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## Nutrition therapy in severe head trauma patients

*Terapia nutricional no traumatismo cranioencefálico grave*

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### ABSTRACT

This article reviews the literature, organizes the major findings, and generates the best evidence-based recommendations on nutrition therapy for head trauma patients. Despite recent advances in head trauma diagnosis and therapy, the mortality associated with this condition remains high. Few therapeutic interventions have been proven to effectively improve this condition. Head trauma causes multiple metabolic and electrolytic disorders; it is characterized by a hypermetabolic state that is associated with intensive catabolism, leading to specific nutritional needs.

The current literature lacks specific guidelines for nutrition therapy in severe head trauma patients, although a substantial

amount of data has been reported and relevant issues are currently being studied; these data may allow better nutrition therapy guidelines for these patients. In addition to a well-trained multi-disciplinary team, the following recommendations appear to improve outcomes: introducing nutrition therapy early; preferred enteral administration; appropriate energy intake; formulations that are tailored to specific patients, including appropriate nutrients; and strict electrolytic and metabolic monitoring. Understanding the pathophysiology and the consequences of therapy is fundamental.

**Keywords:** Craniocerebral trauma; Brain injuries; Nutrition therapy; Nutritional support; Enteral nutrition; Parenteral nutrition

**Conflicts of interest:** None.

Submitted on February 7, 2012

Accepted on March 26, 2012

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### INTRODUCTION

Head trauma (HT) continues to be a highly lethal condition, with an overall mortality of 20% to 50% in the United States of America (USA).<sup>(1)</sup> HT causes 52,000 deaths annually in the USA, with 85% of these deaths occurring within the first two weeks after the trauma.<sup>(2)</sup> Brazilian statistics on HT are sparse and are only available for specific regions. In São Paulo, the 1997 HT admission rate was 0.36 per 1,000 inhabitants, with an estimated mortality rate of 26 to 39 per 100,000 inhabitants.<sup>(3)</sup>

Currently, strategies for maintaining brain perfusion and preventing hypoxemia, hypotension and intracranial hypertension have reduced the risk of death and improved severe HT outcomes.<sup>(4)</sup>

In spite of the limited data on the relevance of nutrition therapy for HT patients, two systematic Cochrane Collaboration reviews have suggested

that nutrition therapy may improve mortality and neurological outcomes.<sup>(5,6)</sup>

Therefore, this article will discuss the most recent evidence on the benefits of nutritional support for craniocerebral trauma patients and make clinical recommendations.

## METHODS

A systematic literature review with a defined search strategy was conducted using the following DeCS (Heath Sciences Descriptors) keywords: traumatic brain injury, head injuries/craniocerebral trauma, nutritional support, nutritional therapy, enteral nutrition and parenteral nutrition. The searches were conducted using the SciELO (Scientific Electronic Library Online) and PubMed (U.S. National Library of Medicine) databases in November 2011. In addition, well-known text books were consulted.<sup>(7-9)</sup>

A total of 703 articles were identified, from which 55 were selected using evidence-based medicine criteria, their possible clinical impact and the relationship between severe head trauma, nutrition support and outcomes. The selection criteria considered the quality and strength of the evidence in descending order. That is, the studies were searched in descending order of relevance: meta-analyses, randomized controlled trials, non-controlled studies, cohort studies, case-control studies, and case report articles. The references were read and analyzed based on the study quality and evidence strength, and the information was summarized to clarify the data and make suggestions based on the most recent relevant evidence.

## METABOLIC SCENARIO

HT triggers hypermetabolic and catabolic states, severely impairing nitrogen homeostasis. It is characterized by disproportional pro-inflammatory cytokine (e.g., tumor necrosis factor- $\alpha$ , interleukin-1 and interleukin-6) production and release that is associated with increased counter-regulatory hormones (e.g., cortisol, glucagon and catecholamines) release. This process leads to increased systemic and cerebral energy needs, even in paralyzed patients.<sup>(10)</sup> The increased energy needs can persist for long periods.

The mechanical forces involved in the initial trauma cause distortion, shearing and destruction of brain tissue, which causes the primary injury.

