Review

Liver dysfunction in the intensive care unit

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SUMMARY

Liver dysfunction plays a significant role in the Intensive Care Unit (ICU) patients' morbidity and mortality. Metabolic, hemodynamic and inflammatory factors contribute in liver damage. Hemorrhagic shock, septic shock, multiple organ dysfunction, acute respiratory dysfunction, metabolic disorders, myocardial dysfunction, infection from hepatitis virus, and therapeutic measures such as blood transfusion, parenteral nutrition, immunosuppresion, and drugs are all recognised as potential clinical situations on the grounds of which liver dysfunction develops.

The liver suffers the consequences of shock- or sepsis-inducing circumstances, which alter hepatic circulation parameters, oxygen supply and inflammatory responses at the cellular level. Moreover, the liver **is an orchestrator of metabolic arrangements which promote the clearance and production of inflammatory mediators, the scavenging of bacteria, and the synthesis of acute-phase proteins. This balance defines the stage upon which the syndrome of "shock liver" develops.**

Ischemic hepatitis develops from shock and is characterised by elevated plasma aminotransferase concentrations. 'ICU jaundice' emerges later in critical illness, mainly in patients with trauma and sepsis. The commonly reported biochemical abnormality is conjugated hyperbilirubinaemia. The clinical setting suggests that hepatic ischemia and hepatotoxic actions of inflammatory mediators are the main aetiological factors. Cross-talk between hepatocytes, Kupffer cells and endothelial cells, leading to an inflammatory response mediated primarily by tumour necrosis factor-alpha, is pivotal for the development of liver injury at that stage.

Although determinations of aminotransferases, coagulation studies, glucose, lactate and bilirubin can detect hepatic injury, they only partially reflect the underlying pathophysiological mechanisms. Both the presence and degree of jaundice are associated with increased mortality in a number of non hepatic ICU diseases.

Therapeutic approaches to shock liver focus on the prevention of precipitating causes. Prompt resuscitation, definitive treatment of sepsis, meticulous supportive care, controlling of circulation parameters and metabolism, in addition to the cautious monitoring of therapeutic measures such as intravenous nutrition, mechanical ventilation and catecholamine administration reduce the incidence and severity of liver dysfunction. Only precocious measures can be taken to prevent hepatitis in ICU.

Key words: shock liver, hypoxic hepatitis, ischemic hepatitis, shock, multiple organs dysfunction.

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1. INTRODUCTION

''Shock liver" is a simplified term used to describe a complex critical ill patient's liver syndrome whose pathophysiology includes haemodynamic, cellular, immunological and molecular mechanisms. Different grades of shock liver affect about 50% of all intensive-care patients.[1] Although hepatic injury plays a significant role in the Intensive Care Unit (ICU) patients' morbidity and mortality, it is underdiagnosed.[2]

"Shock liver" is a consequences of shock- or sepsis-inducing circumstances. Liver dysfunction can also result from multiple organ dysfunction and acute respiratory distress syndrome or develop from myocardial dysfunction, immunosuppresion, metabolic disorders, infection from hepatitis virus and therapeutic measures such as blood transfusion, parenteral nutrition and drugs.[3]

"Shock liver" is, on that ground, a practical term used to describe a pool of critically ill patients in whom the elevation of liver function tests or overt hepatic dysfunction is apparent. In most cases liver dysfunction emerges without any noticeable changes in the patient's clinical profile. 'ICU jaundice' emerges later in critical illness, mainly in patients with trauma and sepsis, whereas the pivotal clinical case is that of mild elevation of liver enzymes. Clinical suspicion of liver complications mainly depends upon abnormal laboratory tests.

