is the leading cause of mortality in patients with cirrhosis. Cirrhosis is the most important risk factor for developing HCC in 80% to 90% of individuals and the annual incidence is 1% to 6 %. It occurs in chronic inflammatory condition of liver and is most closely linked to chronic viral hepatitis infection (hepatitis B or C) or exposure to toxins such as alcohol or aflatoxin. Certain metabolic diseases such as hemochromatosis and alpha 1-antitrypsin deficiency and non-alcoholic steato-hepatitis (NASH) markedly increase the risk of developing HCC.[21] The clinical features are jaundice, abdominal distension, loss of appetite, weight loss, abdominal pain, nausea, vomiting, and malaise. The diagnosis is by liver biopsy, blood levels of α- fetoprotein (AFP), Ultrasound, CT scan and MRI. On CT and MRI, it has three distinct patterns of growth, a single large tumour or multiple tumours or a poorly defined tumour with an infiltrative growth pattern. The most common sites of metastasis are the lung, abdominal lymph nodes and bone. Radio frequency ablation (RFA) is suitable for small tumours (< 5 cm). Liver transplantation is indicated for

patients who are not eligible for resection, especially those within Milano criteria (solitary tumour ≤ 5 cm and up to three nodules ≤ 3 cm).[22]

7) Cholangiocarcinoma: (CCA)

It is a primary neoplasm of the biliary system that arise from malignant transformation of cholangiocytes, the epithelial cells that line the biliary tree. The risk factors are chronic biliary inflammation, cholestasis, primary sclerosing cholangitis, choledochal cyst, caroli's disease and chronic parasitic infection with liverfluke, Clonorchis sinensis. Morethan 90% of them are adenocarcinoma. The clinical features are obstructive jaundice, pruritus, malaise, abdominal pain, weight loss and loss of appetite. Laboratory tests demonstrate increased total and direct bilirubin, alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT). Ulrasonography shows dilatation of intrahepatic bileducts and the presence of intrahepatic metastasis. Endoscopic retrograde cholangio pancreatography (ERCP), shows the biliary strictures and allows brush cytology and biopsy of the bile ducts. CT scan (Computerised tomography) and MRI (Magnetic Resonance Imaging) help in the evaluation of resectability and CA 19-9 is elevated in most cases. Surgical resection and neoadjuvant chemotherapy with liver transplantation is the treatment of choice in stage I and II. In patients with advanced disease, palliative chemotherapy with or without radiotherapy is the treatment of choice.[20]

MELD SCORE (MODEL FOR END – STAGE LIVER DISEASE):[23]

Model for End – Stage Liver Disease or MELD is a scoring system for assessing the severity of chronic liver disease and prioritizing for of Liver transplantation. It was initially used to predict the mortality of trans-jugular intrahepatic porto-systemic shunt (TIPS) surgery.

This score is now used by the United Network for Organ Sharing (UNOS) and Euro-transplant for prioritizing of liver transplants. It uses the patients value of

1) Serum bilirubin,
2) Serum creatinine,
3) International normalised ratio (INR) for prothrombin time.

MELD = 3.78x log e [serum bilirubin (mg/dl)] + 11.2xlog e [INR] +

9.57xlog e [serum creatinine (mg/dl)] + 6.43

MELD scores are reported as whole numbers, so the result of the above equation is rounded. Patient with decompensated liver disease and cirrhosis with Child pugh B/C or MELD score ≥24 are considered for liver transplantation.[24]

Immunology of Transplantation:

Compared with other solid organ transplants, liver allografts have long been considered to be immunologically privileged manifested by an absence of hyper-acute rejection and a low incidence of graft loss due to chronic rejection. The hepatocytes have the potential to regenerate after tissue injury. However, acute liver rejection occurs in approximately 50% to 75% of liver transplant recipients and it is readily reversed with immunosuppressive drugs.

Immunological Basis of Allograft Rejection:

In liver transplantation, grafts originate mainly from different members of the human species. The process of rejection is very complicated and has been shown to be caused by transplantation antigens including major histocompatibility antigens, minor histocompatibility antigens and other alloantigens. The major histocompatibility complex (MHC), encodes the dominant transplantation antigens and were shown to be similar to human leucocyte antigens (HLA) and are responsible for the self-restriction of immunological responses to conventional antigens.[25]

Classification and Effector mechanisms of Allograft Rejection:

Allograft rejection mainly involves host-versus-graft reaction in liver transplantation, which is the rejection of the transplant by the recipient's body. The recipient's lymphocyte mediated reactions to allogeneic cells, leading to

damage or destruction of the graft cells. The graft rejection has been divided into three groups namely hyper-acute rejection, acute rejection and chronic rejection.

Type of rejection	Time taken	Cause
Hyper-acute	Minutes-hours	Pre-existing anti-donor antibodies & complement activation.
Acute	Weeks - months	Primary activation of T cells
Chronic	Months – years	Causes unclear: antibodies, slow cellular reactions, immune complexes, recurrence of disease.

Hyper-acute Rejection:

It often occurs within minutes to hours, after the host blood vessels are anastomosed to graft vessels. The rejection is mediated by preformed antibodies specific to the graft antigens (including ABO blood type antigens and HLA antigens) that can activate the complement of the host leading to damage to the endothelial cells. Studies have reported that the process is often accompanied with platelets activation and results in thrombotic occlusion of the graft vasculature causing ischemia, denaturation and necrosis. This rejection is relatively rare in liver transplantation.[25]

Acute Rejection:

It occurs within days and up to three months after transplantation (80-90% of cases occur within one month). The rejection occurs due to donor HLA interaction with the host T cells, creating a cascade of immune responses. The mechanisms involve humoral and/or cellular mechanisms. Antibodies can injure the graft by activating complement and mononuclear cells with Fc receptors that recognise allo-antigens on the endothelial cells resulting in vasculitis. Cytotoxic T cells (CD8+) will recognise allo-antigens on antigen presenting cells (APC) by direct presentation on the donor tissue and endothelial cells, which promotes the apoptosis of transplanted tissue. It has been shown that CD8+ cells alone are sufficient for the mediation of acute allograft rejection, but with the help of CD4+ cytokines secretion such as IL-2, the expression and clonal expansion of cytotoxic attack molecules will be upregulated.[26] The Fas/Fas ligand (FasL) pathway is another pathway which cause activation of CD8+ cells. The pathological features of acute rejection are acute vasculitis and parenchymal cell necrosis, along with the infiltration of lymphocytes and macrophages. The acute rejection that occurs after liver transplantation is rare.

Chronic Rejection:

It occurs, months or years after acute rejection reactions have subsided. It is an indolent but progressive form of allograft injury that is usually irreversible and results in allograft failure. It affects only 4-8% of patients after 5 years of liver transplant. Chronic rejection is potentially reversible in liver allograft

compared to other solid organ transplants and has been mainly attributed to its unique immunological privilege and its regenerative capacity. Liver biopsy shows decreased number of bile ducts, known as "vanishing bile duct syndrome".[27] Chronic rejection is characterised by vasculopathy, fibrosis and a progressive loss of organ function. The persistent viral infections which induce cellular immune responses may synergise with donor-specific alloreactive T cells within the allograft. It may also reflect chronic ischemia secondary to the injury of blood vessels by antibody or cell-mediated mechanisms.

Prevention and Treatment of Allograft Rejection:

Treatment of allograft rejection refers to immunosuppressive therapy, involving an immunosuppressive drugs selection and regimen.

IMMUNOSUPPRESSANTS:[28]

Survival of both patient and graft following Liver transplantation is made possible through immunosuppression, using immunosuppressive drugs. Studies have shown that standard therapy with steroids and calcineurin inhibitors are highly effective in maintaining immunosuppression.

1) Corticosteroids:

Corticosteroids have been used for induction of immunosuppression since the first successful cases of solid organ transplantation. Almost all patients receive corticosteroids following transplantation. It has potent anti-inflammatory and immunosuppressant action. They cause redistribution of

lymphocytes, causing rapid decrease in peripheral blood lymphocyte count. They bind to receptors inside cells and regulate the transcription of numerous other genes. Additionally, they inhibit activation of NF-kB, which increase apoptosis of activated cells. The pro-inflammatory cytokines such as IL-1, IL-2 and IL-6 are downregulated. T cells activation and proliferation are inhibited. Corticosteroid are administered in high doses, as intravenous injections during the first few days after transplantation in combination with at least one immunosuppressant agent. The typical dosage is 500mg or 1000 mg of methylprednisolone. They are rapidly tapered over the first week to relatively low doses of 10 to 20 mg daily (oral prednisolone) and are usually maintained in immunosuppression regimen for atleast, the first 3 to 6 months after transplant. The use of steroid is associated with many adverse effects like hypertension, cushingoid appearance, weight gain, dyslipidemia, osteoporosis, diabetes, cataracts, and increased risk of infections. There is also concern that higher doses of steroids, increase the risk of disease recurrence in LT patients with chronic viral hepatitis and the risk of organ rejection may increase following early corticosteroid dose reduction or withdrawal.

2) Cyclosporine A:

It is a cyclic polypeptide derived from the fungus, Beauvaria nivea. It acts by binding to cyclophilin, a cytoplasmic protein receptor and the complex binds to calcineurin and inactivate it. This complex inhibit the calcium stimulated

dephosphorylation of the cytoplasmic component of nuclear factor activated T cells (NFAT) and inhibit interleukin 2 (IL-2) production. It is the most effective drug for prevention and treatment of graft rejection by suppressing cell mediated immunity. It is metabolised in liver by CYP3A and its metabolites are excreted through bile into the faeces, with some (6%) excretion in urine. The plasma t½ is biphasic 4-6hrs and 12-18hrs. It is given according to blood levels and renal function. The drug is started at 1-2 mg/kg/day in two divided doses and increased as tolerated, but the maintenance dosage ranges from 1-10 mg/kg/day. Generally, the 2-hour post dose level is measured and is believed to reflect immunosuppression. The major adverse effect is nephrotoxicity, due to intra-renal vasoconstriction and occurs in 40-70% of patients, manifested by acute elevations in blood urea nitrogen and creatinine level which is usually reversible with reductions in dosage. Other adverse effects include hyperkalemia, hypertension, venous thrombosis, tremor, headache, gout, gingival hyperplasia, seizures and hyperlipidemia.

3) Tacrolimus (FK506):

It is a macrolide antibiotic produced by Streptomyces tsukubaensis. Like cyclosporine, tacrolimus also inhibits calcineurin that causes decreased IL-2 production and thereby inhibit T-cell activation and proliferation. The drug acts by binding to intracellular protein, FK 506 binding protein-12 (FKBP-12) and is 100 times more potent than cyclosporine in inhibiting IL-2 synthesis. A

complex of tacrolimus-FKBP-12, calmodulin and calcineurin then forms and inhibit calcineurin phosphatase activity which prevents dephosphorylation and nuclear translocation of NFAT. This, inhibit T- cell activation and proliferation. It is metabolized in the liver by cytochrome P-450 system. The plasma $t½$ is 12 hours. The usual oral dosage is 0.1-0.15 mg/kg/day and was adjusted according to liver function and tacrolimus trough concentration. It requires blood level monitoring for dose adjustment and the ideal serum trough level is 5-10 ng/ml. The adverse effects of tacrolimus are diabetes, neurotoxicity, gastrointestinal disturbances, hypertension and hyperkalemia.

4) Sirolimus:

It is structurally similar to tacrolimus was called as 'Rapamycin' earlier. It binds to FKBP (FK binding protein) as tacrolimus and inhibit a protein kinase called 'mammalian target of rapamycin' (mTOR). The mTOR is an important link in the cascade of signalling pathways that leads to proliferation and differentiation of T- cells activated by IL-2 and other cytokines. It is metabolized by CYP3A4 and excreted through bile in faeces. The plasma t½ is 60 hours. It may be combined corticosteroids and other immunosuppressants. The main adverse effects are bone marrow suppression (thrombocytopenia, anemia, leukopenia), hyperlipidemia, poor wound healing, mouth ulcer, hypokalemia, proteinuria and gastrointestinal effects.

5) Mycophenolate mofetil (MMF):

It is an antibiotic isolated from Penicillium species, that has immunosuppressant properties. It is a prodrug of mycophenolic acid which selectively inhibits inosine monophosphate dehydrogenase, an enzyme essential for denovo synthesis of guanosine nucleotides in the T and B cell. It is a potent inhibitor of B-cell and T-cell proliferation, antibody production and cell mediated immunity. It is used in combination with corticosteroids and cyclosporine / tacrolimus. It is absorbed orally and metabolized in the liver to its active form, mycophenolic acid. It is slowly glucuronidated in the liver to an inactive form, phenolic glucoronide and is then excreted in urine. The plasma t½ is 16 hours. The oral dosage is 2-4 g/day, orally or intravenously and blood level monitoring is not required. The major adverse effects are vomiting, diarrhoea, leucopenia and predisposition to CMV (Cytomegalo virus) infection.

6) Monoclonal Antibodies:

(a) Muromonab:

It is an anti-CD3 monoclonal antibody, primarily used in liver transplantation for steroid resistant acute rejection. It binds to CD3, a monomeric component of T-cell receptor complex involved in antigen recognition, cell signalling and proliferation. It is then followed by depletion and extravasation of majority of T cells from the blood and peripheral lymphoid

organs. It also reduces the production of cytokines like IL-2 and thereby reduce T cell activation and proliferation. The recommended dose is 5mg/day for adults in a single intravenous bolus (<1 min) for 10 – 14 days. The major side effect is cytokine release syndrome which begins 30 minutes after infusion antibody infusion and is assosciated with increased release of cytokines like TNF α, IL-2, IL-6 and IFN ϒ. Common side effects are high fever, chills, rigor, headache, tremor, nausea, vomiting, diarrhoea, abdominal pain, myalgia and arthralgia. Corticosteroids administration before the injection of muromonab, prevents the release of cytokines and reduce the first dose reactions is considered as a standard procedure.

(b) Polyclonal Antibodies:

It includes anti-thymocyte (ATG) and anti-lymphocyte globulins (ALG). They are prepared by inoculating rabbits or horses with human lymphocytes or thymocytes. Their mechanism of action is rapid lymphocyte depletion due to complement mediated cell lysis and uptake of opsonized T cells by reticulo-endothelial cells. Lymphocyte depletion, plays a major role in preparing the recipient's immune system to adapt and recognize the transplanted organ as self and prevent destruction of the allograft. At present, anti-lymphocyte antibodies are used to treat steroid-resistant acute rejection extensively and are successful in 70%-96% of patients. The main side effect is "first-dose reaction" and febrile episode affecting 80% of patients which can often be reduced by pre-medication

with antipyretics, antihistamines and intravenous steroids. Other adverse effects include thrombocytopenia, anaemia, CMV infection, PTLD, pruritic skin rashes, serum sickness and anaphylaxis.

Post-transplant Complications:

The most common complications in the liver transplant recipients are the following:

1) Acute graft rejection
2) Vascular thrombosis
3) Biliary leak or stricture
4) Infection
5) Malignancy
6) Adverse effects of Immunosuppresant drugs.

1) Acute graft Rejection:

Acute rejection occurs in 20-70% of cases, most often at 7-14 days after transplant, and results in graft dysfunction. It is clinically manifested as low grade fever, malaise, jaundice and abdominal tenderness. It may be subclinical, with laboratory abnormalities as the only sign. Bilirubin and alkaline phosphatase levels rise initially, followed by elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). It is most commonly treated with high-dose steroids (methylprednisolone 1 g for 3 days) followed by a rapid taper over 5-7 days. Alternative therapies include

monoclonal antibody therapy with Muromonab or polyclonal antibody (Antithymocyte globulin).

2) Chronic graft Rejection:

It occurs months or years after transplantation and is usually irreversible. It occurs in 5% of patients and is the major cause of late graft failure. It is diagnosed by of liver biopsy, manifested by gradual obliteration of small bile ducts. The laboratory results show persistently elevated serum alkaline phosphatase and bilirubin levels, suggesting a cholestatic liver injury pattern. This may manifest clinically as jaundice and /or pruritus. Tacrolimus has been used to treat refractory cellular rejection and early chronic rejection. When patients fail to repond to tacrolimus rescue therapy, MMF rescue therapy or antiboby (monoclonal or polyclonal) therapy is given. When the above measures fail, retransplantation is done.

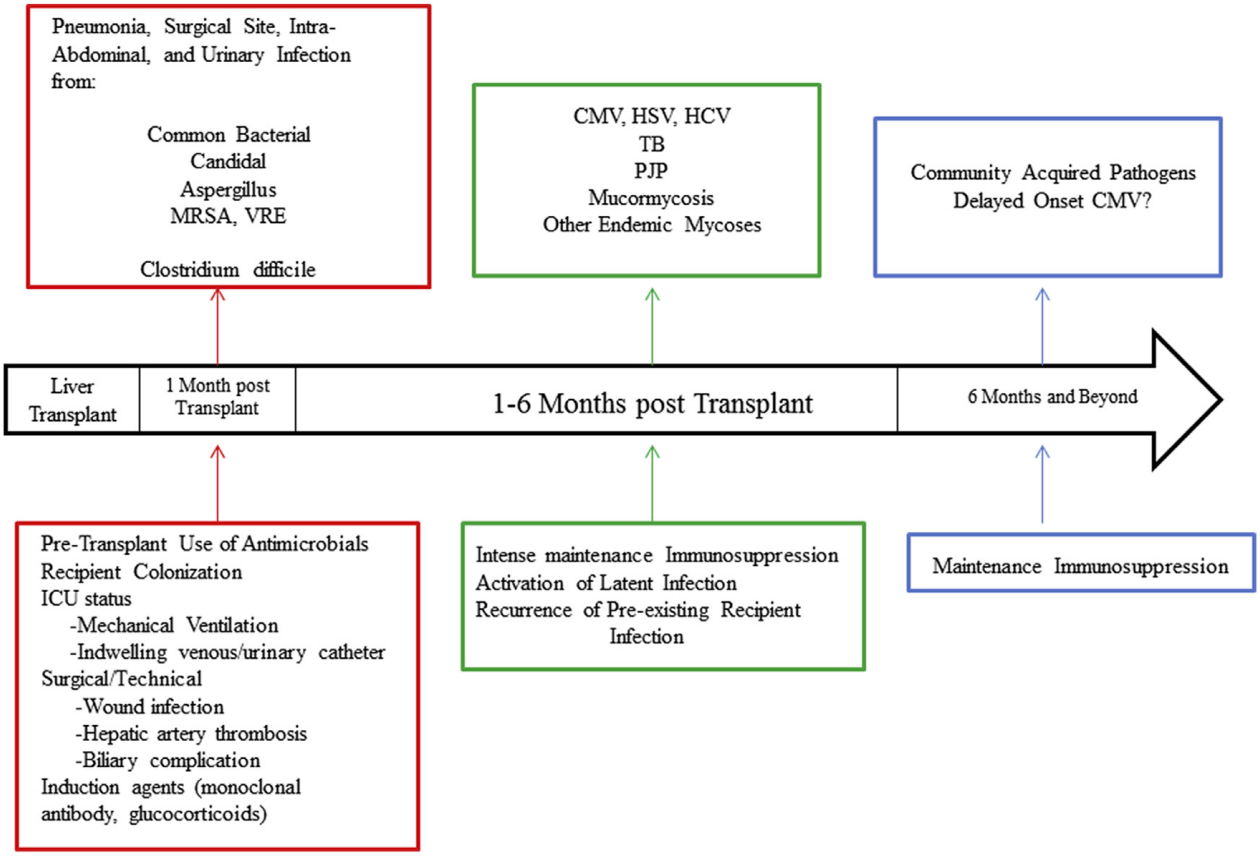
3) Infections after Liver Transplantation:

Infections are the major cause of morbidity and mortality after liver transplantation despite of advances in surgical technique, post-transplant care, hospital environments, immunosuppression and infection prevention.

