INTENSIVE CARE MANAGEMENT OF PATIENTS WITH LIVER DISEASE: proceedings of a single-topic conference sponsored by the Brazilian Society of Hepatology

Paulo Lisboa BITTENCOURT1,2, Carlos TERRA3, Edison Roberto PARISE4, Alberto Queiroz FARIAS5 and Members of the Panel in the 1st Single-Topic Conference of Intensive Care Management of Patients with Liver Disease*

ABSTRACT – Survival rates of critically ill patients with liver disease has sharply increased in recent years due to several improvements in the management of decompensated cirrhosis and acute liver failure. This is ascribed to the incorporation of evidence-based strategies from clinical trials aiming to reduce mortality. In order to discuss the cutting-edge evidence regarding critical care of patients with liver disease, a joint single topic conference was recently sponsored by the Brazilian Society of Hepatology in cooperation with the Brazilian Society of Intensive Care Medicine and the Brazilian Association for Organ Transplantation. This paper summarizes the proceedings of the aforementioned meeting and it is intended to guide intensive care physicians, gastroenterologists and hepatologists in the care management of patients with liver disease.


INTRODUCTION

The mortality rate of patients with cirrhosis admitted to an intensive care unit (ICU) due to organ dysfunction ranges from 34% to 69% depending on the reason for admission, the presence of organ failure (OF) and the severity of the underlying liver disease. Over the last ten years it has markedly decreased from around 90%-100% to 41%-50% in some reports(25, 74).

Besides well-recognized complications of chronic liver disease, such as ascites, infections, variceal bleeding (VB) and hepatic encephalopathy (HE), intensive care physicians now face different clinical scenarios. These include acute-on-chronic liver failure (ACLF), VB with requirement for early transjugular intrahepatic portacaval shunt (TIPS) placement and nosocomial and health-care associated (HCA) infections, particularly spontaneous bacterial peritonitis (SBP) due to multiresistant bacteria(26, 53, 73).

Management of decompensated cirrhosis in ICU has changed due to the emergence of new evidence-based treatments associated with improved survival, tailoring of intensive care measures, availability of artificial and bioartificial liver support systems, as well as the widespread use of liver transplantation (LT) for critically-ill patients, due to the MELD allocation policy, which is based on severity of liver disease(13, 62, 74).

In order to discuss recent advances in this emerging field, the Brazilian Society of Hepatology in cooperation with the Brazilian Society of Intensive Care Medicine and the Brazilian Association for Organ Transplantation sponsored a joint single-topic conference on the critical care management of patients with liver disease, which was held in Rio de Janeiro on May 5th 2014.

This paper summarizes the proceedings of the aforementioned meeting and it is intended to guide intensive care physicians, gastroenterologists and hepatologists in the care management of patients with liver disease.

*Correspondence: Paulo Lisboa Bittencourt. Rua Prof. Clementino Fraga, 220, 1901 – CEP: 40170-050 – Salvador, BA, Brasil. E-mail: plbbr@uol.com.br

declared conflict of interest of all authors: none
Disclosure of funding: no funding received
1 Hospital Português, Salvador, BA; 2 Hospital Universitário Professor Edgard Santos, Universidade Federal da Bahia, Salvador, BA; 3 Hospital Universitário Pedro Ernesto, Universidade do Estado do Rio de Janeiro, RJ; 4 Universidade Federal de São Paulo, SP; 5 Departamento de Gastroentrelologia da Faculdade de Medicina da Universidade de São Paulo, SP; 6 Liver Unit, IMDD, Hospital Clinic, Universidade de Barcelona, IDIBAPS and CIBERehd, 7 Departamento de Gastroenterologia, Hospital Federal do Bonsucesso, Rio de Janeiro, RJ; 8 Universidade Federal de Ciências da Saúde de Porto Alegre e Unidade da Santa Casa de Misericórdia de Porto Alegre, RS.
PART I. MANAGEMENT AND TREATMENT OF PATIENTS WITH CIRRHOSIS IN THE ICU

1) Hyponatremia

Clinically relevant hyponatremia in cirrhosis is defined as a reduction in serum sodium to below 130 mmol/L(4, 3, 44). Recent studies have shown that hyponatremia is an important prognostic marker both before and after liver transplantation (LT)(50, 54, 67). Moreover, hyponatremia has gained attention because of the discovery of the vaptans, which improve solute-free water excretion by counteracting the effects of arginine vasopressin (AVP) in the renal tubules(85). These drugs are currently being assessed for the management of hyponatremia associated with cardiac failure, inappropriate antidiuretic hormone secretion as well as cirrhosis. In clinical practice, hyponatremia is classified into three types: hypovolemic, euovolemic and hypervolemic, with some patients exhibiting a mixture of conditions.

With the exception of a few circumstances of hyponatremia with hypovolemia due to diuretic use or gastrointestinal losses, most of the cases of hyponatremia in cirrhosis result from increased extracellular fluid volume (dilutional hyponatremia)(44). Conditions such as hypotonic fluid administration, heart failure and renal failure frequently seen in the ICUs should be ruled out in the differential diagnosis of dilutional hyponatremia. In cirrhosis, total body water is increased, yet effective arterial volume is decreased ("relative central hypovolemia"). The reduction in effective arterial volume is a consequence of the increased intrahepatic resistance and splanchnic arterial vasodilatation, which is caused by the excessive release of nitric oxide and other compounds such as endotoxin, substance P and endocannabinoids. This process leads to sodium avidity in the proximal portion of the nephron, by activation of the renin-angiotensinaldosterone axis and excessive ADH-mediated free water reabsorption in the collecting tubule.

Arterial baroreceptors, found in the left ventricle and the carotid sinus, have been shown to be a potent regulator of ADH secretion. Their activation counteracts the suppressive effects of hypoosmolality.

In patients with cirrhosis and ascites, the non-osmotic release of ADH from the posterior pituitary becomes the dominant force of water retention, resulting in impaired free water excretion and dilutional hyponatremia(44).

The action of ADH on the kidney occurs predominantly in the principle cells of the collecting tubule. The stimulation of the vasopressin receptor, V2, by ADH leads to downstream activation of a cyclic AMP-based pathway and subsequent up-regulation of the aquaporin channel AQP2 in the apical membrane of the principle cell. This allows the free flow of water from the tubular fluid back into circulation(85).

Low serum sodium levels (<135 mmol/L) are prevalent in both inpatients and outpatients, and are associated with severe ascites, frequent use of large-volume paracentesis, impaired renal function, higher frequencies of HE, SBP, hepatorenal syndrome (HRS), higher rates of in-hospital mortality and poor short-term prognosis(44).

Several lines of evidence show that serum sodium concentration is an independent predictor of survival among liver transplantation candidates(50, 54, 67).

In cases of hyponatremia, water moves into the cells to maintain the osmotic balance, causing cell swelling. Increases of cell volume are particularly important in the brain, as the skull restricts brain enlargement. For this reason, brain cells have defensive mechanisms to limit cerebral edema, which is the extrusion of intracellular solutes to decrease intracellular osmolality, until it matches that of plasma. In the early stages of the development of hyponatremia, there is a rapid loss of intracellular electrolytes, particularly potassium, usually within the first 24 hours. Subsequently, there is a loss of low-molecular weight organic compounds, known as organic osmolytes, including myoinositol, glutamine, choline, and taurine.

The combined losses of both electrolytes and organic osmolytes from the brain cells enable effective regulation of brain volume during hyponatremia. The effectiveness of this mechanism in preventing lethal edema depends, among other factors, on the severity of hyponatremia and rate of reduction of the serum sodium concentration. Adaptation is more efficient in chronic hyponatremia than in acute hyponatremia.

There is evidence that such cerebral adaptation to hyponatremia is also present in cirrhosis. Of similar importance to the central nervous system are the changes that occur after recovery of hyponatremia. When the serum sodium concentration returns to normal, there is restoration of electrolyte and osmolyte levels in brain cells; electrolytes are restored quickly, whereas correction of organic osmolytes is slow, particularly if the duration of hyponatremia has been long. This is a major clinical concern because rapid correction of hyponatremia may lead to severe brain damage, because of a lack of adequate brain adaptation to the normalized osmolality of the extracellular fluid. This is known as osmotic demyelination syndrome(50).

Studies specifically assessing neurological symptoms in cirrhosis with hyponatremia are lacking. However, the clinical experience indicates that significant neurological manifestations such as headache, focal motor deficits, seizures, and cerebral herniation are very uncommon. It is likely that the relatively low incidence of neurological manifestations of hypervolemic hyponatremia in patients with cirrhosis is related to the fact that in most patients hyponatremia is chronic rather than acute. This allows sufficient time for the brain to adjust to the hypo-osmolality of the extracellular fluid.

Apart from hyponatremia, it is believed that low-grade cerebral edema is one of the factors leading to HE, as discussed in section 5 of this manuscript. In patients with HE and low-grade cerebral edema, hyponatremia may represent a second osmotic hit to astrocytes, causing further depletion of osmotic counteractive systems. In this situation, cells would probably not tolerate additional changes in volume, and HE would develop or persist even in the absence of any stimuli(50).

