INTRODUCTION

Portal hypertension commonly accompanies the presence of liver cirrhosis, and the development of esophageal varices (EV) is one of the major complications of portal hypertension ***(De Franchis & Primignani, 2001).*** The prevalence of EV in patients with liver cirrhosis ranges from 35% to 70%, and the reported mortality from variceal bleeding ranges from 17% to 57% ***(Jensen, 2002).***

The frequent occurrence of bacterial infections in cirrhotic patients probably results from deficient defense mechanisms ***(Rosa et al., 2000).*** Accordingly, systemic alterations have been described such as complement deficiency, alterations in immunoglobulins levels ***(Almeida & Mattos, 1997),*** defects in opsonic activity as well as in serum bactericidal activity ***(Wyke, 1987),*** decrease in the phagocytic activity of the reticuloendothelial system ***(Rimola et al., 1981),*** and neutrophilic dysfunction ***(Fiuza et al., 2000)***.

Cirrhotic patients, particularly those with a poor liver function and those admitted with gastrointestinal hemorrhage, are at a high risk of developing acute bacterial infections. Mortality related to infections in cirrhosis has decreased over the years as a result of earlier diagnosis and effective treatment ***(Kamal et al., 2000 and Fernandez et al., 2002).***

In a comparative study of the prevalence of bacterial infections between hospitalized cirrhotic patients with and without upper gastrointestinal bleeding (UGB), it was found that the prevalence of infections was greater among patients with UGB (54%) than in those without UGB (35%) ***(Almeida et al., 2001).***

Diagnostic upper GIT endoscopy, Endoscopic Variceal Sclerotherapy (EVS) and Endoscopic Variceal Ligation (EVL) may contribute to bacterial infections due to associated disruption of the natural barriers ***(Almeida et al., 2001).*** It has been previously reported that the passage of a fiberoptic endoscope into the upper GIT might be associated with mucosal trauma and subsequent translocation of native microorganisms, and that this might be particularly likely to occur when mucosal biopsy specimens were obtained. For simple esophago-gastro-dudenoscopy (EGD), with or without biopsies, the reportedrate of bacteremia ranges from 0% to 8%, with a mean frequency of 4.1% ***(O'Connor et al., 1983).***

Transient bacteremia after injection sclerotherapy of esophageal varices has been reported with a mean frequency of 14.6% (range 0% to 52.5%) ***(Kulkarni et al., 1999).*** Factors implicated to explain this wide variation include contaminated water ***(Brayko et al., 1985),*** length of the injection needle ***(Snady et al., 1985)*** and the presence of acute bleeding (or emergent sclerotherapy) ***(Ho et al., 1991)***. Although usually

lasting less than 30 minutes, bacteremia in some cases has been observed as long as 24 hours ***(Cohen et al., 1983).***

Seven studies have reported bacteremia rates associated with band ligation ranging from 0% to 25%, with a mean frequency of 8.8% ***(da Silveira et al., 1997; Kulkarni et al., 1999 and Lin et al., 2000)***. The designs of these studies were similar to that used to evaluate the frequency of bacteremia after injection sclerotherapy, that is, blood sampling for bacterial culture before, during, and at various intervals after the procedure.

The frequency of bacterial peritonitis reported after ligation ranged from 0% to 15.8%, with a mean rate of 3.7% ***(Kulkarni et al., 1999; ALTraif et al., 1999 and Lin et al., 2000)***. One case of meningitis after EVL had been reported ***(Nagamine et al., 1999).***

Because EVL does not involve the direct penetration of the esophageal mucosa with a needle, there is less opportunity for the direct introduction of bacteria. Also, EVL is done with a protective overtube that prevents the ligation bands from contamination with the oropharyngeal flora on the way ***(Lo et al., 1994).*** Furthermore, the process of ligation itself obliterates the submucosal venous channels; reducing the likelihood of systemic bacteremia. For these reasons, it was believed that EVL is associated with less incidence of bacteremia than EVS ***(Lin et al., 2000).***

AIM OF THE WORK

To compare between incidence bacteremia following injection sclerotherapy and band ligation of esophageal varices, also to determine the most causative organisms and their antibiotic sensitivity pattern.

