INTRODUCTION

Acute liver failure (ALF) is a rare condition in which rapid deterioration of liver function results in altered mentation and coagulopathy in previously normal individuals. U.S. estimates are placed at approximately 2,000 cases per year ***(Hoofnagle et al., 1995).***

The most prominent causes include drug-induced liver injury, viral hepatitis, autoimmune liver disease and shock or hypoperfusion; many cases (~20%) have no discernible cause ***(Ostapowicz et al., 2002).***

Acute liver failure often affects young persons and carries a high morbidity and mortality. Prior to transplantation, most series suggested less than 15% survival. Currently, overall short-term survival with transplantation is greater than 65% ***(Ostapowicz et al., 2002).***

The decision for transplantation depends on the possibility of spontaneous hepatic recovery, which may be estimated by several factors. The most important variables for predicting the need of transplantation in fulminant hepatic failure are the degree of encephalopathy, patient's age and the underlying cause of liver failure ***(Services USDoHaH, 2005).***

Because of its rarity, acute liver cell failure has been difficult to study in depth and very few controlled therapy trials

have been performed. As a result, standards of intensive care for this condition have not been established.

AIM OF THE WORK

The aim of this study is to discuss the most important causes of acute liver failure in critically ill patients, explaining how to diagnose and monitor them and presenting the methods of management, depending on clear understanding of the basic pathophysiology of acute liver failure in critically ill patients.

PATHOPHYSIOLOGY OF FULMINANT HEPATIC FAILURE

Main points

1. Approach to liver anatomy
2. Approach to liver physiology
3. Causes and etiology
4. Pathophysiology

Approach to Liver Anatomy

The liver is the largest organ in the body and lies in the upper part of the abdominal cavity just beneath the diaphragm and mostly under cover of the ribs. It fills the right muirdnohcopyh and extends across the epigastrium into the left hypochondrium ***(Standring et al., 2005).***

The liver is a solid gastrointestinal organ largely occupies the upper quadrant of the abdomen. The costal margin coincides with the lower margin and the superior surface is draped over by the diaphragm. Most of the right liver and most of the left liver is covered by the thoracic cage. The liver extends superiorly to the height of the fifth rib on the right and the sixth rib on the left. The posterior surface straddles the inferior vena cava (IVC). A wedge of liver extends to the left half of the

abdomen across the epigastrium to lie above the anterior surface of the stomach and under the central and left diaphragm. The superior surface of the liver is convex and is molded to the diaphragm, whereas the inferior surface is mildly concave and extends to a sharp anterior border ***(Townsent et al., 2004).***

- **Hepatic Surfaces**

The liver has superior, anterior, right, posterior and inferior surfaces, and has a distinct inferior border. However, superior, anterior, right surfaces are continuous with no definable borders. The superior surface is the largest surface and lies immediately below the diaphragm, separated from it by peritoneum except for a small triangular area where the two layers of falciform ligament diverge. The anterior surface is triangular and convex. It is covered by peritoneum except at the attachment of the falciform ligament. It is covered by peritoneum and lies adjacent to the right dome of the diaphragm which separates it from the right lung, pleura and seventh to eleventh ribs. The posterior surface (Fig. 1) is convex, wide on the right, but narrow on the left. The inferior surface is bounded by the inferior edge of the liver. It is marked near the midline by fissure of ligamentum teres ***(Standring et al., 2005).***