Hyperbilirubinaemia, an increase in serum transaminases, alkaline phosphatase, lactate dehydrogenase, and γ gloutamyl-transpeptidase and a decrease in albumin and coagulation factor levels are the pivotal laboratory parameters on which the diagnosis of hepatic dysfunction is based. Although these parameters lack sensitivity and specificity, they emerge as a result of hepatocellular or bile ducts injury, and consequently they are widely used to detect hepatic injury.[4] Differential diagnosis between hepatocellular and cholestatic injury relies on aminotransferase (transaminases) and alkaline phosphatase levels.[5,6,7] The incidence of liver dysfunction is underestimated when traditional "static" measures such as serum-transaminases or bilirubin as opposed to "dynamic" tests, such as clearance tests, are used to diagnose liver dysfunction. Dynamic tests, such as indocyanine green clearance, which is not available at the bed-side, are useful for the monitoring of perfusion and global liver function.[8] Finally, liver function is not affected by aging processes.[9]

2. HYPOXIC HEPATITIS

The liver benefits from double irrigation: one-third of the blood flow arising from the hepatic artery and two-thirds arise from the portal venous system. The portal venous system combines the effects of splanchnic vasoconstriction, bacterial translocation in the intestine, and mesenteric arterial supply with the portal perfusion. Yet, most of the regulation occurs at the level of the hepatic artery, which has been designated the hepatic artery buffer response. It is the inverse change of hepatic artery flow as a response to changes in portal venous blood flow that maintains a constant overall hepatic blood supply. Hepatic flow during shock situations is regulated by the hepatic artery buffer response, which is capable of ensuring hepatic blood flow by dilatation of the hepatic artery down to a systemic mean arterial pressure of 50 mmHg. When mesenteric and, consequently, portal venous blood flow decreases, hepatic arterial blood flow increases. The compensation of hepatic arterial blood flow for the decreased portal venous blood flow is in the range of 20–30%.[10,11,12] Compensation in terms of oxygen delivery is substantially higher because of the much greater oxygen content in the hepatic artery compared to the portal vein. Thus liver oxygen supply is maintained until blood loss exceeds 30%.[13] The hepatic artery buffer response is abolished early during endotoxaemia when gut blood flow decreases below a critical level and partially recovers after several hours.[14,15,16,17]

Regardless of the underlying mechanism, whenever hepatic microcirculation decreases below a critical threshold, cellular ischemia is induced, and this leads to hepatic injury and dysfunction. At the same time, the potent endothelin causes profound vasoconstriction in vascular beds, including those of the liver, and its actions are antagonised by the synthesis of nitric oxide (NO) by endothelial cells. NO acts as an inhibitor or agonist of cell signalling events in the liver. Constitutively generated, NO maintains the hepatic microcirculation and endothelial integrity, while inducible NO synthase (iNOS)-governing NO production can be either beneficial or detrimental. Whether NO protects or injures is probably determined by the type of insult, the abundance of reactive oxygen species, the source and amount of NO production, and the cellular redox status of liver.[18]

Sixty percent of the liver mass consists of hepatocytes, with the remaining liver mass is composed of Kupffer cells, endothelial sinusoidal cells (dependent upon the state of inflammation) and also neutrophils and mononuclear cells.

The centrilobular liver cell necrosis observed in hypoxic hepatitis is generally attributed to failure of hepatic blood perfusion. Impaired oxygen availability following hemorrhage in ICU promotes liver injury and contributes to delayed mortality.[19],[20] Prolonged low flow/hypoxia induces ATP depletion and pericentral necrosis and restoration of oxygen supply and ATP levels after shorter periods of low flow ischemia propagate programmed cell death or "pericentral apoptosis".[21] Accordingly, liver injury is commonly recognized under the terms "shock liver" or "ischemic hepatitis." In a recently documented study, 142 episodes of hypoxic hepatitis were identified and the role of the hemodynamic mechanisms of tissue hypoxia: ischemia, passive venous congestion, and hypoxemia were assessed.[22] Four different hemodynamic mechanisms responsible for hypoxic hepatitis were recognized: decompensated congestive heart failure (80 cases), acute cardiac failure (20 cases), exacerbated chronic respiratory failure (19 cases), and toxic/septic shock (19 cases). In congestive heart failure and acute heart failure, the hypoxia of the liver was attributed

to decreased hepatic blood flow (ischemia) due to left-sided heart failure and to venous congestion secondary to right-sided heart failure. In chronic respiratory failure, liver hypoxia was the result of profound hypoxemia. In toxic/septic shock, oxygen delivery to the liver was not decreased but oxygen needs were increased. In all conditions underlying hypoxic hepatitis, a shock state was observed in only about 50% of cases. Therefore, the expressions "shock liver" or "ischemic hepatitis" are misleading and should be replaced by the more general term "hypoxic hepatitis".

