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Revisión

Nutritional support for fulminant hepatitis

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Abstract

Introduction: **fulminant hepatitis (FH) is associated with exacerbated hypercatabolism, hypoglycemia and hyperammonemia that are accompanied by the release of proinflammatory cytokines and catabolic hormones into the systemic circulation worsening patient's clinical condition. Nutritional support is a crucial element for the recovery of these patients.**

Objectives: **the aim of this review is to update Nutritional Support for Fulminant Hepatitis.**

Methods: **the review was performed using electronic search on Medline-PubMed using Mesh-terms.**

Results and discussion: **there are not many data available on nutritional support to fulminant hepatitis or acute liver failure. Strategies for initial nutritional intervention are focused on the control of the previously described FH metabolic derangements, and should be individualized according to the severity of patient's clinical condition. Energy and protein can be provided in amounts of 25-40 kcal/kg/day and 0.8-1.2 g/kg/day, respectively. Enteral nutrition therapy is indicated for patients with advancing encephalopathy or for those who cannot be properly fed orally. Euglycemia must be achieved and protein intake can be based on BCAA formulae. Lipids can be administered as energy supplementation with caution. Adequate nutrition therapy can potentially reduce morbidity and mortality of FH patients.**

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Key words: *Fulminant hepatitis. Acute liver failure. Nutrition. Nutrition Therapy.*

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SOPORTE NUTRICIONAL PARA LA HEPATITIS FULMINANTE

Resumen

Introducción: **la hepatitis fulminante se asocia a un exacerbado hipercatabolismo, la hipoglicemia y la hiperamonemia están acompañadas por la liberación de citocinas proinflamatorias y hormonas catabólicas en la circulación sistémica, empeorando la condición clínica del paciente. El apoyo nutricional es un elemento crucial para la recuperación de estos pacientes.**

Objetivos: **el objetivo de esta revisión es actualizar el apoyo nutricional para la hepatitis fulminante.**

Métodos: **la revisión se llevó a cabo mediante la búsqueda electrónica en Medline-PubMed, utilizando malla de términos.**

Resultados y discusión: **no hay muchos datos disponibles sobre el apoyo nutricional para lahepatitis fulminante o fallo hepático agudo. Las estrategias de intervención nutricional inicial se centran en el control de los trastornos metabólicos de la hepatitis fulminante descritos anteriormente, que deben ser individualizadas de acuerdo a la gravedad de la situación clínica del paciente. Energía y proteína se pueden proporcionar en cantidades de 25-40 kcal/kg/día y 0,8-1,2 g/kg/día, respectivamente. La terapia nutricional enteral está indicada en pacientes con encefalopatía avanzada o para aquellos que no pueden ser adecuadamente alimentados por vía oral. Se debe obtener una euglicemia y la ingesta de proteínas puede estar basada en fórmulas de BCAA. Los lípidos se pueden administrar como suplemento energético con precaución. Una terapia nutricional adecuada puede potencialmente reducir la morbilidad y la mortalidad de los pacientes con hepatitis fulminante.**

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Palabras clave: *Hepatitis fulminante. Insuficiencia hepática aguda. Nutrición. Terapia nutricional.*

Abbreviations

AAA
BCAA
DCA
EPA
FH: Fulminant Hepatitis.
HE: Hepatic Encephalopathy.
ICU: Intensive Care Unit.
LT: Liver Transplantation.
MCT: Medium-Chain Triglycerides.

Introduction

Fulminant hepatitis (FH) is a severe condition characterized by rapidly progressive impairment of liver function in previously healthy individuals without pre-existing hepatic disease and with nutritional status usually preserved[1-4]. FH refers to the development of acute liver injury, and may be secondary to a virus, drug, toxin, and autoimmune and metabolic diseases[5]. The processes involved in the liver damage are not well understood, but are multifactorial and depend on the etiology of the disease, age and susceptibility of patients, and extent of hepatic injury. Major pathological liver features include severe necrosis with loss of hepatic architecture, and absence of adequate regeneration[6]. FH is associated with high mortality rates, reported as high as 80%, depending on the etiology of the disease[7]. Early assessment of FH severity and intensive support therapy in a specialized center are crucial for improving survival of these patients[1]. Given that spontaneous recovery is not common, liver transplantation (LT) remains the only life saving treatment in most cases[8].