The secondary injury mechanisms include a wide

range of events, including neuronal depolarization, ion homeostasis changes, glutamate exotoxicity, nitric oxide and oxygen free radical generation, lipid peroxidation, blood-brain barrier disruption, interstitial and cellular swelling, secondary hemorrhage, ischemia, intracranial hypertension, mitochondrial dysfunction, axonal rupture, cell-mediated inflammation and death from both apoptosis and necrosis.<sup>(11)</sup>

This metabolic storm, in conjunction with energy changes, may be caused by systemic conditions (such as post-traumatic inflammatory responses and infections) but can also have a central nervous system component. Brain glucose metabolism rate is increased during this process, likely as a result of mitochondrial dysfunction.<sup>(12)</sup>

Mannitol and hypertonic saline solutions are frequently used to treat increased intracranial pressure because they can modulate brain blood flow rheology and osmolality. Neuromuscular blockers, sedative drugs (such as propofol) and barbiturates (such as thiopental) are also commonly used to suppress brain metabolism and reduce the injured cells' "energy stress". New therapies, including calcium channel blockers, poly ADP-ribose polymerase and cyclosporine, are being currently investigated for their potential to modulate secondary injury mechanics.<sup>(13)</sup>

Recently, preliminary data from three clinical trials have suggested that progesterone reduces brain edema and increases anti-oxidant levels, thereby reducing HT mortality.<sup>(14)</sup> In addition, the role of erythropoietin in restoring memory and the impact of statins after HT are being studied.<sup>(15)</sup> Human trials have indicated that increased glucose utilization may persist for five to seven days after trauma.<sup>(16-18)</sup> The combined effects of these changes, immobility and lack of early nutritional support may lead to rapid and severe lean mass depletion.

Malnutrition has been reported to effect inpatient morbidity and mortality.<sup>(19,20)</sup> Zinc is an important cofactor for substrates associated with metabolism, the immune system and N-methyl-D-aspartate (NMDA) receptor function. Serum zinc levels are reduced in HT patients, due to the liver sequestration and increased renal clearance. Zinc supplementation for up to one month following HT appears to improve protein metabolism and neurological prognosis.<sup>(21)</sup>

Magnesium also appears to be neuro-protective because it modulates cell energy production and calcium inflow through its effects on NMDA receptors.<sup>(22)</sup>

Insulin-like growth factor binding protein-3 (IGFBP-3) is also reduced, which increases clearance and decreases lower insulin-like growth factor-1 (IGF-1) activity. IGF-1 supplementation in HT apparently reduces hyperglycemia and improves protein preservation.<sup>(23)</sup>

Glutamine, which is typically associated with reduced bacterial translocation, may increase glutamate synthesis. Glutamate interacts with NMDA receptors promoting cell death by calcium inflow,<sup>(13,24)</sup> and the risk to benefit ration of L-arginine is currently uncertain.<sup>(25)</sup>

Additional information on the mechanism of action and clinical relevance of electrolyte and amino-acid specific supplementation (such as with magnesium or glutamine) is required to clarify their therapeutic role.

### PRIOR MALNUTRITION IN HT PATIENTS

Alcoholism is frequent in polytrauma patients. Symptoms of alcohol abuse can manifest in any part of the nervous system, including the encephalon, peripheral nerves and neuromuscular junctions.<sup>(26)</sup> Alcohol causes central nervous system changes ranging from psychomotor agitation to coma and death. Chronic alcohol abuse leads to changes in the number and function of receptors, as a compensatory response to alcohol's depressive effects. Type A GABA receptors are downregulated, while NMDA glutamate receptors are upregulated, which can lead to neuronal excitability when alcohol intake is abruptly discontinued.<sup>(26,27)</sup>

Malnutrition is mostly caused by B12 (cyanocobalamin), B1 (thiamine), B5 (riboflavin) and B6 (pyridoxine) vitamin deficiencies. Complex B vitamins are hydrosoluble and have short half lives; therefore, they are easily depleted. In addition, many drugs, including antibiotics, may impair their absorption and metabolism.<sup>(28)</sup> Therefore thiamine, pyridoxine and B12 replacement is recommended for polytrauma patients to prevent certain acute neurological syndromes.

### DRUG CONSIDERATIONS

Many of the drugs used for treating intracranial hypertension (ICH) may affect nutritional support and electrolytic balance.