In most of cases hypoxic hepatitis emerges rapidly after the acute reduction in perfusion caused by shock, hemorrhage, resuscitation or low output septic shock. This rapid primary liver dysfunction is accompanied by high levels of hepatic enzymes and is restored within a few days.

3. SEPSIS

Sepsis is associated with hepatic ischemia and reperfusion injury.[23] Splanchnic blood flow, oxygen delivery and consumption are increased in both acute liver failure and sepsis. The capability of the liver to extract oxygen, even under extreme conditions, renders the liver less prone to hypoxia.[24] In sepsis patients with hyperdynamic circulation, hepatosplanchnic flow increases. Yet, splanchnic tissue oxygenation may be at risk in septic shock due to a major increase in metabolic demand, reflected by increased tissue oxygen consumption and impaired oxygen extraction.[25] Cytokine production and the diversion of oxygen to the generation of reactive oxygen species are both responsible for the increase in oxygen consumption. In addition, the regulation between arterial and venous flow is impaired in sepsis even though cardiac output is increased leading to increased liver blood flow. Adequate oxygen delivery to, and uptake by, the liver appears to be dependent on the oxygen saturation gradient between mixed venous and hepatic venous blood. While oxygen delivery is adequate in most septic patients, those with a high gradient between mixed venous and hepatic vein oxygen pressure exceeding 10% may not meet the actual hepatic oxygen demand and are at risk of hepatic injury. Also, in the intensive care mechanical ventilation, the increase in intrathoracic pressure additionally contributes to the reduction in hepatic flow. In conclusion, endotoxin-induced liver hypoxia relies on the balance of two different pathological issues: defective oxygen delivery versus oxygen consumption.[26] In practical terms hepatic microcirculation initially increases then decreases and the liver functions deteriorates gradually after sepsis is induced.[27]

In terms of cell dysfunction, liver in sepsis has two opposing roles: a source of inflammatory mediators and a target organ for the effects of the inflammatory mediators. The liver is pivotal in modulating the systemic response to severe infection[28] , because it contains the largest mass of macrophages (Kupffer cells) in the body. Activation of Kupffer cells by lipopolysaccharide (LPS) plays a pivotal role in the onset of pathophysiological events that occur during endotoxemia. Because these macrophages can clear the endotoxin and bacteria that initiate the systemic inflammatory response,[29] a reduction in Kupffer cell function may therefore lead to a spill over of bacteria and endotoxin, as well as inflammatory mediators, contributing to the development of an inflammatory response syndrome. In addition, pro-inflammatory mediators, including tumour necrosis factor-alpha (TNF-a), interleukin (IL)-1, IL-8, granulocyte-colony stimulating factor, IL-12, IL-18 and granulocyte-macrophage colony stimulating factor are produced by Kupffer cells. Those pro-inflammatory cytokines can be counteracted by the production of anti-inflammatory mediators, such as IL-4, IL-6, IL-10, transforming growth factor-beta, TNF soluble receptors, and IL-1 receptor antagonists. TNF is a potent endogenous regulator involved in anti-inflammatory responses which aims to maintain normal arterial pressure and protect liver tissue from pathological injury during endotoxin shock.[30] However, an increase in TNF-levels also leads to an increase of anticoagulant activity of endothelial cells, the activation of neutrophils, and (with interferon-gamma) an increase in expression of adhesion molecules. Hepatic injury is increased by the adhesion of neutrophils to the sinusoidal endothelial cells and the resulting radical oxygen species. Thalidomide prevents LPS-induced liver injury via mechanisms dependent on the suppression of TNF-alpha production from Kupffer cells.[31] The balance of the different actions initiated by Kupffer cells determines the severity of hepatic injury in shock situations.