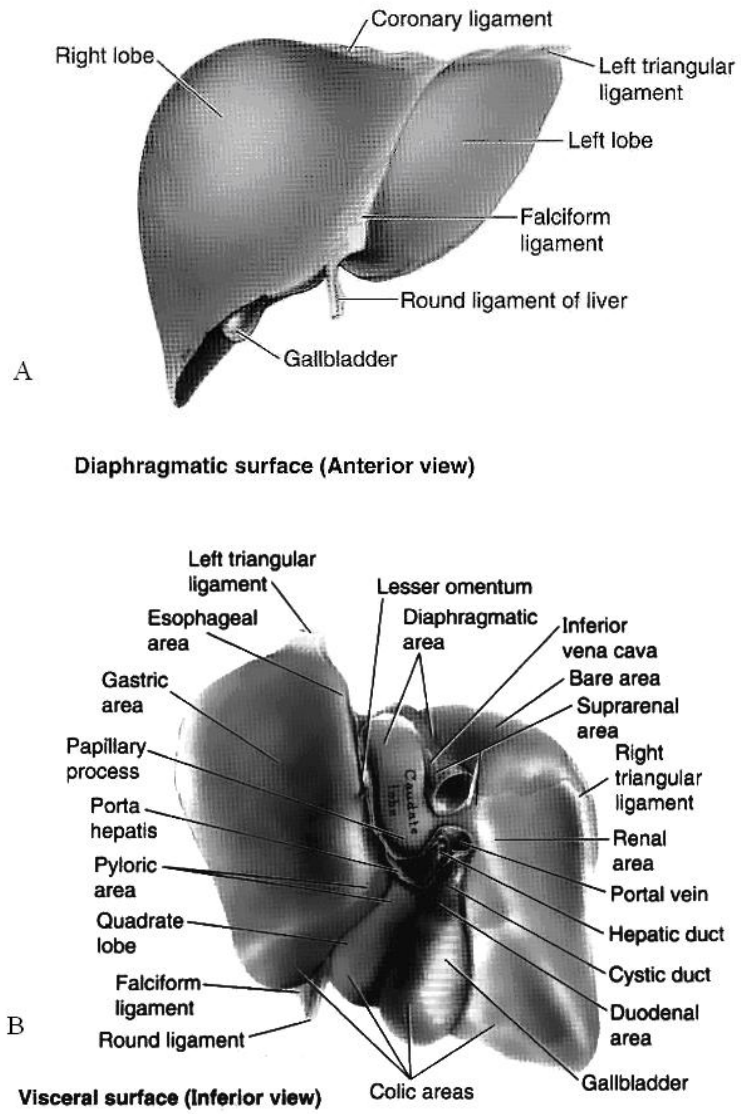

Fig (1): A. Anterior surface of the liver **B.** visceral surface of the liver ***(Moore and Dalley, 2006).***

- **Ligaments of the liver:**

The liver is attached to the anterior abdominal wall by the falciform ligament , except for a small area of the liver against the diaphragm (the bare area), the liver is almost completely surrounded by visceral peritoneum. Additional folds of peritoneum connect the liver to the stomach (hypogastric ligament), the duodenum (hepatodudenal ligament), and the diaphragm (right and left triangular ligaments and anterior and posterior coronary ligaments) ***(Drake et al., 2005).***

- **Important relations:**

Anteriorly: Diaphragm, right and left costal margins, right and left pleura, and lower margins of lungs, xiphoid process and anterior abdominal wall in the subcostal angle.

Posteriorly: Diaphragm, right kidney, hepatic flexure of the colon, duodenum, gallbladder, inferior vena cava, esophagus, and fundus of the stomach ***(Snell, 2004).***

- **The Porta Hepatis**

The porta hepatis is the area of the inferior surface through which all the neurovascular and biliary structures, except the hepatic veins, enter and leave the liver ***(Standring et al., 2005).***

- **Lobes Of The Liver**

The right lobe of the liver is the largest in size and contributes to all surfaces; it exceeds the left lobe by a ratio of 6:1. It occupies the right hypochondrium and is bordered on its upper surface by the falciform ligament, on its posterior surface by the left sagittal fossa and in front by umbilical notch. The left lobe of the liver is the smaller of the two main lobes. It lies in the epigastric and left hypochondrium regions. The caudate lobe is a small lobe visible on the posterior surface. In gross anatomical descriptions this lobe is said to arise from the right lobe, but it is functionally separate. The quadrate lobe is only visible from the inferior surface, it appears somewhat rectangular. In gross anatomical description it is said to be a lobe arising from the right lobe, however, it is functionally related to the left lobe ***(Standring et al., 2005).***

- **The excretory apparatus of the liver consists of :**

i. The common hepatic duct
ii. The gallbladder
iii. The cystic duct
iv. The common bile duct

(Drake et al, 2005)

- **Functional anatomy of the liver (Hepatic segments):**

The functional anatomy of the liver is composed of eight segments, each of which is supplied by a single portal triad (also called a pedicle) composed of a portal vein, hepatic artery, and bile duct. These segments are further organized into four sectors that are separated by scissurae containing the three main hepatic veins. The four sectors are even further organized into the right and left liver. This system was originally described in 1957 by Woodsmith and Goldburne as well as Couinaud and defines hepatic anatomy as it is most relevant to surgery of the liver ***(Townsent et al., 2004).***