Mannitol, an osmotic diuretic, is used as a first line agent for acutely reducing intracranial pressure. Frequent use of mannitol requires osmolality and electrolyte monitoring. Hypertonic saline (HS)

is another frequently used agent. The typical concentrations used for this purpose range from 3% to 23.4% sodium hydrochloride. HS's osmotic effects are similar to those of mannitol, although HS trends to have less diuretic effect. However, serum sodium and chloride level may rise rapidly after repeated doses; therefore acid-base parameters and metabolism should be regularly monitored.

Propofol has become a routine treatment for reducing brain metabolism. It is dissolved in a soybean oil and egg phospholipid emulsion. This lipid vehicle provides extra energy (propofol 10% provides 1.1 Kcal/mL)<sup>(29)</sup> that should be accounted for in nutritional support calculations. A combination of propofol and enteral nutrition enriched with  $\omega$ -3 fatty acids (as eicosapentaenoic acid) can counteract the anti-inflammatory effects resulting from an unbalanced  $\omega$ -6 to  $\omega$ -3 ratio caused by propofol's vehicle.<sup>(8)</sup>

Barbiturate drugs such as thiopental are used to reduce brain metabolism in difficult to manage ICH. The energy requirements of such patients tend to be approximately 80% of their predicted energy expenditures.<sup>(30,31)</sup> Their protein needs may also be reduced, as evidenced by a 40% reduction in their urinary nitrogen.<sup>(31)</sup> A barbiturate coma and narcotics such as fentanyl and morphine also reduce gastrointestinal mobility and gastric emptying, often causing intolerance to enteral nutrition.

Several antiepileptic drugs, such as phenytoin, phenobarbital, primidone and carbamazepine, are frequently prescribed in neurological intensive care units to prevent seizures. All of these drugs may impact folate absorption. However, folate replacement may reduce phenytoin levels and increase seizure risk. Phenytoin may also interact with vitamin D and reduce calcium absorption, which may lead to osteopenia and osteoporosis, especially in chronic cases.

Valproic acid may lead to increased serum ammonia levels and increase the risk of hepatic encephalopathy, especially in liver disease patients.

Given these considerations, routine liver function monitoring (by regular hepatocellular and canalicular liver enzyme measurements), serum ammonia monitoring and serum antiepileptic drug levels are recommended for this type of intensive care patients.

### DRUG-NUTRIENT INTERACTIONS

Interactions between nutrients and drugs should also be considered. Just as enteral administration is

greatly preferred to parenteral administration, enteral administration is also preferable for drugs. Many drugs that are administered intravenously may show appropriate enteral bioavailability; therefore, as soon as enteral function is present and the patient can tolerate enteral nutrition, these drugs may be switched to enteral administration.<sup>(32,33)</sup>

Commonly used phenytoin formulas include sodium phenytoin for parenteral administration and acid phenytoin solutions for enteral use. Independently of the solution used, phenytoin is well absorbed under relatively normal conditions (> 80%).<sup>(34)</sup> However, combining acid phenytoin suspensions and enteral nutrition formulas may lead to reduced phenytoin absorption.<sup>(35)</sup> To prevent concomitant administration, some clinicians recommend no enteral nutrition for 1 to 2 hours before and after each phenytoin dose. Other authors recommend adjusting the acid phenytoin solution dose or using a phenytoin sodium enteral formulation, which can be administered with enteral nutrition.<sup>(36)</sup> Independent of the route through which phenytoin is administered, pharmacokinetic (serum level) monitoring is essential for keeping serum levels within the therapeutic range.

Other drugs administered enterally may not be compatible with nutrition formulas. For example, carbamazepine suspensions and sucralfate form precipitates that may occlude enteral feeding tubes.<sup>(37)</sup> Other incompatibilities may also occur. For example ciprofloxacin bioavailability is reduced by 44% when it is administered with enteral formulations, probably due to polyvalent cation chelation.<sup>(38)</sup>

Therefore, some drugs may affect nutrient and electrolyte concentrations, either by directly increasing them (e.g., intravenous sodium and potassium penicillin salts) or by interfering with absorption, metabolism or elimination, e.g., carbamazepine (hyponatremia), ticarcillin/piperacillin (hypernatremia) and amphotericin B deoxycholate (hypokalemia and hypomagnesemia). Therefore, interactions between drugs and nutrients should be assessed daily, preferably by a multi-disciplinary team that includes nutritionists and clinical pharmacists.