The metabolic disorders documented in the hepatocytes of sepsis patients include alteration of the hepatic expression of inflammatory and acute-phase proteins.[32] Plasma concentrations of C-reactive protein, a-1 antitrypsin, fibrinogen, prothrombin, haptoglobin etc. are increased, while hepatic production of albumin, high-density lipoprotein, transferrin and antithrombin is impaired. The synergistic effects of TNF-, IL-1 and IL-6 appear to regulate this activity. In addition, glycogenolysis and gluconeogenesis are increased. Also the hepatic concentrations of ATP and NADH decrease and gut lactate production increases, but the liver can metabo-

lize this additional load of lactate, so that the hepatosplanchnic area is not a major source of lactate unless the liver becomes profoundly hypoxic.[33] Recent evidence suggests that sepsis may induce an uncoupling of oxidative phosphorylation.[34] In addition, biotransformation, which is found to be impaired during sepsis, leads to a reduced activity of cytochrome P450s and of the hepatobiliary transport rate and bile flow, which results in the impaired elimination of endobiotic and xenobiotic compounds. Endothelial cells can therefore contribute to the pro-inflammatory actions, although the elaboration of small amounts of NO has also been shown. NO may promote systemic antimicrobial activity by inhibiting leukocyte adhesion to hepatic endothelial cells and by reducing superoxide anions. Furthermore, findings of impaired oxygen utilization in septic patients and animals implicate NO-mediated inhibition of the mitochondrial respiratory chain.[35] On the other hand, the acute-phase response leads to considerable changes in the balance of coagulation factors, moving the balance towards coagulation. The increase in a_1-antitrypsin and a_2-macroglobulin inhibits protein C, whereas C4-binding protein, thrombin-activable fibrinolytic inhibitor and tissue factor expression are increased, lowering the levels of free protein S and the synthesis of antithrombin. Low-level synthesis of antithrombin also contributes to procoagulatory activity and is associated with a higher rate of fatal outcome of hepatic injury.

Sepsis commonly emerges with hyperbilirubinaemia and mild elevation of transaminase.[36] A disproportinal increase of bilirubin is found when renal failure, sickle cell anemia or haemolysis (such as in G6PD deficiency) coexist. Aminotransferase elevations are documented in acute and chronic hepatitis, suggesting a possible hepatocellular-cytolytic mechanism. Yet aminotransferase also increase in extrahepatic diseases reported in ICU, including injuries, myositis, thermal injury, rabdomyolysis (differential diagnosis is based on the documented increase in CPK, LDH, and aldolase levels), leukemia, rhabdomyolysis, pancreatitis, etc.[37,38] In those cases, the pivotal increase is that of AST, whereas in hepatocellular injury the increase in ALT is the outstanding laboratory measurement. In cardiac infarction the increase in ALT is attributed to hepatic hypoxia 39 and the increase in transaminase levels does not imply a cytolytic mechanism, but accompanies the formation of immunoglobulin-complexes which are not being metabolized. 40,41 Furthermore, serum should be separated immediately from blood samples to avoid haemolysis. The abnormal hepatic profile is expected to develop within the first 6-8 days after respiratory failure or major surgery. It can also occur even over one week after the onset of septic shock in patients without preexisting liver dysfunction.[42,90] In most cases alteration in the above enzymes goes unnoticed, reducing the awareness of hepatic injury whereas the alteration in prothrombin time without hyperbilirubinaemia may be an indicator of liver dysfunction.[43,44] Several screening tests have been modified in order to quantify liver injury including AST and bilirubin,[90] jaundice, bilirubin and prothrombin time,[92] LDH, AST and bilirubin. Those screening tests are inappropriate for patients with preexisting decompensated cirrhosis. In those patients a mortality of 100% is reported.[45,46]

Patients with sclerosing cholangitis, following septic shock, represent a new variant of vanishing bile duct disorders. In such patients liver disease rapidly progresses to cirrhosis.[47]

4. SURGERY

Jaundice after surgery is documented in approximately 1% of operations in non-cirrhotic patients and it restores automatically within a few days. Its underlying aetiology includes blood transfusions, haematomas, G6PD deficiency, sickle cell anemia, infection and Gilbert syndrome, causing increase of unconjugated bilirubin without increase of transaminase or ALP. Elevation in conjugated bilirubin and in transaminase levels >than 5-fold inflect hepatocellular injury present in hepatic hypoxia, drug induced hepatitis and viral hepatitis. If the increase in conjugated bilirubin is accompanied by increase of ALP, cholestasis of several causes is implied (sepsis, total parenteral nutrition, trauma, Mirrizzi syndrome, chololithiasis, pancreatitis). Differential diagnosis between intra- or extra- hepatic cholestasis cannot be assessed only with those enzymes and ultrasonography is recommended. During the first post-surgical week (usually during the second day), jaundice of intrahepatic obstruction develops, peaking on the 4-10th day (serum bilirubin 24-40 mg/dl) and diminishing in 14-18 days.

