LITERATURE REVIEW

1. VIRAL HEPATITIS

It is the inflammation of liver characterized by the presence of inflammatory cells in the liver. It can be caused by any one of the five viral agents namely virus A, B, C, D, or virus E. This infection of liver is in general, self limiting, but may progress to chronic liver disease with cirrhosis and even to carcinoma (Dienstag & Isselbacher, 2005).

The hepatitis viruses are RNA virus except HBV, which is DNA virus. These hepatitis viruses can be distinguished by their molecular and antigenic properties.
**Hepatitis A virus** is transmitted mainly by orol-faecal route, has incubation period of about 15-45 days, and common in children, adults. There is a spread by person to person contact and it enhances in overcrowded areas, under unhygeinic conditions, and migration of people into endemic areas. HAV appears to be more symptomatic in adults, having no progression to chronicity (Tong et al., 1995). This type of infection is self limiting, but usually has a tendency to relapse, with appearance of symptoms within 6 months after termination of acute condition in 15% of population. Prophylaxis against HAV is through inactivated vaccination. There is no therapy.

**Hepatitis E virus** is also transmitted through oro-faecal route, by ingesting contaminated food and water. Generally, this infection does not spread from infected persons to their close contacts. It favours young adults in age of 20-40y, has incubation period of 14-60 days. Its prognosis is also good. There is no prophylaxis and no therapy known against HEV (Dienstag & Isselbacher, 2005).

**Hepatitis B virus** is transmitted covertly by percutaneous and overtly by blood transfusion routes (Chaudhary, 2004). The non percutaneous routes for HBV, are sexual contact and perinatal transmissions. Its incubation period is 30-180 days and can occur at any age. HbsAg has been isolated from almost all the body fluids of patients. Its progression to chronicity is hardly 10%. The immunization can be through recombinant vaccines and treatment involves the use of interferon.

**Hepatitis C virus** can be transmitted through blood transfusion, percutaneous routes, like injection drug use, occupational exposure to blood, sexual contact, perinatal transmission, as well as to patients under haemodialysis. The incubation period is 15-160 days with any age susceptibility (Dienstag & Isselbacher, 2005). It has high frequency of progression to chronicity up to 50-70%. There is no prophylaxis against HCV and treatment is through use of interferon and ribavarin.

**Hepatitis D virus** infection occurs as a coinfection with HBV or as a superinfection to chronic hepatitis B individuals. The HDV would complicates the outcome of HBV
infection (kumar et al., 2007; Tong et al., 1995). The incubation period for HDV is 30-180 days. The prophylaxis is by HBV vaccine (Dienstag & Isselbacher, 2005).

All types of viral hepatitis produce clinically similar signs and symptoms. The prodromal symptoms of hepatitis starts with low grade fever, malaise, anorexia, nausea, vomiting, coryza. These features continue for 4-6 days.

This stage is followed by icteric stage, characterised by jaundice in skin, mucosa and sclera, and continues for about 4-6 weeks. There is dark urine and clay coloured stools. Prodromal symptoms decreases. Liver becomes tender. There is pain over upper right abdominal quadrant.
Diagram source
(Chaurasia, B.D. Human anatomy)
(2A. FIGURE OF NORMAL LIVER)

Diagram source
(Jain, A.K. Human physiology, 2012)
(2B. FIGURE OF NORMAL LIVER)
2. CIRRHOSIS
The term cirrhosis was first of all introduced by LAENNEC in 1826. Cirrhosis is the chronic, diffuse disorder of varied etiologies and is characterized by hepatic cells necrosis, proliferation of connective tissues and nodular regeneration, thereby leading to abnormal reconstruction of lobular architecture and disturbed hepatic circulation.

Clinical features of cirrhosis vary, according to the severity of cirrhosis as seen in non ascites cirrhosis (compensated cirrhosis) and ascites cirrhosis (decompensated cirrhosis). The common symptoms observed in compensated cirrhosis are indigestion, flatulence, loss of weight, anemia and haematemeses, whereas jaundice, palmer erythema, spider naevi, liver may be palpable, non tender, oedema of extremities, distension of abdomen, anemia, delirium, flapping tremors of hands are present in decompensated cirrhosis (Chung & Podolsky, 2005).