CHAPTER I
CHRONIC LIVER DISEASE

Definition

Chronic liver diseases are described as persistent inflammation of the liver for 6 months or more after initial exposure and/or initial detection of liver disease ***(Dove and Wright., 2004)***.

According to ***Thomas et al. (2001)***, there are 4 main causes of chronic liver diseases. (Table 1)

Table (1): Causes of chronic liver disease.

Persistent viral infection	Auto immune liver disease	Drugs and alcohol	metabolic disorders
1- Hepatitis B: Infection mainly by I.V drug abuse, vertical transmission, blood product, and sexual transmission. In 90% of the patients infected, immune response results in the elimination of the virus but in some cases, chronic infection can lead to cirrhosis and liver carcinoma (HCC).	1- Auto immune (lupoid) hepatitis: Commonly seen in females, histologically classified by appearance of chronic active hepatitis dominated by numerous plasma cells and swollen liver cell arranged in rosette-like forms, auto antibodies to smoth muscle antigens are often present.	• Alcohol liver injury: Ethyl alcohol is a common cause of acute and chronic liver injury. Alcohol is directly cytotoxic at high concentration, injuring hepatocytes and causing inflammatory reaction. In addition, alcohol stimulates collagen synethesis and	1- Alpha 1-antitrypsin deficiency: Congenital defect of synthesis, with hyaline globular inclusion in liver. Patients have increased risk of emphysema and cirrhosis. 2-Wilson's disease: Inherited disorder of copper metabolism. Copper accumulate in liver and brain, also cause kayser-fleischer rings at the corneal limbus, low serum caeruloplasmin (a copper containing protein). 3- Hemochromtosis Inherited as autosmal recessive disorder.

Persistent viral infection	Auto immune liver disease	Drugs and alcohol	metabolic disorders
2- Hepatitis C: Transmitted parenterally, following infected blood transfusion and IV drug abuse. 50% of acute infection leads to chronic infection, 10% of that having cirrhosis (with or without HCC).	2-Primary biliary cirrhosis: Chronic disorders affects mainly middle-aged females. Liver biopsy shows bile duct obstruction, granulomas, ductular proliferation, fibrosis and eventual cirrhosis.	leads to fibrosis and cirrhosis	Iron absorption is inappropriately high for dietary intake thereby leading to progressive accumulation of storage iron, iron deposite primarily in hepatecytes as ferritin and subsequently also as hemosiderin with a decreasing gradient of iron deposition from peripheral (zone 1) to pericentral (zone 3) hepatocyte.

(Thomas et al., 2001)

Other causes of chronic liver disease (CLD):

- Secondary biliary cirrhosis.
- Granulomatous disease (eg. Sarcoidosis).
- Type IV glycogen storage disease.
- Drug-induced liver disease (eg, methotrexate, alpha methyl-dopa, amiodarone).
- Venous outflow obstruction (eg, Budd-chiari syndrome, venooclusive disease).
- Chronic right-sided heart failure.
- Tricuspid regurgitation.

(Wolf, 2005)

Histological Grading and Staging:

A standardized scale for the interpretation of histology in chronic hepatitis was developed by ***Batts and Ludwig, (1995)***. The grading scale measures the necroinflammatory process; the staging scale measures the degree of fibrosis (Table 2 & 3)

Table (2): Grading of disease activity in chronic hepatitis:

Grade	Descriptive	Lymphocytic piecemeal necrosis	Lobular inflammation and necrosis
0	Portal inflammation	None	None
1	Minimal	Minimal, patchy	Minimal, occasional spotty necrosis.
2	Mild	Mild, involving some or all portal tracts	Mild, little hepatocellular damage
3	Moderate	Moderate	Moderate, with noticeable hepatocellular damage
4	Severe	Severe	Severe, with prominent diffuse, hepatocellular damage

(Dove and Wright, 2004)

