**CIRRHOSIS**

**DEFINATION**

Irreversible chronic injury of hepatic parenchyma with associated extension fibrosis in association with the formation of regenerative liver nodules. These features result from hepatocyte necrosis , collapse of the supporting reticulin network with subsequent connective tissue deposition, distortion of the vascular bed and nodular regeneration of remaining liver parenchyma. The pathological process is a final common pathway of many types of chronic liver injury.

AETIOLOGY

Post-hepatitis or post necrotic cirrhosis represents the final common pathway of many types of chronic liver disease. Post necrotic liver cirrhosis may be of specific or unknown causes.

The causes include:-

1. Viral Hepatitis –B, C, and, CMV, EBV
2. Alcoholic Hepatitis
3. Primary Biliary Cirrhosis
4. Primary sclerosing cholangitis
5. Non alcoholic fatty liver Disease (Steatohepatitis)
6. Drugs
7. Amiodarone
8. Arsenicals
9. Pyrolidazine alkaloids and
10. Anti-neo plastic agents

Internal and Metabolic disorder:-

1. Galactosemia
2. Haemochromatosis
3. Wilson’s Disease
4. Biliary Atresia
5. Antitrypsin Deficiency
6. Alagilles Syndrome
7. Glycogen Storage diseases

OTHERS

1. Chronic Biliary Obstruction
2. Cystic fibrosis
3. Graft – versus – host disease
4. Sarcoidosis
5. NAFLD
6. Primary Sclerosing Cholangitis
7. Chronic autoimmune hepatitis

Clinical features of Cirrhosis derive from the morphological alteration and often reflect the severity of hepatic damage rather than the aetiology of the underlying liver disease. Loss of functioning liver cell mass may lead to loss of major functions of liver namely excretory, synthetic, storage and filtration leading to jaundice, oedema, coagulopathy, variety of metabolic abnormalities, vascular distortion leading to portal hypertension and its sequalae i.e. varices, splenomegaly, Ascites, hepatic encephalopathy result from hepatocellular insufficiency and portal hypertension.

Cirrhosis is classified into the following categories

1. Alcoholic
2. Cryptogenic and post hepatitic
3. Biliary
4. Cardiac
5. Metabolic, inherited and drug induced

**PATHOLOGY**

Post hepatitis liver is typically shrunken in size distorted in shape and composed of nodules of liver cells separated by dense and broad band of fibrosis. The microscopic picture is consistent with the gross impression. Cirrhosis is characterized morphologically by i) Extensive confluent loss of liver cells 2) Stromal collapse and fibrosis resulting in broad bands of connective tissue containing the remains of portal triads, 3) Irregular nodules of regenerating hepatocytes varying in size from microscopic to several centimeters in diameter.

**ALCOHOLIOC CIRRHOSIS**

Commonly referred to as Laennec’s Cirrhosis.

Characterized by diffuse scarring, fairly uniform loss of liver cells, small regenerative nodules, but sometimes larger nodules may occur with time.

Pathology and Pathogenesis

With alcohol intake and destruction of liver cell (including activated hepatic stellate cells that have transforming properties to myoblasts with contractile properties) appear at the site of injury and deposit collagen. Web-like septae of connective tissue appear in periportal and pericentral zone and eventually connect tissue network surrounds small masses of remaining liver cells which regenerate and form nodules. Cell loss eventually exceeds regeneration leading to liver destruction, collagen deposition and liver shrinkage. Concomitant Hepatitis C viral infections accelerates development of alcoholic cirrhosis.

**CLINICAL FEATURES**

The clinical manifestations are usually an extension of the manifestations of the primary process. Clincal features are usually related to

1. Portal hypertension and its sequelae such as ascites, splenomegaly hypertension , encephalopathy bleeding, gastroesophageal varices, SBP
2. Reduced cell mass

These include:-

1. Jaundice
2. Palmar Erythema
3. Spider Naevi
4. Parotid and lacrimal gland enlargement
5. Clubbing of fingers
6. Shranken Nodular liver
7. Splenomegaly
8. Muscle wasting.
9. Ascites with or without peripheral oedema
10. Gynaecomastia (males)
11. Testicular Atrophy, reduce body hair (males)
12. Dupuytren’s Contractures
13. Virilization in women

**LABORATORY FINDINGS**

1. Anaemia - Iron deficiency from bleeding
* Hypersplenism
* B12 and folate deficiency – Nutritional
1. High Bilirubin
2. High Alkaline Phosphatase
3. High Transamineses
4. Raised Prothrombin time
5. Hypoalbuminaemia
6. High Ammonia – Encephalopathy
7. Glucose intolerance more common
8. Low mg and phosphate due to loss
9. Low potassium due to secondary hyper aldosteronism

**DIAGNOSIS**

1. High index of suspicion
2. Shrunken liver
3. Confirmation by liver biopsy and histology

**PROGNOSIS**

Depends on progression and complication include:-

1. Variceal Haemorrhage
2. Hepatic encephalopathy
3. Development of Hepatocellular carcinoma

**ASCITES**

**DEFINATION**

Abnormal fluid accumulation within the peritoneal cavity; usually above 100ml of fluid. It is divided into transudative and exudative depending on the protein content of the fluid based on protein concentration or on high or low serum – Ascites albumin gradient (SAAG). High albumin gradient or Ascites fluid protein of less than 2.5g/dl suggest a transudative Ascites and low albumin gradient or Ascites protein concentration of ≥2.5g suggests exudative ascites.

