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Management of Therapy in Hepatic Cirrhosis

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Abstract
The liver is the largest organ of the human body with many important functions. The presence of histopotologis conditions, such as the formation of fibrosis in the liver will affect liver function. Hepatic cirrhosis is characterized by diffuse fibrous formation and nodular formation, accompanied by various clinical manifestations and complications.Sirosis is the 12th leading cause of death in the United States which accounted for 29,165 deaths in 2007, with mortality of 9.7 per 100,000 people. Various pharmacological treatments in hepatic cirrhosis are used to treat underlying causes, preserve nutrients and overcome the emerging complications, including portal hypertension, variceal haemorrhage, splenomegaly, ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome and hepatic encephalopathy. This review aims to describe the pharmaceutical aspects of pharmacological therapy used in the management of hepatic cirrhosis.

Keywords*: hepatic cirrhosis, management theraphy*

I. LIVER DISEASES

Evaluation in patients with liver disease is performed when: establishing the etiology of diagnosis, grading severity (acute / chronic, active / inactive, mild / moderate / severe / very severe), staging the disease (early / advanced, precirrhotic, cirrhotic)**.** Liver biopsy is the most accurate examination to determine the grading and staging of liver disease. Serum aminotransferase is more comfortable and non-invasive than biopsy, but it is not always reliable in describing the disease grade. Staging of cirrhosis can be done clinically using the Child-Pugh classification system (score 5-15). Scores 5 and 6 describe Child-Pugh class A (consistent with "compensated" cirrhosis), score 7-9 (class B), score 10-15 (class C).

Child-Pugh score is a reliable survival predictor in some liver diseases and predictors of possible major complications of cirrhosis, such as variceal bleeding and SBP (Spontaneous Bacterial Peritonitis). Recently, the child-pugh scoring system has been replaced with the Model for End-Stage Liver Disease (MELD). MELD is prospectively designed to predict the prognosis of patients with liver disease and portal hypertension calculated from three noninvasive variables, ie prothrombin time as INR, bilirubin serum, and serum creatinine.

Table 1. **Metode *Child-Pugh Classification Sirosis***

Factor	Units	Points Toward Total Score		
		1	2	3
Serum bilirubun	µmol/L	< 34	34 -51	> 50
	mg/dL	< 2.0	2.0-3.0	> 3.0
Serum albumin	g/L	> 35	30-35	< 30
	g/dL	> 35	3.0-3.5	< 3.0
Prothrombin time	Second prolonged	< 4		
	INR (International Normalized Ratio)	< 1.7		
Acites		None	Easily controlled	Poorly controlled
Hepatic Enchepalophaty		None	Minimal	Advanced

Table 2. Metode *Model for End-Stage Liver Disease (MELD* score) [2]

MELD score	One-year Survival Rate Depending On	
	One-year survival (%)	
	No complications	Complication
< 9	97	90
10-19	90	85
20-29	70	65
30-39	70	50
MELD from SI units		
10 x (0,378(In serum bilirubn (µmol/L) + 1,12 (In INR) + 0,957 (In serum creatinine (µmol/L)) + 0.643		
MELD from non SI units		
3,8 (ln serum bilirubn (µmol/L) + 11,2 (In INR) + 9,3 (ln serum creatinine (µmol/L)) + 6,4		
Ln = natural log.		
Complication means the presence at ascites, encephalophathy or variceal bleeding		

II. HEPATIC CIRRHOSIS

Hepatic cirrhosis characterized histopathologically (diffuse hepatic fibrosis and nodule formation) has various clinical manifestations and complications. Cirrhosis is the 12th leading cause of death in the United States that accounted for 29,165 deaths in 2007, with mortality rates of 9.7 per 100,000 people. The overall cirrhosis prognosis is bad. Many patients come when the disease is advanced and or with serious complications with a high mortality rate. The incidence of complications such as jaundice, ascites, encephalopathy, infection, renal dysfunction, variceal bleeding requires hospitalization with increased risk of death by 40-50% within 5 years. Some patients (significant amounts) require intensive management and care (ICU) with supportive organs and still show high mortality rates in Hospital.