The FH was described in 1970 by Trey & Davidson[2] as an acute disease that emerges with jaundice and within 8 weeks the patient develops encephalopathy. Later, in 1993, O'Grady et al.[3] proposed a classification according to the interval between jaundice and encephalopathy; namely hyperacute hepatitis when encephalopathy develops within 7 days after the onset of jaundice, acute when encephalopathy develops within 8 days to 4 weeks, and subacute, when encephalopathy develops within 5 to12 weeks[3]. The prognosis is less favorable for acute and subacute types than for hyperacute FH, which is associated with a higher rate of spontaneous recovery without LT[3]. LT is indicated for patients with a poor chance of spontaneous survival according to established prognostic criteria. In our Center, LT candidates are selected according to the King's College Hospital criteria that is based on evaluation of five variables: patient age, jaundice-to-encephalopathy time interval, etiology, serum total bilirubin and prothrombin time[9]. However, because LT is of limited immediate availability and patients can rapidly develop multiple organ failure, supportive therapies play an essential role in stabilizing these candidates while waiting for transplantation, as well as in cases with chance of spontaneous recovery[10,11].

The liver is a metabolic organ par excellence that performs several nutrition-related functions, particularly energy metabolism, protein and lipid synthesis, and glycemic control[12]. In FH, acute liver failure is associated with severe metabolic disorders such as exacerbated hypercatabolism, hypoglycemia and hyperammonemia. Hypercatabolism is accompanied by the release of proinflammatory cytokines and catabolic hormones into the systemic circulation worsening patient's clinical condition. Intensive care and nutritional support are key elements for the recovery of FH patients[13]. Nutritional interventions in these patients aim at maintaining the energy-protein balance in order to preserve body mass, cell functions and immunocompetence, taking into account that severe liver failure with rapid progression to multiple organ failure are likely to occur in most cases. Nonetheless, there are few studies to guide nutritional therapy for patients with FH in terms of nutritional load, supplements administration, and delivery routes[14,15]. The aim of this review is to update Nutritional Support for Fulminant Hepatitis.

Methods

Study selection

The review was performed using electronic search on Medline-PubMed, preferably in English, looking for relevant information on nutritional support for acute liver failure. The search was performed through www.ncbi.nlm.nih.gov/pubmed with the terms and Mesh-terms acute liver failure, fulminant hepatitis, fulminant hepatic failure, liver failure, liver transplantation, nutritional support and nutrition

Results and discussion

Etiology and clinical presentation of fulminant hepatitis

FH can result from various etiologies, being drug-induced and viral hepatitis the most common causes. Acetaminophen is the leading etiology in some Western countries, accounting for 46% of all FH cases in United States[16]. In Brazil and other countries, drug-induced hepatitis is the etiology in up to 30% of FH cases. In these countries other drugs than acetaminophen triggers FH highlighting alpha-methyldopa, rifampin, isoniazid, flutamide, carbamazepine, anti-thyroid agents, nonsteroidal anti-inflammatory drugs, sulfonamide, valproate, anorexigens, halothane and ecstasy. Viral hepatitis is also an important cause, being hepatitis B in most cases. Less frequent etiologies includes autoimmune hepatitis, metabolic hepatitis, Budd-Chiari syndrome and exogenous poisoning

with agents like trichloroethylene, tetrachloroethane, and Amanita phalloides mushroom. However, in 20% to 30% of patients the etiology of hepatitis cannot be determined[17,18]. Table I shows the etiology in 100 patients with transplant indication for FH admitted to the Liver Unit at Hospital das Clínicas from University of Sao Paulo Scholl of Medicine between 2002 and 2011 (unpublished data).