Patients with cirrhosis have a 1% to 10% risk of developing central pontine myelinolysis after LT. Higher frequencies (5% - 25%) are demonstrated in hyponatremic transplant recipients.
Hyponatremia before LT has also been associated with an increased risk of renal failure and infectious complications, higher use of blood products, longer duration of hospital stay, and, most importantly, increased short-term mortality rates after LT(50, 54, 67).

Conventional treatment of ascites in cirrhosis includes sodium restriction, diuretic therapy, and large-volume paracentesis. Fluid restriction in combination with orally administered aldosterone antagonists and loop diuretics is currently the primary approach for treatment of hypervolemic hyponatremia in cirrhosis.

However, in recent years, a number of vasopressin receptor antagonist agents, which inhibit the effects of AVP and increase free water excretion, have been assessed for treatment of hyponatremia in cirrhosis(7, 35). The oral selective vasopressin V2-receptor antagonist tolvaptan is approved for treating hypervolemic and euvolemic hyponatremia, including that caused by cirrhosis. It has proved to be effective, safe, and improves short-term quality of life (one month) in cirrhosis.

However, there are no long-term data on efficacy and safety, nor are there data on other outcomes such as HE or survival. Tolvaptan is a high cost drug, approved in USA for the management severe hypervolemic hyponatremia (<125 mmol/L) in cirrhosis, cardiac failure and SIADH, while in Europe it is approved only for the management of SIADH(85).

Patients who can benefit the most from treatment with tolvaptan are those with severe hyponatremia awaiting liver transplantation. Treatment with tolvaptan should be started in the hospital with low doses and serum sodium should be closely monitored to avoid rapid correction of hyponatremia to less than 10 mmol/day. This is relevant because patients with very low sodium concentration are at greatest risk of neurological complications. Patients with type-1 hepatorenal syndrome and hyponatremia should be treated with terlipressin or other vasoconstrictors and albumin(85).

2) Circulatory failure

Diuretics, antibiotics, and human serum albumin (HSA) are the most frequently used treatments for the management of patients with cirrhosis. According to the CANONIC study database(71), a prospective European investigation of 1348 patients with decompensated cirrhosis, HSA was prescribed for 60% of the patients during hospital admission. Prevention of paracentesis-induced circulatory dysfunction, prevention of type-1 HRS associated with bacterial infections and treatment of type-1 HRS are the main intended aims of therapy(78, 79). In these cases, treatment with HSA is associated with improved survival(88).

 Decompensated cirrhosis is a condition associated with systemic inflammation, which plays an important role in the pathogenesis of organ failure. Although, the beneficial effects of HSA have been traditionally attributed to plasma volume expansion, they could also relate to its effects modulating systemic and organ inflammation(35).

Three major features characterize decompensated cirrhosis. The first is multi-organ dysfunction. The second is a systemic inflammatory reaction with increased plasma and ascitic fluid concentration of cytokines and C-reactive protein (CRP). The third is an increased systemic oxidative stress with high levels of oxidized HSA and other markers of oxidative stress(7). Systemic inflammation, oxidative stress, and organ dysfunction are moderate in patients with decompensated cirrhosis and severe in patients with acute-on-chronic liver failure (ACLF)(71). Translocation of bacterial products (i.e., lipopolysaccharide, bacterial DNA) or of viable organisms from the intestinal lumen to the circulation due to quantitative and qualitative changes in gut microbiota, impairment in intestinal mucosal barrier, increased epithelial permeability, and impaired intestinal immunity are important mechanisms of systemic inflammation in cirrhosis(7). Systemic inflammatory response can be triggered by bacterial antigens (Pathogens-Associated Molecular Patterns, PAMPs) or by intrinsic factors released into the circulation as a result of trauma or cell injury (Damaged Associated Molecular Patterns, DAMPs). Specialized receptors of the innate immune system recognize these factors and release inflammatory mediators such as cytokines, and reactive oxygen (ROS) and nitrogen species (RNS). However, systemic inflammation may also occur in response to acute liver damage (i.e., acute alcoholic hepatitis) or other mechanisms(7). Close interactions exist between bacterial translocation, local inflammation, and cardiovascular dysfunction in decompensated cirrhosis. Activation of the intestinal immune system by bacterial translocation causes local release of NO and other vasodilators, leading to the characteristic hyperdynamic circulation of cirrhosis.

At more advanced stages, there is effective hypovolemia, activation of the renin-angiotensin system (RAS), sympathetic nervous system (SNS), antidiuretic hormone (ADH) and asces formation. The activated sympathetic nervous system induces changes in the gut microbiota and impairs intestinal immunity, thus producing a vicious circle promoting the progression of cardiovascular dysfunction(7). A slow but progressive impairment of left ventricular function and cardiac output also develops in decompensated cirrhosis and contributes to circulatory dysfunction. Recent experimental data suggest that impairment in cardiac function in cirrhosis is related to inflammation, tumor-necrosis factor alpha (TNF-alpha)-related activation of inducible NO-synthase and oxidative stress in cardiac tissue(87). ACLF is characterized by acute organ failure(s) (liver, renal, brain, coagulation, circulation, and respiration) in patients with compensated or decompensated cirrhosis. ACLF develops in the setting of severe systemic inflammatory reaction due to bacterial infection, acute alcoholic hepatitis or other precipitating factors. The frequency of organ failure correlates directly with the degree of systemic inflammation(71). Therefore, whereas systemic inflammation is chronic and moderate in decompensated cirrhosis, it is acute and severe in ACLF. The mechanism of organ failure in ACLF is complex. Acute impairment in cardiovascular function leading to intense organ hypoperfusion is a major characteristic. However recent studies in sepsis suggest the contribution of the extension
of systemic inflammation to organs, leading to abnormal distribution of blood-flow within the microcirculation and cell dysfunction related to mitochondrial oxidative stress \(^{7, 71}\). Bacterial infection is a frequent precipitating factor of HE. Peripheral inflammation may affect cerebral function through afferent vagal nerves activated by cytokines at the site of inflammation, by lipopolysaccharide or cytokines which interact with the brain in areas lacking the blood-brain-barrier or by diffusion to the brain of endothelial mediators. Activation of microglia and synthesis of pro-inflammatory cytokines in the brain have also been demonstrated in experimental models of liver failure. Circulatory dysfunction in patients with systemic inflammation reduces brain perfusion. Systemic inflammation increases the inhibitory effect of ammonia in brain function. There are marked differences in HE between patients with decompensated cirrhosis and patients with ACLF. In the first group HE is of low severity and diuretics are the most common precipitating cause. By contrast, HE in ACLF is severe and bacterial infection or acute liver injury are the main precipitating factors. Organ dysfunction in cirrhosis therefore varies according to the mechanism and degree of systemic inflammation \(^{7, 24, 71}\).

Considering the potential role of systemic inflammation in cirrhosis and the effect of HSA in innate immune response and oxidative stress, it is reasonable to suggest that some effects of HSA (prevention and treatment of type-1 HRS, treatment of SBP) might be related to these properties \(^{7}\). In patients with cirrhosis and SBP, treatment with intravenous albumin in addition to an antibiotic reduces the incidence of renal impairment and mortality in comparison to treatment with an antibiotic alone \(^{80}\). It is known that in patients with HRS type 1, the association of albumin with analogues of vasopressin improves renal function and survival \(^{108, 81}\). In this regard, albumin infusion was reported to be superior to hydroxyethyl starch in improving hemodynamics, including left ventricular function, cardiac output, and peripheral vascular resistance in patients with SBP without complications \(^{89}\).

Circulatory dysfunction in cirrhosis is related to systemic inflammation leading to arterial vasodilation and impairment of left ventricular function. The differences in circulatory dysfunction between patients with type-1 HRS and those with decompensated cirrhosis and/or type-2 HRS are related to differences in time-course and grade of systemic inflammation. In type-1 HRS, systemic inflammation is acute and severe. In decompensated cirrhosis and/or type-2 HRS it is moderate and prolonged. Albumin is probably effective in the prevention and treatment of HRS by regulating the systemic inflammatory reaction \(^{7}\).

### 3) Renal failure and hepatorenal failure

Renal failure (RF) is seen in 39% to 49% of the patients with cirrhosis admitted to the ICU \(^{19, 23}\). The most common causes of RF are hypovolemia, bacterial infection, parenchymal kidney disease and hepatorenal syndrome (HRS). They are identified as causes of RF in 40%, 32%, 15% and 12% of the cases, respectively \(^{19}\). Hepatorenal syndrome is usually seen in patients with advanced cirrhosis and ascites. It is characterized by an intense renal vasconstriction, which leads to very low renal perfusion and glomerular filtration rate (GFR) \(^{46, 80}\). The development of portal hypertension in cirrhosis is associated with arterial vasodilation in the splanchnic circulation due to the local release of nitric oxide and other vasodilatory substances. These circulatory changes induce arterial hypotension that is compensated by the development of a hyperdynamic circulation (increased heart rate and cardiac output). As the disease progresses, arterial vasodilation increases, leading to activation of high pressure baroreceptors, reflex stimulation of the renin-angiotensin and sympathetic nervous systems, increase in arterial pressure to normal or near normal levels, sodium and water retention and ascites formation. Splanchnic circulation is resistant to the effect of angiotensin-II, noradrenaline and vasopressin, due to the local release of nitric oxide and other vasodilators. The maintenance of arterial pressure is due to vasoconstriction of extra-splanchnic vascular territories such as the kidneys. HRS develops in the final phase of the disease, when there is extreme deterioration in effective arterial blood volume, severe arterial hypotension and intense renal vasoconstriction. Several lines of evidence suggest that cardiac dysfunction may also play a role in the pathogenesis of this syndrome \(^{58, 78}\).