1) Bacterial Infections:

They are the most common causes of infection after liver transplantation and the highest incidence occurs during the first month after transplantation and

these infections involve the surgical site, the abdominal cavity, bloodstream, urinary system, and the respiratory tract, predominantly.



Most of the infections are caused by nosocomial organisms, the patient's normal flora and can also be transmitted from the donor. During the second to sixth months after LT, opportunistic infections may occur, depending on patients' risk factors and the intensity of immunosuppression. At 6 months after LT, infections are related to environmental exposure, late biliary complications, graft function and combined viral hepatitis. At 12 months after LT, urinary tract infections, intra-abdominal infections and pneumonia are the major types of infection in solid organ transplant recipients. Shifts in nosocomial pathogens, increasing antibiotic resistance, potent

immunosuppression, improved diagnostic methods, grafts from marginal donors and broader epidemiologic exposure, influence the risk and outcomes of bacterial infections.[29]

(A)Surgical Site Infections:

It is one of the most common bacterial infections found to manifest itself early after liver transplantation. It is most often manifested as erythema, induration, tenderness and drainage at the surgical site. Leukocytosis and fever may occur in some cases. It is more common in liver recipients who require a large number of blood transfusions and prolonged duration of the surgery.[1]Currently, the overall incidence of SSI ranges from 18% to 37%. They are most commonly caused by gram positive cocci (Staphylococcus aureus and enterococcus), gram negative pathogens (like Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter baumannii), anaerobe and fungi. Treatment consists of surgical debridement and pathogen directed antimicrobial therapy.[29]

(B)Intra-abdominal Infections:

It accounts for 27%-47% of early bacterial infections after liver transplantation. Intra-abdominal abscesses, peritonitis, and cholangitis are commonly present during the first few weeks after liver transplant as fever, leukocytosis and abdominal pain. They may be asymptomatic clinically which are manifested as elevated liver enzymes are common. The pathogens are most

often polymicrobial and at present, often include multi-drug resistant isolates.1 Some of the important bacteria causing intra-abdominal infections are enterococci, including VRE, Staphylococcus aureus including MRSA, Candida species, and Gramnegative bacilli such as Pseudomonas species, Klebsiella species, Acinetobacter species and Enterobacter species.[31,32] They are associated with increased mortality, graft loss and re-transplantation. When suspected clinically, CT scan or Ultrasound is done to diagnose the presence of fluid collections. Treatment consists of percutaneous or open surgical drainage combined with antimicrobial therapy.

(C)Bloodstream Infections:

It may occur at any time after transplantation and the majority occurs during the first post-operative month. Risk factors include intra-abdominal infection, prolonged use of indwelling vascular catheters, the need for reoperation and acute allograft rejection. Clinical manifestations most often include fever and rigors, accompanied by leucocytosis and organ-specific or localizing symptoms such as erythema and drainage at vascular catheter sites, cough and dyspnoea (pneumonia), dysuria and suprapubic and flank pain (urosepsis).[29] The most common source of bloodstream infections are due to enterococcus, viridans streptococcus, gram-negative bacilli or may be poly-microbial.[33,35] Now, there is an increasing prevalence of multi-drug resistant bacteria such as methicillin resistant staphylococcus aureus, which may cause

50% of bloodstream infections in some centres. Transplant candidates who are carriers of MRSA have a higher risk of bloodstream infection and may be decolonized prior to transplantation.[34] Escherichia coli is the most common organism causing bloodstream infection after liver transplantation, followed by Klebsiella pneumoniae and Pseudomonas aeruginosa.[35] There is increasing resistance among these gram negative pathogens and the prevalence of extended spectrum β lactamases (ESBL) producing Gram-negative bacilli is 13% in some centres. Treatment consists of elimination of the predisposing factor and pathogen directed antimicrobial therapy. For persistent bloodstream infections, endocarditis should be evaluated by means of a trans- esophageal echocardiogram.

(D)Pneumonia:

Because of the prolonged surgery, frequent use of mechanical ventilation, immunosuppression, massive transfusions, fluid overload and underlying malnutrition, liver transplant recipients are more prone to respiratory tract infections. It occurs in 11%-28% of liver transplant recipients with nosocomial pneumonia occurring in 50%-75% and community-acquired pneumonia in 25%-50%.[36] Currently, bacterial pneumonia is the most common infection followed by fungal pneumonia, during the first month after liver transplantation.[37] Treatment consists of pathogen-specific antimicrobial therapy with or without reduction of immunosuppressive agents. After, One month of

transplantation, the bacterial pneumonia occur less common. At 6 months after LT, in patients with good graft function and immunologically stable, the bacterial pneumonia is similar to that of non-LT patients.[38]

(E)Urinary Tract Infection:(UTI)

It was the most common primary source of bacterial infection, for 6 months after solid organ transplantation. The risk factors are age, female sex, diabetes and long term urinary indwelling catheter. The most common pathogens are Escherichia coli, Enterococcus species, Klebsiella species, Staphylococcus aureus and Enterobacter species.[40,41] Urinary tract infections are the common sources of antibiotic resistant bacterias such as ESBL producing Enterobacteriaceae, vancomycin-resistant enterococci (VRE) and methicillin resistant staphylococci (MRSA).[42,43]

2) Viral Infections:

Liver transplant recipients are unique among other transplant recipients because they are commonly chronically infected with hepatitis B or C viruses. Among the opportunistic viral pathogens, the most commonly occurring are members of the herpes virus group, of which cytomegalovirus is the most important infection.

(A)Cytomegalovirus Infection (CMV):

The seroprevalence rate of CMV infection in humans ranges from 45% to 100%. The high infection rate in transplant recipients is due to its ability to establish latency inside the cells. The immunocompetent hosts are usually asymptomatic and the liver recipients often present with severe clinical presentation. The most common symptoms are fever and bone marrow suppression (CMV syndrome). The severe infection present as gastritis or colitis and manifests itself as abdominal pain and diarrhoea. Endoscopic findings, consists of mild hyperemia, mucosal erosions and ulcerations or even normal mucosa. The second clinical symptom is CMV hepatitis, which usually presents with abnormal liver function tests and can be confirmed by means of biopsy, where inclusion bodies with clusters of polymorphonuclear cells are seen.[44,45] Other system such as the central nervous system and the respiratory system may be infected and presents as headache, delirium, changes in mental function, cough and dyspnoea respectively. Currently, biologic markers such as CMV pp65 antigens or CMV DNA by polymerase chain reaction are used as the earliest indicators of infection.[44,45] Treatment of CMV disease is with intravenous ganciclovir (5 mg/kg every 12 hours) or oral valganciclovir (900 mg orally twice daily), combined with reduction in immunosuppression. Mild to moderate cases are treated with oral valganciclovir. For severe cases, along with intravenous ganciclovir, hyperimmunoglobulin is used as an adjunct treatment.

The efficacy of treatment is guided by serial weekly monitoring of viral load or antigenemia levels.[1]

(B)Epstein Barr Virus Infection (EBV):

It can present in a variety of ways after liver transplantation. Acute infection is manifested as fever, malaise with leukopenia, atypical lymphocytosis or thrombocytopenia. Primary EBV infections, occurs predominately in children and it is estimated that 90% of adults are EBV seropositive due to previous subclinical infection. In adults post liver transplant with active EBV infection, reactivation is presumed to be the predominant pathophysiologic process.[46] Acute illness is usually self-limited. EBV infection can lead to post transplant lymphoproliferative disorder (PTLD) in the liver recipient. EBV associated PTLD is an uncommon but is a serious complication of liver transplantation with an incidence in adults of less than 3%.[47,48] Risk factors include, primary EBV infection, presence of CMV disease and increased immunosuppression. The EBV assosciated PTLD include lymphadenopathy, pancytopenias, fever, and disturbances of gastrointestinal tract, lungs, spleen, and central nervous system. Radiographic studies can identify the involvement of pulmonary or intra-abdominal sites. The detection of EBV viremia with nucleic acid testing is not diagnostic of EBV associated PTLD. The treatment is a reduction of immunosuppression.[49] When there is no clinical response within 2–4 weeks, anti-CD20 monoclonal antibodies (rituximab) may be required.

3) Fungal Infections:

Among the various fungal infections after liver transplant, the most common are the Candida species followed by Aspergillus species.

(A) Candida Infection:

Candidiasis is the most common fungal infection after liver transplantation and is the leading cause of invasive fungal infection. The Superficial and invasive candidiasis occurs often during the first 1-3 months after liver transplantation. Candida albicans is the most common species and now, the non-albicans candida species are being reported from blood cultures more frequently. The most common symptom is mucosal candidiasis but the more fatal illness is invasive candidiasis. Invasive candidiasis can be primary or secondary to infected catheters or surgical wounds.[51] Risk factors for invasive candidiasis, include prolonged surgery, surgical procedure, increased blood transfusions, previous Candida species colonization and renal failure after liver transplantation.

The American Society of Transplantation recommends antifungal prophylaxis against Candida to high-risk liver recipients[50,52] and the duration of prophylaxis is for 4 weeks in many centres. Clinical studies have shown that fluconazole, itraconazole or amphotericin B prophylaxis markedly reduced the incidence of invasive candidiasis in liver recipients. Treatment of invasive

candidiasis after liver transplantation, is a combination of antifungal therapy and reduction of immunosuppression.

(B) Aspergillus Infection:

After Candida species, the second most common fungal infection is invasive aspergillosis occurring in 1% - 9.2% in liver recipients. The most important risk factors are retransplantation, renal failure, prolonged stay in intensive care unit, CMV disease and fulminant hepatic failure.[53] Aspergillus fumigatus is the most common species whereas Aspergillus niger, Aspergillus flavus and Aspergillus tereus are less common.[54] In a recent study of the clinical features of invasive aspergillosis from 23 United states transplant centres, the most common clinical presentation (90%) was lung infection and occur during the first year after transplant.[53] The liver recipients with invasive fungal infection had the highest mortality reported, because of the severity of the illness and the underlying immune-compromised status. The possibility of invasive aspergillosis should be suspected in the presence of risk factors and clinical findings, and should be confirmed by any one of the following, (1) lower respiratory tract infection symptoms and CT images showing well circumscribed lesions with or without the halo sign, air-crescent sign or cavity, (2) central nervous system infection with focal lesions on imaging or (3) recovery by culture of the mold. The American Society of Transplantation, recommends the use of a amphotericin B (3-5 mg/kg per day) or an

echinocandin for high risk patients and the duration of prophylaxis is for 4 weeks after liver transplantation.[53] The current guideline recommends, voriconazole as the first-line of choice for the treatment of invasive aspergillosis.[54]

Evaluation Of Infections after Liver Transplantation:[55]

Infection in the early post-transplant period (<1 month) is most commonly bacterial and are primarily nosocomial such as enterococci, staphylococci, gram-negative aerobes, anaerobes or candida species. They are most commonly intra-abdominal (cholangitis, liver, and other abdominal abscesses) and are observed during the post-transplant hospitalization. Infected transplant patients may present with fever, abdominal pain or jaundice or they may be possibly asymptomatic because of immunosuppression. A complete blood investigation, liver function tests, renal function test, coagulation profile, urine analysis were done. Symptomatic investigations are done for culture. Further investigations may include radiological investigations, abdominal ultrasonography, computerised tomography (CT), endoscopic retrograde cholangio-pancreatography (ERCP) and liver biopsy.

During 1-6months, the infections are most commonly due to viruses or opportunistic organisms. After 6 months of transplant, the risk of infection is similar to that of the general population. The most common causes of infection in the outpatient setting are the typical community-acquired pathogens which

are treated with the antimicrobials, typically prescribed for non-immunosuppressed patients (with caution regarding drug interactions). Incidence declines after 6-12 months, if the recipient is on a stable immunosuppressant regimen.

Symptoms and Signs of Infection:

The classic signs and symptoms of infection are often absent because of immunosuppression. Fever is the most common symptom caused by infection or may also be due to rejection or drugs. Fever may be low-grade or absent and leukocytosis may not be present. Pain at sites of infection may be minimal because of the patient's decreased ability to mount an inflammatory response. Infection may progress more rapidly than in the normal patient and may be more difficult to eradicate. A complete blood investigation, radiological investigations, abdominal ultrasonography and liver biopsy were done to rule out infections.

Folllow Up:

The patient was reviewed in the surgical gastroenterology department every month in OPD (Outpatient department). Since most liver transplant patients are immunosuppressed and come to medical attention as a last resort, every complaint should be taken seriously and the patients infected require admission because they will need a decrease in their immunosuppressants and are at risk of

rejection. Fever of unknown origin or suspicion of rejection should be considered for admission for further evaluation. Symptomatic investigations and complete blood investigations are done. If bacterial infection was suspected, cultures are obtained and antibiotics initiated, based on culture and sensitivity as in the non-immunocompromised patient. Broad-spectrum antibiotics are given, if the source is unknown because these patients are on long-term corticosteroids and should be prescribed only after reviewing the information of drug interactions.

MATERIALS AND METHODS:

STUDY PLACE:

1) Department of Microbiology, Government Stanley Medical College, Chennai.
2) Department of Surgical Gastroenterology, Government Stanley Medical College, Chennai.

STUDY DESIGN:

Prospective study.

SAMPLE SIZE:

15 in numbers.

STUDY PERIOD:

October 2016 – July 2017.

ETHICAL CONSIDERATION:

Ethical and research clearance was obtained from the Ethical committee, Stanley medical college. Permission to conduct the study was sought from the respective hospital department authorities. An informed consent was obtained from the patient before enrolment into the study.

STATISTICAL ANALYSIS:

The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe about the data, descriptive statistics, frequency analysis, percentage analysis were used for categorical variables and the mean & Standard deviation (S.D) were used for continuous variables.

INCLUSION CRITERIA:

All patients undergoing liver transplant surgery at Institute of Surgical Gastroenterology in Govt. Stanley Medical College, during the study period.

SAMPLE COLLECTION AND LABORATORY TESTING:

DONOR:

Complete blood investigations, Throat swab c/s, Nasal swab c/s, Blood c/s & Urine c/s were done to rule out infections.

RECIPIENT:

Throat swab c/s, Nasal swab c/s, Blood c/s & Urine c/s before surgery to rule out infections. Symptomatic investigations are done daily and biochemical tests include, Complete blood investigations, Liver function test, Renal function test, Coagulation profile, Serum pro-calcitonin, Tacrolimus or Cyclosporine assay.

SAMPLE COLLECTION:[5]

THROAT SWAB:

It was made sure that the patient was not treated with antibiotics, 8 hours before swabbing. In a good light from over the shoulder, the patient is instructed to tilt the head back and breathe deeply. The tongue is depressed using a tongue depressor to visualize the tonsillar fossae and posterior pharynx. The tonsillar area and the posterior pharyngeal wall are rubbed using a sterile cotton wool swab. Two swabs were taken, one for gram's stain and other for culture.

NASAL SWAB:

Nasal swabs are obtained under direct vision using over-the-shoulder illumination. With the thumb of one hand gently lift the tip of nose. Moisten the tip of sterile cotton swab with sterile water or saline and gently insert into one of the nares. Guide the swab backward and upward along the nasal septum until a distinct feel of resistance indicates that a posterior pharynx has been reached.

URINE CULTURE:

After cleaning the external genitalia with soap and water, then rinse with water and a clean voided mid-stream urine is collected in a sterile wide mouthed container. In indwelling catheter (Foley's catheter), disinfect the catheter collection port and aspirate 5 – 10 ml of urine with sterile needle and syringe and add it into sterile screw cap container.

BLOOD CULTURE:

The blood should be collected before antimicrobial treatment has started.To increase the chances of isolating the pathogen, it is usually recommended that at least two specimens are collected at different times and cultured. Under strict aseptic precautions, about 5 – 10 ml of blood is collected using a sterile syringe and needle in a sterile screw capped liquid culture bottle containing 50ml 0f brain heart infusion broth. It is then incubated at 37^{o} C for 1 week. When growth is suspected, sub-culturing is done on blood agar and macconkey agar and the organism was isolated.

CENTRALVENOUS CATHETER TIP CULTURE:

Disinfect the skin before removal and the catheter tip is collected in a sterile screw cap container. It is cultured qualitatively by rolling the tip back and forth across the blood agar and macconkey agar with sterile forceps four times.

BODY FLUIDS CULTURE: (Abdominal, peritoneal, bile, pleural and drainage fluid)

Disinfect the skin before aspiration and aspirate about 2 – 3ml using a sterile needle and syringe into a sterile test tube.