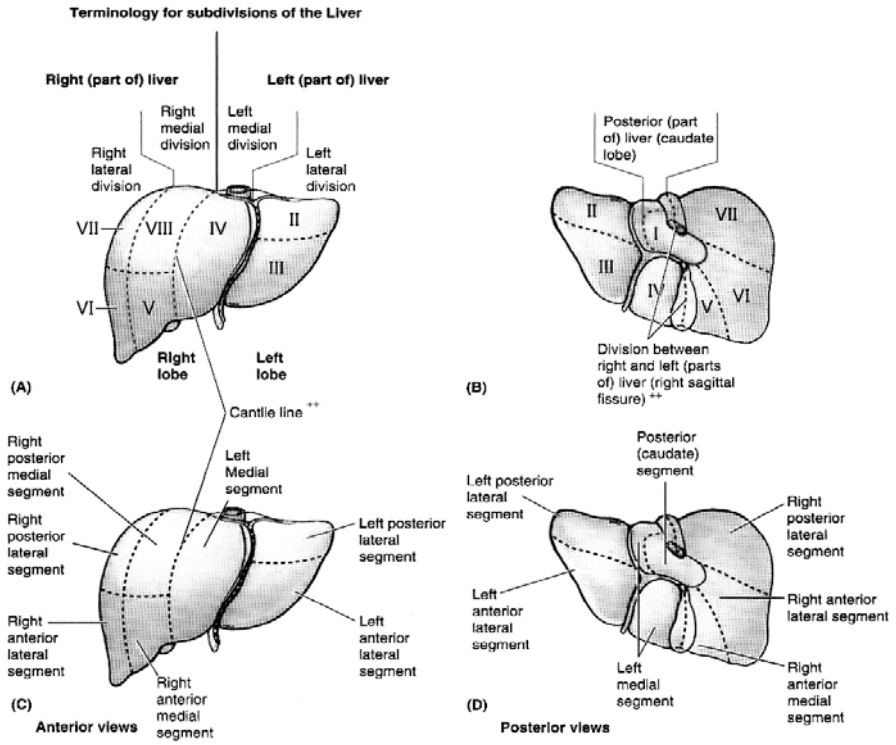

Figure (2): Functional division of the liver ***(Moore and Dalley, 2006).***

PHYSIOLOGY OF THE LIVER

The liver is the largest organ in the body, contributing about 2 % of the total body weight, or about 1.5 kg in the average adult human. The basic functional unit of the liver is the liver lobule, which is a cylindrical structure several millimeters in length and 0.8 to 2 millimeters in diameter. The human liver contains 50,000 to 100,000 individual lobules. It is also a large, chemically reactant pool of cells that have a high rates of metabolism, sharing substrates and energy from one metabolic system to another, and performing other metabolic functions ***(Guyton and Hall, 2006).***

Principle functions of the liver:

1. Bilirubin metabolism
2. Amino acid and protein metabolism
3. Carbohydrate metabolism
4. Lipid and lipoprotein metabolism
5. Hormone metabolism
6. Vitamin metabolism
7. Biotransformation and detoxification function
8. Coagulation
9. Blood reservoir
10. Blood cleansing function

(Kuntz and Kuntz, 2006)

Definition of fulminant hepatic failure: The term fulminant hepatic failure (FHF) was first introduced more than 40 years ago by Trey and Davidson ***(Trey et al., 1968)*** to describe the onset of altered mental status within 8 weeks of initial symptoms in an otherwise healthy individual with no previous history of liver disease. the term *fulminant* hepatic failure be reserved for cases in which encephalopathy developed within 2 weeks of the onset of jaundice and that *subfulminant* hepatic failure be applied to cases in which encephalopathy developed more insidiously, between 2 weeks and 3 months after the onset of jaundice. *Late-onset* hepatic failure has been used to describe patients in whom hepatic encephalopathy occurred between 8 and 24 weeks after the onset of symptoms ***(Gimson et al., 2006).***

The "umbrella term" of *acute liver failure* was proposed by ***(O'Grady et al.,*****2009)** Based on a retrospective analysis of 539 patients, they suggested a further subclassification comprising 3 distinct syndromes depending on the jaundice-to-encephalopathy time interval. Thus categorizing liver failure as *hyperacute* (onset within 1 week), *acute* (between 8 and 28 days), and *subacute* (between 29 days and 12 weeks). This classification reflected differences in survival rate for th groups, the best prognosis paradoxically being in the hyperacute group.