5. MYOCARDIAL DYSFUNCTION

Liver dysfunction frequently accompanies heart diseases such as pericarditis, acute myocardial infarction and heart failure, presenting in patients admitted to the coronary care unit and resulting in low cardiac output.

In patients suffering from congestive cardiac failure, liver dysfunction is associated with a decrease in cardiac

supply and passive hepatic venous congestion. Symptoms of liver disease may include right upper quadrant pain, encephalopathy and hypoglycaemia. The liver is enlarged and tender when palpated in 95-99% of cases, splenomegaly is documented in 20-80%, ascites consisting of high quantities of leukoma (> 3 gr/dl) is present in 25% of patients, and jaundice is involved in the clinical manifestation in 20% of all cases reported. Liver abnormalities may be typical of hepatic congestion with disproportionate elevation of bilirubin (up to 10-fold) in 25-80% of cases, and prothrombin time (2 to 6 seconds) in 80-90%. Yet, modest aminotransferase elevations (less than threefold) are reported in 30-60% of patients. Mild elevations of LDH and γGT are present in 30-60%, and decrease in immunoglobulin IgG is documented in 50% of patients.

Differential diagnosis of jaundice in patients with cardiac failure involve, for example, sepsis, haemolysis, gallbladder obstruction, pulmonary embolism, liver congestion-low blood flow and drugs. Ultrasonographic examination is usually reliable in differentiating the underlying pathological feature through the recognition of dilated intrahepatic venous system and post-cava.

Hypoxic hepatitis develops from systemic hypotension after an episode of cardiac arrest or arrhythmia, emerging as a striking elevation in liver function tests.[48] Severe acute rises of transaminase levels (>1000 iu/l), accompanied by similar elevation of lactate dehydrogenase (ALT/LDH <1,5), and a mild increase in bilirubin and alkaline phosphatase are documented. Differential diagnosis includes acute virus hepatitis and drug induced hepatitis. Recovery is usually rapid and complete within a week if the hemodynamic abnormalities are corrected. The histological picture is that of periportal zonal necrosis and the clinical presentation is that of cardiac failure with high rates of mortality (60%).[49] Whenever chronic congestive cardiac failure preexists a new episode of hypotension may cause fulminant liver failure.

In constrictive pericarditis, problems of differential diagnosis arise while splenomegaly, ascites, and hepatomegaly are common clinical features also developing in Badd-Chiari syndrome and cirrhosis.[50] The typical physical examination reveals jugular venous distention, hepatojugular reflux, pulsus paradoxus and Kussmaul's sign, all symptoms indicating cardiac tamponade.

Liver complications may also develop after cardiopulmonary bypass surgery and the timing of the onset of jaundice with that of surgery helps the differential diagnosis. In practical terms, during the first week after heart surgery, jaundice develops in approximately 20% of patients, usually during the 2nd post-surgery day, maximizes in 4-10 days (24-40 mg/dl) and diminishes in 14-18 days. Its prognosis is poor.[51] Intrahepatic cholestasis is responsible for the elevation of bilirubin whilst transaminases increase extensively and alkaline phosphatase remains normal.[52] The elderly seem to be more susceptible developing post surgical jaundice whilst other factors synergistically contributing are the number of valves replaced, the number of blood transfusions, preexisting chronic hepatic congestion, low blood supply, surgical hypothermia, sepsis, haemolysis, renal failure and the absorption of haematomas. Drug or virus-induced hepatitis should be excluded. On the other hand, jaundice developing on the 2nd or 3rd post surgical week is attributed to acute hepatitis from Cytomegalovirus (CMV), and, rarely, Hepatitis C Virus (HCV) or Hepatitis B Virus (HBV) infection. It is accompanied by a severe increase in transaminase levels and should be differentiated from drug-or heart induced hepatitis.