PUS CULTURE:

Pus from an abscess is best collected at the time, it is incised and drained, or after it has ruptured naturally. Using a sterile technique, aspirate or collect

from a drainage tube up to 5 ml of pus and transfer to a leak-proof sterile container.

WOUND SWAB:

Using a sterile cotton-wool swab, sample is collected from the infected site. Immerse the swab in a container of Amies transport medium. Usually, 2 swabs are collected, one for culture and the other for gram staining.

SPUTUM CULTURE:

A sterile, dry, wide-necked, leak-proof container was given to a patient and requested to cough deeply to produce a sputum specimen. Sputum is best collected in the morning soon after the patient wakes and before any mouth-wash is used. When pulmonary tuberculosis is suspected, up to three specimens may need to be examined to detect acid fast bacilli.

BRONCHO ALVEOLAR LAVAGE:

Bronchial and alveolar washings (broncho-alveolar lavage), are collected using a bronchoscope. The specimen must contain alveolar exudate if cysts are to be found.

ANTIBIOTIC SUSCEPTIBILITY TEST BY KIRBY BAUER'S DISC DIFFUSION METHOD:

The Muller Hinton agar is the standard agar based medium used for testing of most bacterial organisms. The appropriate concentrations of drug for each disk is determined by the United states, Food and Drug Administration (FDA). Before disk placement, the agar plate is inoculated using a swab that has been submerged in a bacterial suspension standardised to match the turbidity of 0.5 Mcfarland turbidity standard equivalent to 1.5×10^8 CFU/ml. The surface of the plate is swabbed in 3 directions to ensure even and complete distribution of the inoculum. Within 15 minutes of inoculation, the antimicrobial disks are placed and incubated at 37^{o} C for 16 – 18 hrs. The incubation time may be increased beyond 16 hours for certain resistant organisms like methicillin resistant in staphylococcus aureus and vancomycin resistant in enterococci. After incubation, a dark background and reflected light are used to examine a disk diffusion plate. A ruler or caliper can be used to measure the diameter of zone of inhibition of each antimicrobial agent. Interpretive criteria for antimicrobial agent / organisms may be tested by disk diffusion are provided in the Clinical and Laboratory Standard Institute (CLSI- M2 series), "Performance Standard for Antimicrobial Disk Susceptibility Tests (M 100 supplements)".

E-TEST (Epsilometer Test):

It is a type of disc diffusion method used to detect the minimum inhibitory concentration of particular organisms against particular drug that is commercially in plastic strips. The one side of the strip contains antimicrobial agent concentration gradient and the other side contains a numerical scale that indicates the drug concentration. Muller Hinton plate was inoculated as for disk diffusion and the strips are placed on the inoculum lawn. Several strips may be placed radially on the same plate. After overnight incubation, the plate is examined and the number present at the point where the border of growth inhibition intersects the E- strip is taken as the minimum inhibitory concentration (MIC) of the drug. In this study, this test was done to detect the MIC of vancomycin against Methicillin resistant Staphylococcus aureus. Vancomycin with MIC $\leq$ 2mm is sensitive, 4 – 8 mm intermediate sensitive and $\geq$ 8mm resistant according to CLSI M-100, S 26.

COMPLETE BLOOD INVESTIGATIONS:[6]

It includes, total white blood cell (WBC) count, differential count, red blood (RBC) cell count, platelet count, haemoglobin (Hb), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) and blood sugar.

URINE COMPLETE ANALYSIS:

It includes specific gravity, pH, colour, appearance, WBC esterase, protein, glucose, ketones, occult blood, bilirubin, urobilinogen and nitrite.

SERUM ELECTROLYTES:

It includes serum sodium, potassium, chloride, calcium, magnesium and phosphorus.

LIVER FUNCTION TEST:

It includes measurement of serum alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gama- glutamyl transferase (GGT), total protein, serum albumin, serum globulin, total bilirubin, direct and indirect bilirubin levels.

RENAL FUNCTION TEST:

It includes measurement of blood urea nitrogen (BUN) and serum creatinine.

COAGULATION PROFILE:

It includes prothrombin time (PT), international normalised ratio (INR), activated partial thromboplastin time (APTT) and serum fibrinogen.

TACROLIMUS ASSAY:

It is a chemi-luminescent microparticles immunoassay (CMIA), used for the quantitative measurement of tacrolimus in human whole blood on the ARCHITECT *i* system. The ARCHITECT Tacrolimus assay is used as an aid in the management of liver allograft patients receiving tacrolimus therapy. The tacrolimus trough levels should be within the therapeutic range (5-10 ng/ml) because acute rejection and toxic side effects, are common at the lower and upper extremes of this range.

CYCLOSPORINE LEVEL:

It is used to measure cyclosporine level in whole blood, to maintain adequate immunosuppression. It is a high performance liquid chromatography method. About 2ml of blood was collected in an EDTA (Ethylene diamine tetra-acetic acid) added tube immediately to the next dose. The therapeutic reference range for liver transplant patient is 150 – 200 µg/ml for 6 months after liver transplant and 100 – 150 µg/ml for > 6 months of transplantation.

REAL-TIME PCR:

It is a variation of standard polymerase chain reaction (PCR) technique that is commonly used to quantify DNA or RNA in a sample. By measuring the amount of amplified product at each stage during the PCR cycle, quantification is possible. The nucleic acid must be extracted first from the clinical specimen

as with conventional PCR. The denaturation of double stranded nucleic acid by heating at 94^{o} C followed by primary annealing and extension are performed in one cycle. The sequence of the primers and probes were selected from the EBV-encoded RNA (EBER) gene for EBV. The forward and reverse primer sequences for EBV were 5´-AAACCTCAGGACCTACGCTGC-3´ and 5´-AGACACCGTCCTCACCAC-3´ respectively. EBNA LP1 region (Nuclear Antigen Leader Protein), was selected for amplification and detection. The detection of specific amplification product indicates the presence of ENV DNA in the specimen.

FOLLOW UP INVESTIGATIONS:

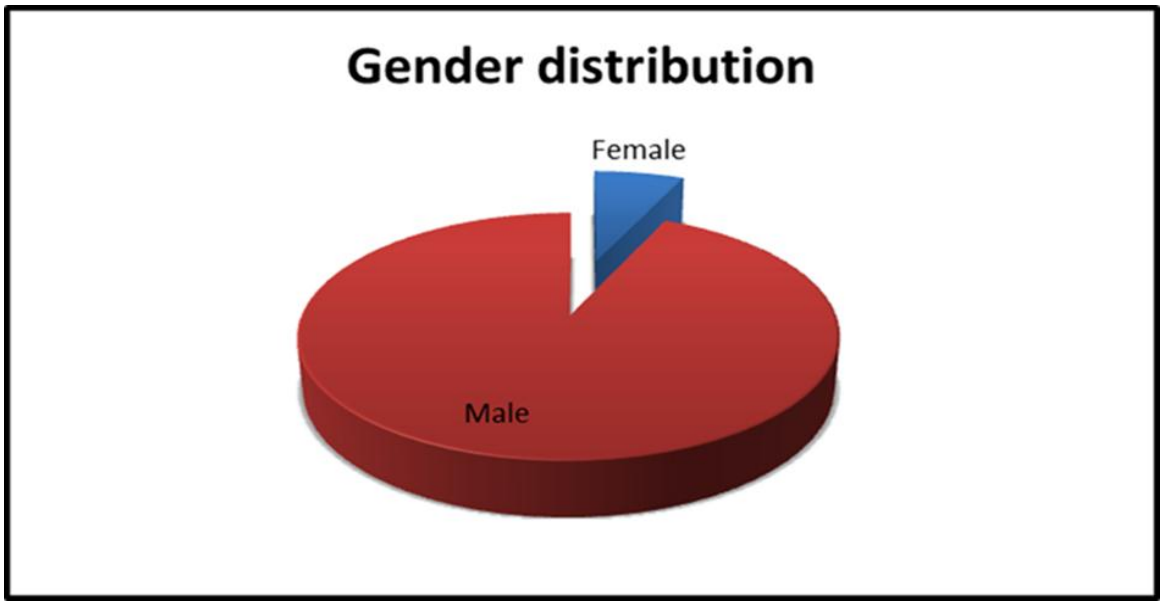
After discharge from the hospital, the recipients need lifelong follow up. Initially patient was reviewed weekly for the first 1 month, then monthly for 6 months and then every 3 months. If the patient had any symptoms after discharge was admitted immediately. Complete blood investigations, Liver function test, Renal function test and coagulation profile was done. The trough level of tacrolimus was also monitored. Culture was done depending on the symptoms and antibiotics were given based on antibiotic sensitivity report.

OBSERVATION AND RESULTS

About 15 Liver transplant patients were followed during the study period, in the department of Surgical Gastroenterology, Stanley Medical College. Specimens taken include throat swab, nasal swab, blood culture, urine culture, wound swab, central venous tip culture, drainage fluid culture and blood for serological test. All the specimens were processed in the department of Microbiology in our institute and the results obtained were analysed.

SEX DISTRIBUTION: (Table 1)

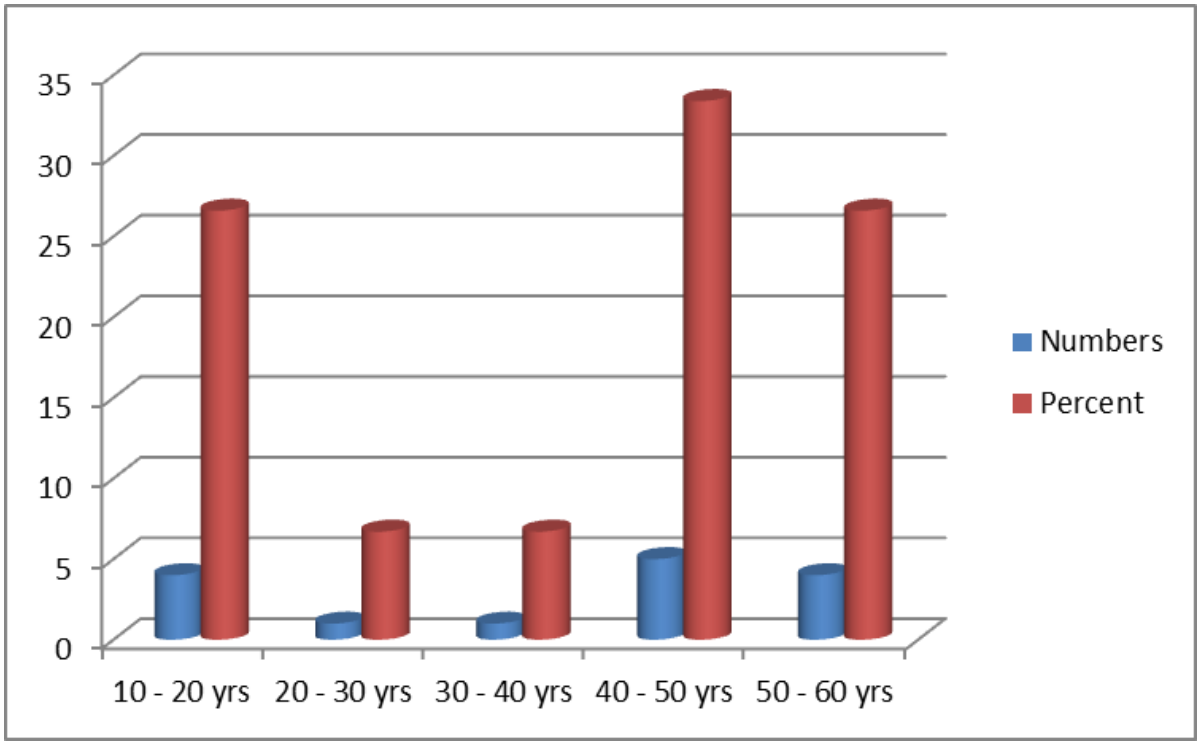
Sex	Frequency	Percent (%)
Female	**1**	**13.3**
Male	**14**	**93.7**



AGE OF STUDY POPULATION:

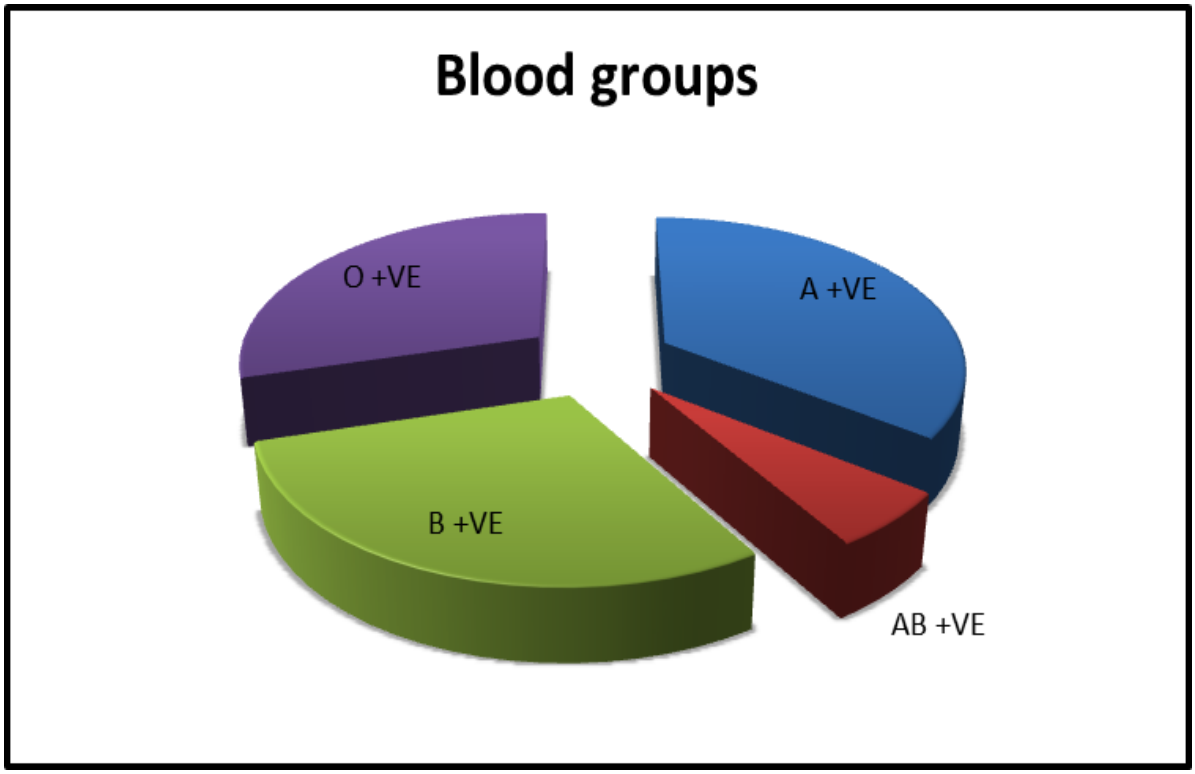
Table 2

Age Group (years)	Numbers	Percentage (%)
10 – 20	4	26.6
20 – 30	1	6.7
30 – 40	1	6.7
40 – 50	5	33.4
50 – 60	4	26.6



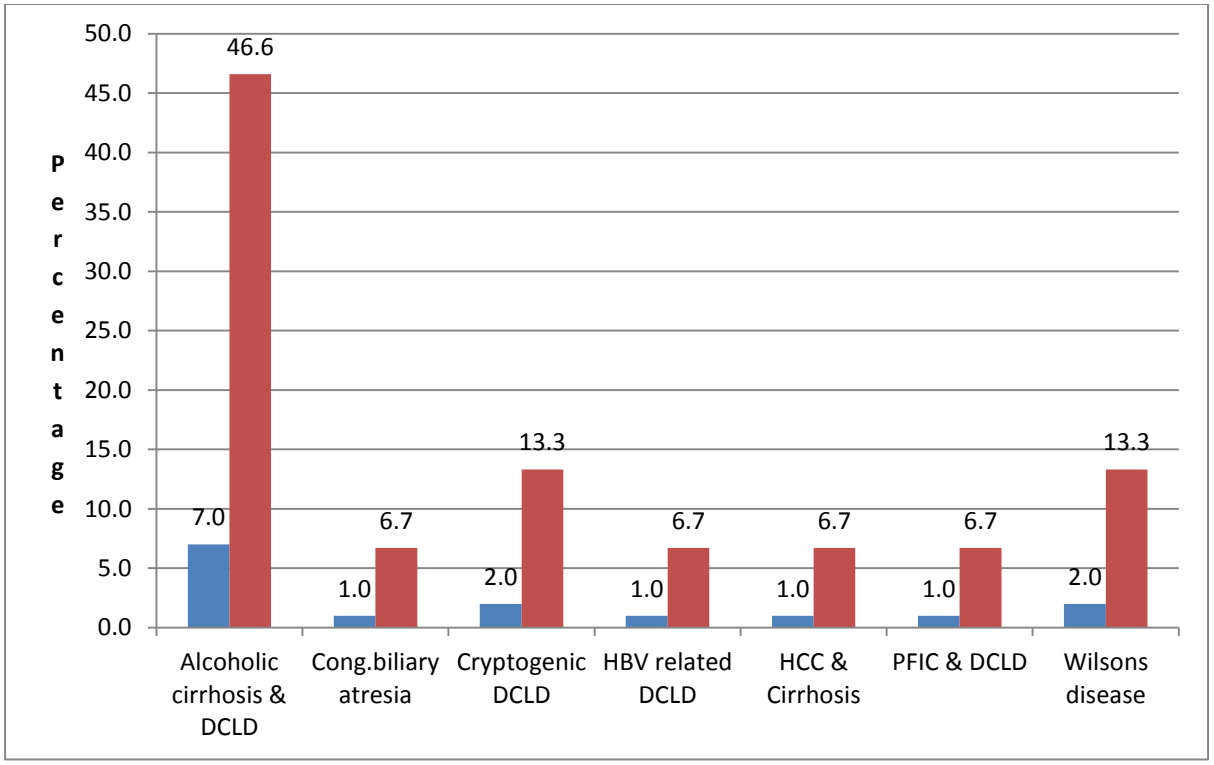
Blood Groups: (Table 3)