There are two different types of HRS. Type-2 HRS develops in non-azotemic patients with cirrhosis and refractory ascites with moderate and relatively steady renal failure. By contrast, Type-1 HRS is characterized by increasing serum creatinine levels, reaching a value greater than 2.5 mg/dL in less than two weeks \(^{80}\). Type-1 HRS frequently occurs in a closed relationship with a precipitating factor such as bacterial infection, mainly SBP, gastrointestinal hemorrhage, a major surgical procedure or an acute hepatitis flare in a patient with cirrhosis.

The diagnosis of HRS is based on the exclusion of other types of renal failure that may occur in patients with cirrhosis. The criteria required for diagnosis are reported below \(^{80}\):
- Cirrhosis with ascites.
- Serum creatinine > 133 mmol/L (1.5 mg/dL).
- No improvement of serum creatinine (decrease to a level of ≤133 mmol/L) after at least 2 days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
- Absence of shock.
- No current or recent treatment with nephrotoxic drugs.
- Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhaematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography.

HRS is the complication of cirrhosis associated with the worst prognosis. The median survival time for type-1 HRS is 15 days. Patients with type-2 HRS have a median survival time about 6 months.

Liver transplantation is the treatment of choice for HRS,
because it allows both the liver disease and renal failure to be treated. The long-term survival of patients with HRS who undergo liver transplantation is good, with a three-year probability of survival higher than 60%. This survival rate is only slightly reduced compared with that of transplantation in patients without HRS (which ranges between 70% and 80%). The main problem of liver transplantation in type 1 HRS is its applicability. Due to their extremely short survival time, most patients die before transplantation.

Vasoconstrictors improve circulatory function by inducing vasoconstriction of the splanchic arterial bed, thereby suppressing the activity of endogenous vasoconstrictor systems and improving renal perfusion. In combination with intravenous albumin, this pharmacological approach may reverse HRS in approximately 40%-50% of patients. Different vasoconstrictors have been used, including terlipressin, midodrine and noradrenaline. Although data on other vasoconstrictors are promising, terlipressin is the most studied, and should be used in progressive dosage starting with 0.5 mg / 4 hours. If serum creatinine does not decrease by more than 30% in 3 days, the dose should be doubled. Albumin should be administered starting with a priming dose of 1g/kg of body weight followed by 20-40 g/day. Midodrine and noradrenaline, which have been shown to be effective and safe, can also be used. A recent randomized study including forty-six patients with HRS type-1, evaluated the safety and efficacy of terlipressin and noradrenaline (starting with 0.5 mg/h) in the treatment of HRS. The main conclusion of this study was that noradrenaline is as safe and effective as terlipressin, but less expensive in the treatment of HRS. These conclusions were confirmed by a recent meta-analysis of four studies comprising 154 patients.

The treatment of HRS with vasoconstrictors increases the risk of potentially serious adverse events, such as myocardial infarction. Assessment of potential contraindications and close monitoring of adverse events is essential.

Currently, few patients with HRS have been treated by transjugular intrahepatic portacaval shunt (TIPS).

Published data suggest that TIPS is effective in normalizing serum creatinine in a significant proportion of patients with HRS, rendering it an alternative treatment of type-1 HRS. The applicability of transplantation is relatively low, since it is usually contraindicated in patients with severe liver failure or severe HE. At the time of writing, no studies had compared TIPS and vasoconstrictors in the treatment of HRS.

The use of MARS in patients with type 1 HRS was not associated with beneficial effects and therefore should not be given outside clinical trials.

4) Adrenal failure

Adrenal insufficiency (AI) is the clinical manifestation of deficient production or action of glucocorticoids. Cortisol is the major endogenous glucocorticoid secreted by the adrenal cortex and has several biological effects. Glucocorticoids modulate immune response by stimulation of anti-inflammatory cytokine production and inhibition of proinflammatory cytokine production, inflammatory cell migration, and expression of inflammatory mediators. They are also responsible for maintenance of myocardial contractility and vascular tone by modulating reactivity to renin-angiotensin-aldosterone and sympathetic nervous systems, regulating vascular permeability and decreasing production of vasodilators. The synthesis and secretion of cortisol is regulated by the hypothalamic-pituitary-adrenal axis' production of adrenocorticotrophic hormone (ACTH) and corticotropin-releasing hormone (CRH).

In patients with decompensated cirrhosis, increased production of cytokines due to bacterial translocation, hypoperfusion of the adrenal gland and reduced serum levels of cholesterol (the main precursor of adrenal steroids), may lead to reduced cortisol synthesis. These findings may explain the increased frequency of AI observed in patients with cirrhosis when compared to the general population.

Diagnosis of AI is most commonly established by the ACTH stimulation test. The test uses 250μg of synthetic ACTH given IV, with cortisol measured at baseline and after 60 minutes (peak cortisol). The difference between baseline and peak cortisol is called delta cortisol. Most studies use a delta cortisol level lower than 9 μg/dL as the diagnostic criterion. In critically ill patients, a baseline serum cortisol lower than 15 μg/dL is also considered indicative of AI.

In patients with decompensated cirrhosis, the prevalence of AI ranges between 26% and 39%. There is no clear relationship between liver and adrenal function, as evidenced by the equal proportion of patients with Child-Pugh C score and comparable values of MELD scores between patients with and without AI. Nevertheless, lower serum levels of cholesterol (but not triglycerides) were reported in patients with AI. Adrenal insufficiency was also associated with greater impairment of circulatory and renal functions, as evidenced by lower mean arterial pressure and serum sodium, and higher values of BUN and plasma renin activity.

Interestingly, patients with AI had a higher probability of sepsis and type-1 HRS and lower survival rates. These data indicate that, in patients with decompensated cirrhosis, AI is a common complication that develops independently of the degree of liver function and is associated with greater morbidity and mortality when compared with patients with normal adrenal function. In patients with cirrhosis and septic shock, the prevalence of AI ranges between 51% and 76%, a frequency almost double the one observed in patients with decompensated cirrhosis and almost 50% greater than the one observed in non-cirrhotic subjects with septic shock.

These data suggest that presence of both conditions greatly increases the probability of the patient developing AI. In patients with cirrhosis and septic shock, presence of AI was associated with greater impairment in liver, circulatory and renal functions. Patients with AI also had more severe infection, as evidenced by higher frequency of bacteremia and leucocyte counts. There was also a correlation between the prevalence of organ failure and adrenal function. Prevalence of AI increased progressively with the number of organ system failures. Together with APACHE III score, adrenal
insufficiency was shown to be an important prognostic factor and an independent predictor of hospital mortality. Previous studies have shown that administration of low doses of hydrocortisone improves shock reversal and survival in septic shock. Two studies have specifically addressed this issue in patients with cirrhosis. In a prospective study, 25 patients with septic shock had adrenal function evaluated, and those who had AI received 50 mg IV hydrocortisone every 6 hours. Results were compared with a retrospective cohort of 50 patients with septic shock not treated with steroids. Shock resolution was more frequent and faster in the group treated with hydrocortisone. This group also showed a lower frequency of renal failure in the ICU, with a comparable incidence of new infections and GI bleeding. Survival was significantly higher for the group treated with supplementary steroids, indicating a beneficial effect of the treatment of AI in patients with cirrhosis and septic shock.

Recently, a randomized, double blind trial evaluated the effects of low doses of hydrocortisone versus placebo in a group of 75 patients with cirrhosis. The authors showed a similar beneficial effect on shock reversal, but a higher frequency of gastrointestinal bleeding was observed in the hydrocortisone group. Both groups showed similar survival rates after 28 days.

In summary, adrenal insufficiency is common in patients with cirrhosis and is correlated with higher morbidity and mortality. However, more studies are needed to better clarify possible role of stress-dose corticosteroid supplementation in the management of this condition.

5) Cerebral dysfunction and hepatic encephalopathy

Hepatic encephalopathy is an important multifactorial neurological syndrome that can occur in patients with chronic liver disease and acute liver failure (ALF), related or unrelated to portosystemic shunts. It represents a progressive but potentially reversible cause of cerebral dysfunction with a wide array of neuropsychiatric, cognitive and motor symptoms, ranging from minor signs of altered brain function to deep coma. Hepatic encephalopathy was shown to increase mortality and to diminish the quality of life of patients with cirrhosis. The probability of transplant-free survival after the first episode of acute HE is only 42% at 1 year and 23% at 3 years. Those with severe HE in the ICU carry, respectively, a 35% and 54% in-hospital and 1-year mortality.