About 40% of the cirrhotics are asymptomatic. A damage of about 80% of the liver parenchyma will result into clinical manifestations of ascites, skin changes, renal dysfunction, encephalopathy and thus, will end up into a stage called decompensated cirrhosis. About half the ascites cirrhosis patients die if the liver transplantation is not done (Watring & Deane, 2007).

3. ALCOHOLIC CIRRHOSIS
It is referred to as Laennec’s cirrhosis. It is one of many after effects of chronic alcohol consumption. It is characterised by diffuse fine scarring, loss of liver cells, small regenerative nodules. It is also called as micronodular cirrhosis. Alcoholic cirrhosis with time may progress to macronodular cirrhosis.
Chronicity of alcohol consumption and quantity are the most important risks factors for the development of alcoholic cirrhosis. The threshold of developing cirrhosis in men is the intake of more than 60-80g/day of alcohol for more than 8 years.
The chronic HCV infection in patients consuming alcohol beyond the threshold, increases the risk for development of alcoholic cirrhosis. These patients may develop ascites cirrhosis at the younger stage (Mailiard & Sorrell, 2005).

Alcohol, itself, is a hepatotoxin. The prolonged consumption of alcohol, initiates a number of pathogenic processes like lipid peroxidation, body’s altered immune response, production of aldehyde-protein adducts and release of pro inflammatory cytokines (Chaudhary, 2004; Lieber, 1994).

The alcohol is absorbed into circulation and is metabolised in liver. The alcoholic dehydrogenase enzyme in liver, helps oxidise the alcohol in liver. It is converted into Acetaldehyde. This compound is unstable and highly toxic to tissues. It reacts with the proteins molecules and forms acetaldehyde-protein adducts. The acetaldehyde is further, oxidised into acetate. This oxidation process, produces extra NADPH molecules, hence, synthesis of Reactive oxygen species, takes place in mitochondria. This results into oxidative stress.

The ROS brings about lipid peroxidation, protein molecules degradation and DNA damage, hence liver cells necrosis.

Alcohol increases intestinal permeability to bacterial toxins, which, further sensitizes the kupffer cells in liver. This sequence leads to production of inflammatory cytokines, thereby, activating stellate cells and enhanced fibrogenic activities in liver.

Alcoholic cirrhosis starts as a micronodular cirrhosis with nodules less than 3mm in diameter. The disease progresses into macronodular cirrhosis. Liver shrinks to less than 1 kg. in weight. The surface of liver appears nodular (Mohan, 2012). The cut section shows angular nodules with fibrous septa.
PROLONGED ALCOHOL CONSUMPTION

ACETALDEHYDE

↑ R.O.S. IN LIVER CELLS
Lipid Peroxidation
DNA damage
↑ PRODUCTION OF INFLAMMATORY CYTOKINES

PROTEIN ADDUCTS

↑ LIVER CELL INJURY

NECROSIS

↑ PERMEABILITY OF INTESTINE

BACTERIAL ENDOTOXINS (LIPOPOLYSACCHARIDES)
SENSITIZATION OF KUPFFER CELLS
↑ LEVELS OF TNF alpha, TGF-beta
ACTIVATES STELLATE CELLS

↑ FIBROTIC RESPONSE

(3. FLOW CHART OF SEQUELA OF PROLONGED ALCOHOL CONSUMPTION)
Diagram source
(Chaurasia, B.D. Human anatomy, 2005)

(2C. FIGURE OF NORMAL LIVER)

Diagram source
(Mohan, H. Essential Pathology for dental students, 2012)

(4. FIGURE OF CIRRHOSIS OF LIVER)

4. PORTAL HYPERTENSION IN CIRRHOSIS
PHT is the high blood pressure in portal vein and its tributaries and is defined as the portal pressure gradient (difference in blood pressure between Portal vein and Hepatic vein) of 10 mm or greater than 10 mm of hg.

Applying ohm’s law to portal venous system,

**Portal pressure gradient** \( (\Delta P) = Q \times R \)

Where \( \Delta P \), is the change in portal pressure,

Q is the blood flow within the entire portal venous system,

And R is the vascular resistance of the same venous system,

Therefore, the \( \Delta P \), portal pressure gradient is the result of the product of the blood flow within the entire portal venous system and the vascular resistance of the same venous system.