Table (3): Stages of chronic hepatitis:

Stage	Descriptive	Criteria
0	No fibrosis	Normal connective tissue
1	Portal fibrosis	Fibrous portal expansion
2	Periportal fibrosis	Periportal or rare portal-portal septa
3	Septal fibrosis	Fibrous septa with architectural distortion, on obvious cirrhosis
4	Cirrhosis	Cirrhosis

(Dove and Wright, 2004)

Chronic liver diseases generally progress slowly from hepatitis to cirrhosis, often over 20 to 40 years. Some forms of liver diseases are non progressive or only slowly progressive. Other, more severe forms are associated with scarring and architectural disorganization, which, if advanced, lead to cirrhosis ***(Thomas et al., 2001)***.

Liver cirrhosis

Definition:

Cirrhosis represents an irreversible state of chronic liver injury. Cirrhosis is defined as fibrosis of the liver with the formation of regenerative nodules. Once a liver has been scarred to the point of cirrhosis, it will probably never return to normal. (Figure 1) ***(Sandowski, 2000)***. It can be also defined as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal modules that lack normal lobular organization ***(Cheney et al., 2004).***

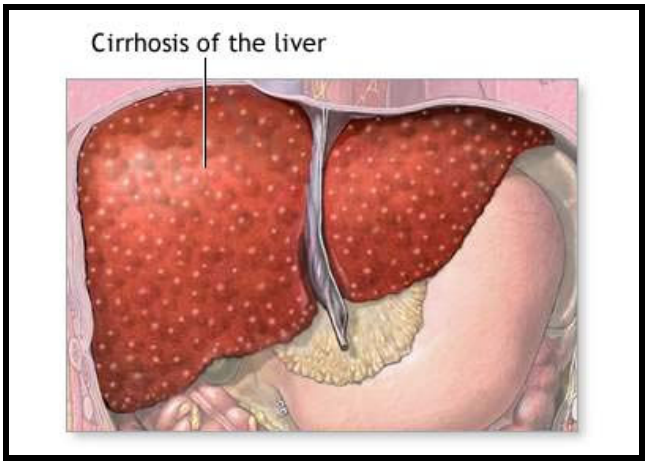

Figure (1): Liver cirrhosis.

Classification of Cirrhosis

1- Morphological classification: less useful because of considerable overlap. (Figure 2).

a. Micronodular cirrhosis. Uniform nodule <3 mm in diameter: causes include alcohol, hemochromatosis, biliary obstruction, hepatic venous outflow obstruction, jejunoileal bypass, indian childhood cirrhosis.

b. Macronodular cirrhosis. Nodular variation >3 mm in diameter: causes include chronic hepatitis C, chronic hepatitis B, alpha-1 antitrypsin deficiency, primary biliary cirrhosis.

c. Mixed cirrhosis. A combination of micronodular and macronodular cirrhosis. Micronodular cirrhosis frequently evolves into macronodular cirrhosis ***(Cheney et al., 2004)***.

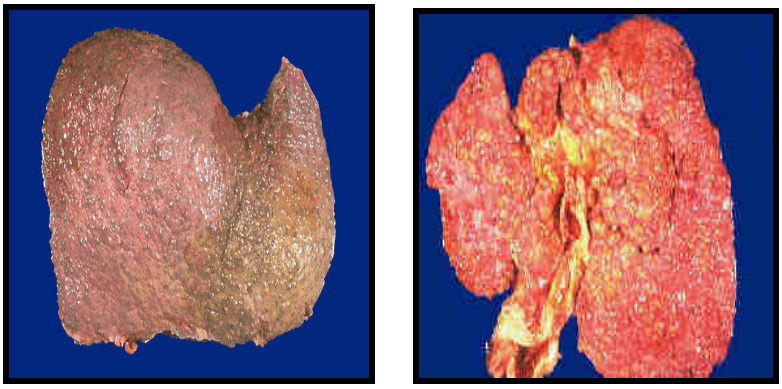

Figure (2): Macronodular cirrhosis & Micronodular cirrhosis

2- Etiologic classification: (preferred)

- This method of classification is the most useful clinically, by combining clinical, biochemical, histologic, and epidemiologic data, the likely etiologic agent can be ascertained.
- The two most common causes of cirrhosis are excessive alcohol use and viral hepatitis ***(Cheney et al., 2004)***.