Blood Group	Frequency	Percentage (%)
1) A positive	6	40
2) AB positive	1	6.7
3) B positive	5	33.3
4) O positive	3	20
Total	15	100



INDICATIONS FOR LIVER TRANSPLANTATION: (Table 4)

Diagnosis	Frequency	Percentage (%)
Alcoholic cirrhosis with DCLD	7	46.6
Congenital biliary atresia	1	6.7
Cryptogenic DCLD	2	13.3
Hepatitis B virus related DCLD	1	6.7
Hepatocellular carcinoma & Cirrhosis	1	6.7
PFIC & DCLD	1	6.77
Wilsons disease	2	13.3



DESCRIPTIVE STATISTICS OF RECIPIENT BEFORE SURGERY AND AFTER SURGERY: Table 5A

Datas	Minimum	Maximum	Mean	Standard Deviation
Hemoglobin	9.00	12.00	10.3000	1.04881
INR	1.80	3.00	2.4200	.35496
Serum Creatinine	1.40	2.60	2.0200	.35697
Total Bilirubin	90.00	190.00	136.0667	32.25671
Direct Bilirubin	90.00	180.00	145.3333	30.17252
AST	300.00	420.00	372.1333	32.35267
ALT	1.80	4.20	2.9867	.66102
ALP	.50	2.00	1.2400	.42728
Total Protein	9.00	12.00	10.5667	.94239
Serum Albumin	5.00	6.80	5.9733	.50351
Serum Globulin	3.60	5.50	4.5933	.58121

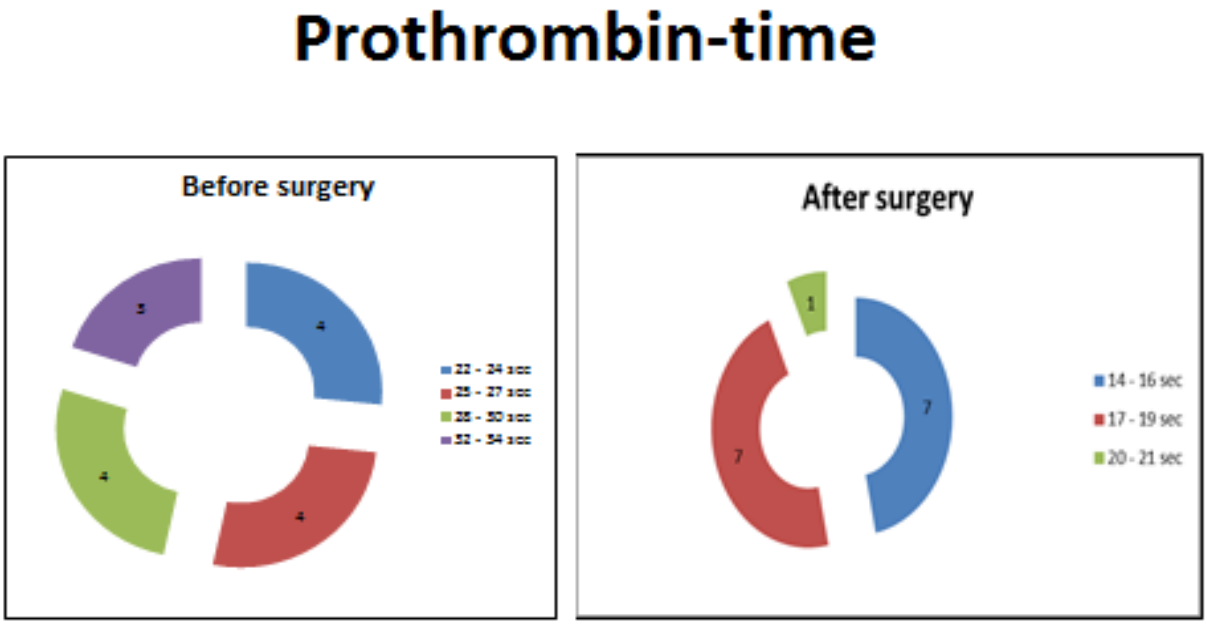
Table 5B:

Datas	Minimum	Maximum	Mean	Standard Deviation
Hemoglobin	9	12	10	1.12
INR	1.0	1.6	1.3	0.173
Serum Creatinine	.5	1.3	0.9	.249
AST	32	50.0	41.5	5.655
ALT	24	80.0	50.0	12.043
ALP	160	280.0	228.0	37.291
Total Bilirubin	.7	1.9	1.1	0.267
Direct Bilirubin	.18	.40	.25	.0806
Total Protein	4.8	7.0	6.0	0.729
Serum Albumin	3.0	5.0	4.0	0.509
Serum Globulin	0.6	2.9	1.9	0.541

Descriptive statistics of recipients before surgery and after surgery including Hemoglobin, Liver function test, serum creatinine and INR. They were raised before surgery and within normal limits after surgery.

PROTROMBIN TIME OF RECIPIENT: (Table 6)

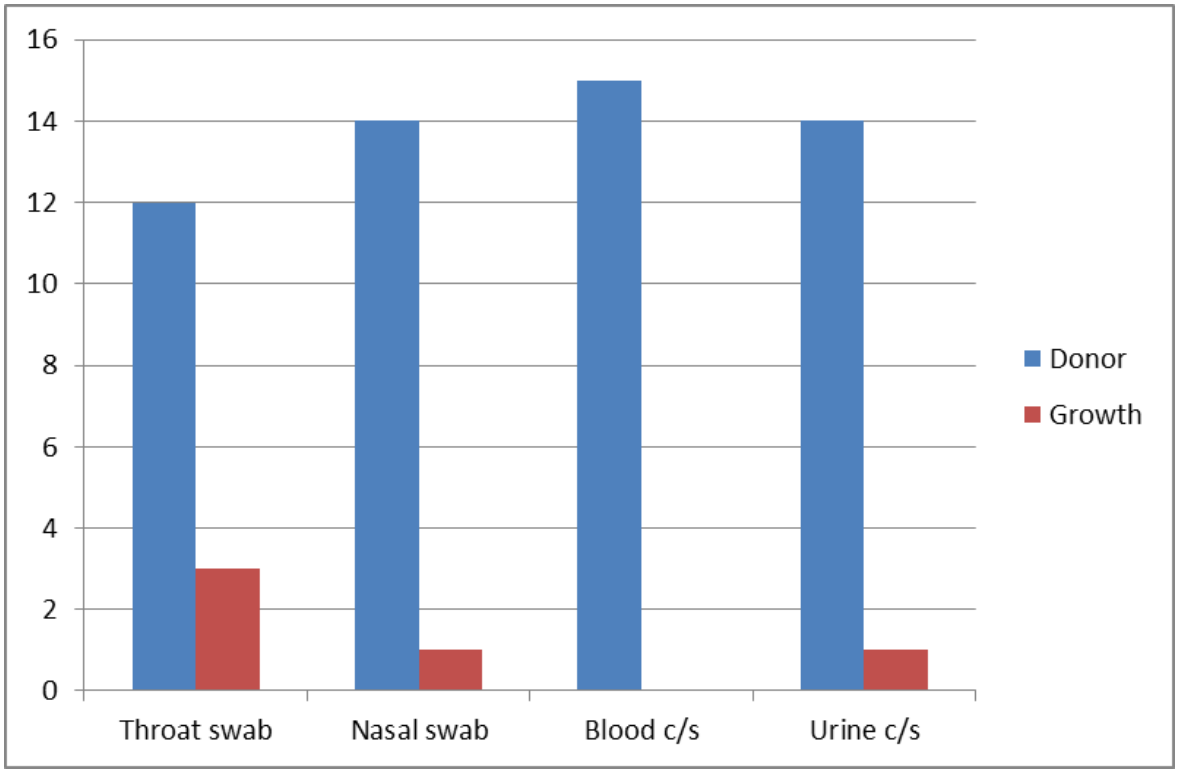
Prothrombin Time(seconds)	14 – 16	17 - 19	20 - 21	22 - 24	25 - 27	28 - 30	32 - 34
Before surgery	0	0	0	4	4	4	3
After surgery	7	7	1	0	0	0	0



CULTURE OF DONOR BEFORE SURGERY:

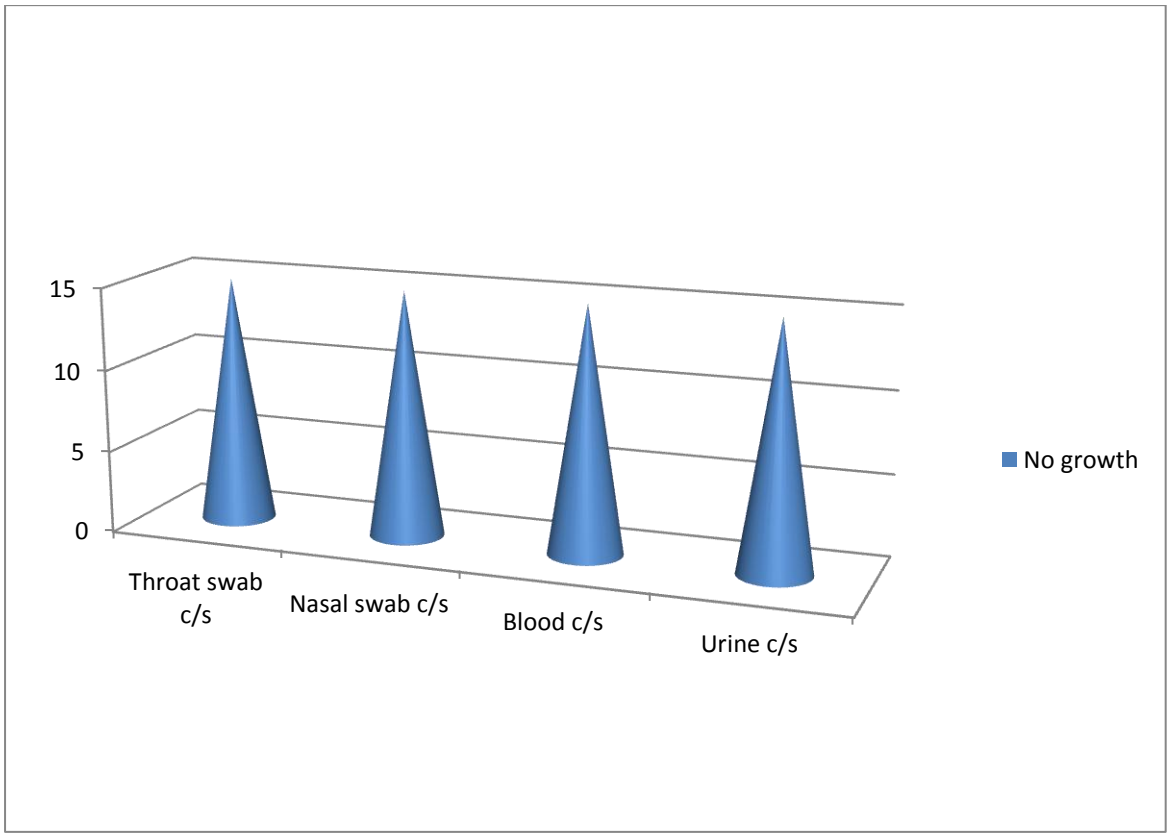
(Table 7)

Culture	Donor	Growth
Throat swab culture/sensitivity	12	3
Nasal swab culture/sensitivity	14	1
Blood culture/sensitivity	15	NIL
Urine culture/sensitivity	14	1



CULTURE OF LIVER TRANSPLANT RECIPIENT BEFORE SURGERY: (Table 8)

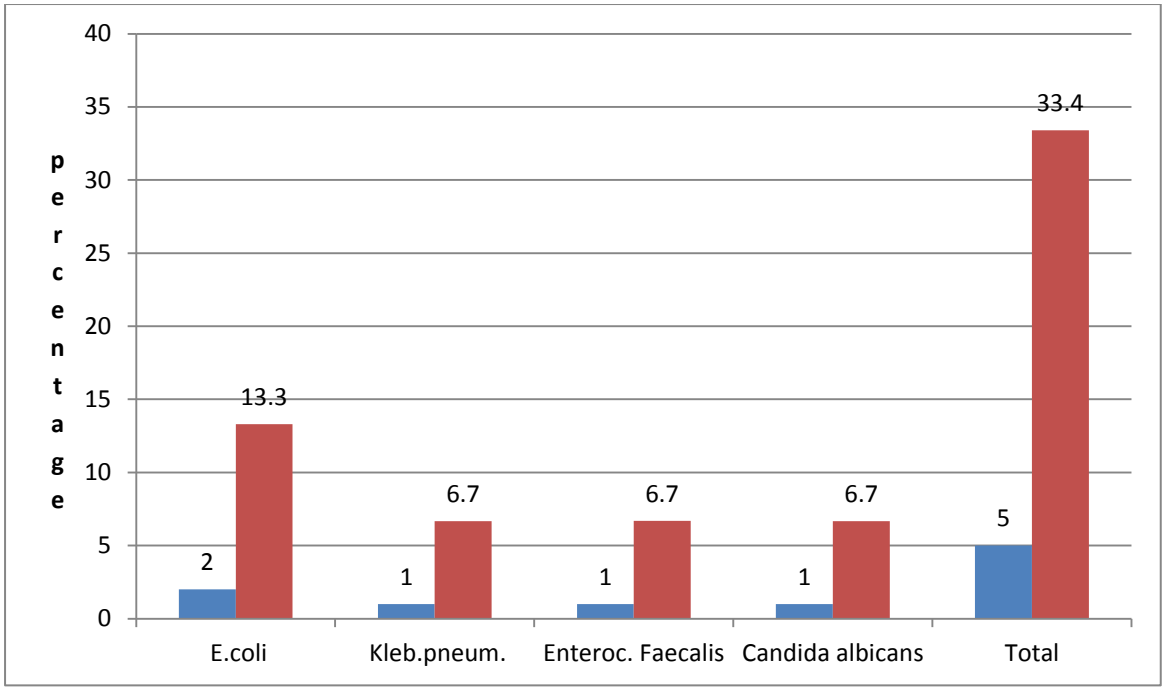
Culture	Total	Growth
Throat swab culture/sensitivity	15	NIL
Nasal swab culture/sensitivity	15	NIL
Blood culture/sensitivity	15	NIL
Urine culture/sensitivity	15	NIL



POST OPERATIVE INFECTIONS:

Catheter Assosciated Urinary Tract Infections: (Table 9)

Catheter Associated UTI	Frequency	Percentage (%)
Escherichia coli	2	13.3
Klebsiella pneumoniae	1	6.7
Enterococcus faecalis	1	6.7
Candida albicans	1	6.7
Total	5	33.4



Antibiotic Sensitivity: (Table 9A)

Organisms	Amikacin	Gentamycin	Cafazolin	Cefatoxime	Cotrimoxazole	Nitrofurantoin	Norfloxacin	Imipenem	Meropenem	Amox.clav	Tigecycline	Colistin
Escherichia coli 1	S	R	R	R	R	S	R	S	R	S	S	S
Escherichia coli 2	S	S	R	R	R	S	S	S	S	S	S	S
Klebsiella pneumoniae	S	S	R	R	R	S	R	S	R	S	S	S

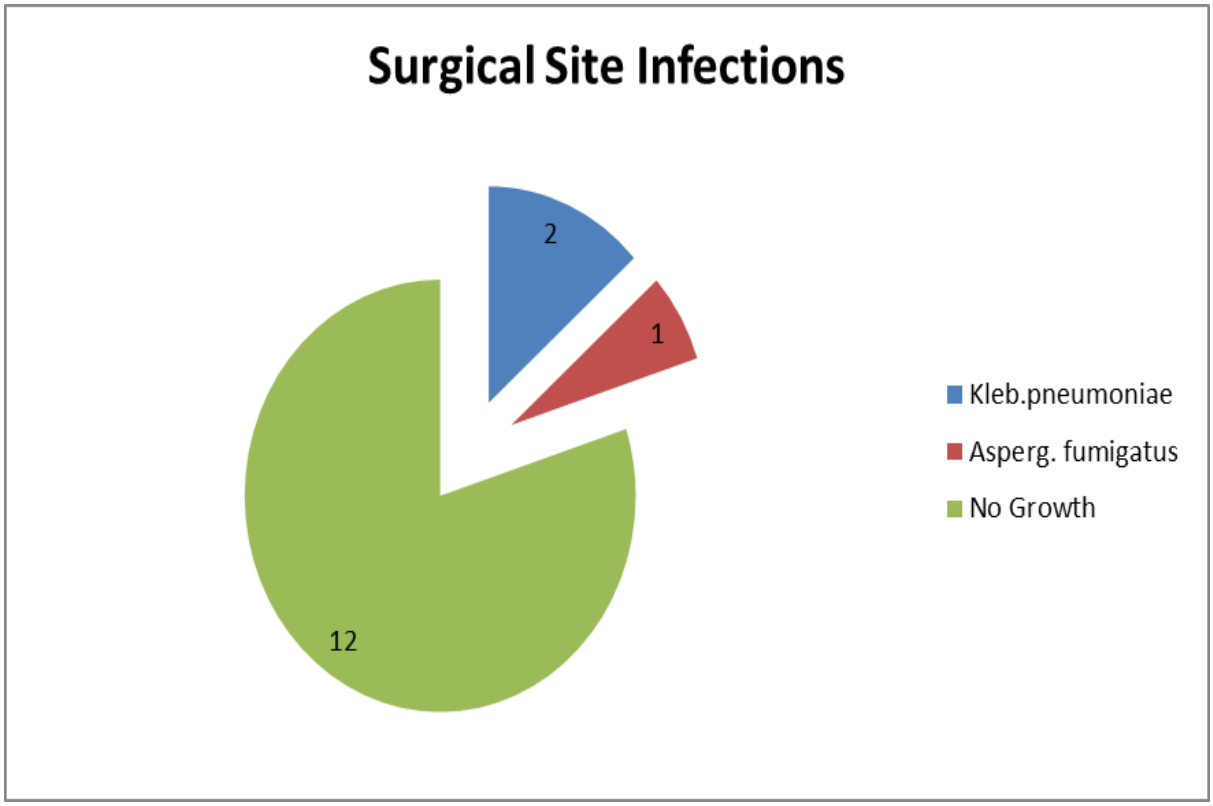
Amox.clav – Amoxicillin clavulanate

Antibiotic Sensitivity of Gram positive Organism: (Table 9B)