Causes and etiology:

Etiology of ALF provides one of the best indicators of prognosis and also dictates specific management options.

1- Acetaminophen Hepatotoxicity

Acetaminophen hepatotoxicity is suggested by historic evidence for excessive ingestion either as an intended suicidal overdose or the inadvertent use of supra-therapeutic quantities of pain medications. Acetaminophen is a dose related toxin; most ingestions leading to ALF exceed 10 gm/day. However, severe liver injury can occur rarely when doses as low as 3-4 gm/day are taken ***(Schiodt et al., 2004).***

Very high aminotransferases may be seen; serum levels exceeding 3,500 IU/L are highly correlated with acetaminophen poisoning and should prompt consideration of this etiology even when historic evidence is lacking.

2- Mushroom Poisoning

Mushroom Poisoning (usually *Amanita phalloides*) may cause ALF, and the initial history should always include inquiry concerning recent mushroom ***(Klein et al., 2005).***

3- Drug Induced Hepatotoxicity

A variety of medications have been associated with acute liver injury. Before implicating a particular substance, history should include careful listing of all agents taken, the time period involved, and the quantity ingested. Drugs other than acetaminophen rarely cause dose-related toxicity. Most examples of idiosyncratic drug hepatotoxicity occur within the first 6 months after drug initiation. A potentially hepatotoxic medication that has been used continually for more than 1 to 2 years is unlikely to cause de novo liver damage. Certain herbal preparations and other nutritional supplements have been found to cause liver injury, so inquiry about such substances should be included in a complete medication history ***(Stedman, 2007).***

Other causes of ALF should still be ruled out even if a drug is suspected. Any presumed or possible offending agent should be stopped immediately where possible. Classes of drugs commonly implicated include antibiotics, non-steroidal anti inflammatory agents and anti-convulsants (Table 1).

Table (1): Some Drugs Which May Cause Idiosyncratic Liver Injury Leading to ALF

Isoniazid	Isoflurane
Sufonamides	Lisinopril
Phenytoin	Nicotinic acid
Statins	Imipramine
Propylthiouracil	Gemtuzumab
Halothane	Amphetamines/Ecstasy
Disulfiram	Labetalol
Valproic acid	Etoposide
Amiodarone	Flutamide
Dapsone	Tolcapone
Herbals*	Quetiapine
Didanosine	Nefazodone
Efavirenz	Allopurinol
Metformin	Methyldopa
Ofloxacin	Ketoconazole
PZA	
Troglitazone	
Diclofenac	
Combination agents with enhanced toxicity:	
Trimethoprim-sulfamethoxazole	
Rifampin-isoniazid	
Amoxicillin-clavulanate	
*Some Herbal products/dietary supplements that have been associated with hepatotoxicity include:	
Kava kava Chaparral	
Skullcap Germander	
Pennyroyal Jin Bu Huan	
Heliotrope Rattleweed	
Comfrey Sunnhemp	
Senecio Impila	
Greater celandine Gum Thistle	
He Shon Wu Ma Huang	
LipoKinetix Bai-Fang herbs	

(Julie and William, 2005)

4- Viral Hepatitis

Hepatitis serological testing should be done for identification of acute viral infection (Table 2) even when another putative etiology is identified. Viral hepatitis has become a relatively infrequent cause of ALF (United States: 12%; hepatitis B – 8%, hepatitis A – 4%) ***(Ostapowiz et al., 2008).***

Acute hepatitis D may occasionally be diagnosed in a hepatitis B positive individual. Although controversial, hepatitis C alone does not appear to cause ALF. Hepatitis E is a significant cause of liver failure in countries where it is endemic, and tends to be more severe in pregnant women ***(Schiodt et al., 2007).***

This virus should be considered in anyone with recent travel to an endemic area such as Russia, Pakistan, Mexico, or India.

5- Wilson disease

Wilson disease is an uncommon cause of ALF. Early identification is critical because the fulminant presentation of Wilson disease is considered to be uniformly fatal without transplantation. The disease typically occurs in young patients, accompanied by the abrupt onset of hemolytic anemia with serum bilirubin levels > 20 mg/dL. Due to the presence of