A. Etiology

As for several causes of hepatic cirrhosis are presented in the following table:

Table 3. Causes of Cherrosis

Causes of sirosis	
- Alcohol	- Genetic
- Chronic viral hepatitis (B or C)	> Haemochromatosis
- Non-alcoholic fatty liver desease	> Wilson's disease α1-antithrypsin
- Immune	deficiency
➢ Primary sclerosing cholangitis	- Cryptogenic (unknow-15%)
➢ Autoimmune liver disease	- Chronic venous outflow obstruction
- Billary	- Any chronic liver disease
➢ Primary billary sirosis	
➢ Secondary billary sirosis	
➢ Cistic fibrosis	

III. PATHOPHYSIOLOGY

Following liver injury, stellate cells are activated by cytokines produced by Kupffer cells and hepatocytes. Transformation of stellate cells into myofibroblast-like cells, can produce collagen, pro-inflammatory citokynes and other mediators that cause hepatocyte damage and tissue fibrosis. Cirrhosis is a histologic diagnosis that has developed over the years as a widespread progressive fibrosis. Fibrosis may be centrilobular, pericellular, or periportal. When fibrosis reaches a certain grade, it causes a normal distortion of the liver architecture and replacement of hepatocytes by regenerative nodules that interfere with hepatic

vascularization. These changes affect the liver overall, but in billiary cirrhosis (eg PBC) is not the case. Histopathologically, cirrhosis can be classified into: micronodular cirrhosis (small diameter ± 1 mm), found in alcoholic cirrhosis and macronodular cirrhosis (nodules appear to be larger in varying sizes).

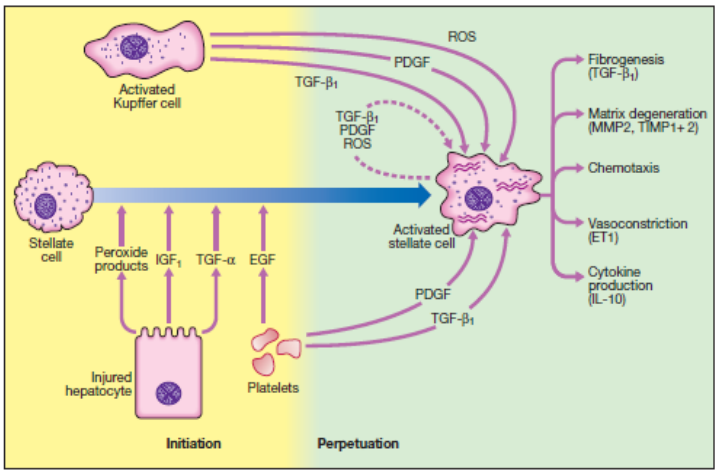


Figure 1. Pathogenic Mechanism of Fibrosis

A. Clinical Manifestations

Clinical manifestations of hepatic cirrhosis vary widely. In some patients asymptomatic and upright diagnoses during ultrasound or surgical examination, there are also manifestations such as hepatomegaly, splenomegaly, signs of portal hypertension, or hepatic insufficiency. Common non-specific symptoms are weakness, fatigue, muscle cramps, weight loss, nausea, vomiting and upper abdominal discomfort. Hepatomegaly generally occurs in cirrhosis due to ALD (Alcoholic Liver Disease) or haemochromatosis. Destruction of progressive hepatocytes and fibrosis that gradually lead to reduced liver size generally occur in cirrhosis due to viral hepatitis or autoimune liver disease.

IV. MAJOR COMPLICATION

The clinical course of patients with cirrhosis is complex with a number of sequelae, such as portal hypertension and consequent of esophageal varices haemorrhage, splenomegaly, ascites, escephalopathy, SBP, hepatorenal syndrome and hepatocellular carcinoma. The forms of complications comprise of:

a. Portal hypertension: Defined as an increase in hepatic venous pressure gradient (HVPG)> 5 mmHg, caused by two simultaneous hemodynamic processes, namely: increased of intrahepatic resistance due to cirrhosis and increased of splanchnicecular blood flow resulting in splancnic vasodilation of blood vessels. In the USA, more than 60% of patients with cirrhosis have portal hypertension. Portal hypertension is directly responsible for the occurrence of ascites and variceal hemorrhage. Coagulation disorders due to cirrhosis can lead to portal venous thrombosis including polycythemia vera, protein C deficiency, protein S, antithrombin 3, leiden V factor and gene-regulating prothrombin production abnormalities