## NUTRITION BASES

### Assessment of swallowing

Dysphagia is frequent in HT patients; it may be found in up to 61% of the cases.<sup>(39)</sup> Therefore, a specialized deglutition assessment should be

performed before oral nutrition is initiated. Speech therapists should be part of the assessment team.

Patients with severe HT are usually not able to effectively communicate due to reduced consciousness and/or tracheotomies. Information on the trauma mechanism, injury severity, feeding difficulties and weight loss can be retrieved from medical records and caregivers. Findings suggesting dysphagia include coughing and choking during or after a meal, a history of tube feeding, pulmonary complications, weight loss, sialorrhea and a need for suctioning.

Deglutition rehabilitation, using compensatory strategies and specific exercises, is an overall principle when managing dysphagia patients. The compensatory strategies attempt to change feeding behavior by changing food bolus size and texture as well as head and body posture. Rehabilitation exercises attempt to induce structural changes by intensifying afferent motor and sensory stimuli.<sup>(40)</sup>

For an updated review, please refer to the 2011 I Brazilian Consensus on Nutrition and Dysphagia.<sup>(41)</sup> Increased aspiration risk due to reduced consciousness and/or the need for intubation to maintain respiration frequently prevent oral nutrition in severe HT cases. Therefore, only two options are available for early enteral nutrition: gastric and jejunal.<sup>(42)</sup>

### Nutrition status assessment

Before prescribing nutritional support, the current and prior nutritional status, the underlying disease progression, severity and time and the associated catabolic effects should be assessed.

Several methods and techniques may be used for nutritional assessment; however, no single method is sufficiently accurate to be considered the gold standard in critically ill patients.

An overall subjective assessment is a simple, affordable and reproducible technique.<sup>(7,8)</sup> Such an assessment should consist of anamnesis and an objective physical examination conducted within 3 days of admission. The subjective nutritional assessment is based on a scoring system that incorporates several factors. The patient is rated as well-nourished if the total score is between 1 and 17 points, moderately underfed if it is between 17 and 22 points, and severely underfed if it is above 22 points.

### Nutrition status indicators

Measures such as body weight, height, body mass index (BMI) and physical constitution should

be obtained.<sup>(7)</sup> Blood values such as serum albumin, prealbumin, transferrin and a lymphocyte count may be used for nutritional status assessment.<sup>(33)</sup> However, blood proteins are influenced by hydration and hypercatabolic states and change markedly during the first two weeks after severe HT.

Nitrogen balance (NB) is a practical and affordable method for assessing protein nutrition status. Nitrogen balance may be determined by collecting a 24-hour urinary urea (Uu 24 h) sample from a patient with adequate renal function and calculating the dietary nitrogen ingested (NI).

## NUTRITION REQUIREMENTS

### Energy requirement calculation

Indirect calorimetry continues to be the gold standard for assessing the energy expenditure of severe HT patients. However, the energy requirements of severe brain injury patients with intermittent muscle contractions, sympathetic storming or fever may not be accurately measured by indirect calorimetry.

Severe HT patients may have energy requirements as high as 120% to 250% above their basal energy expenditure estimate from the Harris-Benedict equation.

Sedative, paralyzing and barbiturate drugs may reduce this need to 76% to 120% of the estimated basal energy expenditure. Providing 140% of the estimated energy expenditure may be a good starting strategy.

Equal attention should be paid to overfeeding, i.e., providing more energy than the patient needs. Excessive or prolonged overfeeding may be harmful. It can result in metabolic issues such as hyperglycemia and a refeeding-type syndrome with electrolytic disorders, liver steatosis, pulmonary issues that complicate ventilator weaning and even obesity in long-term cases.<sup>(33)</sup>

Energy expenditure in severe HT cases may be predicted using several validated published equations.<sup>(33)</sup> A simple bedside "pocket formula" for calculating energy requirements allows 25 to 30 Kcal/Kg desirable weight/day when following the European recommendations and 20 to 25 Kcal/Kg desirable weight/day when following the American and Brazilian recommendations (which emphasize reducing the overfeeding risk).

The current guidelines recommend 1.5 to 2.0 g protein/Kg body weight/day for acute HT patients.