In normal liver, the intrahepatic resistance changes with the variations in portal blood flow, thereby the portal pressure remains within normal limits, Hence, the Portal hypertension is the result of either the increase in the blood flow or and the increase in vascular resistance (Martell et al., 2010).

Since, cirrhosis, eventually results into fibrosis, scarring and formation of regenerative nodules and altered state of hepatic circulation. These changes will raise the intra hepatic vascular resistance to flow of portal blood through liver, in the initial stages and in later stages, seen a rise in splanchnic circulation (Tsao, 2003). These events predispose to decreased compliance and increased portal blood flow, thus would end into portal hypertension.

The nodules and scarring compress the veins in the liver, thus the blood pressure within the liver rises. It occurs in about 60% of cirrhotic patients. The portal hypertension may cause bleeding in the intestine. It causes pooling of blood in veins of stomach and oesophagus, hence resulting into enlargement of veins called varicose veins or varices. These dilated veins rupture and bleeding occurs
Diagram source

(Netter, F.H. The CIBA Collection of Medical Illustrations, Volume 3: Digestive System, Part III, 1957)

(5. FIGURE OF CIRRHOTIC LIVER, OESOPHAGEAL VARICES, SPLEENOMEGALY)

into the stomach and oesophagus. This eventuality may predisposes to morbidity and mortality of patients.
Later on, GROSSMANN and co-worker changed this concept. They proposed the presence of increased number of specialized contractile elements in cirrhotic liver that would by way of their contraction, modulate the intrahepatic resistance to portal blood flow.

5. ROLE OF HEPATIC STELLATE CELLS IN PORTAL HYPERTENSION

Hepatic stellate cells (HSC) represent 5-8% of human liver cells and about 13% of the volume of sinusoidal cells. The HSC are located in the perisinusoidal space of Disse beneath the endothelial layer. These cells have long cytoplasmic processes running parallel to sinusoidal endothelial walls. Secondary processes shoot out from these processes and penetrate between hepatocytes in the neighbouring sinusoids. HSCells contain neuropeptides, calcitonin–gene related peptides, somatostatins (Burt et al., 1993; Stoyanova II et al., 2000).

In normal liver, these cells store vitamin A, synthesise extracellular matrix components, matrix degrading metalloproteins cytokines and growth factors (Geerts, 2001). Following acute liver injury, HSC are activated and trans-differentiated into myofibroblastic phenotype. These cells now release proinflammatory, profibrogenic, promitogenic cytokines, fulfilling needs for tissue repair. These changes, in acute conditions are transient, while in chronic conditions, lead to accumulation of extracellular matrix resulting in liver fibrosis (Friedman, 2000).

In the diseased state, these cells undergo transition in their morphology and functions. The HSC, now in activated state, acquire myofibroblast like phenotype, thus having both pro- fibrogenic and contractile activities around sinusoidal space, it would thus, narrow down the diameter of sinusoidal space. This phenomenon, collectively contribute to portal hypertension (Laleman, 2006; Tsao, 2003).
Diagram source
(Laleman, 2006)

(6.FIGURE OF ROLE OF HEPATIC STELLATE CELLS IN PORTAL HYPERTENSION)

6. COLLATERAL CIRCULATION
Progressive hepatic hyperemia and splanchnic pooling of blood coupled with raised intrahepatic vascular resistance result in the formation of collateral circulation. Blood from the portal vein is shunted away into systemic circulation by the formation of porto-systemic collaterals. These collaterals drain away about 80% of the portal blood. This ends into an arterial and venous steal phenomenon (Newby & Hayes, 1995).

Arterial steal occurs from systemic circulation to splanchnic circulation and venous steal takes place from portal blood to porto-systemic collaterals. The progressive liver disease produces a rise in cardiac output and azygous blood flow and reduced hepatic perfusion (Braillon et al., 1990).
Portosystemic shunts are responsible for increased absorption and impaired neutralization of Gut endotoxins, which induce the overproduction of cytokines namely interleukins and tumour necrosis factor (TNFa) (Myers et al., 2000; Martin et al., 1998; Mitchel et al., 1993).