**CAUSES**

Transudative Ascites (SAAG) ≥1.1g/dl)

1. Chronic liver disease mainly Cirrhosis
2. Hypoproteinic state e.g Neptrotic syndrome

Malnutrition, protein losing enteropally

1. Congestive Cardiac failure

Exudative Ascites (SAAG ≤1.1g/dl)

Also referred to Non Cirrhosis Ascites

1. Malignancy related Ascites
2. High Protein content
3. Chylonis - Post Surgery
* Lymphoma
* Carinomations blockage of lymphatic
1. Inflammatory Causes
2. Infections
3. Tuberculosis
4. Ordinary bacteria
5. Fungal infection
6. Chlamydia infection
7. Spontaneous bacterial peritonitis
8. Pancreative inflammation
9. Biliary Inflammation
10. Post Surgery

**PATHOGENESIS**

Secondary to liver Disease (Cirrhotic) Ascites forms in the settings of Cirrhosis as a result of the sequence detailed below.

The most resent theory of Ascites formation the peripheral arterial vasodilation hypothesis, proposes that older hypotheses, the under full and overflow theories are corrected, but that each is operative at a different stage.

The first abnormality that develops in portal hypertension is portal pressure increases above a critical threshold and nitric oxide levels increase. Nitric oxide leads to vasodilation. As the state of vasodilation worsens, plasma levels of vasoconstrictor - sodium – retentive hormones increase and renal function deteriorates; Ascites develops (decompensation)

However, animal ability to detect changes in intravascular volume (especially volume overload) is limited and is linked to pressure receptors. The neuro humoral response by vasopressin, renin-angiotensin – aldosterone and sympathetic nervous systems are activated.

**NON CIRRHOTIC ASCITES**

The mechanism of fluid retention in patients with malignancy related Ascites depends on the location of the tumour. Peritoneal carcinomatosis causes Ascites through the production of proteinaceous fluid by tumour cells lining the peritoneum. Extracellular fluid enters the peritoneul cavity to establish oncotic balance. Fluid accumulates in patients with massive liver metastases because of portal hypertension caused by stenosis or occlusion of portal veins by tumour nodules or tumour emboli. In patients with hepatocellular carcinoma, Ascites forms because of the underline cirrhosis related portal hypertension, tumour induced portal vein thrombosis or both. Chylous Ascites in patients with malignant lymphoma appears to be lymph node obstruction by tumour and rupture of chyle containing lymphatics. Ascites can complicate high output or low output heart failure or nephrotic syndrome. As in cirrhosis, effective arterial blood volume appears to be decreased and the vasopressin, renin-angiotensin – aldosterone and sympathetic nervous systems are activated. These changes lead to renal vasocontriction and sodium and water retention. Fluid then weeps from them congested hepatic sinusoids as lymph as in Cirrhotic Ascites, tuberculosis, chlamydia infection coccidoidomycosis causes ascites through the production of proteinaceous fluid as in peritoneal carcinomatosis . Spontaneous bacterial peritonitis does not appear to cause fluid to accumulate; infection develops only in pre-existing ascites

Pancreatic and biliary ascites fluid forms by leakage of pancreatic juice or bile into the perotoneal cavity followed by chemical induced inflammation.

**DIAGNOSIS**

History

1. Abdominal Swelling
2. History of alcohol intake
3. History of previous liver disease, acute hepatitis
4. Previous blood transfusion
5. Previous and current IVDU, previous/current obesity
6. Weight loss
7. Heart failure
8. Fever and abdominal pain
9. Diabetes mellitus and symptoms of low thyroid functions
10. Corrective tissue disease e.g. joint pain, muscle pain and skin/facial rush

Physical Examination

1. Abdominal distension, more in the flunks.
2. Flunk dullness on percussion that shifts on change of posture (Require 1500ml fluid)
3. Palmar Erythema
4. Large pulsatile spider augramata
5. Large abdominal wall collateral veins
6. Immobile mass in the umbiliars the Sister Joseph nodule suggests peritoreal carcinomatesis
7. Congested, distended neck vein – heart disease mainly constrictive pericarditis or CCF
8. Peripheral oedema –CCR Nephrotic syndrome.