The underlying mechanisms involved in the pathogenesis of HE are not completely understood, but it is speculated that the failure to detoxify nitrogen-derived products (especially ammonia) predominantly found in the intestine is involved. This may be related both to impaired hepatic clearance and portosystemic shunting. Hepatic encephalopathy is classified as type A when associated with ALF, type B when related to portosystemic bypass or shunting and type C when associated with cirrhosis. Type C is further divided into episodic, persistent and minimal HE. Episodic HE can be triggered by recognized risk factors; spontaneous and recurrent HE (more than two episodes in a year) in the absence of these triggering events. Persistent HE is defined by the presence of chronic neuropsychiatric signs and symptoms, usually graded as mild, severe or controlled only with drug therapy. Minimal HE is a pre-clinical syndrome that can be diagnosed only with neuropsychological or complex neurophysiological tests. All types are associated with some degree of cerebral dysfunction due to astrocyte ammonia swelling, impaired glial and neuronal function, mainly due to hyperammonemia, which may disrupt synapsis and lead to HE symptoms. In contrast to ALF, HE in cirrhosis occurs without cerebral edema and intracranial hypertension and is usually triggered by some precipitant factors. The West Haven classification is commonly used to assess severity of HE in four grades. However, recently the International Society for Hepatic Encephalopathy and Nitrogen Metabolism proposed another classification named SONIC that encompasses minimal and grade I HE as covert HE and grade II to IV HE as clinically apparent HE. Common signs and symptoms include somnolence, confusion, bradykinesia, asterixis, dysarthria, ataxia, progressive alterations in muscular reflexes and coma. Seizures, transient focal deficits and nystagmus are uncommon. Myelopathy as well as extrapyramidal symptoms may be predominant in some patients.

The diagnosis of HE is usually straightforward in subjects with cirrhosis, but it should be pointed out that it is important to exclude other causes of brain dysfunction, particularly in patients that failed to recover promptly post treatment. Blood ammonia may be useful in those patients, but one should keep in mind that its concentration was shown to vary in individual patients and can be in the normal range of 10% of patients with overt HE. Computed tomography scans may be useful to rule out intracranial hemorrhage, infarction, abscess or tumors. Furthermore, magnetic resonance imaging of the brain can depict typical abnormalities seen in subjects with HE, such as deposition of paramagnetic substances in the basal ganglia, decrease in brain size, increase in brain water and changes in organic osmolytes. Electroencephalogram triphasic waves are very common but not specific for HE.

Admission to the ICU is usually restricted to patients with grade III to IV HE who need quick intervention for protection of airways and ventilation. However, grades I and II HE are common in critically ill patients with cirrhosis and other complications such as sepsis, HRS and VB. The management strategies for HE include: 1) exclusion of other causes of encephalopathy, 2) identification of triggering factors, and 3) empirical treatment with agents known to reduce production and/or absorption of ammonia or enhance its clearance. These agents are non-absorbable disaccharides (NAD) including lactulose and lactitol; poorly absorbable antibiotics, including neomycin, metronidazole and rifaximin; and L-ornithine L-aspartate (NAD). Either lactulose or lactitol are the first-line treatments of HE. Neomycin, and to a lesser extent metronidazole are associated with adverse events that preclude their routine use. In this regard, either metronidazole or LOLA are usually prescribed in association with NAD in those subjects that failed to respond after 24-72 hours of treatment. Rifaximin is not available in Brazil but is highly
It should be pointed out that most patients with HE could recover only with the withdrawal of triggering factors (Figure 2). According to clinical judgment, it is important to rule out infection; discontinue diuretics and administer intravenous fluids for those who are volume depleted, correct electrolyte disturbances, stop offending drugs such as benzodiazepines and narcotics, restore or enhance bowel movements in those patients with obstipaton or gastrointestinal hemorrhage. Equally important but generally neglected, are general supportive measures, such as adequate care to protect those patients from self-inflicted injury and/or aspiration pneumonia, to provide nutrition in order to avoid hypoglycemia as well as malnutrition. In this regard, it is important to guarantee a minimal caloric intake of 35-40 Kcal/Kg/day. Protein restriction does not have an apparent benefit in episodic HE. With cirrhosis, despite the fact that protein could contribute to HE, patients should receive 1.2-1.5g/Kg/day of protein. This is important in order to prevent further depletion of muscle mass in an already malnourished patient. For those with severe HE, solutions containing branched chain amino acids (BCAAs) and reduced amounts of aromatic amino acids seem to improve neurological symptoms.

The management of HE in ALF is discussed part III section 1 of this manuscript.

### PART II: INFECTIONS, SEPSIS, SEPTIC SHOCK AND SURVIVAL SEPSIS CAMPAIGN GUIDELINES (SSCG) IN PATIENTS WITH CIRRHOSIS

#### 1) Infections

The prevalence of infections in cirrhosis is reported to be 25%-35% in hospitalized patients and as high as 59% in subjects admitted to the ICU(32, 36, 47). In decreasing order of frequency, intra-abdominal infections, particularly SBP; urinary tract infections (UTI); pneumonia; bacteremia and cellulitis are the most frequent types of infections seen in patients with cirrhosis(36). However, in the ICU, pneumonia is the most common infection observed in patients with cirrhosis. Isolation of causative organs is possible in 50% to 70% of those patients(47). Gram-negative bacilli (GNB) and Gram-positive cocci (GPC) are the cause of community-acquired infections in, respectively, 60% and 30%-35% of the patients, whereas CPC is seen in 60% of nosocomial infections and usually associated with invasive clinical procedures(32, 36, 47). Multiresistant bacterial infections are reported with higher frequency in health care associated (HCA) and nosocomial acquired infections with increasing prevalence from 10% to 23% over the last decade. Multiresistant strains are now isolated from 20% of HCA and 39% of nosocomial infections(32, 36, 47). The presence of infections due to multiresistant bacteria is associated with a two-fold increase in mortality(32). Fungal infections are also particularly common in ICU(32, 36, 48). When compared to ICU patients without chronic liver diseases, subjects with cirrhosis and infections have a significantly higher incidence of septic shock and organ failure, require renal replacement therapy (RRT) more often and suffer decreased survival rates(47). Mortality of patients with...
cirrhosis and septic shock admitted to the ICU is reported to be 76%. Delay in administration and/or inappropriate use of antibiotics, as well as initial employment of a single antibiotic agent as empirical therapy, were all associated with decreased survival rates\(^6\).

The frequency of infection due to multiresistant bacteria and its impact on survival has led to changes in infection preventative measures and a modification of antibiotic guidelines\(^3, 34\). Empirical antibiotic therapy should be selected by considering the type of infection, the site of acquisition (nosocomial, HCA or community-acquired), the severity of infection (sepsis, severe sepsis or septic shock) and local epidemiological pattern of resistant bacteria. It is important to emphasize the importance of antibiotic prophylaxis in subjects with VB in order to prevent subsequent infectious complications and the employment of albumin to prevent HRS in order to improve short-term survival in patients with SBP\(^3\)\(^4\).

In summary, bacterial infections in patients with cirrhosis admitted to the ICU are very prevalent and associated with poor prognoses. Prompt and appropriate antibiotic treatment is essential in the management of infected patients with cirrhosis admitted to the ICU. Third-generation cephalosporins continue to be the gold-standard antibiotic treatment of many of the infections acquired in the community. Empirical treatment of nosocomial and possibly some HCA infections should be adapted to the local epidemiological pattern of antibiotic resistance and should be also defined according to the severity of the infection.

2) Fluids and vassopressors

In order to improve survival\(^27\), the survival sepsis campaign guidelines (SSCG) recommend administration of broad-spectrum antibiotics in patients with severe sepsis and septic shock (after blood cultures collection) within the first hour after the recognition of sepsis. Early resuscitation should be carried out in the first 6 hours with crystalloids (at least 30 mL/kg) in subjects with hypovolemia or tissue hypoperfusion, to achieve hemodynamic improvement based on either dynamic or static variables including mean arterial pressure (MAP) higher than 65 mmHg, central venous pressure of 8-12 mmHg or 12-15 mmHg in mechanically-ventilated subjects, urinary output >0.5 mL/Kg/hour, central venous oxygen saturation (ScvO2) >70% and lactate restoration to normal levels. It is notable, however, that in patients with cirrhosis ScvO2 levels higher than 70% could occur in hypovolemic subjects due to the presence of hyperdynamic circulation, and slowed lactate clearance is commonly ascribed to the reduction in its excretion by the liver.

Fluid challenge with albumin can also be considered in patients who continue to require substantial amounts of crystalloid to maintain adequate mean arterial pressure. Its use, in association with crystalloids, was associated with a significant higher mean arterial MAP and lower heart rate (HR) when compared to crystalloid resuscitation alone, but no improvement in survival was observed\(^17\). In addition to providing volume expansion, albumin also acts as a potent antioxidant and detoxifying substance capable of restoring endothelial function in cirrhosis. Albumin use in subjects with cirrhosis and SBP was shown to prevent HRS and to improve systemic hemodynamics and survival\(^8\). The use of hydroxyethyl starch, was shown to be detrimental in the treatment of septic shock and should be avoided.

Norepinephrine is considered the first-choice vasopressor. Vasopressin (0.03 U/min) can be added to norepinephrine to raise MAP to desired levels, but its use should not be recommended as initial therapy. Dobutamine infusion can be added to norepinephrine in the presence of myocardial dysfunction or ongoing signs of hypoperfusion despite resuscitation.