The main cardiovascular changes in cirrhosis are due primarily to the splanchnic steal and the progressive, unavoidable vasodilation of splanchnic vascular bed. The body homeostatic mechanism tends to correct these malfunctionings. The main mechanism are the activation of SNS and release of epinephrine and role of angiotensin II. These produce peripheral vasoconstriction.

Collaterals devoids the liver from portal blood. It shrinks in size and its capacity to regenerate is impaiered. Porto-systemic shunts contribute to hepatic encephalopathy, increased absorption of intestinal organisms and endotoxins and other circulatory and metabolic effects (Sherloch & Dooley, 2002).
Diagram source

(Newby et al., 1995)

( 7. FIGURE OF PORTO SYSTEMIC SHUNTS)

7. ROLE OF VASODILATING SUBSTANCES AND SPLANCHNIC ARTERIAL VASODILATION
In cirrhosis, there is accumulation of vasodilating substances in the body. The most prominently influencing ones are, the Nitric oxide, Endothelin, Glucagon, Calcitonin gene related peptide (CGRP), endotoxins, Tumour necrosis factor (TNFa), bile salts and prostacycline (Moller et al., 2001; Fernandez et al., 1997). These substances are not metabolised by disease liver (Groszmann, 1994). These vasoactive substances are implicated in the hyperdynamic circulation in cirrhosis (Moller et al., 2001; Vallance & Moncada, 1991). These substances have pronounced vasodilating effect on the splanchnic circulation (Groszeman, 1998).

The nitric oxide has more significant effect on the circulation than other substances. It is a chemical produced by the enzyme nitric oxide synthetase (NO synthetase) on L-arginine in the vascular endothelium and NO free radicals are produced along with the citrulline as bye products.

Bacteria and endotoxins from the GIT find entry into the systemic circulation via collaterals. This condition stimulates NO synthetase activity in endothelium. Albornoz et al. reported increased production of nitric oxide in splanchnic circulation and high NO synthetase activity in hepatic artery (Albornoz et al., 2001).

The assumption behind the elevated levels of vasodilating substances, is the impaired hepatic metabolism and their escape through porto systemic collaterals into systemic circulation. The splanchnic vasodilation results into pooling of blood in the splanchnic vascular bed and subsequently, aggravates the portal hypertension (Bendt et al., 1991).

8. HYPERDYNAMIC CIRCULATION
The symptoms of hyperdynamic circulation were described in 1950. Hyperdynamic circulation is characterized by ↑ cardiac output, ↓ peripheral vascular resistance, low systolic arterial blood pressure (Groszmann, 1994).

This increase in cardiac output and stroke volume are now a days, characterized as mild, asymptomatic heart dysfunction and is labeled as Cirrhotic Cardiomyopathy (Ma & Lee, 1996). It is a subclinical stage of heart problem and at rest, patients have no symptoms. Norepinephrine attaches to receptors located on S A node. It results into increased heart rate and cardiac output, decreased systemic vascular resistance, hypotension, and aggravates renal vasoconstriction. As the cirrhosis progresses, it favours splanchnic vasodilation, that enters into a vicious circle to enhance the systemic vasodilation and renal vasoconstriction.

9. REDUCED EFFECTIVE CIRCULATORY BLOOD VOLUME
Splanchnic and peripheral vasodilation reduce the effective circulatory blood volume, which in turn activates the high pressure baroreceptors located in carotid sinus and aortic arch. As a consequence, the sympathetic nervous system is stimulated and it induces the release of Norepinephrine from adrenal medulla. It is a potent vasoconstrctor and tends to restore the peripheral vascular tone. This vasoconstrictor also influences the renal circulation.
The degree of activation of sympathetic nervous system is correlated to the severity of cirrhosis.

The reduced effective circulatory blood volume induces renal hypoperfusion. This is a stimulus for kidneys to release rennin by the juxtaglomerular apparatus. The rennin activates the angiotensinogen into angiotensin I and II. The angiotensin II causes renal vasoconstriction and induces the releases of aldosterone from adrenal cortex.