b. Variceal Hemorrhage: Approximately 5-15% of patients with cirrhosis per year experience esophageal varices and it is estimated that the majority of patients will experience it during their lifetime. The presence of varices can be identified through endoscopy. Abdominal imaging, CT and MRI may assist in nodular identification and alteration of the portal tension with intraabdominal collateral circulation. Patients with ascites and HVPG> 12mmHg increased risk of variceal hemorrhage

c. Splenomegaly and Hypersplenism: Hypersplenism with thrombocytopenia is a common clinical feature of cirrhotic patients and is usually the first indication of portal hypertension. Congestive splenomegaly is common in patients with portal hypertension.

d. Ascites: It is defined as the accumulation of fluid in the peritoneal cavity, commonly due to portal hypertension due to cirrhosis. However, malignancy or infection can also cause ascites. The intrahepatic resistance and splanchnic vasodilation lead to increased venous porta blood flow. These hemodynamic changes result in sodium retention caused by RAAS activation hyperaldosteronism occurs. Sodium sensibility leads to fluid accumulation and expansion of extracellular fluid volume resulting in peripheral edema and ascites. Sodium retention is a consequence of homeostatic response caused by underfilling of arterial circulation. Hipoalbuminemia resulting in decreased oncotic pressure also contributes to the discharge of fluid from the vascular compartment to the peritoneal cavity.

e. Spontaneous Bacterial Peritonitis (SBP): SBP is a complication of ascites characterized by spontaneous infection of ascites fluid with no source of abdominal infection. Bacterial removal of the intestine through the intestine to mesenteric lymph node triggers bacteremia and develops in ascites fluids. Common bacteria infecting are Escherichia coli, gram-positive bacteria (Streptococcus viridans, Staphylococcus aureus, and Enterococcus sp). Diagnosis of SBP is established when in ascites fluid samples are found neutrophil absolute> 250μ.

f. Hepatorenal Syndrome (HRS): HRS is a functional renal failure without renal pathology, characterized by impaired circulation of the renal artery occurring in 10% of patients with advanced cirrhosis or acute liver failure.

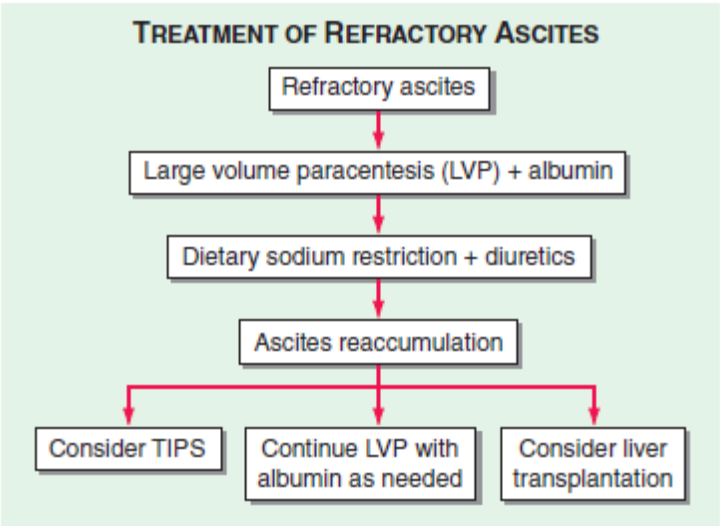
g. Hepatic Encephalopathy: Defined as a change in mental status and cognitive function that occurs when there is a liver failure, due to the neurotoxins of the intestine that can not be excreted by the liver. Ammonia levels are usually elevated in patients with hepatic encephalopathy, but the severity of liver disease and high ammonia levels are often uncorrelated. HE can be triggered by antidepressant medication, infection, hypocalcemia, constipation, increased protein load.