The extrahepatic complications of liver failure are mainly cardiovascular and renal failure, and encephalopathy related to the development of brain edema. Patients with FH present a hyperdynamic condition with increased cardiac output and high systemic energy expenditure that can lead to subclinical myocardial injury and hypercatabolism[19]. The development of acute renal failure may be associated with dehydration, hepatorenal syndrome or manifestation of acute tubular necrosis. The failing liver is unable to perform its normal synthetic and metabolic functions. In patients with FH, depletion of hepatic glycogen stores associated with glyconeogenesis impairment may lead to hypoglycemia in the more severe cases. Also the decreased ammonia metabolism with consequent hyperammonemia, plays a key role in the development of cerebral edema, and the decreased hepatic synthesis of coagulation factors and fibrinogen is likely to induce coagulopathy. Both the resulting renal failure hypervolemia and the hyperammonemia contribute to the development of cerebral edema, which is characterized by hepatic encephalopathy (HE) progressing to coma and culminating with intracranial hypertension in the more severe cases. Furthermore, acute lung injury with adult respiratory distress syndrome, and impaired glycocorticoid production (which induces arterial hypotension) may be observed[13,19,20]. When looking into the immune system, FH patients may present an immune deficiency with impairment of monocytes, neutrophils, Kupffer cells and macrophages, and a imbalance of pro-inflammatory and antiiflammatory cytokines. As a result, the immunity does not function properly increasing the risk of sepsis[21].

Table I
Causes of liver failure in 100 patients admitted to Hospital das Clinicas from University of Sao Paulo School of Medicine

Etiology of liver failure	*Patients*
Drugs	32%
Autoimmune hepatitis	15%
Hepatitis A virus	3%
Hepatitis B virus	13%
Wilson disease	4%
Budd-Chiari syndrome	1%
Indeterminate	32%

HE manifests through symptoms that range from mild confusion to deep coma, and can be classified on the basis of clinical findings. According to the West Haven Criteria, it is graded as follows: grade I - slowing of the ability to perform mental tasks, euphoria, anxiety, irritability, decreased attention, and fine tremor; grade II - lethargy or apathy, minimal disorientation, subtle personality change, flapping, and slurred speech; grade III - confusion, disorientation, somnolence to semistupor, but responsive to verbal stimuli; and grade IV - coma (unresponsive to verbal/noxious stimuli)[22]. HE grade is directly related with the intensity of cerebral edema and the severity liver disease[13,20,22].

FH patient's survival and prognosis vary according to etiology, grade of encephalopathy and disease subtype. Patients with virus-induced hepatitis present better prognosis while in those with encephalopathy grade 4 associated with cerebral edema have a worse prognosis. Moreover, patients with subacute FH present poorer prognosis despite the absence of cerebral edema[13]. Between 1984 and 2008, one-year survival rate increased from 38% to 77% after liver transplantation. However, patients with encephalopathy grades III and IV, renal failure and signs of infection (sepsis) still have the poorest prognosis[1-3,9,19].

Nutritional recommendations

Energy support and administration routes

Strategies for initial nutritional intervention are focused on the control of the previously described FH metabolic derangements, and should be individualized according to the severity of patient's clinical condition[23]. Artificial nutrition is indicated to patients unable to be sufficiently fed orally within the next 5-7 days. The use of supplementary parenteral nutrition therapy is considered when patients cannot be fed adequately by enteral nutrition[4]. Energy and protein can be provided in amounts of 25-40 kcal/kg/day and 0.8-1.2 g/kg/day, respectively. Excessive protein restriction must be avoided[14,24-26]. Patients with grade I encephalopathy are usually fed orally. Nasoenteric tubes are the route of choice for enteral nutrition therapy for patients with advancing encephalopathy or for those who cannot be properly fed orally[23]. Total parenteral nutrition therapy is not routinely indicated in cases of encephalopathy, as it is associated with risk of sepsis, particularly with fungal pathogens[13,25]. Preemptive therapy with broad-spectrum antibiotics must be administered in cases of encephalopathy grades III and IV, renal failure, parenteral feeding, and in the presence of signs of systemic inflammatory response syndrome[27,28].

FH variations in etiology and clinical presentation preclude any recommendation concerning a disease-specific composition of enteral nutrition formulae. Glucose, lactate, triglycerides, ammonia, sodium, potassium, calcium, magnesium, phosphate, and zinc

plasma levels, as well as pH, should be monitored to guide the use of substrates in nutrition formulae[23]. Ideally the nutrition monitoring should be case-specific according to the severity of catabolism and subclinical metabolic derangements, as well as the patient's clinical condition.