10. RENAL HYPOPERFUSION
The reduced effective circulatory blood volume induces renal hypoperfusion. This is a stimulus for kidneys to release rennin by the juxtaglomerular apparatus. The rennin activates the angiotensinogen into angiotensin I and II. The angiotensin causes renal vasoconstriction and induces the releases of aldosterone from adrenal glands. Norepinephrine also aggravates the renal hypoperfusion by inducing renal vasoconstriction.

Despite the presence of circulating vasodilating substances like prostaglandins, kallikarins, renal vasoconstriction continues and becomes intense as the cirrhosis advances and terminates into hepatorenal syndrome (Epstein et al., 1988; Rimola et al., 1990).

The angiotensin II directly influences proximal tubules to reabsorb sodium and also induces the release of Aldosterone from adrenal cortex. It favours sodium retension through distal convoluted tubules. Anti diuretic hormone is released non-osmotically, from hypothalamus-neurohypophysis. ADH acts on collecting tubules and results in water retension.

11. HAEMODILUTION
The renal retension of free water and sodium, raises the plasma volume, decreases plasma osmolarity and cause haemodilution. There is dilution of cells, solid componsants of plasma, even electrolytes. This favours a fall in serum albumin level, haemoglobin conc. The total body water rises more than total body sodium, favouring a rise in extra cellular volume, oedema formation and ascites (Gines et al., 2005).
Diagram source

( wadei et al., 2006)

(8. FIGURE OF PATHOPHYSIOLOGY OF RENAL DYSFUNCTION )

12. ROLE OF ATRIAL NATRIURETIC PEPTIDES IN CIRRHOSIS
Atrial natriuretic peptides and brain natriuretic peptides are released in high concentration in cirrhosis. These peptides have natriuretic, vasorelaxing, RAAS-ADH-SNS inhibitory effect (Flora, 1990). The effects of these peptides is blunted in cirrhosis partly due to increased renal endopeptidase activity which degrade them, and partly to down regulation of renal natriuretic peptides receptors.

13. ASCITES FORMATION

The pioneering work by Farnsworth & Kraukusin and Eigenmenger et al., documented that sodium retension is the main abnormality of kidney function.

Two major explanations for the ascites formation and sodium retension have been implicated.

In the first explanation, the primary abnormality is seen in renal sodium excretion in patients suffering from cirrhosis. This condition leads to plasma volume expansion along with raised extra cellular fluid volume. The fluid leaks into interstitial space and peritoneal cavity producing ascites and oedema. Plasma volume expansion lead to ↑ cardiac output, suppression of vasoconstrictors, RAAS and SNS activities but remain uneffective due to impaired and non responsiveness of kidneys to humoral substances.

In the second explanation, there are haemodynamic changes in body circulation, resulting into activation of SNS and RAAS activities. This result in sodium retension and ascites formation.

The receptors in cardiac atria and pulmonary arteries are sensitive to blood volume changes, whereas the receptors in carotid sinus, aortic arch and juxtaglomerular apparatus detect changes in pressure in arterial circulation. These receptors send signal via glossopharyngeal nerve and vagus nerve to medulla and hypothalamus.

14. THEORIES TO EXPLAIN ASCITES FORMATION IN CIRRHOSIS
Three theories have been propounded to describe changes in body in cirrhosis that result in sodium retension and ascites formation. 

14A. UNDER FILLING THEORY OF ASCITES FORMATION

In cirrhosis, there occurs “Backwards” increase in hydrostatic pressure in hepatic and splanchnic circulation. This happens due to raised intrahepatic vascular resistance. Hence, the fluid infiltrates into the interstitial space. The lymphatic system would tend to compensate it by draining the fluid into thoracic duct.

As the cirrhosis progresses, the excess fluid from interstitial space accumulates into the peritoneal cavity. So intravascular compartment has lesser of fluid, causing hypovolemia, thereby, initiating sodium retension activity. In extreme hypovolemia, renal vasoconstriction develops, that results into hepatorenal syndrome (Braunwald et al., 1997).

This theory does not correlate with the clinical data of cirrhotic ascites patients. If this theory was correct, than the changes in systemic circulation would consist of ↓ plasma volume, ↓ cardiac output, ↑ peripheral vascular resistance. But the patients findings, however, on the contrary are ↑ plasma volume, ↑ cardiac output and ↓ systemic vascular resistance (Schrier et al., 1994; Gines et al., 2001). The oedema developed under this theory is secondary oedema.