3) Corticosteroids and glicemic control

Cortisol is known to be responsible for vascular tonus, endothelial integrity, vascular permeability, total corporal water distribution and also for decreasing the levels of cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor-alpha\(^2, 93\). Patients with cirrhosis are predisposed to develop adrenal insufficiency (AI) due to low levels of cholesterol synthesis (which is the substrate for cortisol production), and to the high frequency of concurrent endotoxemia and coagulopathy that can induce adrenal hemorrhage or infarction\(^2, 93\). Relative AI is defined as inadequate cellular response to corticosteroid activity in critically ill patients. Its prevalence in patients with cirrhosis varies from 10% to 87% according to the presence of severe sepsis or shock septic, severe upper gastrointestinal bleeding and liver transplation. Moreover, AI is associated with conditions such as liver and renal failure, refractory septic shock and hospital mortality\(^2, 93\).

These discrepancies in the frequency of AI in cirrhosis are caused by different laboratorial diagnostic criteria encountered to establish AI. An International Task Force has standardized the AI definition in the ICU as a delta (peak minus basal) cortisol level less than 250 nmol/L (9 μg/dL) after standard ACTH test or random serum total cortisol less than 276 nmol/L (<10 μg/dL)\(^2, 9\).

Latest surviving sepsis campaign guidelines suggest the use of intravenous hydrocortisone (200 mg/day) for refractory septic shock with an evidence grade of 2C\(^27\). In this respect, two previous trials have reported distinct results regarding the use of corticosteroids in septic shock with either reduction in or with no effect on mortality\(^27\). Up to 8% of the patients in both trials had liver disease. Recently, Tsai et al.\(^9\) enrolled 101 critically ill patients with cirrhosis and severe sepsis or septic shock. They found that the group with AI had a higher hospital mortality rate when compared with patients without AI (81% compared with 37%, respectively). The trial also showed that independent factors that predicted AI were mean arterial pressure, serum bilirubin, vasopressor dependency, and bacteremia. Fernández et al.\(^9\) retrospectively evaluated 75 critically ill patients with cirrhosis and found that 68% of them had AI. Administration of low doses of hydrocortisone was associated with a significant increase in reversal of shock and increased hospital survival. Arabi et al.\(^9\) conducted a prospective trial to evaluate the beneficial effects of hydro-
cortisone in septic shock, enrolling 75 patients with cirrhosis within 24 to 48 hours of shock. This study was stopped for futility even in the presence of improvement of hemodynamic status in the treated group of patients due to the fact that they had also higher rates of severe hyperglycemia and gastrointestinal bleeding. Shock relapse was also frequently reported after weaning of corticosteroid in the treated group of subjects. In summary, more large-scale trials are needed to settle the potential benefits of corticosteroids in patients with cirrhosis and AI.

Hyperglycemia leads to impairment of neutrophil function, apoptosis and may be a procoagulant. The NICE-SUGAR trial randomized 6,030 critically ill patients in intensive (with goals for glucose levels between 81-108 mg/dL) and conventional (with goals for glucose levels between 140-180 mg/dL) insulin therapy. Even though 30% of those patients had some liver dysfunction, it was unclear how many were diagnosed with cirrhosis. The study showed that the intensive group had a higher mortality rate and incidence of hypoglycemia when compared to conventional therapy. As there are no trials reported to address this question in patients with cirrhosis, most papers suggest a less strict glucose target (140-180 mg/dL) in critically ill patients with cirrhosis.

PART III: CONTROVERSIES IN THE MANAGEMENT OF PATIENTS WITH LIVER DISEASE IN THE ICU

1) Acute liver failure

Acute liver failure (ALF) is a life-threatening critical illness that occurs in patients without previously known liver disease. It is characterized by the sudden onset of jaundice followed by HE and signs and symptoms of liver dysfunction. It is potentially reversible but carries a high mortality rate. Trey and Davidson have defined ALF, also known as fulminant hepatic failure, as onset of HE within 8 weeks of the first symptoms, usually jaundice, in the absence of pre-existing liver disease. Others have suggested different time frames between disease onset and the development of HE, as well as different terminology (Figure 4). The American Association for the Study of Liver Diseases defines ALF as the presence of HE and coagulopathy expressed as an INR higher than 1.5, in the absence of pre-existing cirrhosis within 26 weeks of the onset of the first symptoms.

The main etiologies of ALF are summarized in Figure 5. There is a striking geographical heterogeneity in the epidemiology of ALF worldwide. Hepatotoxicity due to acetaminophen is the most common cause of ALF in the United States of America and United Kingdom, followed by idiosyncratic hepatotoxicity due to other drugs and indeterminate etiology. Viral hepatitis is uncommon in the West. Hepatitis A, B and E are the most common causes of ALF in Asia and Africa.

To determine the etiology of ALF it is important to obtain a comprehensive clinical history and a detailed physical examination to guide laboratory and imaging evaluation, including: INR, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, glucose, AST, ALT, alkaline phosphatase, GGT, total bilirubin, albumin, urea, creatinine, arterial ammonia, amylase, lipase, arterial blood gas, arterial lactate, complete blood count, blood type, toxicology screen with acetaminophen level, viral serologies (anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HEV, anti-HCV, HCV RNA, Herpes simplex virus IgM, Varicella zoster virus, HIV), ceruloplasmin levels, antinuclear antibody, anti-smooth muscle antibody and anti-liver kidney microsome type 1 antibody, abdominal ultrasound and or computed tomography scan or magnetic resonance imaging if appropriate by clinical judgment.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FHF (0-14 days)</td>
<td>FHF (0-14 days)</td>
<td>FHF (0-14 days)</td>
<td>Hiperacute FHF (0-7 days)</td>
</tr>
<tr>
<td>Subfulminant</td>
<td>Subfulminant</td>
<td>Subfulminant</td>
<td>Acute</td>
</tr>
<tr>
<td>HF (15-60 days)</td>
<td>HF (15-90 days)</td>
<td>HF (15-60 days)</td>
<td>FHF (8-28 days)</td>
</tr>
<tr>
<td>Late-onset (61-180 days)</td>
<td></td>
<td>Late-onset (61-180 days)</td>
<td>Subacute</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FHF (28-72 days)</td>
</tr>
</tbody>
</table>

FIGURE 4. Definitions of Acute Liver Failure

FHF: Fulminant hepatic failure, HF: Hepatic failure.

Viral hepatitis
Other Viruses
Paracetamol*
Other drugs
Amanita phalloides*
Vascular disorders*
Acute fatty liver of pregnancy, HELLP syndrome, eclampsia
Autoimmune hepatitis*
Malignant involvement of the liver*

Hepatitis A, B*, C, E and delta
Herpes simplex virus*, Varicella zoster virus*, Epstein Barr virus, Cytomegalovirus,
Isoniazid, NSAIDs, Valproic acid, etc
Budd-Chiari syndrome, ischemic hepatitis, heart failure
Acute fatty liver of pregnancy, HELLP syndrome, eclampsia
Acute fatty liver of pregnancy, HELLP syndrome, eclampsia
breast, lung, lymphoma, melanoma

FIGURE 5. The main causes of acute liver failure

* Causes of ALF that may benefit from specific therapy.
Differential diagnosis of the cause of ALF is important to rule out chronic liver disease, acute on chronic liver failure, to evaluate therapy directed for the underlying disorder and to assess prognosis. In this regard, patients with either hepatitis A or paracetamol induced ALF carry a transplant-free survival rate higher than 50%, whereas their counterparts with non-paracetamol drug-induced or Wilson disease ALF have mortality rates as high as 90% to 100%.

It is important to consider treatment of the confirmed or presumed cause of ALF, including cessation of possible offending drugs. N-acetylcysteine should be considered in paracetamol overdose and in the initial phase of non-paracetamol ALF, when HE is grade I or II[61]. Immediate delivery should be recommended in acute fatty liver of pregnancy. In cases of suspected autoimmune hepatitis AIH or Wilson disease, a trial of corticosteroids or D-penicillamine respectively is recommended. In case of *Amanita Phalloides* intoxication penicillin is prescribed, and in ALF due to herpes virus or hepatitis B antivirals are recommended. Other diverse measures such as hemodynamic support, chemotherapy or TIPS may be required for ischemic hepatitis, massive neoplastic involvement of the liver and acute Budd-Chiari syndrome[13, 62].

The causes of ALF that require evaluation for treatment are highlighted in Figure 5.

Besides etiology, other prognostic factors include age, time interval between EH and jaundice, pH, INR, factor V, creatinine and bilirubin, MELD score, serum lactate, serum phosphate, alpha-1-fetoprotein, galactose elimination capacity, C-13 methacetin breath test, GC globulin, liver volume by CT scan and indocyanine green clearance. Several of those aforementioned parameters were combined into prognostic systems, like Kings College and the Clichy criteria (Figures 6 and 7) in order to identify those patients with higher mortality without LT. The most employed worldwide and in Brazil is the Kings College system, whose specificity is good, but is somewhat limited in its sensitivity[13, 62].

Once the diagnosis of ALF has been established, the patient should be referred to a liver unit to allow a definite etiological diagnosis, to initiate specific treatments and evaluate the criteria for possible OLT.

Systemic complications of ALF include intracranial hypertension (ICH) due to cerebral edema, particularly seen in mechanically ventilated subjects with grades III or IV HE, circulatory and renal failure, metabolic and hydroelectrolytic abnormalities, coagulopathy, infections, sepsis and septic shock[60, 90].