Organism	Penicillin	Ampicillin	High level gentamycin	Nitrofurantoin	Norfloxacin	Doxxcycline	Vancomycin	Linezolid
Enterococcus faecalis	R	S	S	S	S	R	S	S

SURGICAL SITE INFECTIONS: (TABLE 10)

Organisms	Frequency	Percentage (%)
Klebsiella pneumoniae	2	13.3
Aspergillus fumigatus	1	6.7
Total	3	20.0



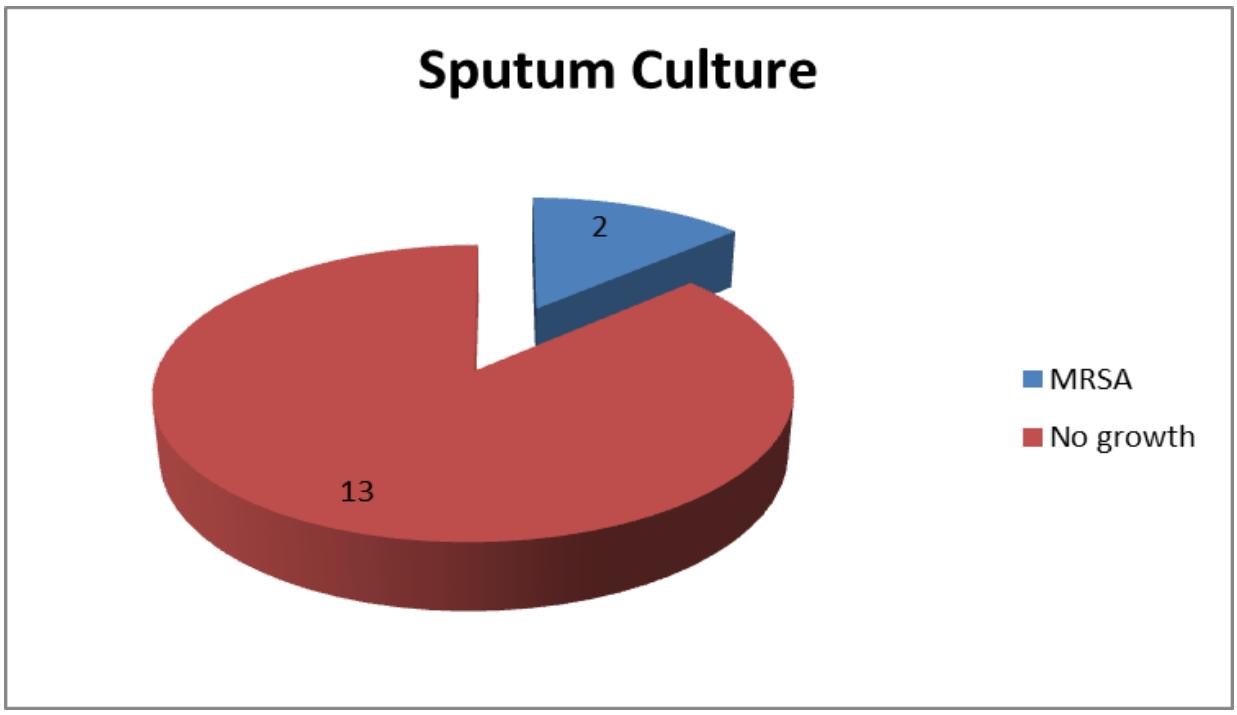
SURGICAL SITE INFECTIONS :

Antibiotic Sensitivity: (Table 10A)

Organism	Amikacin	Gentamycin	Cefazolin	Cefatoxime	Cotrimoxazole	Ciprofloxacin	Imipenem	Meropenem	Tigecycline	Colistin
Klebsiella pneumoniae 1	S	S	R	R	R	R	S	R	S	S
Klebsiella pneumoniae 2	R	R	R	R	R	R	R	R	S	S

SPUTUM CULTURE: (Table 11)

Organisms	Total	Percent (%)
Methicillin Resistant Staphylococcus aureus (MRSA)	2	13.3
No Growth	13	86.7

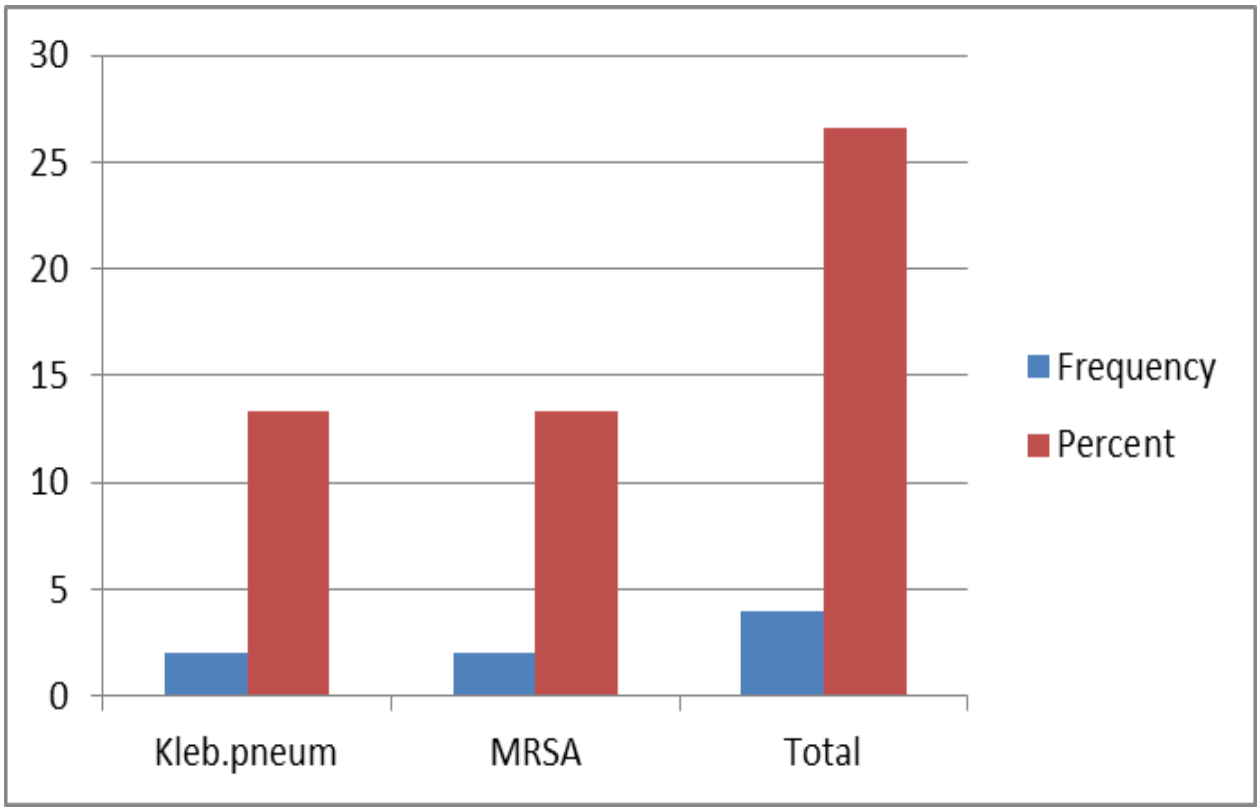


Antibiotic Sensitivity: (Table 11A)

Organism	Penicillin	Cotrimoxazole	Cefoxitin	Erythromycin	Clindamycin	Vancomycin	Linezolid	Levofloxacin	Teicoplanin	Amikacin
MRSA 1	R	S	R	R	R	S	S	S	S	S
MRSA 2	R	R	R	S	S	S	S	R	S	S

CENTRAL VENOUS TIP CULTURE: (Table 12)

Organisms	Frequency	Percentage (%)
Klebsiella pneumoniae	**2**	**13.3**
Methicillin Resist. Staphylococcus aureus	**2**	**13.3**
Total	**4**	**26.6**



CENTRAL VENOUS TIP CULTURE:

Antibiotic Sensitivity: (Table 12A)

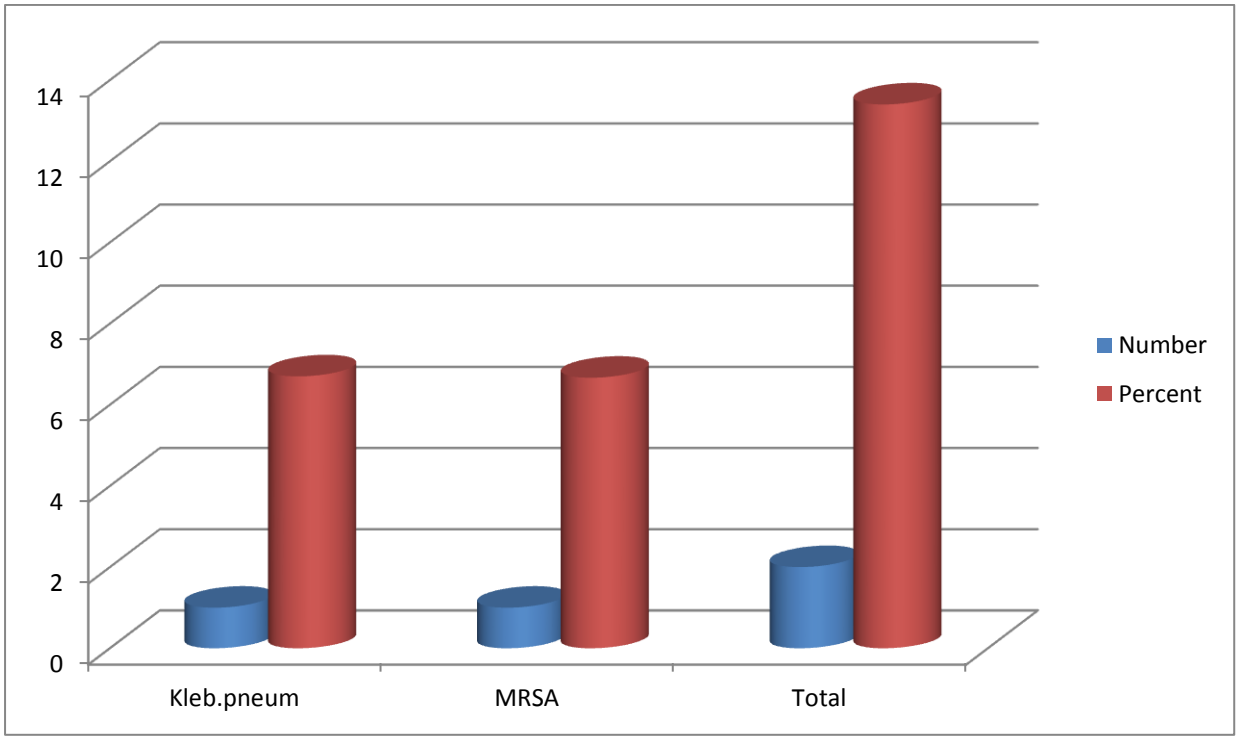
Organism	Amikacin	Gentamycin	Cefazolin	Cefatoxime	Cotrimoxazole	Ciprofloxacin	Imipenem	Meropenem	Tigecycline	Colistin
Klebsiella pneumoniae-1	S	S	R	R	R	R	S	R	S	S
Klebsiella pneumoniae-2	S	S	R	R	R	S	S	S	S	S

Antibiotic Sensitivity of Gram Positive Organism: (Table 12B)

Organism	Penicillin	Cotrimoxazole	Cefoxitin	Erythromycin	Clindamycin	Vancomycin	Linezolid	Levofloxacin	Teicoplanin	Amikacin
MRSA - 1	R	R	R	S	S	S	S	R	S	S
MRSA – 2	R	S	R	S	S	S	S	S	S	S

DRAINAGE FLUID CULTURE: (Table 13)

Organisms	Numbers	Percentage (%)
Klebsiella pneumoniae	1	6.7
Methicillin Resistant Staphylococcus aureus (MRSA)	1	6.7
Total	2	13.4



DRAINAGE TUBE CULTURE:

Antibiotic Sensitivity: (Table 13A)

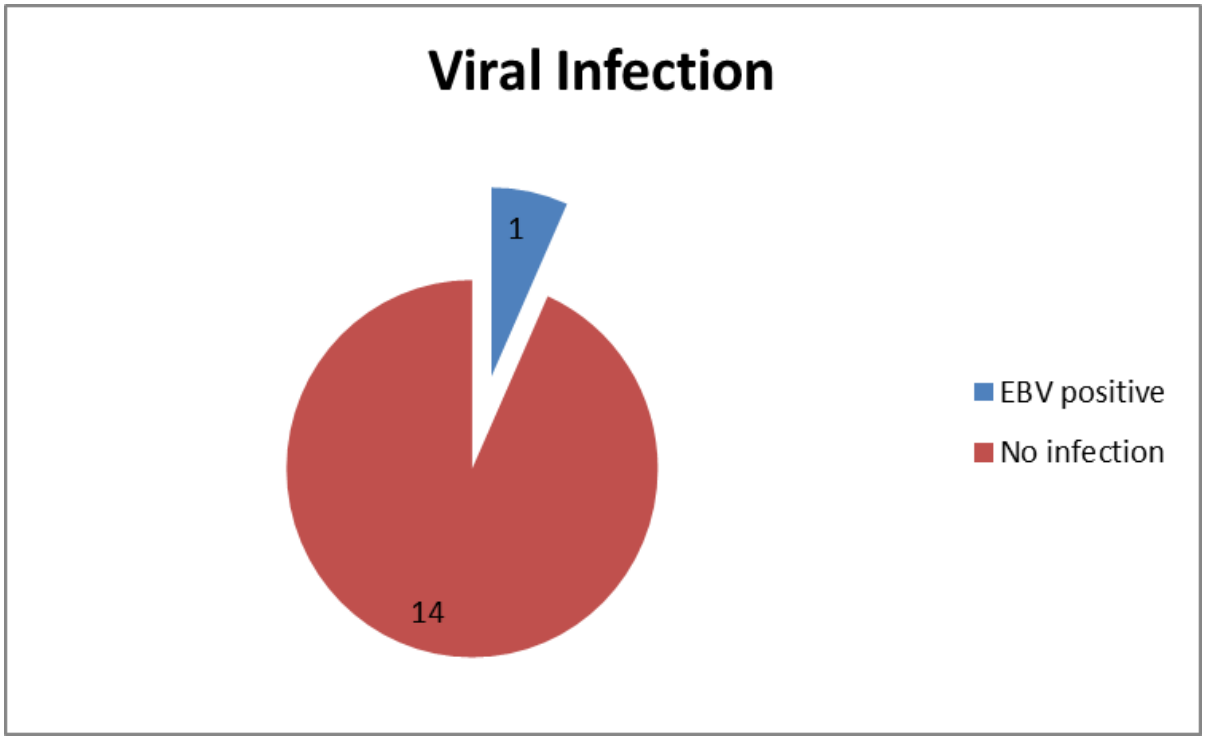
Organism	Amikacin	Gentamycin	Cefazolin	Cefatoxime	Cotrimoxazole	Ciprofloxacin	Imipenem	Meropenem	Tigecycline	Colistin
Klebsiella pneumoniae-1	R	R	R	R	R	R	S	R	S	S

Antibiotic Sensitivity of Gram Positive Organism: (Table 13B)

Organism	Penicillin	Cotrimoxazole	Cefoxitin	Erythromycin	Clindamycin	Vancomycin	Linezolid	Levofloxacin	Teicoplanin	Amikacin
MRSA	R	S	R	R	R	S	S	S	S	S

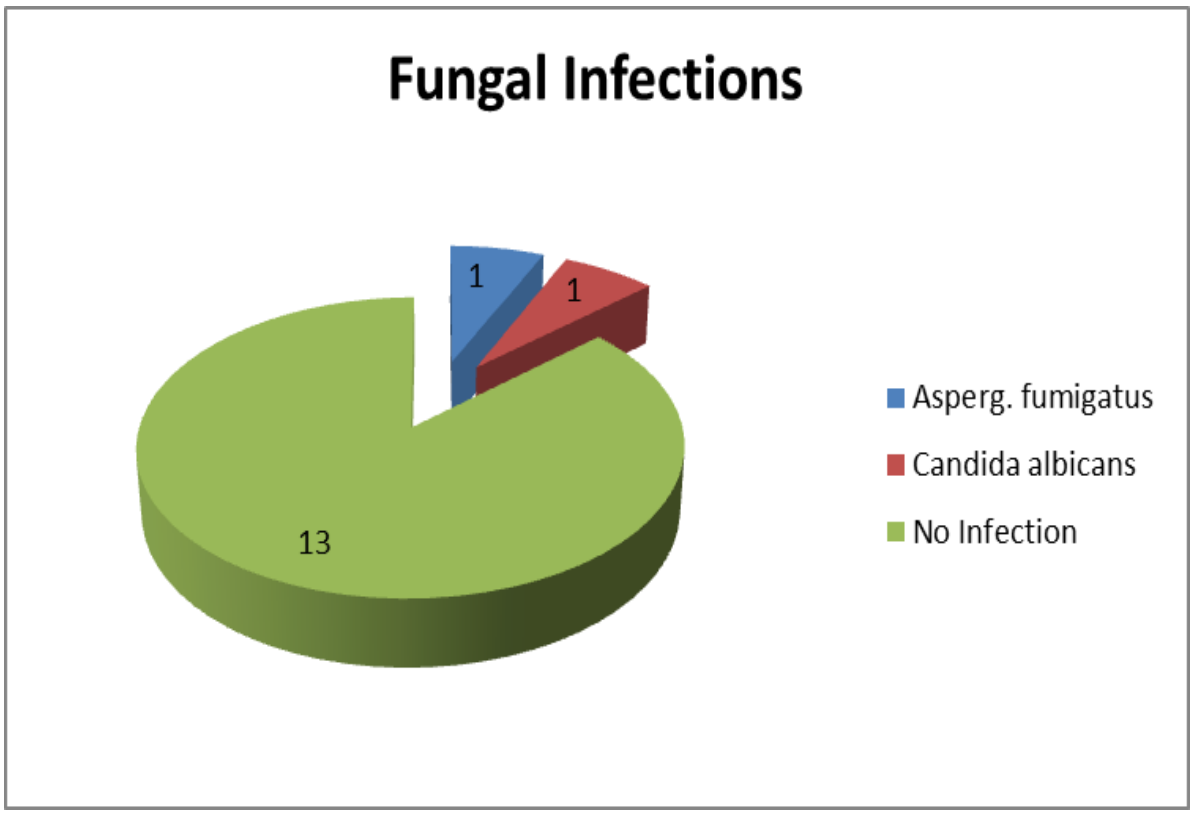
VIRAL INFECTION: (Table 14)