Glucose

Patients with liver failure are likely to progress to a hypermetabolic state, characterized by increased sympathetic activity and catabolism, associated with marked systemic inflammation and inadequate glucocorticoid production[14,19]. FH patients are prone to hypoglycemia, especially due to loss of glycogen stores, glycogenolysis impairment, and increased insulin serum levels[14,24,29]. Hypoglycemia can be treated with continuous glucose infusion. Glucose levels must be tightly controlled to ensure euglycemia[25,30]. Hypoglycemia must be avoided as it may impair intracranial hypertension control and worsen the neurological prognosis in multiple scenarios related to cerebral ischemia[24,31]. Hypoglycemia can be prevented with intravenous infusion of glucose at a rate of 2-3 g/kg/day. Hyperglycemia, in turn, can be managed with reduced intravenous glucose infusion associated with intravenous insulin administration in specific cases[19]. Glycemic control must be performed strictly according to the protocol for capillary blood glucose monitoring in critically ill ICU patients adopted by the institution concerned.

Lipids

In FH, liver glycogen depletion leads to gluconeogenesis increasing protein metabolism for glucose production[14]. Fatty acid oxidation and ketogenesis are the main non-glucose energy yielding processes for the liver. Therefore, adequate lipid supplementation should be considered in FH cases[30]. During triglyceride supplementation, triglyceride plasma levels should be carefully monitored, given that acute liver failure may compromise the use of fatty acids by the liver[23,30]. When insulin resistance is present, the use of lipids (0.8-1.2 g/kg/day) associated with glucose to meet energy requirements should be considered with caution[19]. Preference should be given to medium-chain triglycerides (MCTs), as they do not undergo lipid peroxidation and do not require much energy for absorption, utilization, or storage. Moreover, MCTs are enterally absorbed as free fatty acids without resterification, are not packaged into chylomicrons, and are readily available for energy metabolism. In patients with impaired hepatic beta-oxidation, special attention should be paid to lipid load, particularly to ICU patients receiving continuous sedation with propofol that contains fatty acid triglycerides. In such cases, lipid administration may worsen the hepatic injury[30].

Amino acids

FH patients develop hypercatabolism with significantly impaired protein metabolism depending on FH type and severity. The early introduction of enteral nutrition is advantageous in attenuating tissue protein catabolism[32]. In these cases, the use of amino acids at 0.8-1.2 g/ kg/day is recommended[4,19]. The administration of proteins at 1.0 g/kg/day does not seem to increase hyperammonemia[24].

Hyperammonemia is one of the major causes of encephalopathy. Ammonia and glutamine are thought to be the main substrates responsible for the development of cerebral edema in FH[30,33]. Amino acids released by protein hypercatabolism are converted into ammonia in the intestine. The failing liver has decreased capacity to synthesize urea from ammonia produced in the splanchnic region, leading to hyperammonemia in spite of extrahepatic ammonia detoxification. In the brain, ammonia cross easily the blood-brain barrier by passive diffusion, being metabolized to glutamine in perivascular astrocytic spaces. Glutamine, which has a powerful osmotic effect, shifts extracellular fluid into astrocytes causing glial edema and interneural communication alterations in the brain[33,34]. Increased ammonia concentration and cerebral glutamine efflux have been reported in FH patients that died due to neurological complications[33].

Normal dietary protein has not been associated with worsening of hepatic encephalopathy. Protein restriction, however, may have adverse effects on protein metabolism and should be avoided, unless encephalopathy can be related to excessive protein intake[26,35].