14B. OVERFILL THEORY OF ASCITES FORMATION

In cirrhosis, the primary abnormality remains in renal sodium excretion and water retension by renal tubules. This results into plasma volume expansion, hence leads to ↑ cardiac output, ↓ vascular resistance as adaptive circulatory mechanism against excess of intravascular fluid volume.

This hypervolemia would ensure overflow of fluid into peritoneal cavity and interstitial space. The stimulus for sodium retension arises from liver as a consequence of either
portal hypertension or liver failure. The former condition of liver activates hepatic low pressure baroreceptors, while in latter condition, there would occur ↓ hepatic clearance of sodium retaining factors (Wood et al., 1990; Wensing et al., 1990; Ahloulay et al., 1996; Levy, 1992).

The edema developed, as per this theory, is of primary edema.

14C. PERIPHERAL ARTERIAL VASODILATION HYPOTHESIS

It was proposed by SCHRIER and co worker in 1988. Peripheral arterial vasodilation is the earliest manifestation in cirrhosis and it would propose to renal sodium retension and diminished ability of kidney to excrete free water and thus, causing plasma volume expansion that would precede the development of ascites.

This theory also explains the hyperdynamic circulation in cirrhosis. Cirrhotic patients exhibit palmer erythema, spider naevi, flushed extremities.

The vasodilators exert more on the splanchnic vascular bed and produce hypoperfusion in extra splanchnic viscera, including Brain (Dillon et al., 1995).

Many vasoconstrictors are produced in body namely catecholamines, angiotensin II and tend to raise the peripheral tone of body (Helmy et al., 2000).

This theory encompasses the features of above two theories by assuming that in initial stage, there is underfilling of intravascular compartment, whereas in later stages of cirrhosis progression, there operates overfill theory.
portal hypertension

↓

Splanchnic arterial vasodilation

↓

↓Effective arterial blood volume

↓

Activation of receptors in carotid sinus, Aortic arch, juxtaglomerular apparatus in kidney

↓

Activation of

Renin-angiotensinogen and sympathetic nervous system and release of antidiuretic hormone

↓

Sodium, water retention

↓

HEPATORENAL SYNDROME

(9. FLOW CHART OF HEPATO RENAL SYNDROME)
15. ACUTE RENAL FAILURE

Acute renal failure is characterized by rapid decline in glomerular filtration rate (over hours to days), retention of nitrogenous waste products, perturbation of extracellular fluid volume, electrolytes and acid-base homeostasis. It is usually asymptomatic and is
diagnosed when biochemical investigation of hospitalized patients reveals a rise in blood urea nitrogen, serum creatinine concentrations (Kathleen, 2008).

The renal failure can be classified into three types, as follows:

1. Pre Renal ARF: Renal hypoperfusion resulting in decreased glomerular filtration rate without any histological alteration in kidneys (Pre Renal ARF ≈ 55%).
2. Intrinsic ARF: Disorder that affect renal parenchyma (intrinsic ARF ≈ 40%).
3. Post renal ARF: Disorder that cause urinary tract obstruction (Post renal ARF = 5%) (Kathleen, 2008; Lameire et al., 2005).

Renal failure was designated as renal dysfunction by ADQI work group in 2004. In an Indian tertiary hospital, the most common cause of acute renal dysfunction was Acute Tubular Necrosis (ATN ≈ 44.4%), followed by pre renal azotemia (36.6%) and HRS (19.9%) (Madaan & Mehta, 2004).

16. HEPATORENAL SYNDROME

It is the functional renal failure that develops in patients with advanced cirrhosis of liver. It is characterized by intense vasoconstriction leading to low renal perfusion and fall in glomerular filtration rate. Renal ability to excrete free water and sodium is decreased in cirrhosis. Patients exhibit dilutional hyponatremia.