In order to prevent cerebral edema, it is important to maintain ICP lower than 20 mmHg and cerebral perfusion pressure equal or higher than 50 mmHg with SaO2 >95%. It is advisable in subjects with grades III or IV HE to keep the head elevated, to avoid stimulation, hypotension, fever, hyponatremia and hypoglycemia. To protect airways, tracheal intubation and mechanical ventilation may be warranted. Placement of ICP monitoring devices can be useful for early detection of ICH and to guide therapy. However, it should be pointed out that their use was not associated with enhanced survival. The frequency of bleeding adverse events associated with the placement of ICP devices is reported to be around 10% and occur more often with the insertion of intracerebral or subdural ICP catheters. ICP monitoring is useful in the presence of urgent requirement for liver transplantation according to Kings College criteria, seizures or pupillary abnormalities, more than two criteria for SIRS, ammonia levels higher than 150 mmol/L, hyponatremia, need for vasopressors or evidence of highly decreased or highly increased cerebral blood flow by jugular venous O2 saturation or transcranial Doppler. Whenever possible, it is preferable to use extradural ICP transducers[13, 90].

Whenever clinically suspected or detected by ICP monitoring, ICH should be aggressively treated with intravenous mannitol. Short-term hyperventilation may be useful in cases of impending brainstem herniation. Prophylaxis of seizures with phenytoin is no longer recommended but treatment should be aggressive whenever ICH is present due to its undesired effects in ICP. Appropriate sedation, whenever possible with propofol is recommended. Hypertonic saline is of value to maintain sodium levels between 145-155 mmol/L, hyponatremia, need for vasopressors or evidence of highly decreased or highly increased cerebral blood flow by jugular venous O2 saturation or transcranial Doppler. Whenever possible, it is preferable to use extradural ICP transducers[13, 90].

Sepsis is common in the course of ALF and may lead to impaired hepatic regeneration and ICH due to SRIS. Surveillance for infection is required as well as prompt antimicrobial treatment whenever it is suspected. Antibiotic prophylaxis is possibly helpful but not proven. Circulatory failure must be treated cautiously with intravenous fluids and vasopressors, preferably noradrenaline, to maintain adequate organ perfusion, particularly CPP. Electrolyte and metabolic disturbances are common and must be avoided or corrected. It is advisable to start enteral nutrition as early as possible. Coagulation abnormalities should not be corrected in the absence of bleeding and invasive procedures. Continuous venous-venous hemodialysis is the best approach for renal replacement therapy in those subjects with renal failure[43].

<table>
<thead>
<tr>
<th>Non-paracetamol ALF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin time higher than 100 seg (INR higher than 6.5) independently of the grade of HE or at least three out of four parameters: age less than 10 or higher than 40 years, drug-induced or unknown etiology, time interval between EH and jaundice higher than 7 days, bilirubin higher than 300 mmol/L and INR higher than &gt;3.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Paracetamol ALF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH &lt;7.3 after resuscitation and or</td>
</tr>
<tr>
<td>Combination of grade of HE equal or higher than 3, creatinine equal or higher than 300 mmol/L and INR higher than 6.5</td>
</tr>
</tbody>
</table>

**FIGURE 6. King's College prognostic system**

| Presence of grade III or IV of HE and |
| Age less than 30 years and factor V lower than 20% |
| Age higher than 30 years and factor V lower than 30% |

**FIGURE 7. Clichy prognostic system**
The evaluation for LT remains a major dilemma. The most common criteria used worldwide for identification of those ALF subjects with a survival benefit with LT are the Kings College and the Clichy prognostic systems. In Barcelona, patients with the HE grade III or IV, sub fulminant or sub acute course or lack of improvement with conventional treatment are regarded as appropriate candidates for LT. In most programmes, a pragmatic case-by-case evaluation of the risk benefit profile is employed. Other strategies besides cadaveric LT include auxiliary heterotopic LT, living-donor LT and artificial and bioartificial support systems. Auxiliary heterotopic LT and living-related LT are usually infeasible in critically ill subjects with ALF. Data concerning liver support systems are presented elsewhere in this manuscript. Their use is controversial, and there is no undisputed evidence that they improve survival, but instead they may play a temporary role providing a bridge for LT\(^{(13, 62)}\).

In summary, ALF is a life threatening illness usually associated with a dismal prognosis without LT. It is important to search carefully for its cause in order to establish prognosis and to evaluate introduction of specific therapy for the underlying disorder. All patients with ALF should be referred to an ICU for advanced life support in a tertiary care center for prompt evaluation for LT.

2) Prognostic scores: Child-Pugh Score (CPS), Model for End-stage Liver Disease (MELD), sofa and clif-sofa

The occurrence of the first episode of liver decompensation marks a change in the prognosis of the liver disease. Variceal bleeding, SBP, HRS and sepsis are the main complications requiring admission to the ICU. A major proportion of these patients develop organ failure. The mortality rate of critically ill patients with cirrhosis is very high due to poor prognosis related to end-stage liver disease, late referral for organ support, lack of knowledge of the management of cirrhosis, absence of a liver transplantation program, as well as reduced availability of ICU beds and the high cost of treatment\(^{(65)}\).

The main objectives of prognostic scores in patients with cirrhosis are to estimate the probability of mortality within a given time interval, to determine which therapeutic option is the most appropriate with respect to the patient’s condition, whether a patient has an acceptable chance of survival after a given treatment and whether a resource-spending treatment such as OLT is justified.

Various prognostic models have been developed and applied to patients with cirrhosis, including ICU scores such as SOFA, RFH score, SAPS II, APACHE II, which were shown to predict outcomes better in the ICU, when compared to conventional liver scores such as MELD and Child-Pugh scores\(^{(5, 22)}\). MELD variants that included Na were not shown to predict ICU mortality better than MELD alone in such patients\(^{(63)}\). Some authors found that a modified SOFA for cirrhosis, named CLIF-SOFA and leukocyte counts were independent predictors of mortality in patients with acute-on-chronic liver failure (ACLF)\(^{(71)}\). Cut-off levels are essential for determining outcomes. A French study showed that mortality was best correlated with SOFA \(\geq 10.5\) and MELD \(\geq 28.5\) after the first day of ICU admission\(^{(65)}\). Mortality of patients with cirrhosis has reportedly decreased on the ICU in recent years. This improvement in survival may be a consequence of new therapies such as terlipressin or TIPS\(^{(22, 45)}\). An aggressive treatment initiated at an earlier stage may also account for improving results. Early referral to the ICU would reduce the risk of disease worsening and maybe improve the survival rate.

Although outcomes have improved over time, mortality rates for critically ill patients with cirrhosis remain high. Studies showed that patients admitted to the ICU with VB or HE had better survival rates when compared to patients admitted with sepsis. The presence of infection is associated with poor survival at 2 months. Fungal infection significantly impacts on ICU mortality. Bilirubin at admission, infection at admission or acquired during ICU stay, mechanical ventilation and vasopressor therapy are all independently related to mortality\(^{(63, 64)}\).

There is a correlation between the number of organs requiring support and ICU mortality. Patients have a mortality rate of over 90% if they experience failure of three or more organs or if they require more than three types of organ support or replacement therapy (mechanical ventilation, vasopressor therapy, renal replacement therapy, MARS), unlike the mortality rate, estimated at 2%, for patients with cirrhosis but without organ failure\(^{(63)}\).

Some authors suggest that all critically ill patients with cirrhosis should be admitted to the ICU at an earlier stage of decompensation, to optimize their management. Reassessment of these patients with ICU scores should take place 2 to 4 days thereafter. The persistence of three or more organ failures and the need for three or more organ supports may lead to consideration of the limitations of invasive treatments, as unfavorable results are almost certain in this setting\(^{(63, 64)}\).

3) Artificial and bioartificial liver support systems

The artificial and bioartificial support systems were designed to enhance short-term survival of patients with acute liver failure and acute on chronic liver failure in order to provide a bridge to liver transplantation or liver regeneration in the case of ALF\(^{(62)}\). The Molecular Adsorbent Recirculating System (MARS), the fractionated plasma separation and adsorption (Prometheus), the single-pass albumin dialysis and the Hepa Wash procedure are artificial liver support systems that are commercially available and reported to be safe\(^{(97)}\). The rationale for their use is the removal of albumin-bound toxins. Their benefit is limited to secondary endpoints in randomized clinical trials such as improvement of HE and mean arterial pressure, increased cerebral blood perfusion, reduction in ICP and cerebral edema, removal of pro-inflammatory cytokines in ALF, but without any effect on mortality either in ALF or in ACLF\(^{(11, 62, 59, 97)}\). Furthermore, several other bioartificial liver support systems using human or other mammalian hepatocytes have been developed, including the Hepa-
tAssist, the extracorporeal liver support device (ELAD), the modular liver support system (MELS), the bioartificial liver support system (BLSS) and the Amsterdam Medical Center bioartificial liver (AMCBAL). When compared to the artificial liver support systems, they appear to be less effective and much more complex and expensive. At present, their use has not been associated with improved transplant-free survival, and the use of either liver support system is not recommended outside clinical trials\(^{43, 62}\).