Organism	Number	Percentage (%)
Epstein-barr virus	1	6.7
No infection	14	93.3



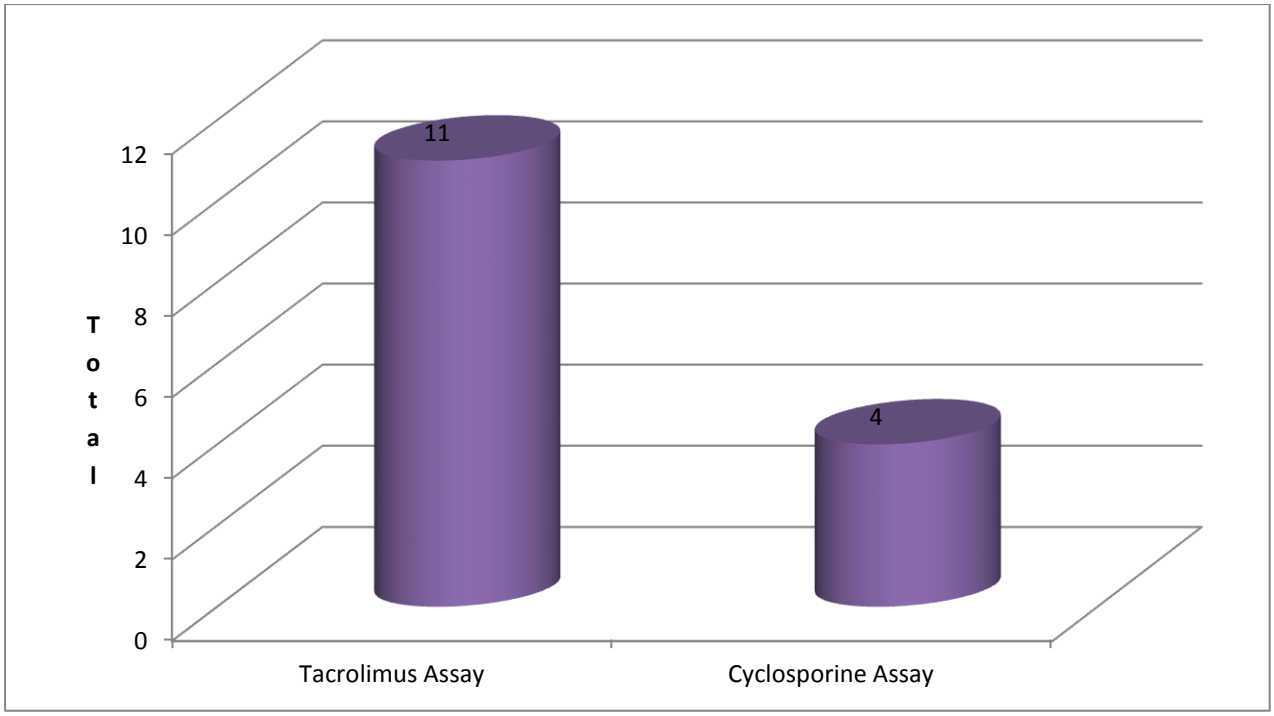
FUNGAL INFECTIONS: (Table 15)

Organism	Number	Percentage (%)
Aspergillus fumigatus	1	6.7%
Candida albicans	1	6.7%
Total	2	13.4%



IMMUNOSUPPRESSANTS ASSAY: (Table16)

IMMUNOSUPPRESSANT ASSAY	TOTAL
Tacrolimus assay	11
Cyclosporine assay	4
Total	15



In liver transplant patients, tacrolimus was given post- operatively along with corticosteroids to maintain immunosuppression. The trough level of tacrolimus was measured on alternate days. In about 15 patients, 4 patients developed increased blood sugar level and elevated liver enzymes due to tacrolimus. The trough level was also raised. So tacrolimus was stopped and changed to cyclosporine A to prevent the drug toxicity. Cyclosporine blood level was measured daily. The therapeutic reference range of cyclosporine A for liver transplant patient is 150 – 200 µg/ml for 6 months after liver transplant and 100 – 150 µg/ml for > 6 months of transplantation.

DISCUSSION

The incidence of infection in liver transplant recipients were analysed in our hospital, in about 15 patients during the study period.

The sex distribution is shown in Table 1. Among 15 patients in this study, one patient was female and the others were male. Liver disease is two-fold more common in males than females. [60] Hence the incidence of Liver transplant is more common in males which correlates in our study.

The age group patterns are shown in Table 2. The most common age group for liver transplantation is 40-60 years, who are more prone for liver diseases particularly in males due to alcoholism in accordance with Varma et al.[16]

The blood group distribution in our study is shown in Table 3. The common blood groups involved in liver transplantation were six A positive blood group and B positive blood group.

The indications for liver transplantation is shown in table in Table 4. The most common indication for liver transplantation is Alcoholic cirrhosis with decompensated liver diseases (46.7%) in accordance with Varma et al.[16] After viral hepatitis, alcoholic liver disease is the second common indication for liver transplantation, overall in the United States and Europe. Alcoholic liver disease accounts for 17%-25% of all transplants performed in the United States and

Europe. Without transplant, in patients with alcoholic liver disease, 5-year survival is as low as 23% which improves to 88% with transplantation. The 1year, 5 years, and 10 years patient survival rates for alcoholic liver diseases were 96%, 88%, and 76% respectively, as compared to 97%, 80%, and 72% respectively, for patients with other indications for LT. Significantly better survival rates were observed for patients who remained abstinent when compared to those, who resumed drinking after LT. Further they observed that patients who resumed abusive drinking following LT had the lowest survival. Recurrent alcoholic liver disease was responsible for the majority of deaths (87.5%) among patients who resumed abusive drinking

Descriptive statistics of recipient before and after surgery is shown in Table 5A and 5B involving Hemoglobin, Liver Function test, Serum creatinine and INR (International Normalised Ratio). The results were increased before surgery and within normal limits after surgery.

Prothrombin time of recipients before surgery and after surgery, during discharge is shown in Table 6. It is prolonged before surgery due to liver diseases and normal, after surgery.

The cultures of donor before surgery are shown in Table 7, including Throat swab, Nasal swab, Blood culture and Urine Culture. Among 15 donors, β- hemolytic Streptococcal was isolated in Throat swab of 3 donors. Methicillin

resistant Staphylococcus aureus was isolated from nasal swab of one donor. Candida albicans was isolated from Urine culture of one donor.

The culture of recipients before surgery is shown in Table 8. No growth was observed in Throat swab, Nasal swab, Blood culture and Urine culture before surgery. Coagulase negative Staphylococcus aureus (CONS) was isolated from nasal swab in most patients which were commensals.

Catheter assosciated Urinary tract infection of recipients is shown in Table 9 and it was 33.4% in this study. The most common organism isolated after transplantation was Escherichia coli. They belong to Extended spectrum β lactamases (ESBL) producing organism in accordance with Sang Il Kim.[29] Urinary tract infections are the common source of antibiotic resistant bacterias, such as extended spectrum β lactamases (ESBL) producing Enterobacteriaceae, vancomycin resistant enterococci (VRE) and methicillin resistant Staphylococcus aureus (MRSA). Prolonged use of indwelling urinary catheter is one of the most common risk factor for UTI. The ESBL producing E. coli was confirmed by standard disk diffusion method in Muller Hinton agar, using cefotaxime and ceftazidime alone and in combination with clavulanate incubated at 37^{o}C for 16 – 18 hours. An increase in zone of diameter of ≥ 5mm was noticed for antimicrobial agent tested alone and in combination with clavulanate. Enterococcus infection was seen in 13.3% of patients and sensitive to norfloxacin, nitrofurantoin, vancomycin and linezolid.

Surgical site infection of liver transplant patients is shown in Table 10. The incidence of surgical site infection in this study is 20% in accordance with Sanger Il kim.[29] In previous studies, the incidence of surgical site infections ranged from 9% to 21.5% as wound infection, from 6% to 18% as cholangitis, from 6.3% to 9% as peritonitis and from 4% to 12.9% as abscess. LT recipients differ from other transplant recipients with regard to underlying poor nutrition, bleeding tendencies, difficulties and longer surgical durations. The common organisms isolated in this study was, Klebsiella pneumonia (13.3%). The antibiotic sensitivity pattern shows that one organism is sensitive to Imipenem and resistant to Meropenem. The other organism (Klebsiella species) is a multi-drug resistant, sensitive to Tigecycline and Colistin only. The surgical site infection, is the most common cause of bacterial infection and manifest itself early after liver transplantation. Treatment consists of surgical debridement and pathogen directed antimicrobial therapy.

Sputum culture positive organism of recipients is shown in Table 11. Bacterial pneumonia occurs in 13.3% of patients after transplantation which were caused by Methicillin Resistant Staphylococcus aureus in accordance with Sanger Il Kim.[29] Antibiotic sensitivity pattern shows, one organism sensitive to Vancomycin, Linezolid and Teicoplanin. The other organism is sensitive to all except Penicillin and Cotrimoxazole. The sensitivity to Vancomycin was detected by minimum inhibitory concentration (MIC) by E- test method. Liver

transplant recipients are more prone for respiratory tract infections because of prolonged surgical duration, frequent use of post-transplant mechanical ventilation and immunosuppression. In a study by Ikegami et al,[39] gram negative bacilli were the predominant pathogens, causing up to 84% of bacterial pneumonia, and the short-term mortality rate was 42%. Pathogen-specific antimicrobial therapy is done for the treatment of bacterial pneumonia, with or without reduction of immunosuppressive agents. After the immediate post-operative period, the opportunistic bacterial pneumonia may occur less common.

Central venous tip culture of post liver recipient is shown in Table 12. The incidence of infection in this study is 26.6% and the most common organisms isolated are Methicillin resistant Staphylococcus aureus (13.3%) and Klebsiella pneumoniae (13.3%). Among the Klebsiella pneumoniae, one organism is sensitive to Imipenem and resistant to Meropenem. The MRSA isolates were sensitive to all drugs except penicillin. The sensitivity to Vancomycin was detected by MIC by E- test method.

Drainage tube culture of post liver transplant recipient is shown in Table 13. The incidence is 13.4% in this study and caused by Klebsiella pneumoniae and Methicillin resistant Staphylococcus aureus (MRSA). The Antibiotic sensitivity pattern of Klebsiella pneumonia, shows that is sensitive to Imipenem, Tigecycline, Colistin and resistant to Meropenem. The MRSA organism was

sensitive to Vancomycin, Linezolid, Teicoplanin and Levofloxacin. The sensitivity to Vancomycin was detected by MIC by E- test method.

The viral infection of post liver transplant recipient is shown in Table 14. It was seen in only one patient (6.7%), diagnosed as Epstein- barr virus with assosciated post-transplant lymphoproliferative disorder (PTLD). The patient reported to the hospital with complaints of fever, malaise and symptoms suggestive of lower respiratory tract infection, 4 months after transplantation. Blood investigations showed leucopenia, thrombocytopenia, anaemia and raised ESR. CT scan of thorax shows multiple mediastinal lymphadenopathy and CT scan of thorax and neck were normal. Real time PCR (Polymerase Chain Reaction) was done for Epstein-barr virus DNA and found to be to be positive. The patient was treated with chemotherapy with reduction of immunosuppression.

The fungal infection of post liver transplant recipient is shown in Table 15. It was seen in 13.4% of patients. The organisms isolated were Candida albicans from catheter assosciated urinary tract and Aspergillus fumigatus from wound tissue. In accordance with Pappas PG and Silveria FP, Candida species accounts for over half of all invasive fungal infections in liver recipients. Superficial and invasive candidiasis occurs early and often during the first 1-3 months after liver transplantation.[50] Invasive candidiasis could be primary or secondary to infected catheters or surgical wounds. The American Society of

Transplantation recommends antifungal prophylaxis against Candida to high-risk liver transplant recipients with many centres providing it for 4 weeks.[1]Aspergillus species is the second most common fungal infection in liver recipients, with invasive aspergillosis occurring in 1%-9.2%. Antifungal prophylaxis against Aspergillus species could result in reduction in superficial and invasive infection, as well as the mortality. The current guidelines recommend voriconazole as the first line of treatment for 12 weeks. Surgical excision or debridement remains an integral part of the management of invasive aspergillosis.[1]

The immunosuppressant assay is shown in Table 16. In liver transplant patients, tacrolimus was given post- operatively along with corticosteroids. The tacrolimus trough level was measured on alternate days to maintain immunosuppression. In about 15 patients, 4 patients developed increased blood sugar level and elevated liver enymes due to tacrolimus about 3- 4 days after transplantation. The trough level of tacrolimus were also raised. The drug was stopped and changed to cyclosporine A to prevent the drug toxicity. Cyclosporine A blood level were measured in 4 patients. In most centres, tacrolimus is preferred over cyclosporine because of its greater potency and organ protective effects. It is usually started with a low dose of 0.1- 0.15 mg/kg per day divided in 2 doses, orally on the first day after transplant and the dose is gradually increased to reach the desired trough level. Usually, the levels of 10-

15 ng/ml were targeted for the first 4-6 weeks and 5-10 ng/ml were accepted thereafter by many centres to prevent acute rejections and renal protection.[56] When cyclosporine A has to be used, the recommended dose is 10-15 mg/kg per day in 2 divided doses. The trough level (C0 level) in the early post-transplant period, is 250 µg/ml and 150 µg/ml later on. For cyclosporine, C2 levels (2 hour after dose) monitoring has also been implemented at some centres. The C2 level may be in the range of 800-1400 µg/ml for the first 3 months, 600-1000 µg/ml after 6 months and 500-700 µg/ml after 1-year post transplantation.[57]

Acute graft rejections were seen in 3 patients (20%) after liver transplantation and were treated with high dose (intravenous) corticosteroids for 3 – 5 days (Pulse therapy) in combination with immunosuppressants, according to Jens encke et al. The typical dosage of Methyl prednisolone is 500 or 1000mg for 3 days and gradually tapered to oral prednisolone. Acute rejection occurs 5 – 15 days after liver transplantation. It is clinically suspected by elevation in serum aminotransferase and alkaline phosphatses which typically preceeds jaundice and fever. Diagnosis should be confirmed by liver biopsy prior to initiation of treatment for rejection. Approximately 75% of episodes of acute cellular rejection resolve after a course of high dose corticosteroids (3 – 5 days of 500 -1000 mg of Methyl prednisolone) and a second course is effective in additional 10% of cases. Monoclonal antibodies (Muromonab) seems to be beneficial in steroid resistant rejections.[58]

Bacterial pathogens differ between the post-transplant period. Most of the bacterial infections occur within 2 months of transplantation. Enteric gram negative bacilli and gram positive cocci are the major causative organisms. Enterobacteriaceae are the major pathogens in Liver transplant recipients. The gram negative bacteria can also cause surgical site infections including deep intra-abdominal infections, bacteremia, pneumonia, urinary tract infections and catheter-related infections. Enterobacteriaceae are the major pathogens in liver tranplant recipients in this study and a high rate of drug-resistant were seen. The prevalence of ESBL producing gram negative bacilli, carbapenem-resistant klebsiella pneumoniae (CRKP), multi-drug resistant Acinetobacter and Pseudomonas are increasing and are related to higher rates of treatment failure.[59] The risk factors for multi-drug resistant gram negative bacilli (MDR-GNB) infections include, prolonged hospitalization, antibiotic exposure, surgical complications and the need for invasive devices and are associated with increased rates of allograft failure and mortality.

The gram positive bacteria are the major cause of superficial and deep surgical site infections, bacteremia and pneumonia, predominantly during the first 2 months after LT. They are the most common causes of early post-transplant surgical site and bloodstream infections. Among the gram positive bacteria, the common organisms include Staphylococci, Streptococci and Enterococci. The incidence of Methicillin resistant Staphylococcus aureus

(MRSA) were more common in this study and were sensitive to vancomycin, linezolid and teicoplanin. Enterococcus faecalis infection was found in catheter assosciated urinary tract and sensitive to norfloxacin, nitrofurantoin, vancomycin and linezolid.

SUMMARY

- Out of 15 Liver Transplant patients in this prospective study, 14 patients were male and one patient was female.
- The most common age group was between 40 – 50 years.
- The most common indication for Liver transplantation was Alcoholic cirrhosis with decompensated liver disease and it is 46.6% in this study.
- The common organism isolated in catheter assosciated urinary tract infection was Escherichia coli and was 13.3% in this study. They were ESBL producing organism.
- Surgical site infections were caused by Klebsiella pneumoniae during the post- operative period. They are multi drug resistant, with sensitivity to Imipenem, Tigecycline and Colistin. and it was 13.3% in this study.
- Bacterial pneumonia was seen in 13.3% of patients and was caused by Methicillin resistant Staphylococcus aureus (MRSA) with sensitivity to Vancomycin, Linezolid and Teicoplanin.
- Central venous tip culture shows growth in 26.6% of patients, the isolates were Klebsiella pneumoniae and Methicillin resistant Staphylococcus aureus.
- Drainage tube culture was positive in 13.4% of patients, caused by Klebsiella pneumoniae and Methicillin resistant Staphylococcus aureus. The Klebsiella pneumoniae was multi-drug resistant, sensitive to

Tigecycline and Colistin. The MRSA isolate was sensitive to Vancomycin, Linezolid and Teicoplanin.