6. ADULTS RESPIRATORY DISTRESS SYNDROME

Both post-traumatic respiratory failure and acute respiratory distress syndrome have been associated with liver dysfunction. The impact of hepatic dysfunction is less obvious than that of pulmonary failure (prolonged mechanical ventilation) but it has been estimated that the presence of hepatic injury significally alters outcome by contributing to increased intensive care unit length of stay and mortality in patients with acute respiratory distress syndrome and in critically ill adults.[53, 54, 55]

7. TRAUMA

Posttraumatic liver failure is a rather sinister complication developing in ICU associated with a mortality of 15 to 50%. Reduction of liver perfusion due to hypotension, catecholamines or increased intraabdominal pressure, parenteral nutrition, endotoxemia, and potentially hepatotoxic drugs contribute to the development of hepatic injury. The Child classification and the APACHE score may predict prognosis before surgery and serum bilirubin levels thereafter. It is desirable to quantify hepatic injury to allow for an assessment of prognosis and therapeutic intervention such as an aggressive medical and surgical approach mainly aiming at the prevention of tissue hypoxia.[56] Trauma patients who develop hepatic dysfunction are older, more severely injured,

more frequently in shock, and require more blood transfusions.

8. VIRAL HEPATITIS INFECTION

There is inadequate documented data regarding the potential danger for the transmission of hepatitis virus in the ICU and its contribution to the remodelling of the mortality rates in the critically ill patients. Length of stay, number of blood transfusions, number of re-surgery, inadequate hygienic and isolation practices (including hand washing, subsequent oral contamination and food contamination) are recognized as potential risk factors.

A nosocomial outbreak of hepatitis A is a potential danger in the ICU environment, mainly due to the inadequate administration of immunoglobulin among health care workers. Up to one third of community acquired cases of hepatitis A have been linked to day-care centres.[57] The majority of HAV outbreaks reported in the literature involve exposure to thermally injured patients, multi-traumatized patients and infants from a neonatal intensive care unit.[58] In each case the time of exposure to the asymptomatic carrier who silently transmitted the virus in the preclinical phase of the disease determines the acquisition rates (dose-response relationship). Problems identified upon reviewing the reported cases of hepatitis A outbreak were inadequate terminal cleaning of equipment (abstersion of the endoscopes is achieved with gloutaraldehyde 2%, while commonly used equipment is disinfected by heating 75^0 C for 20 minutes or the use of formaldehyde[59]), food consumption in the ICU and inadequate hand-washing practices. Implementation and maintenance of standard infection control practices is vital if further outbreaks of hospital-acquired hepatitis A and other enteric infections are to be avoided.[60] Blood products and fresh frozen plasma transfusions have also been identified as potential risk factors.[61] Self-reported data indicates non-routine hand washing by approximately 25% of health care workers, non-routine use of gloves by 37% and conservative estimates of compliance with standard hygienic procedures.

Concerning HBV infection, its prevalence among health care workers has decreased, mainly due to the establishment of vaccination practices.[62,63] In the ICU environment it is estimated that the danger of transmission from chronic carriers is small, on the ground that infection control practices are applied and there is no contact between patients and doctors or nurses with acute HBV infection. In China a decrease in the prevalence of HBV infection was reported from 20,9% to 3,3% after the implementation of single-use syringes and needles[65] without any documented change in the probability of parturient transmission of the disease.

Precautionary measures include single-use devices, and use of gloves, while in high risk departments such as operating theatres, labs and haemodialysis units smoking and consumption of food should also be avoided. Among 246 documented cases of patients initially exposed 483 times to 9 HBsAg positive staff member (doctors or nurses) not a single incident of HBV transmission has been reported, and the relative danger of transmission has been estimated to be <1%.[65] Yet the implementation of extensive vaccination practises is necessary due to the fact that the danger transmission is 5-10 times higher in health care centres in comparison to the general population. Disinfection of equipment is accomplished by heating at 100^0C for 10 minutes, with formalin 20% in 70% alcohol, with 2% alkaline gloutaraldeyde and finally standard infection control practices include hand washing for >3 minutes followed by the use of a decontaminant for 2 minutes.[65]

Multi-traumatized patients who are submitted to multiple surgery and blood transfusions are the target group as far as HCV infection is concerned. 3-4 cases of infected blood samples per 10000 transfused blood units are reported.[65, 64] On that ground, the implementation of restrictive indications for transfusion, the use of autologic blood products, and the serological screening of all blood samples are considered adequate precautions. Disinfection can be achieved with the same practices used for HBV virus with formalin or chloroform.