V. MANAGEMENT OF THERAPY

Management of cirrhosis involves addressing underlying causes, nutritional maintenance and complication therapy. The most important is alcohol abstinence. Diets should be adequate, calories (25-35 kcal / kg / day in compensated cirrhosis and 35-45 kcal / kg / day in malnutrition) protein (1-1.5g / kg / day in compensated cirrhosis and 1.5g / kg / day in malnutrition) .When HE occurs, the protein intake is reduced to no more than 60-80g / day.) Special branch-chain amino acid supplements to prevent / treat HE or prevent liver failure progression is generally not necessary. Patients with cirrhosis should receive HAV, HBV and pneumococcal vaccines and influenza vaccine annually. Management of cirrhosis complication therapy is presented in the following table

Table. Management Therapy of Hepatic Chirrosis Complication

Complication	Management
Portal Hypertension	The treatment focus on prevention of varices esophageal bleeding a.Primary prevention variceal bleeding beta blocker nonselektif (propranolol 80-160 mg, nadolol, carvedilol) b.secondary prevention of variceal bleeding
Varices Hemorrhage	Management of acute variceal bleeding - Pharmacology : - Colloid fluid therapy, vasopressor-terlipresin (rarely used), vasoconstrictor (somatostatin, octreotide), prophylactic antibiotic to prevent SBP (cephalosporin iv), PPI to prevent peptic ulcer, enema phosphae and/or lactulose to prevent encephalopathy - Emergency endoscopy (confirmation of bleeding source : variceal/ulcer) - Balloon tamponade (use in patient that can undergo emergency endoscopy or need to stabilize before endoscopy) or TIPSS (transjugular intrahepatic portosystemic stent shunting) or esophageal transection - variceal band ligation to stop the bleeding,
Ascites	a. sodium restriction (<2 g/day) b. spironolacton 100-200 mg single dose in the beginning and combine with furosemide 40-80 mg/day in patient with peripheral edema. If ascites still persist, increased spironolactone dose 400-600 mg/day and furosemid 120-160 mg/day c. if ascites is still persisten after therapy from point a and b, then refractory ascites therapy (diuretic resistance or intolerance to diuretic) with alternative large volume paracentesis (> 5L) d. Goal of therapy in ascites without peripheral edema: decrease of body weight 0.5-0.7 kg/day

	 **Figure** . Algorithm Therapy in Refractory ascites a. paracentesis diagnostic is indicated in new patient with ascites and hospitalized because of chirrosis complication. This can reduce mortality especially if it is done under 12 hours in hospital. b. Vaptan can increase sodium levels in the serum in ascites and chirrosis patient, but rarely used because of the cost, potential risk and clinical outcome in the patient.
Spontaneous bacterial peritonitis	therapy begins with cefotaxim 2g every 8-12 hours for at least 5 days, ceftriaxon and amoxicillin-clavulant acid or piperacillin / tazobactam as an alternative. SBP relaps are common but can be decreased by ciprofloxacin prophylaxis iv 200 mg every 12 hours for 2 days followed by ciprofloxacin 2x500 mg po for 5 days
Sindroma hepatorenal	midodrine (α agonist) 3x7.5 mg po with octreotide and albumin iv. The best therapy of HRS is liver transplant, renal function will generally improve afterwards.
Hepatic Encephalopathy	GI bleeding must be controlled and blood should be cleared from GIT. 120 ml of magnesium citrate or NGT every 3-4 hours until the faeces are free of gross blood, or by lactulose administration. The initial dose of lactulose for acute hepatic encephalopathy is 30 mL three or four times daily. The use of lactulose may be continued after acute encephalopathy may decrease the frequency of recurrence

VI. CONCLUSION

Various pharmacological therapies are used to address the underlying causes of hepatic cirrhosis, overcoming complications and maintaining patient nutrition. Non-selective beta blockers are a therapeutic option for dealing with portal hypertension, vasoconstrictors such as somatostatin and octreotide are selected to treat acute variceal bleeding.Restriction of sodium, diuretic (single spironolactone and furosemide combination) is commonly used as ascites therapy with large volume paracentesis and albumin as an alternative when refractory ascites or ascites resistant diuretics. To treat SBP, a third-generation cephalosporin antibiotic or a penicillin-β lacatamse inhibitor may be selected, whereas quinolone may be selected as prophylaxis. Hepatorenal syndrome is recommended to be treated with midodrine α agonists along with octreotid and iv albumin. Lactulose is chosen as a therapy and prophylaxis of hepatic encephalopathy.

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