Pathogenesis:

Liver cirrhosis represent a continuous disease spectrum characterized by an increase in total liver collagen and other matrix proteins which disrupt the architecture of the liver and impair liver function ***(Friedman, 2000)***.

High quality experimental evidence supports the hypothesis that the final common pathway of fibrosis is mediated by the hepatic stellate cells ***(Friedman, 2000)***. Hepatic stellate cells in normal liver store retinoids and reside in the spaces of disse. In injured area of the liver, hepatic stellate cells undergo a remarkable transformation: they resemble myofibroblasts and express contractile proteins, hepatic stellate cells proliferate and are known to be the major source of the fibrillar collagens that characterize fibrosis and cirrhosis (figure 3) ***(Iredale, 2003)***.

Activated stellate cells proliferate, with the result that increases in numbers of hepatic stellate cells, in addition to increases in secretion of fibrillar (or scarring) collagens, results in the deposition of excess fibrotic matrix ***(Iredale, 2003)***.

Stellate cells, and other cells involved in the fibrotic process, including macrophages and kupffer cells, secrete a repertoire of matrix degrading metalloproteinase enzymes (MMPS), these enzymes degrade collagen and other matrix molecules, and their presence in the fibrotic liver highlights the potential dynamic nature of scarring with the liver ***(Benyon and Arthur, 2001)***.

In addition, activation of hepatic stellate cells is associated with the expression of contractile intracellular proteins such as α smooth muscle actin, and activated cells become sensitive to the potent vasoactive substance endothelin. Endothelin concentrations increase after fibrotic livery injury, promoting contraction of hepatic stellate cells. In parallel, injury results in a reduction in nitric oxide derived from hepatic endothelial cells, which antagonizes the effect of endothelin. The net result of this imbalance is that stellate cell contraction is stimulated, and the consequent increases in intrahepatic sinusoidal resistance contribute to portal hypertension ***(Rockey, 2002)***.

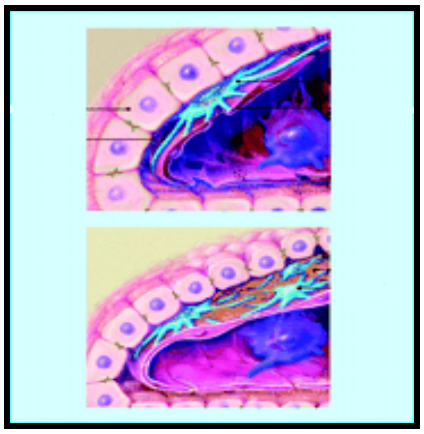

Figure (3): Normal liver (top) and liver injury (bottom).

Clinical picture:

The natural history of cirrhosis is divided into compensated and decompensated stages. Some patients never progress to the decompensated stage and die of other cause after a normal life expectancy. Usually these are patients with alcoholic cirrhosis who stop drinking before decompensation. Decompensation is defined as development of ascites, hepatic encephalopathy, or gut bleeding caused by portal hypertension, usually from esophageal varices, jaundice is sometimes included as a manifestation of decompensation but is not nearly as important sign as the three main defining features ***(Sandowski, 2000)***.

The severity of cirrhosis is determined based on laboratory tests and findings on physical examination. The liver biopsy plays no role in determining the severity of the cirrhosis. Factors that are taken into account to determine the severity of cirrhosis include the serum albumin, the PT or INR (Prothrombin Time or International Normalized Ratio), and the level of serum bilirubin. In addition, the presence or absence of ascites and encephalopathy are also used to grade the severity of cirrhosis. A point system known as the Child-Pugh-Turcotte score or modified Child-Pugh score, has been devised to determine the severity of the cirrhosis. Depending on the total score, a patient is classified as class A (early cirrhosis) through class C (advanced cirrhosis) (table 4) ***(Roynard et al., 2003)***.