4) Limiting intensive care support in patients with cirrhosis

It is a challenge to limit intensive care support in patients with liver disease in light of the recent improvement in patient survival in ICUs, the availability of liver support systems and liver transplantation (LT). In this regard, the survival benefit of LT is seen most markedly in patients with MELD scores higher than 15\(^{83}\). However, critically ill subjects with cirrhosis and organ dysfunction usually have a poor prognosis. In those patients, the presence of more than two organ failures, defined by Sequential Organ Failure Assessment (SOFA) score, is associated with a mortality risk of 50\% that approaches almost 100\% in the presence of more than three organ failures\(^{46, 71}\). The requirement for inotropic support, mechanical ventilation or RRT was also associated with adverse prognosis. In the presence of acute on chronic liver failure (ACLF), CLIF-SOFA was also reported to be a reliable prognostic parameter with better performance when compared to MELD and Child-Pugh score, showing that extra-hepatic organ failure is more important than liver failure in prediction of overall mortality. In this respect, patients with ACLF grades 2 and 3 have a 28-day mortality, respectively, of 32\% and 77\%\(^{71}\).

5) Sedoanalgesia

The management of pain and analgesia of patients with cirrhosis is concerning even for hepatologists, because side effects of analgesics and narcotics can be severe in subjects with cirrhosis. The most common complications include HE, AKI and gastrointestinal bleeding. There is a paucity of high-quality, prospective data regarding the pharmacology, the profiles of many analgesics and their adverse effects in patients with end-stage liver disease.

The International Association for the Study of Pain defines pain as a disagreeable emotional and sensory experience associated with actual or potential tissue damage. The use of scales to monitor pain improves the clinical outcome of those patients in distress, including reduction of their time on mechanical ventilation and shorter length of stay in an ICU\(^{123}\).

Treatment of non-neuropathic pain

The main cause of ALF in the US is the acetaminophen. Due to this fact, the use of this drug is usually incorrectly considered unsafe in patients with cirrhosis. However, the Food and Drugs Administration (FDA) recommends the use acetaminophen in subjects with liver diseases, in doses between 2-3 g/day, without concurrent consumption of more than three alcoholic drinks per day\(^{20}\). Hepatotoxicity due to nonsteroidal anti-inflammatory drugs (NSAID) is well documented. Besides, they also inhibit prostaglandin synthesis, which may precipitate HRS. Opiates also offer risks of toxicity. Tramadol, fentanyl, oxycodone and hydromorphone are the best options and may be used in reduced dosages in cirrhosis. The association with laxatives is recommended in order to avoid constipation and HE.

Treatment of the neuropathic pain

Patients with cirrhosis may feel pain due to neuropathies caused by diabetes, alcoholism, thiamine deficiency and/or cryoglobulinemia, needing adjuvant drugs for treatment of pain\(^{29}\). Anticonvulsants, such as gabapentin and pregabalin are suitable drugs, since they are neither metabolized in the liver, nor do they bind to plasma proteins. Use in conjunction with laxatives is recommended.

Sedation

Frequently, agitation in the ICU is treated with sedatives by mistake. Instead, it is advisable to immediately identify and treat the causes of the agitation, such as delirium, HE, pain, hypoxemia, hypotension, hypoglycemia, alcohol or drug abstinence. When they are needed, the sedatives must be used to induce only mild sedation, and the use of the monitoring sedation scales and light sedation protocols are associated with improvement in the clinical outcomes of the ICU. The most reliable sedation scales are The Richmond Agitation-Sedation Scale (RASS) and the Sedation-Agitation Scale (SAS), the target for the sedation being between -2 and 0 on the RASS or 3-4 on the SAS, or consciousness during the day.

Benzodiazepine is metabolized in the liver and in those with cirrhosis it may trigger HE. Non-benzodiazepine sedatives are recommended to improve the clinical results of those in mechanical ventilation and to reduce the incidence of delirium. Propofol is useful to provide low-level sedation with quick awakening after drug interruption, but smaller dosages are usually required. Dexmedetomidine is the only sedative permitted for patients that are not intubated in ICU in the United States, and its infusion does not need to be discontinued during weaning for extubation. Its metabolism is hepatic and those with severe hepatic dysfunction have their clearance reduced, therefore smaller dosages are required as stated for propofol.

Analgesia should be used cautiously before sedation. Sedation, when needed, should be light and linked to daily awakening protocols when clinically prescribed. In addition, scales of pain and sedation monitoring improve clinical outcomes. The use of analgesics and sedatives in patients with cirrhosis still needs to be further studied.
PART IV: COMMON COMPLICATIONS OF LIVER DISEASE
IN THE ICU

1) Acute variceal bleeding

Esophageal varices are present in patients with compensated and decompensated cirrhosis in 30% to 40%, and in up to 60% of cases respectively. The annual incidence of VB is around 4% (15% if varices are of medium or large size), with a recurrence rate of bleeding in two years of 60% (10). Mortality from VB is 20% during the acute episode and over 50% after 1 year (43). Therefore, it is very important to provide evidence-based strategies for treatment of VB, due to its short and long-term impact on patient survival.

Patients with VB should be ideally managed in the ICU due to the increased risk of death, rebleeding and sepsis. Fluid overload may worsen portal hypertension and induce persistent bleeding or rebleeding. In this regard, Villanueva et al. (96) have shown that a restrictive transfusion policy in VB aimed at maintaining hemoglobin levels between 7-9 g/dL, with a transfusion threshold for hemoglobin levels lower than 7 g/dL, was significantly associated with lower rebleeding and higher 6-week survival when compared to a more liberal transfusion strategy. When necessary, endotracheal intubation should be carried out for airway protection before endoscopy. Prevention of HE with NAD is controversial in VB, but a recent RCT showed that lactulose was more effective when compared to a placebo this setting (80). The use of prophylactic antibiotics is fundamental in order to prevent infection (81, 82). In this respect, a recent meta-analysis from the Cochrane group (59) that evaluated 12 RCT involving 1241 patients with VB has reported a reduction of bacterial infection (RR 0.35); mortality related to bacterial infection (RR 0.43), rebleeding (RR 0.53) and overall mortality in those subjects who received antibiotic prophylaxis. Oral norfloxacin (400 mg bid) was shown to be effective, but intravenous ceftriaxone 1g qid was reported to be superior to oral quinolones in subjects with advanced cirrhosis (37). Patients with Child A cirrhosis have a low risk of infection after VB. Prophylactic antibiotics may not offer additional benefit in this group of patients, but more data is still needed before withholding antibiotic administration in patients without advanced cirrhosis (91).

The standard therapy for VB should be a combination of endoscopic and pharmacological treatments. Endoscopic variceal ligation (EVL) is associated with better outcomes when compared to sclerotherapy and should be performed in the first 12 hours after VB. Vasoactive drugs should be administered as early as possible (10, 14). Combined endoscopic and pharmacological therapy is superior to either endoscopic or pharmacological therapy alone (10). Terlipressin, somatostatin and octreotide are the most frequently vasoactive drugs used for the treatment of VB (84, 82). The efficacy of octreotide has been challenged (81), but a recent meta-analysis has not disclosed any differences in efficacy of the aforementioned drugs in VB (86). Hubmann et al. (51) have proposed the use of esophageal self-expanding metallic stents for patients with massive VB with promising results. This device may be a future option to replace the Sengstaken-Blakemore balloon, but controlled data are still lacking. Recently, the use of early transjugular intrahepatic portosystemic shunts (TIPS) has been recommended in association with standard endoscopic and pharmacological treatment for patients with Child B cirrhosis with active VB or Child C with less than 14 points (41).

In this group of subjects, TIPS performed in the first 72 hours was shown to be associated with lower rebleeding or failure to control VB with a significant impact on survival. These results were subsequently confirmed in one observational study with similar results (42).

Transjugular intrahepatic portosystemic shunts is also considered the rescue treatment of choice for those patients who failed standard endoscopic and pharmacological treatment, in whom early TIPS was not considered. In this regard, employment of polytetrafluoroethylene-covered stents was shown to be superior to conventional stents. They are more expensive, but their use is associated with improved TIPS patency (RR = 0.28), reduction in the frequency of HE (HR = 0.65) and lower mortality (HR = 0.76) (99).

In summary, according to the First Brazilian Consensus of Variceal Bleeding of the Brazilian Society of Hepatology (40) and the V Baveno Faculty Consensus Workshop (56), for patients with VB the following is recommended: 1) to start as early as possible vasoactive drugs; 2) to perform GI endoscopy in the first 12 hours with intervention, whenever needed, preferably with EVL or alternatively with sclerotherapy; 3) to maintain pharmacological therapy for 2-5 days; 4) to begin antibiotic prophylaxis as early as possible; 5) to assess for early TIPS within 72 hours in patients of Child-Pugh class C, less than 14 points or B with active bleeding on endoscopy.

2) Prevention and treatment of coagulopathy

The notion that cirrhosis can induce severe coagulation disorders was established several decades ago. Such disorders are usually complex and multifactorial, resulting from the dynamic interactions between procoagulant and anticoagulant factors and fibrinolysis. Although compensatory mechanisms are activated to restore hemostasis, these interactions lead to hypocoagulability in most patients. Several disorders are identified in patients with chronic liver diseases, such as a reduction in the number and functioning of platelets, decreased levels of plasmatic procoagulant factors, vitamin K deficiency, dysfibrinogenemia, reduced levels of protein C and S, and reduced vascular tone and vasoconstrictor response. All proteins involved in fibrinolysis, with the exception of the tissue plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1), are synthesized in the liver. In cirrhosis, the plasma levels of plasminogen, alpha2-antiplasmin and factor XIII are reduced, while the levels of tPA are increased (18, 65).