In FH, there is no consensus regarding optimal nutritional supplementation with nitrogen substrates or methods for monitoring the use of amino acids[30]. Imbalance between aromatic amino acids (AAA) phenylalanine, tyrosine, and tryptophan and branched chain amino acids (BCAA) leucine, isoleucine, and valine may play a role in hepatic encephalopathy. The modify protein metabolism that go along with liver failure leads to an increase in the levels of total amino acids and AAAs, and a reduction in BCAAs. BCAAs are not metabolized in the liver, and are, therefore, preferentially used by the liver in liver failure. AAAs, in turn, require the liver for metabolism, and accumulate excessively in the body fluids. AAA transport occurs across the blood-brain barrier. Once AAAs cross the blood-brain barrier, the metabolism of phenylalanine and tyrosine produces octopamine. That inhibits excitatory stimulation of the brain by acting as a false neurotransmitter, while tryptophan is metabolized to serotonin, which can worsen encephalopathy[14,36]. In view of the imbalance between AAAs and BCAAs and its role in the development of encephalopathy in liver failure, providing nutritional supplementation with branched chain amino acids to patients with FH seems reasonable despite lack of consensus[36]. Nonetheless, in patients with hyperacute FH, who frequently show cerebral edema

complicated by intracranial hypertension, amino acid administration is not mandatory[14]. In acute or sub-acute FH, however, amino acids at a dose of 0.8–1.2 g kg1 d1 should be used[14]. Supplementation with glutamine should be avoided in FH due to the role of glutamine in the development of cerebral edema, and also because of the increased serum levels of glutamine found in such cases[24,37].

Nutritional recommendations after liver transplantation

In the post-transplant period, enteral nutrition should be restarted for patients unable to resume normal oral intake promptly, preferably 12-24 hours after transplant[14,23]. This practice is associated with reduced postoperative viral infections, improved nitrogen retention, and decreased incidence of bacterial infections[36,38]. The same nutritional goals should be targeted before and after liver transplant. Adequate nutritional therapy, including correction of micronutrient and vitamin deficiencies, reduces morbidity and mortality[14]. In table II it is summarized the main recommendations to guide the nutrition support for FH patients.

Immunonutrition

Immunonutrition refers to the use of specific nutrients, including arginine, Omega-3 fatty acids EPA and DHA, antioxidants and others, in order to regulate immune response and control inflammatory response in malnourished critically ill ICU patients in the postoperative period. In surgical patients, the use of enteral formulae supplemented with immunonutrients decreases infectious complications and length of hospital stay[39,40]. In patients undergoing liver transplantation, enteral formulae enriched in arginine, Omega-3 acid and nucleotides are associated with improved recovery of protein stores and a lower rate of postoperative infectious complications[41,42]. In an experimental study, Omega-3 polyunsaturated fatty acids reduced the severity of acute liver injury and promoted liver regeneration as an anti-inflammatory agent after 90% hepatectomy in rats[43]. However, a randomized trial to evaluate immunonutrition in liver transplantation did not find any benefits in postoperative outcome[44]. And there are no studies supporting recommendations for intervention with immunonutrients in FH.

Conclusion

FH is a condition that leads to acute multisystem failure and is commonly associated with high mortality rates. Keeping patients with FH stabilized while waiting for liver transplantation requires intensive care, including individualized metabolic support and nutritional interventions. The goals of nutritional interventions are to preserve and maintain pre- and postoperative body mass and immunocompetence. Adequate nutrition therapy with correction of micronutrient deficiencies can potentially reduce morbidity and mortality in patients with FH.

Table II
Guide for nutrition support for patients with fulminant hepatitis from Hospital das Clínicas – University of Sao Paulo School of Medicine

General	Preference should be given to enteral nutrition (via nasoduodenal tube). Individualized nutrition therapy.
Total energy	25-40 kcal/kg/day
Proteins	0.8-1.2 g/kg/day Formulae enriched in BCAA and poor in AAA. Avoid supplementation with glutamine, methionine and tryptophan. Amino acid supplementation should be used in acute and sub-acute FH, but is not mandatory in hyper-acute FH.
Lipids	0.8-1.2 g/kg/day Preference should be given to medium-chain triglycerides. Keep plasma triglycerides ≤ 4 mmol/L. Avoid the administration of propofol and lipids when hepatic beta-oxidation impairment is suspected.
Intravenous glucose	2 - 3 g/kg/day when there is risk of hypoglicemia. Avoid hyperglycemia.
Monitoring	Glucose, ammonia, sodium, potassium, calcium, magnesium, phosphate, zinc, triglycerides, lactate and pH.
After liver transplantation	Follow recommendations above. Resume enteral diet as soon as 12-24 hours after surgery.

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