Table (4): Modified Child-Pugh classification

	Points assigned to laboratory values and signs*		
Parameters laboratory value	**1**	**2**	**3**
Total serum bilirubin level	< 2 mg per dL (34 µmol per L)	2 to 3 mg per dL (34 to 51 µmol per L)	>3 mg per dL
Serum albumin level	> 3.5 g per dL (35 g per L)	2.8 to 3.5 g per dL (28 to 35 g per L)	<2.8 g per dL
International Normalized Ratio	<1.70	1.71 to 2.20	>2.20
Signs			
Ascites	None	Controlled medically	Poorly controlled
Encephalopathy	None	Controlled medically	Poorly controlled
** -- Based on total points, a patient with cirrhosis is assigned to one of three classes: Child class A = 5 to 6 points; Child class B=7 to 9 points; Child class C = 10 to 15 points.*			

(Pugh et al., 1973)

A patient with cirrhosis may present with none, some or all of the findings listed below:

1- General Features:

Fatigue, anorexia, malaise, weight loss, muscle wasting, fever ***(Cheney et al., 2004)***.

2- Gastrointestinal manifestations:

Parotid enlargement, diarrhea, cholelithiasis, gastrointestinal bleeding (Esophageal, gastric, duodenal, rectal, stomal varices portal hypertensive gastropatly, colopathy) ***(Cheney et al., 2004)***.

3- Hematologic manifestations:

Anaemia, thrombocytopenia, leucopenia, impaired coagulation, disseminated intravascular coagulation, hemosiderosis ***(Cheney et al., 2004)***.

4- Pulmonary manifestations:

Decrease oxygen saturation, altered ventilation-perfusion relationships, portopulmonary hypertension, hyperventilation, reduced pulmonary diffusion capacity, hepatic hydrothorax, hepato-plumonary syndrome ***(Cheney et al., 2004)***.

5- Cardiac manifestations:

Hyperdynamic circulation. ***(Cheney et al., 2004)***.

6- Endocrinologic manifestations:

Hypogonadism, feminization, diabetes. Up to 80% of cirrhotics have glucose intolerance, and 10-20% are truly diabetic, most patients with liver diseases are clinically euthyroid, although there may be changes in the serum level of thyroid hormones. Hypo- and hyperthyroidism may be associated with liver diseases and experimentally influence the severity of experimental liver injury ***(Zein et al., 2000)***.

Complications of Cirrhosis

1- Portal Hypertension

Portal hypertension is defined as a portal venous pressure exceeding 10 mm Hg. Portal hypertension in cirrhosis is determined by an increase in both intrahepatic vascular resistance and portal venous inflow. Intrahepatic vascular

resistance is caused by the architectural distortion of the liver resulting from fibrosis and by increased sinusoidal tone. Portal venous inflow results from a combination of a hyperdynamic circulatory state and increased plasma volume. In response to the increased portal pressure, collateral circulation develops by the opening of preexisting vascular channels and possibly neoformation of vessels ***(Menon and Kamath, 2001).***

Clinical consequences of portal hypertension:

A- Esophagogastric varices:

Esophagogastric varices develop as portal blood flow is shunted from the liver by way of low-resistance collaterals through the coronary vein into the esophagus and proximal stomach, ultimately draining into the systemic circulation via the azygos vein. The location of many of these collaterals near the surface of the gastric fundus and distal esophagus explains the propensity of varices in this area to blood. Rupture with subsequent bleeding from these varices is a grave complication and is associated with a high mortality rates as it accounts for approximately one fifth to one third of all death in cirrhotic patients ***(Fevery and Nevens, 2000)***.

B- Portal Hypertensive Gastropathy (PHG):

Portal hypertensive gastropthy is a common feature of cirrhosis, and its prevalence parallels the severity of portal hypertension and liver dysfunction. Portal hypertensive