- Viral infection was seen in one patient, diagnosed as Epstein-barr virus assosciated post-transplant lymphoproliferative disorder.
- Fungal infection was seen in 13.4% of patients. The isolates were Candida albicans from catheter assosciated urinary tract and Aspergillus fumigatus from wound . They were treated with antifungal drugs. Surgical wound debridement was done for aspergillus fumigatus infection.
- Acute graft rejections were seen in 3 patients (20%) after liver transplantation and were treated with high dose steroids (intravenous methyl prednisolone) for 3-5 days.
- Bacterial infections were more common in the post-operative period in this study. The infections due to gram negative organisms were common when compared to gram positive organisms. Most of the organisms isolated were multidrug resistant.

CONCLUSION

- A study on the incidence of infections was done in 15 liver transplant patients, during the study period October 20l6 – July 2017 and the role of immunosuppressants on immunosuppression studied.
- Alcoholic cirrhosis with decompensated liver disease was the most common indication for liver transplantation and was seen in 46.6% of patients.
- Catheter assosciated urinary tract infection was seen in 5 patients. They are commonly caused by Escherichia coli and are ESBL producers.
- Surgical site infections were seen in 13.3% of patients, caused by Klebsiella pneumoniae. They are multi-drug resistant and treated with Imipenem, Tigecycline and Colistin.
- Bacterial pneumonia was seen in 13.3% of patients, caused by Methicillin resistant Staphylococcus aureus (MRSA). They are sensitive to Vancomycin, Linezolid and Teicoplanin.
- Central venous tip culture was positive in 26.6% of patients, caused by Klebsiella pneumoniae and Methicillin resistant Staphylococcus aureus.
- Drainage tube culture was positive in 13.3% of patients, caused by Klebsiella pneumoniae and Methicillin resistant Staphylococcus aureus (MRSA). Klebsiella pneumoniae was multidrug resistant with sensitivity

to Tigecycline and Colistin only. MRSA was sensitive to Vancomycin, Linezolid and Teicoplanin.

- Fungal infections were caused by Candida albicans from catheter assosciated urinary tract and Aspergillus fumigatus from surgical wound. They were seen in 13.3% of patients and treated with anti-fungal drugs.
- Viral infection was seen in one patient, diagnosed as Epstein-barr virus assosciated with post-transplant lymphoproliferative disorder (PTLD).
- Acute graft rejections were seen in 3 (20%) patients and were treated with high dose intravenous corticosteroids, Methyl prednisolone 500 or 1000mg for 3 – 5 days (Pulse therapy).
- Infections after liver transplantation are the common cause of morbidity and mortality. Evaluation of common nosocomial infection and avoidance of unnecessary indwelling catheters can prevent early morbidity. Frequent use of antibiotics prior to surgery for varying indications (e.g. infection and SBP prophylaxis) render liver transplant recipients vulnerable to multi-drug resistant strains of bacteria

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PROFORMA

Name : Serial No.

Age : DOA -

Sex : DOS -

IP. No : DOD -

Provisional Diagnosis:

HISTORY DETAILS:

6) H/O pain over the wound site (Yes/No) 7) H/O discharge from the wound site (Yes/No) 8) H/O fever or any other symptoms (Yes/No) 9) H/O intra operative complications (Yes/No) 10) H/O antibiotics and immuno- (Yes/No) Suppressants during the Post-operative period 11) H/O comorbid illness (Yes/No) GENERAL EXAMINATION: Anaemia (Yes/No) Jaundice (Yes/No) Pedal edema (Yes/No)	

SYSTEMIC EXAMINATION:

RESPIRATORY SYSTEM:

CARDIOVASCULAR SYSTEM:

PER ABDOMEN:

CENTRAL NERVOUS SYSTEM:

INVESTIGATIONS:

POST- OPERATIVE PERIOD:

Antibiotics and Immunosuppressants course:

ADVICE:

பங்குபெறுபவரின் அறிவிப்பு

.....ஆகிய எனக்கு இந்த ஆய்வினை பற்றியும், அதன் நோக்கம் என்ன என்பதையும், என்னுடைய மொழியில் தெளிவாக ஆய்வு செய்பவரின் மூலம் விளக்கப்பட்டது.

மேலும், ஆய்வினை பற்றி நான் கேட்ட எல்லாவிதமான கேள்விகளுக்கும் எனக்கு திருப்தியடையும் விதத்தில் ஆய்வு செய்பவரால் பதிலளிக்கப்பட்டது; மற்றும் என்னுடைய விவரங்களை இரகசியமாக பாதுகாக்கப்படும் என உறுதி அளிக்கப்பட்டுள்ளது. ஆகையால், நான் இந்த ஆய்வில் பங்குபெற தானாக முன்வந்து ஒப்புதல் அளிக்கின்றேன்.

பங்குபெறுபவரின் பெயர் :

பங்குபெறுபவரின் கையொப்பம் (அ) இடது பெருவிரல் பதிப்பு :

ஆய்வு செய்பவரின் பெயர்:

ஆய்வு செய்பவரின் கையொப்பம்:

KEY TO MASTER CHART

IP.NO. - Inpatient number

DCLD – Decompensated Liver Diseases

HCC – Hepatocellular carcinoma

HBV – Hepatitis B virus

PFIC – Progressive Familial Intrahepatic Cholestasis

Total WBC Count – Total White Blood Cell Count

E/ B/ M – Eosinophils/ Basinophils/ Monocytes

RBC Count – Red Blood Cell Count

PCV – Packed Cell Volume

MCV – Mean Corpuscular Volume

MCH – Mean Corpuscular Haemoglobin

MCHC – Mean Corpuscular Haemoglobin Concentration

Hb – Hemoglobin

PT – Prothrombin time

INR – International Normalised Ratio

Sr. creat. – Serum creatinine

AST – Aspartate transaminase

ALT – Alanine transaminase

ALP – Alkaline phosphatase

Total BR – Total bilirubin

Direct BR – Direct bilibubin

Na – Sodium

K – Potassium

Cl – Chloride

Ca – Calcium

Mg – Magnesium

P – Phosphorus

c/s – culture / sensitivity

MRSA – Methicillin Resistant Staphylococcus aureus

UTI – Urinary tract Infection

CV TIP – Central venous tip

DT Fluid – Drainage tube fluid

E.coli – Escherichia coli

Kleb. Pneumonia – Klebsiella pneumonia

EBV – Epstein barr virus

Ak – Amikacin

G – Gentamycin

NIT – Nitrofurantoin

Nor – Norfloxacin

Cz – Cefazolin

IMP – Imipenem

MRP – Meropenem

AmxC – Amoxicillin Clavulanic acid

Ba – Cotrimoxazole

Ctx – Cefotaxime

Cip – Ciprofloxacin

Levo – Levofloxacin

Amp – Ampicillin

TGC – Tigecycline

Colis – Colistin

HLG – High level gentamycin

Dox – Doxycycline

Pen – Penicillin

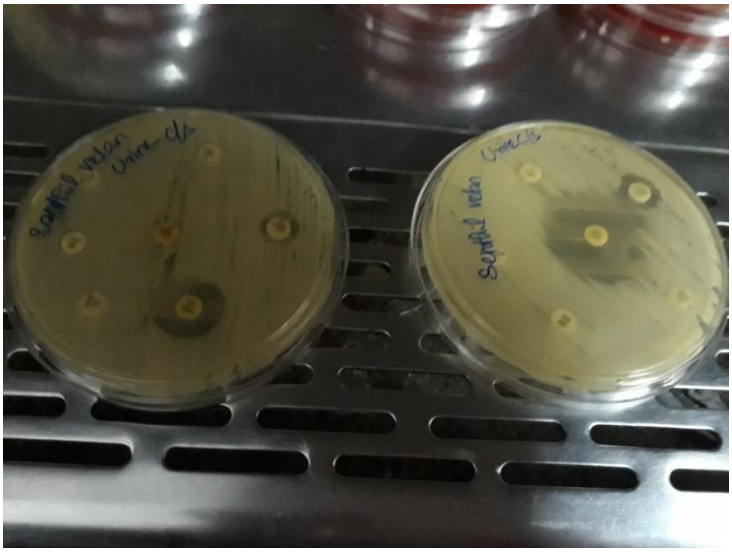
Ery – Erythromycin

CD – Clindamycin

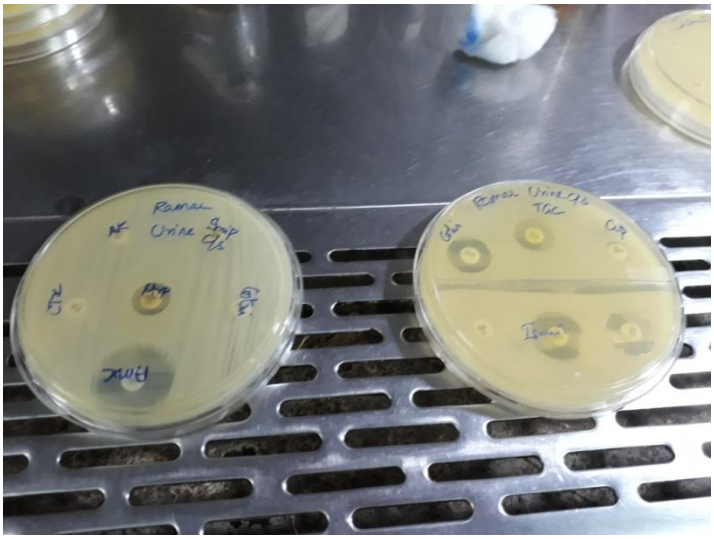
Van – Vancomycin

Lz – Linezolid

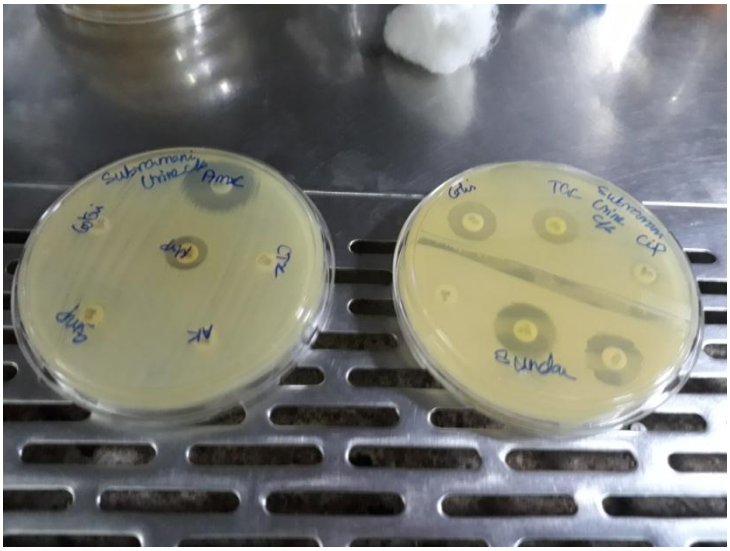
Teico – Teicoplanin



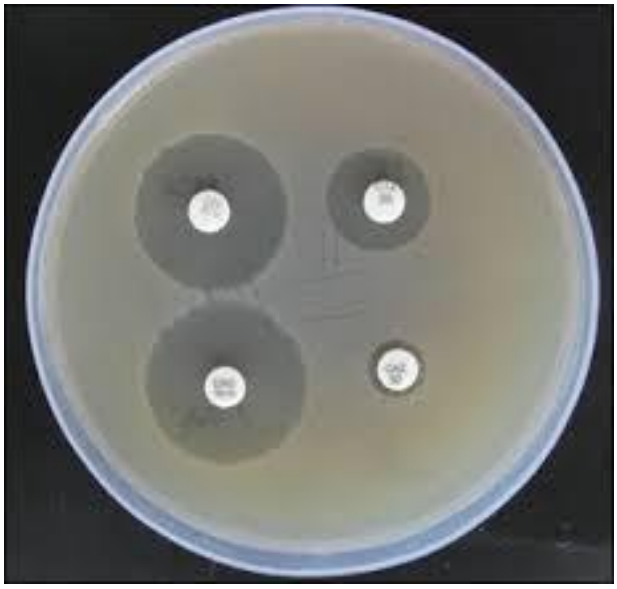
SENTHIL VELAN URINE C/S



RAMAR URINE C/S

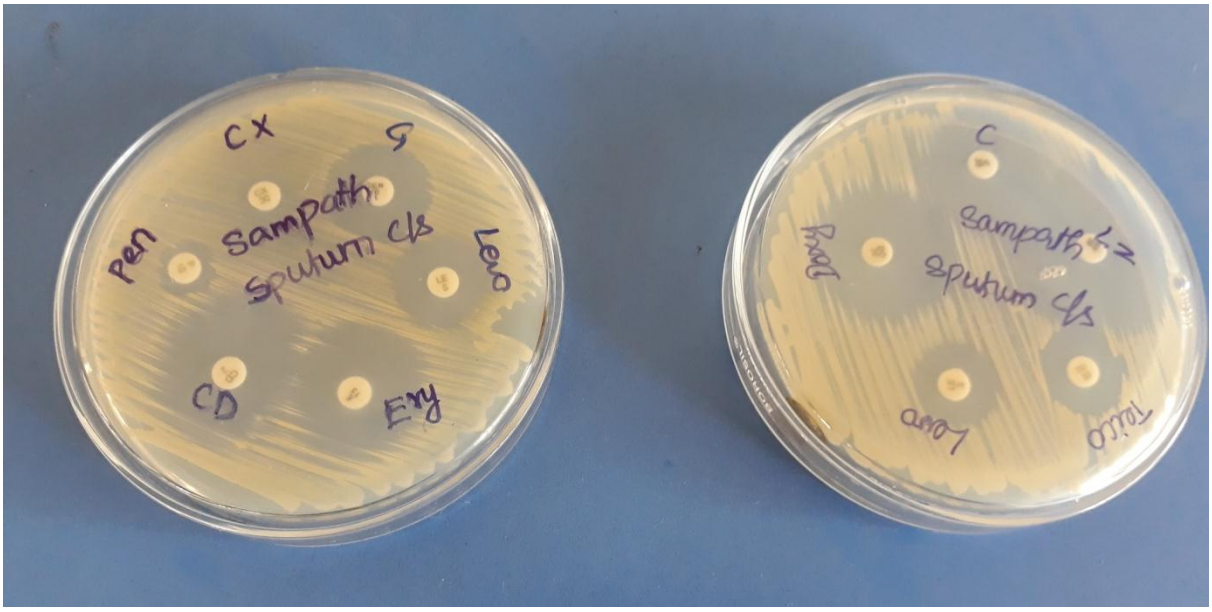


SUBRAMANI URINE C/S

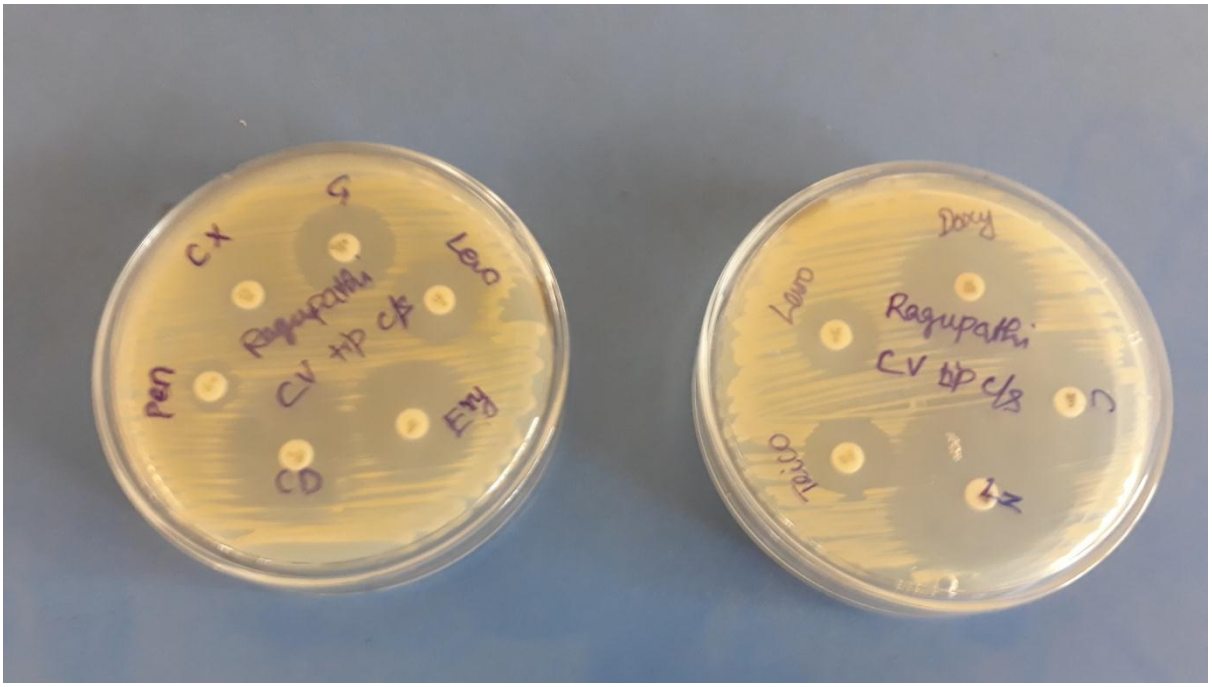


ESBL PRODUCING E.coli (Ramar)

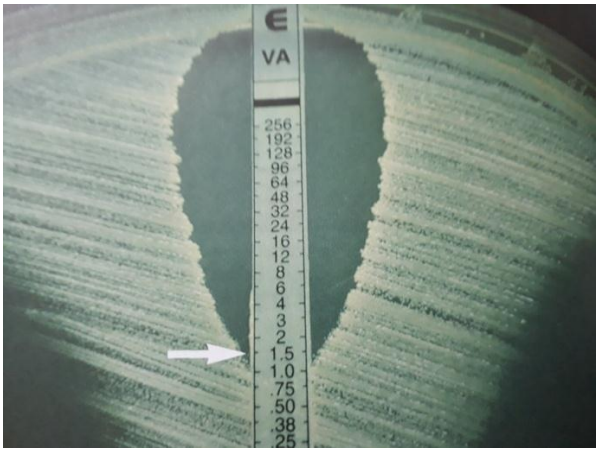
ESBL PRODUCING E.coli (Subramaniam)