**ASCITIC FLUID ANALYSIS AFTER PARACENTEISS: To determine cause of Ascites**

Gross appearance

1. Clear suggests low protein
2. Content
3. Turbid high protein/neutrophils chylcons
4. Cloudy – High neutrophils chyle
5. David Brown – Blood and Bilirabu
6. Bloody

Ascitic Fluid Tests

1. Cell count (Submitted in EDTA bottle)
* White cell count is less than 500 cells/mm3, (0.5 x 10g/d) in uncomplicated Cirrhotic Ascites. Note Predimesis
* Increase White cell count found a) Infection – WBC
* Increase in RBC
1. Protein Level need for calculating serum –Albumin gradient (SAAG

SAAG has been proved to categorize Ascites better than either the total protein concentration or other parameters. SAAG is based on oncotic – hydrostatic balance. Partial hypertension results in an abnormally high hydrostatic pressure gradient between the partial bed and Ascites fluid. Albumin exerts greater oncotic force per gram tan do other proteins. Therefore, the difference between the serum and Ascetic fluid albumin concentration correlates directly with partial pressure.

SAAG is calculated by measuring albumin concentration of serum and Ascetic fluid. The gradient is calculated by subtraction and is not a ratio. If the SAAG is greater than or equal to 1.1g/dl, the patient can be diagnosed with partial hypertension with an accuracy of 97%.

**CULTURE**

The most common infection of Ascetic fluid (SBP) is usually of single bacterial cause and with low bacterial concentration (1 organism/ml)

Bedside inoculation fluid in blood culture bottles has the best yield.

**TOTAL PROTEIN**

Measurement of combination of Ascetic fluid total protein, glucose, LDH are useful in distinguishing SBP from gut perforation into Ascites.

Surgical peritonitis

* High protein content (>lg/dl)
* Glucose less than 2.8mmnol/l
* LDH greater than upper limit of normal for serum

Glucose

Amylase

Gram stain

AAFB/ TB culture

PCR for TB

Cytology

Tryglyceride levels where chylous Ascites is suspected

Bilirubin should be measured in Ascetic fluid that is dark brown.

Level of greater than 102umml/l and greater than serum bilirubin or upper gut perforation into Ascites

**TREATMENT OF ASCITES**

Appropriate treatment o patient with ascites depends on the causes of the fluid retention. Accurate determination of the aetiology of the Ascites is crucial. The SAAG is helpful diagnostically as well as in therapeutic decision –making. Patients with low SAAG usually do not have portal hypertension and do not respond to salt restriction and diuretics (except nephrotic syndrome). Patients with a high SAAG have portal hypertension and usually are responsive to low salt diet bed rest and – diuretics.

**LOW ALBUMIN GRADIENT ASCITES**

Peritoneal Carcinomatosis is the most common cause of low SAAG ascites. Peripheral oedema responds diuretic treatment. Patients without peripheral oedama who are treated with diuretics only lose intravascular fluid not Ascites. The main stay of non-ovarian peritoneal Carcinomatosis is therapeutic paracentesis.

Ascites caused by tuberculosis peritonitis is treated by anti-TB medication –diuretics are only helpful if there is associated portal hypertension with Cirrhosis

Pancreatic Ascetic will require endoscopic stept insertion in pancreatic duct or surgical intervention or may resolve spontaneously or with treatment with somatostatin or its analogues. Chlamydia peritonitis commonly referred to Fitz – Hugh – Curtis syndrome, responds to tetracycline Ascites due to serositis from connective tissue disease response to steroids dialysis related Ascites may respond to aggressive dialysis.

 **HIGH ALBUMIN-GRADIENT ASCITES**

Cirrhosis is the most common cause management should focus on

1. Treatment of underline cause eg Alcohol stoppage, Autoimmune hepatitis, Haemochromatosis, Wilson’s Disease – should receive specific therapy.

Many patients with large volume Ascites require hospitalization for definitive diagnosis and management of fluid overloads as well as the underlying liver disease. A large number may have

1. GI bleeding
2. Encephalopathy
3. Infection
4. Hepatocellular Carcinoma

Patient Education

Focuses on:-

1. Precipitating factors
2. Diet education – sodium intake
3. Fluid restriction not useful on its own
4. Bed Rest has only limited value

**DIURETICS**

Spironolactone acts slowly, long half life, Single dosing per day, increases sodium excretion and water excretion as well.

Furosemide: Not useful alone but works better with sipronolactone.

Amiloride : Works faster than Spironolactone.

Maintain Ration of Spironolactone/Furosemide 100:40. This reduces chances of hypokalaemia

Diuretic doses and dietary sodium intake are adjusted to achieve weight loss and negative sodium balance.

**REFRACTORY ASCITES**

Refractory Ascites is defined as Ascites unresponsive to sodium restricted diet and a high dose diuretic treatment. This will be associated with no weight loss despite high doses of diuretics and will be associated with diuretic complications. This category comprises less than 10% of patients on treatment.

Viable options patients with refractory to routine medical therapy includes

1. Liver transplantation
2. Therapeutic paracentesis (Serial with colloide replacement
3. TIPS
4. Peritoneal – venous shunts
5. Terlipressin.