Renal failure is commonly associated with advanced liver disease and worsens platelet dysfunction. Bacterial infections lead to the release of substances that act as endogenous heparinoids, which explains the deterioration of various coagulation parameters during episodes of sepsis.

In recent years, there has been a substantial shift in the
understanding of hemostasis in cirrhosis. The current concept of rebalanced coagulation indicates that the decrease in serum levels of both plasma procoagulant factors and natural anticoagulant proteins (protein C, protein S, antithrombin and tissue factor inhibitor) run parallel to the decline of liver function.

The reduced levels of fibrinolysis inhibitors are at least partially counterbalanced by the reduction of the levels of profibrinolytic factors, particularly plasminogen. The final result is a rebalanced hemostasis, which remains functioning, but highly unstable when compared to that found in individuals without liver dysfunction. The capacities of adhesion and aggregation of platelets may be preserved by a compensatory mechanism in cirrhosis characterized by an increased production of endothelial von Willebrand factor and decreased liver synthesis of the protease ADAMTS-13.

Due to the multiple mechanisms that contribute to the development of coagulopathy in cirrhosis, the need to implement monitoring strategies is a major concern, especially when invasive procedures are considered. There is strong published evidence that perioperative monitoring and hemostatic therapy should be performed with point-of-care equipment and using validated treatment algorithms. These strategies range from prevention to intensive monitoring of hemostasis. The prophylaxis of hemostasis disorders should be offered for all patients and with the intention to maintain normothermia, correct calcium metabolism disorders and hemodynamic stabilization, preferably in association with a blood component restrictive strategy.

Conventional coagulation tests (PT, aPTT) as methods for assessment of coagulopathy in patients with liver diseases have received criticism. Published evidence emphasizes that the results of these tests do not correlate well with the risk of bleeding and therefore should not be used to guide treatment of acute coagulopathy. The current method of choice is the thromboelastography. Thromboelastography has the advantages of speed and ease of interpretation of graphs, accurate differential diagnosis of the cause of the bleeding, assessment of platelet activity and rapid assessment of the effectiveness of therapy used.55, 77

Five parameters of the formation of clot lysis are measured in thromboelastography (Figure 8): R (time lag to initial fibrin formation); K (speed that a certain level of resistance of the clot is reached), α (speed of fibrin formation); MA (clot strength); and LY30 (rate of reduction of the resistance of the clot or fibrinolysis). Each parameter indicates an aspect of hemostasis that is abnormal and may be used to guide the targets of therapy (Figure 9).

In massive bleeding the therapeutic goals are: 1) hemodynamic goals: systolic blood pressure between 80-100 mmHg and heart rate ≤120 bpm; 2) metabolic targets: normothermia, lactate clearance, normalization of base excess, ionized calcium >1.0 mmol/L and adequate urine output; 3) targets of hemostasis: hemoglobin 7-10 g/dL, platelet count >100,000/mm³, fibrinogen >1.0 g/L. After hemorrhage control, the resuscitation should continue guided by conventional goals and the administration of blood products should be guided by thromboelastography, according to therapeutic algorithms (Figure 9). In severe refractory coagulopathy, consider administering rVIIa (recombinant activated factor VII). As the action of rFVIIa depends on the patient’s own clotting system, some requirements must be met for its administration: temperature >35°C, pH >7.2, platelets >100,000/mm³, fibrinogen >1.0 g/L, ionized calcium >1.0 mmol/L and hemoglobin of 7-10 g/dL.55, 77

3) Alcoholic hepatitis

Alcoholic liver disease (ALD) includes a spectrum of damage, ranging from simple steatosis to cirrhosis. These are not distinct stages of evolution of disease, but multiple overlapping stages that could be present simultaneously in the same patient. Genetic factors and environmental factors (binge drinking, viral hepatitis, HIV, obesity, insulin resistance, cigarette smoking) modify the clinical course of ALD. A proportion of patients who progress to alcoholic steatohepatitis (ASH) have a worse short-term prognosis.30

Alcoholic steatohepatitis represents a spectrum of disease, ranging from mild to severe damage, and it appears acutely against a background of chronic liver disease. ASH may be present in 10%-35% of hospitalized alcoholic patients.
Concomitant cirrhosis is seen in more than 50% of cases. It is defined by the coexistence of steatosis, hepatocyte ballooning, inflammatory infiltrate with neutrophils, Mallory’s hyaline and perisinusoidal fibrosis in the centrilobular area. AST levels are elevated to 2-6 times the upper limit, with AST:ALT ratio greater than 2. Increased bilirubinemia and neutrophilia are also observed. Recent onset of jaundice and/or ascites in a patient with ongoing alcohol misuse are the main observable features of symptomatic ASH. Fever, hepatomegaly, weight loss and malnutrition can occur. In severe cases, ASH may induce liver decompensation with variceal hemorrhage or encephalopathy. Patients with severe forms of ASH are prone to develop bacterial or fungal infections\(^{47}\), acute renal failure due to type 1 HRS or acute tubular necrosis and ultimately to progress to ACLF with multisystem organ failure and high mortality.

Although considered the gold standard for diagnosis of ASH, opinions are divided on the role of liver biopsy, since coagulopathy is common in this group of patients and the transjugular approach is not easily available. The lack of availability of liver biopsy should not delay treatment in severe cases\(^{69}\).

Prognostic models have been designed to identify patients with high risk of death 1-2 months after hospitalization, including: The Maddrey discriminant function (DF), MELD (Model for End Stage Liver Disease), the GASH (Glasgow ASH Score) and the ABIC score (age, bilirubin, INR, creatinine score). Several groups showed that spontaneous short-term survival of patients with DF ≥32 fluctuated between 50% and 65%, whereas 28-day survival of patients with DF <32 is close to 90%.

Regardless of severity, abstinence is key aspect of therapy. Nutritional support is also important. Corticosteroids (prednisolone 40 mg qid) were shown to significantly reduce mortality in patients with ASH who have DF ≥32, GASH ≥9 (prednisolone 40 mg qid) were shown to significantly reduce mortality in patients with ASH who have DF ≥32, GASH ≥9 and 65%, whereas 28-day survival of patients with DF <32 is close to 90%.

Patients failing to respond to medical therapy have a 6-month survival rate of around 30%, with most deaths occurring within 2 months. Early transplantation is an attractive option, but highly controversial as it challenges the 6-month abstinence rule\(^{70}\). New strategies are required to improve the probability of survival of patients with severe ASH.

4) Initial poor graft and primary non-function after liver transplantation

Initial poor graft dysfunction (IPGD) and primary graft non-function (PGNF) are diagnosed in the first days after liver transplantation, caused by a poorly functioning graft with no detectable vascular abnormalities. Despite all advances in immunosuppression and surgical preservation techniques, they are still major determinants of postoperative morbidity and mortality.

Either IPGD or PGNF are the most severe consequences of ischemia-reperfusion injury with hepatic sinusoidal endothelial damage. Histopathological findings include inflammatory infiltrates, hepatocellular damage with coagulation necrosis, hepatocyte ballooning and aggregation\(^{59}\). These findings have been associated with an elevation of cytokine levels, specifically GM-CSF, IL-6 and IL-2R\(^{59}\). Incidence post LT has been estimated between 2% and 23%, both are reported to be a common cause of liver retransplantation. PGNF differs to IPGD in the degree of dysfunction, time elapsed from LT and the probability of retransplantation. In most severe cases there is no possible graft recovery, which is classified as PGNF. Diagnosis still lacks objective criteria, and there is no consensus for the timing of retransplantation. Consequently, there is a great concern whether the patient will survive the efforts of graft recovery or whether early retransplantation should be recommended.

Most authors over the past 20 years define IPGF as an elevation of AST or ALT of more than 1500 UI and the need of clotting support within the first days after LT\(^{49}\). Once the MELD criterion for organ allocation was established, the combination of elevated bilirubin (>10 mg/dL), INR (>1.6) and AST/ALT levels (>2000 UI/mL) after the first week of liver transplantation clearly define the patients at the greatest risk of developing PGNF and the need for retransplantation\(^{75}\).

Risk factors for IPGF and PGNF include donor clinical status and age, marginal grafts (including steatosis), cold ischemia time, ischemia-reperfusion injury, small for size syndrome and the clinical condition of the recipient\(^{75}\). The
expansion of the organ donor pool due to increasing waiting lists and deaths leads to variability in early graft function.

However, the diagnosis criteria currently used for their diagnosis are based upon clinical and biochemical blood parameters. There is promising research in novel dynamic liver function tests, such as indocyanine green plasma disappearance rate, the monoethylglycinexylidide test, and several metabolic noninvasive breath tests. These may, in the near future, improve monitoring and prediction of IPGF and PGNF(16).

In summary, technical and non-technical complications may arise early after LT. When IPGF and PGNF are suspected, timing for transplantation is still based on experience, clinical and biochemical parameters.

REFERENCES


ERRATUM

In article “Intensive care management of patients with liver disease: proceedings of a single-topic conference sponsored by the Brazilian Society of Hepatology” published in journal Arquivos de Gastroenterologia, 2015(Suppl 1):55-72, on page 55 which was read:

which was read: Angelo Matos

read: Angelo Alves de Mattos

DOI: 10.1590/S0004-28032015000500004