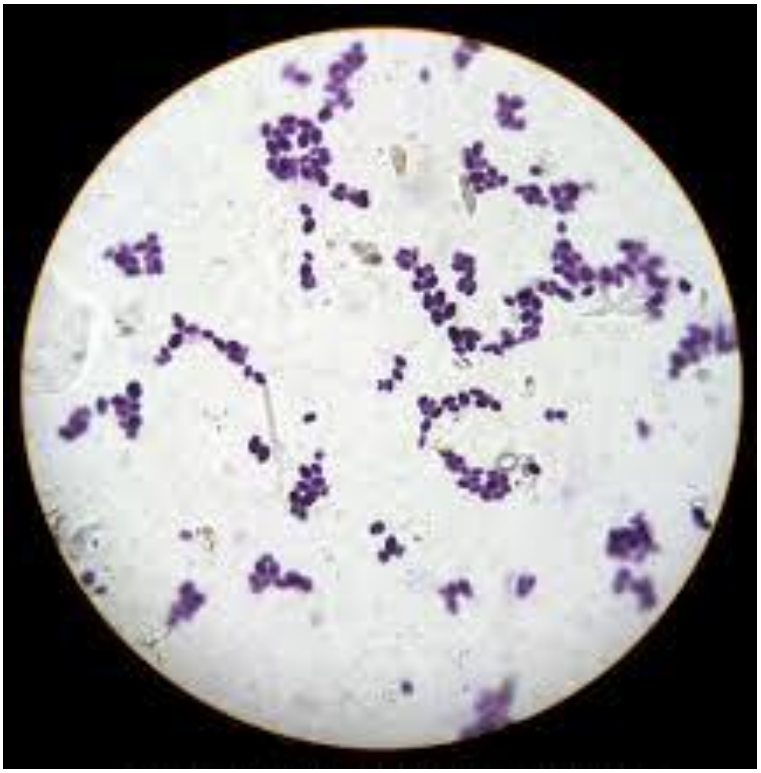
SAMPATH SPUTUM C/S



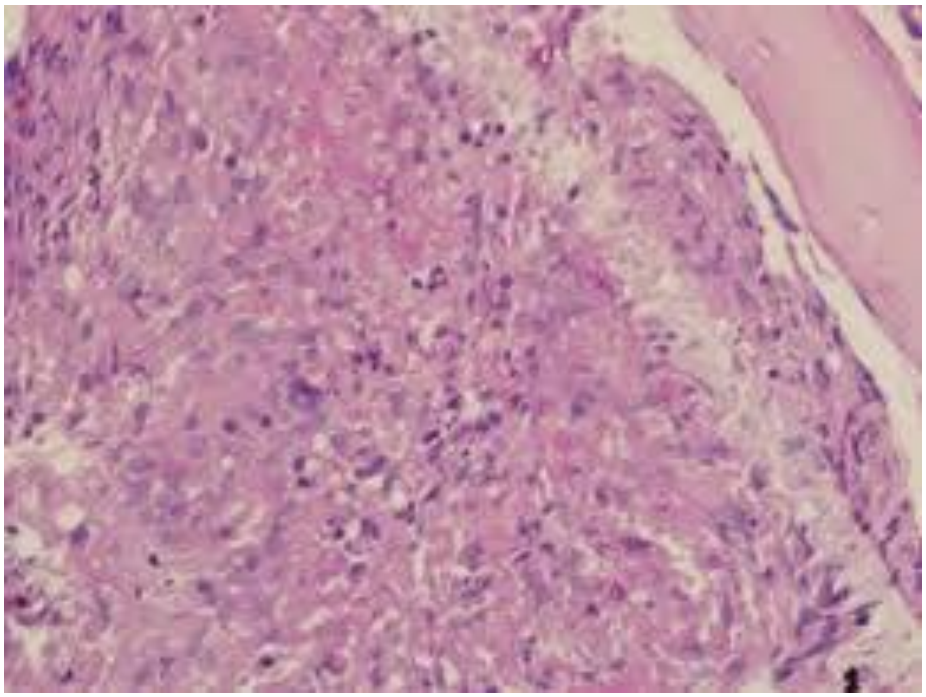
RAGUPATHI CV TIP C/S



VANCOMYCIN MIC – Staphylococcus Aureus



CANDIDA ALBICANS – URINE (GRAM STAIN)



ASPERIGILLUS FUMIGATUS – HPE SLIDE

S.No.	Category	Name	IP.NO.	Age/Sex	Blood group	Diagnosis	Platelet count	Total WBC count	Differential count			RBC count	PCV	MCV	MCH	MCHC	Hb	PT /sec	INR	Bd.Sugar
							cells/cu.mm	cells/cu.mm	Neutrop.	Lymphoc.	E/B/Mon	million/µl		Fl	pg	g/dl	g/dl			mg/dl
1	Donor	Mohan	1651076	45/M	A +VE		200000	9400	70%	24%	6%	4million	40%	84Fl	28pg	36g/dl	10	14-16sc	1.4	140
	Recipient	Sampath	1651032	58/M	A +VE	Alcoholic cirrhosis & DCLD	180000	7800	80%	18%	2%	3.8million	34%	80Fl	26pg	30g/dl	9	12-14sec	1.2	124
2	Donor	Chitra	1656160	38/F	A +VE		220000	10400	74%	22%	4%	3.8million	36%	84Fl	30pg	32g/dl	11	14-16sec	1.4	136
	Recipient	Arun kumar	1656125	18/M	A +VE	Wilsons disease	190000	9000	76%	20%	4%	3.6million	34%	80Fl	28pg	30g/dl	11	14-16sec	1.4	105
3	Donor	Sumathi	1660125	36/F	B +VE		190000	9600	68%	30%	2%	5million	42%	90Fl	36pg	42g/dl	14	12-14sec	1.2	110
	Recipient	Ramar	1660086	45/M	B +VE	Alcoholic cirrhosis & DCLD	214000	8100	84%	14%	2%	4.2million	38%	86Fl	34pg	30g/dl	10	16-18sec	1.6	136
4	Donor	Pradeep	1671605	27/M	O+VE		180000	8600	70%	26%	4%	4.2million	40%	86Fl	38pg	42g/dl	10	12-14sec	1.2	96
	Recipient	Ravichandran	1671576	43/M	O +VE	Alcoholic cirrhosis & DCLD	166000	9600	76%	18%	6%	3.2million	30%	80Fl	30pg	34g/dl	9	14-16sec	1.4	140
5	Donor	Murugesan	1668625	48/M	O +VE		220000	10600	70%	24%	6%	4.6million	42%	88Fl	36pg	38g/dl	12	16-18sec	1.6	125
	Recipient	Subramaniam	1668591	57/M	O +VE	Cryptogenic DCLD	214000	8700	86%	12%	2%	3.8million	34%	80Fl	28pg	32g/dl	10	14-16sec	1.4	160
6	Donor	Krishnakumar	1708536	36/M	A +VE		240000	9600	68%	26%	6%	4million	40%	85Fl	38pg	40g/dl	10	14-16sec	1.4	100
	Recipient	Udayakumar	1708510	36/M	A +VE	HCC& Cirrhosis	220000	11000	78%	28%	2%	3.6million	35%	82Fl	30pg	34g/dl	9	12-14sec	1.2	121
7	Donor	Baskar	1709840	30/M	B +VE		190000	9800	76%	20%	4%	5.2million	42%	80Fl	38pg	42g/dl	14	12-14sec	1.2	90
	Recipient	Senthilvelan	1709826	42/M	B +VE	Alcoholic cirrhosis & DCLD	180000	6400	66%	24%	10%	4million	36%	76Fl	26pg	34g/dl	10	14-16sec	1.4	106
8	Donor	Rajkumar	1717446	45/M	A +VE		220000	11000	78%	28%	4%	5.4million	40%	85Fl	36pg	42g/dl	14	14-16sec	1.4	160
	Recipient	Krishnan	1717429	54/M	A +VE	Cryptogenic DCLD	190000	8400	84%	11%	5%	3million	30%	78Fl	32pg	36g/dl	9	12-14sec	1.2	120
9	Donor	Rajasekar	1632545	55/M	A +VE		210000	8500	70%	26%	4%	4.6million	42%	82Fl	34pg	40g/dl	12	16-18sec	1.6	145
	Recipient	Raguraman	1632533	47/M	A +VE	Alcoholic cirrhosis & DCLD	246000	11400	74%	16%	10%	3.5million	32%	80Fl	28pg	32g/dl	9	14-16sec	1.4	120
10	Donor	Saranya	1637594	27/F	B +VE		210000	10200	76%	28%	6%	3.6million	36%	80Fl	34pg	40g/dl	10	14-16sec	1.4	102
	Recipient	Arthi	1637570	20/F	B +VE	Wilsons disease	180000	7800	80%	16%	4%	2.8million	28%	78Fl	28pg	34g/dl	9	12-14sec	1.2	130
11	Donor	Durairaj	1734442	36/M	AB +VE		190000	9000	70%	26%	4%	4million	40%	84Fl	36pg	42g/dl	11	12-14sec	1.2	116
	Recipient	Radha Krishnan	1734429	53/M	AB +VE	Alcoholic cirrhosis & DCLD	160000	5800	73%	21%	6%	3.6million	30%	74Fl	30pg	34g/dl	10	14-16sec	1.4	140
12	Donor	Bhoopesh kumar	1738696	36/M	O +VE		180000	10400	76%	30%	4%	5.4million	42%	82Fl	36pg	42g/dl	14	14-16sec	1.4	96
	Recipient	Abinesh	1738671	18/M	O +VE	Congenital biliary atresia	115000	8100	60%	32%	7%	3.8million	35%	80Fl	30pg	34g/dl	10	12-15sec	1.2	92
13	Donor	Irudhayaraj	1741204	50/M	B +VE		225000	9600	68%	30%	2%	5million	42%	80Fl	36pg	40g/dl	14	14-16sec	1.4	156
	Recipient	Gopala Krishnan	1741191	43/M	B +VE	Alcoholic cirrhosis & DCLD	166000	6400	62%	26%	12%	3.4milli0n	30%	74Fl	32pg	36g/dl	9	16-18sec	1.6	162
14	Donor	Anand	1744910	42/M	B +VE		240000	11200	78%	20%	2%	5.2million	42%	86Fl	36pg	42g/dl	14	16-18sec	1.6	124
	Recipient	Ragupathi	1744884	28/M	B +VE	HBV related DCLD	208000	9000	73%	17%	10%	3.9million	36%	80Fl	32pg	36g/dl	10g/dl	12-14sec	1	110
15	Donor	Dhanushkodi	1749425	18/M	A +VE		210000	8400	74%	30%	6%	4.2million	40%	85Fl	36pg	42g/dl	10g/dl	12-14sec	1.2	92
	Recipient	Alwin deepak	1749406	18/M	A +VE	PFIC & DCLD	180000	5400	72%	24%	4%	3.6million	32%	80Fl	30pg	34g/dl	10	14-16sec	1.4	100

Urea	Sr.Creat.	Liver Function Test								Electrolytes:						Culture of Donor & Recipient Before Surgery			
mg/dl	mg/dl	Total BR	Direct BR	AST	ALT	ALP	Total Protein	Albumin	Globulin	Na	K	Cl	Ca	Mg	P	Throat swab c/s	Nasal swab c/s	Blood c/s	Urine c/s
		mg/dl	mg/dl	µ/dl	µ/dl	µ/dl	g/dl	g/dl	g/dl	mEq/L	mEq/L	mEq/L	mg/dl	mg/dl	mg/dl				
28	0.8	1	0.2	45	44	140	5.5	3.5	2	140	4.5	102	9	4	2.5	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
34	1	1	0.2	50	48	250	6	4.5	1.5	145	4	109	10	2.8	2	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
32	1	1.2	0.2	50	50	160	5.6	3.6	2	138	4.5	100	11	3.5	2	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
36	0.9	1	0.2	42	54	215	6.5	4.5	2	150	5	110	10	2.5	2	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
24	0.8	1	0.2	40	48	170	6	4	2	140	5	98	10	4	2.5	β-Streptococci	NO GROWTH	NO GROWTH	NO GROWTH
22	1.2	1.2	0.4	45	50	260	5	4.4	0.6	137	4.8	104	10	2.4	2	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
34	0.9	1	0.2	40	40	154	5.4	3.4	2	145	5	98	10	4	2	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
30	1.2	1.15	0.4	35	55	210	5.8	3.6	2.2	142	4.3	108	9	2	1.8	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
30	1	1.2	0.2	46	38	145	5	3	2	138	4.5	102	9	4.2	1.8	NO GROWTH	MRSA	NO GROWTH	NO GROWTH
28	1.02	1.08	0.2	45	54	220	4.8	3	1.8	143	3.2	98	8.5	2.2	1.9	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
36	0.8	1	0.2	36		160	5	3	2	140	4.5	106	11	4.8	1.9	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
32	0.9	1.2	0.2	50	35	180	6.5	4.2	2.3	142	4	103	10	2.4	1.7	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
28	1	1.2	0.2	42		120	5.5	3.5	2.5	142	5	100	11	3.8	2	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
26	1.2	0.7	0.26	38	44	160	6.8	4.5	2.3	135	4.8	95	10	2.4	1.7	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
34	0.8	1	0.2	40	40	180	6	4	2	136	4.5	104	10	3.6	2.5	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
32	1.2	0.8	0.2	32	45	260	6.2	4.3	1.9	130.5	5	99	9	2.3	2	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
32	0.8	0.8	0.2	42	42	180	5	3	2	140	5	106	10	3.6	2	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
32	0.8	0.8	0.2	42	42	180	5	3	2	140	5	106	10	3.6	2	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
30	0.8	1.2	0.4	45	40	240	5.6	3.7	1.9	136	4.6	102	9	2.3	1.6	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
34	0.7	1	0.2	45	42	190	6	4	2	138	4.5	100	11	3.8	2.5	β-Streptococci	NO GROWTH	NO GROWTH	NO GROWTH
30	0.68	1.2	0.2	40	50	260	5	3.6	1.4	135	4.3	106	10	2.4	1.6	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
28	1	0.9	0.2	40	46	160	5	3	2	140	4.5	102	10	4	2	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
32	1.09	1.02	0.22	46	80	246	7	4.1	2.9	134	4	109	9.6	2.4	1.8	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
26	1	1	0.2	38	40	176	5.5	3.5	2	145	4.5	104	11	4.2	2.5	β-Streptococci	NO GROWTH	NO GROWTH	NO GROWTH
28	0.8	0.95	0.18	40	24	194	7	5	2	140	4.2	100	10	2.2	2	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
34	1	0.9	0.2	50	50	150	6	4	2	138	5	106	10	4.4	2	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
30	0.8	1.2	0.25	35	38	178	6.5	4	2.5	136.5	4.6	101.2	10	2.5	1.6	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
38	0.8	0.8	0.2	45	48	180	5	3	2	145	5	102	11	3.8	2.5	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
34	0.9	1.2	0.25	35	55	268	5.4	3.7	1.7	142	4.8	98	11	2.5	2	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
34	0.8	0.9	0.2	40	45	160	5.5	3.5	2.5	145	5	106	11	3.6	2.4	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH
28	0.8	1	0.2	45	50	280	6	4.5	1.5	138	4	103	11	2	1.9	NO GROWTH	NO GROWTH	NO GROWTH	NO GROWTH

RECIPIENT, Post Operative Infections						
Catheter Assos. UTI	Sputum culture c/s	Central Venous Tip c/s	Drainage Fluid c/s	Wound swab c/s	Viral Infection	Fungal Infections
NO GROWTH	MRSA,S-Ak,G,Ba,Van,Lz,Teico,Levo	NO GROWTH	-	-	-	-
	R-Pen,Ery,CD,Cip					
NO GROWTH	NO GROWTH	NO GROWTH	-	-	EBV Positive	-
E.coli, S- AK,NIT,IMP,AmxC,TGC,Colis	NO GROWTH	Kleb.pneum,S- Ak,Gen,IMP,TGC,Colis	-	Kleb.pneum, S- Ak,Gen,IMP,TGC,Colis	-	-
R-G,PT,LZ,MRP,Ba,Nor,Cip,Ctx		R-MRP,Ba,Cip,Ctx		R-MRP,Ba,Cip,Ctx,Cpm		
NO GROWTH	NO GROWTH	NO GROWTH	Rt.- MRSA,S-Ba,Ak,G,Van,Lz; R-Pen,Ery,CD	Aspergillus fumigatus	-	Aspergillus fumigatus
			Lt.-Kleb.pneum,S-IMP; R-Ak,G,Cip,Ctx,MRP			
E.coli,S-Ak,Gen,NIT,IMP,AmxC,TGC,Colis	MRSA-Ak,G,Ery,CD,Van,Lz,Teico	MRSA,S-Ak,G,Ery,CD,Van,Lz,Teico	-	Kleb.pneum, S-TGC,Colistin	-	-
R- Ba,Ctx,CZ,Nor,Cip, Amp	R-Pen,Ba,Levo	R-Ba,Levo		R-Ak,G,Ctx.Cz,Ba,Cip,IMP,MRP		
NO GROWTH	NO GROWTH	NO GROWTH	-	-	-	-
Kleb.pneum,S-Ak,G,NIT,IMP,TGC,Colis	NO GROWTH	NO GROWTH	-	-	-	-
R-PT,Ba,MRP,Cip,Ctx,Cpm						
NO GROWTH	NO GROWTH	NO GROWTH	-	-	-	-
NO GROWTH	NO GROWTH	NO GROWTH	-	-	-	-
NO GROWTH	NO GROWTH	Kleb.pneum,S-Ak,G,Cip,IMP,MRP,TGC, Colis	-	-	-	-
		R-Ba,Ctx,Cz				
NO GROWTH	NO GROWTH	NO GROWTH	-	-	-	-
Candida albicans	NO GROWTH	NO GROWTH	-	-	-	Candida albicans
NO GROWTH	NO GROWTH	NO GROWTH	-	-	-	-
Entero. Faecalis,S- Amp,HLG,NIT,Nor,Van,Lz	NO GROWTH	MRSA-Ery,CD,Ba,Cip,Van,Lz,Teico,Levo	-	-	-	-
R- Pen,Dox		R- Pen				
NO GROWTH	NO GROWTH	NO GROWTH	-	-	-	-