The prevalence of HCV infection in ICU health care workers was estimated in a recently conducted survey and according to the conclusions, among the 874 participants 19 (2%) were HCV positive diagnosed by enzyme immunoflorescence (ELISA). In 14 (1,6%) of them the diagnosis was further established by recombinant immunoblotting technique (RIBA) and in 11 cases viraemia was confirmed by polymerase chain reaction (PCR). Furthermore, in 7 [50%] of the diagnosed cases, a contact with an HCV positive patient was self-reported. Finally, 10 people [1,1 %] had no other potential risk factor.[65] In another study in ICU 0,9% (4 out of 416 participants) were HCV positive while the identical percent in the control group was 1,6%.[66] On a similar study conducted in Peru, where 2769 health care workers were serologically tested 32 (1,16%) HCV positive samples were confirmed.[67] Finally, from a series of multi-transfusioned patients a percentage of 8,3% was found positive for HCV after serological screening, a percentage

that is 10-fold higher than that of the control group.[65]

9. THERAPY INDUCED LIVER DISEASES

Surgical, medical and nursing procedures in critically ill patients may also interfere with the ability to maintain adequate liver function. Implementation of drugs, blood transfusions, haemodialysis, parenteral nutrition, immunosuppressive factors, and changes in metabolic parameters synergetically cause hepatic injury.

Liver disease emerging as cholestasis ranging in severity from mild increases in plasma conjugated bilirubin to progressive liver failure that results in the death of the patient is relatively common during parenteral nutrition. Elevation of transaminase and alkaline phosphatase levels are expected to restore within 20 days. When the liver is enlarged and tender, fatty filtration of the liver should be suspected. A physician should also expect complications from the bile duct. Severity of liver disease depends primarily on the magnitude of the underlying intestinal problem that indicated parenteral nutrition. Transient ileus resulting from a non-intestinal disorder usually results in trivial, self-limiting liver injury. Removal of a large segment of the intestinal tract because of necrotizing enterocolitis or a congenital malformation predicts a more prolonged course with a guarded prognosis, particularly when initially complicated by sepsis.[68]

Haemodialysis with ultra-filtration has been recently associated with a significant reduction in systemic, splanchnic and femoral blood flows responsible for hepatic hypoxia.[69]

Polypharmacy and alterations in drug disposition are common in the ICU whilst critically ill patients have limited physiologic reserves to deal with adverse drug events.[70] Drug-induced hepatitis in ICU is attributed to antimicrobial agents, antitubercular drugs,[71] nonsteroidal antiinflammatrory drugs, antiepileptic and suppressive drugs, inotropic and other cardiac drugs. Cardiac drugs are associated with multiple types of hepatic injury due to the changes they cause to systemic arterial blood flow, including granulomatous hepatitis (quinidine, methyldopa, hydralazine), fibrosis (amiodarone), acute hepatitis (amiodarone, berapamil, diltiazem, lavetalol, atenolol, propranolol, lisinopril, enalapril, captopril, quinidin, hydralazine), chronic hepatitis (methyldopa, statines), cholestasis (nifedipin, chlorothalidon, disopyramide, ouarfarin) or mixed changes (ticlodipin, procainamide). Among the antimicrobial agents erythromycin, clindamycin, soulfonamides, oxacillin, amfotericin B[72], ketoconazol and nitrofourantoin have been identified as potential causes of hepatitis. Mixed cholestatic-hepatocellular type of hepatic injury has been associated with phenytoin, halothane, cyclopropane, and chloroform. Finally, a case of acute hepatic steatosis due to excessive administration of glucose in the setting of massive insulin overdose (usually on the ground of hypoglycaemic shock) has been reported.[73] This complication is completely reversible if glucose infusion is rapidly tapered.