Renal histology shows no lesion. Detailed description of HRS was given in 1950 by Sherlock, Paper, Vessin. Their studies emphasized the functional nature of renal failure, along with the co-existence of circulatory disturbances and poor prognosis of HRS. Investigations carried out during 1960-70 particularly by Epstein, documented, renal failure in HRS is due to extreme vasoconstriction in renal circulation. HRS is a frequent problem seen in patients suffering from advanced liver disease and ascites. The incidence of HRS is estimated to be about 8% annually. It is associated with intense renal vasoconstriction and decreased renal perfusion and glomerular filtration rate. The renal ability to excrete sodium and free water is reduced and patients show dilutional hyponatremia (Arroyo et al., 2008; Schepke, 2004).
Types of HRS:
HRS – I  This type has features of rapid onset and poor prognosis and is characterized by serum creatinine level more than 2.5 mg/dl in less than two weeks.
HRS – II  This type has features of slow onset and better prognosis and characterized by serum creatinine level more than 1.5 mg/dl (Gines et al., 1993).

17. SPONTANEOUS BACTERIAL PERITONITIS

It was first of all recognized by HAROLD CONN in 1960.

It is the infection of ascitic fluid that occurs in the absence of visceral perforation and in absence of any intra abdominal inflammatory focus as abscess, acute pancreatitis or cholecystitis (Caruntu & Benea, 2006). It is the most common complication in ascites cirrhotic patients.

The major proportion (70%) of the SBP patients fall in class C of Child Pugh Score. In ascites, the frequency of SBP may be 18-30% in hospitalized patients (Syed et al., 2007). Enteric organisms mainly aerobic, gram positive as streptoccoci and gram negative as E. coli, have been isolated from ascitic fluid of more than 90% of the SBP patients.

The preponderance of enteric organisms in SBP has favoured the hypothesis of Bacterial Translocation, where direct transmural migration of microbes from the intestinal lumen into mesentric lymph nodes and extraintestinal organs of body takes place.

But the exact mechanism of bacterial inoculation of ascetic fluid is still a controversy. The key predisposing factors which influence the bacterial translocation are lowered local and systemic immune response in cirrhotic patients, impaired phagocytic function and decreased activity of reticulo endothelial system collectively result in proliferation of microbes and their reduced clearance from blood. The transient bacteremia becomes pronounced and stays for prolonged period into ascitic fluid (Syed et al., 2007; Tsao, 2008).
The bacteremia and bacterial endotoxins in ascites cirrhosis worsen the hyperdynamic circulation due to cytokines mediated aggravation of vasodilation. Therefore, SBP can lead to renal dysfunction (Folla, 1994).

17. ACUTE TUBULAR NECROSIS
It is the most common cause of acute renal dysfunction in cirrhosis. This disorder is the continuum of renal hypoperfusion as observed in pre renal failure. The prolonged renal ischemia results in renal tubule epithelial cell injury and cell death. Proximal tubule and ascending loop of Henle are the major areas of ischemic cell necrosis. ATN is manifested in three phases as initiation, maintainance and recovery phases. The initiation phase is characterized by apical blebs, loss of brush border margins, loss of polarity and integrity of tight junctions (Gill et al., 2005).

18. CAUSES OF RENAL FAILURE IN ASCITES CIRRHOSIS
Following causes, based on clinical findings and analysis are found in renal failure:

1. Renal failure associated with infection
In this category, the renal failure is considered secondary to an infection when patient had an ongoing infection in the absence of other causes of renal failure. The most common infection is the spontaneous bacterial peritonitis and is diagnosed clinically by the presence of polymorphonuclear neutrophil count of more than 250/cumm in the ascites fluid (Rimola et al., 2000; Llahi et al., 2011).

2. Hypovolumia related renal failure
When patient had a history of fluid loss in the preceeding days, due to GIT fluid loss, renal fluid loss due to diuretics and there is absence of other cause of renal failure (Needham, 2005).
3. **Intrinsic renal failure:**
   The cause of this form of renal failure is the alterations in the renal parenchyma. This is diagnosed clinically either by the presence of proteinuria > 500mg/24h, or RBC count > 50 under HPF, or presence of Casts as seen in urine sediment analysis (Needham, 2005).

4. **Hepato renal syndrome**
   It is diagnosed when serum creatinine conc. rises > than 1.5 mg/dl, along with the exclusion of all other causes of renal dysfunction, namely, absence of signs of infection, shock, hypovolumia, proteinuria, haematuria and urinary casts (Gines et al., 2003).