10. TREATMENT

The disturbance of some liver functions, such as synthesis, excretion, or biotransformation of xenobiotics, are important for prognosis and ultimate survival in patients presenting with multiple organ dysfunction on ICU. Although many important aspects of hepatic function may be difficult to measure clinically and dysfunction of other organ systems including lung and kidney has a more visible impact on the patients clinical profile, liver injury has also been proved to independently contribute to mortality rates and determine length of ICU stay.[74]

Therapeutic measures are aimed at a speedy elimination of the precipitating events leading to shock liver. Stabilization of infectious and circulation parameters, monitoring of mechanical ventilation, administration of catecholamines, and metabolic monitoring are included in our therapeutic strategy.

Recently, the haemodynamic effects of fenoldopam (a dopamine-1 receptor agonist) were investigated before and after induction of splanchnic ischaemia by haemorrhage.[75] After haemorrhage, this drug restored portal vein blood flow to near baseline, maintained the splanchnic fraction of cardiac output, and attenuated the rise in gut mucosal partial carbon dioxide tension. Fenoldopam also redistributed the blood flow away from the serosal to the mucosal layer both at baseline and during haemorrhage. Dopamine is used to support cardiac output and blood pressure in patients with cardiac failure and septic shock.[76],[77] Small doses of dobutamine seem to restore gut mucosal perfusion and improve hepatic arterial blood flow in those circumstances. Yet total hepato-splanchnic blood flow cannot be maintained with either dobutamine or dopamine. A decrease in splanchnic oxygen consumption during dopamine infusion has recently been reported in patients with acute hepatic failure.[78] A reduction in hepato-splanchnic oxygen uptake despite increased perfusion may indicate blood flow redistribution. Alternatively, some metabolic functions of the hepato-splanchnic region may have been impaired. Dopamine may directly inhibit isoenzymes of the cytochrome P450

complex.[79] The different effects of dopamine infusion on splanchnic oxygen consumption in the two patient groups could possibly be explained by different baseline activities of P450 isoenzymes. The indications and safety of dopamine in sepsis should therefore be re-evaluated. Finally, supraphysiological doses of corticosteroids reduce norepinephrine requirements in hypotensive liver failure. They do not improve survival but may buy time to find a suitable donor in those awaiting urgent liver transplantation.[80]

Administration of N-acetylcysteine,[81] albumin dialysis and application of Molecular Adsorbents Recirculating System (MARS) are modern therapeutic approaches liver failure. MARS utilises selective hemodiafiltration with countercurrent albumin dialysis aiming to selectively remove both water-soluble and albumin-bound toxins of the low and middle molecular-weight range. It helps as a bridge to liver transplantation.[82,83] In a recent survey postburn treatment with the vasodilator prostacyclin was assessed with beneficial results for hepatic perfusion and oxygenation during the late postburn endotoxic phase.[84] Nevertheless, liver transplantation remains the treatment of choice for fulminant hepatic failure when expected survival is $<20\%$.[85]

11. CONCLUSIONS

The liver is a victim of shock inducers, and can also be the orchestrator of the inflammatory response syndrome. Synthetic activity, biliary transport, bile flow and glucose metabolism are all impaired due to major hepatocellular injury. Massive blood transfusion, effects of nutritional support, immunosuppression, metabolic abnormalities, impaired drug oxidation and myocardial dysfunction may contribute to the poor prognosis

Hepatic injury in ICU can emerge either as a rapid primary episode caused by an acute reduction in perfusion after shock, hemorrhage, resuscitation or low output septic shock, or as a late-onset form of hepatic injury emerging secondarily to multiple septic episodes and medical treatment strategies. The rapid primary liver dysfunction is accompanied by high levels of hepatic enzymes and is restored within a few days. In late-onset liver injury lower elevations of serum liver enzymes or of serum bilirubin levers are documented reflecting the hepatotoxic action of inflammatory mediators. Both the presence and degree of jaundice are associated with increased mortality and length of stay in ICU.

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