These requirements should be routinely reassessed and appropriately adjusted based on the observed nitrogen balance.<sup>(43)</sup>

## ENTERAL OR PARENTERAL NUTRITION SUPPORT

Enteral administration is preferred for acute neurological patients. Six meta-analyses have compared enteral versus parenteral nutritional support in general populations of critically ill patients and have found that enteral administration is associated with significantly reduced infectious morbidity.<sup>(43-45)</sup> However, this association has not been established in a population consisting only of HT patients.<sup>(43)</sup> Additionally, experimental data suggest that parenteral nutrition may increase brain swelling; however, this is apparently not a clinical issue.<sup>(43)</sup>

Gastrostomy and jejunostomy have been studied as alternatives to nasal and oral feeding tubes since the 1990s. Improved surgical techniques and undesirable effects from nasal and oral feeding tubes contribute to the interest in this topic.<sup>(40)</sup>

## STARTING NUTRITION THERAPY

Nutrition therapy should start early: within 24 to 48 hours of admission to the intensive care unit. The feeding should be adjusted based on the patient's nutritional requirements over the next 48 to 72 hours. This process is often challenging in severe HT patients. The Brain Trauma Foundation recommends that total nutritional support should be achieved within 7 days of the injury.<sup>(42)</sup> Installing enteral access and starting enteral nutrition should be attempted as soon as volume resuscitation is complete and the patient is hemodynamically stable.<sup>(45,45)</sup>

Early nutritional support is able to reduce the secretion of catabolic hormones, which is already increased in this setting. It is also able to at least partially preserve the previous nutritional conditions and partially preserving body weight and muscle mass. Additionally, it is associated with less intestinal bacterial proliferation and therefore less translocation.

## INTOLERANCE TO ENTERAL NUTRITION SUPPORT

A considerable fraction of severe HT patients cannot tolerate enteral nutrition within the first two



weeks of their injuries.<sup>(33,47)</sup> Intolerance to enteral nutrition is generally manifested by increased gastric residue, gastro-esophageal reflux, vomiting, abdominal distension and diarrhea. These complications may result in ineffective enteral nutrition, increased risk of aspiration pneumonia, prolonged ICU stays and increased mortality.<sup>(47)</sup>

There are several reasons for intolerance to enteral nutrition in HT patients: reduced gastrointestinal mobility, which is characterized by decreased inferior esophageal sphincter pressure, prolonged and altered gastric emptying with antral hypermotility and motor complexes disorders; hyperglycemia; inflammation; medications; electrolytic disorders; hypoalbuminemia; reduced colon absorption; and changes in the normal intestinal flora.<sup>(47)</sup>

## TECHNIQUES TO IMPROVE ENTERAL NUTRITION TOLERANCE

**1. Early enteral nutrition:** The American Society for Parenteral and Enteral Nutrition (ASPEN) and the Canadian Clinical Practice Guidelines (CCPG) recommend that enteral nutrition to be started within 24 to 48 hours of admission to the ICU, as soon as the patient is stabilized. The European Society for Parenteral and Enteral Nutrition (ESPEN) recommends starting enteral nutrition within 24 hours whenever possible.<sup>(38-40,42,44)</sup>

**2. Enteral formulas:** Complete and isotonic formulas should be initially chosen. Given their high price, minimally improved tolerance and increased incidence of diarrhea, peptide-based formulas are not recommended by ESPEN and CCPG.

**3. Feeding routes and methods:** Patients who cannot tolerate gastric feeding may benefit from a post-pyloric small bowel tube, with improved achievement of energy targets. When the different techniques were compared, however, no significant differences in mechanical ventilation-associated pneumonia or mortality were detected.<sup>(45,47-49)</sup> Continuous infusion is recommended by ASPEN for intolerant or high-risk patients. A 10 to 40 mL/h infusion rate can be used initially. It can be increased by 10 to 20 mL/h every 8-12 hours, as tolerated, until the energy target is reached. It is critical to adopt protocols with clear target energy intakes and infusion rates, early starting times and specific techniques for measuring gastric residue and infusion frequencies and for detecting cases where the infusion should be discontinued or adjusted.

## 4. Monitoring gastrointestinal function:

Symptoms such as nausea, vomiting, abdominal distension, intestinal sounds, flatus and feces elimination and diagnostic techniques such as abdominal radiographs and gastric residue measurements may suggest gastrointestinal motility disorders. ASPEN recommends that gastric residue be measured every 4 hours during gastric feeding and recommends avoiding withholding the infusion for residues of less than 500 mL in the absence of other signs of intolerance. There are two ways to measure gastric residue volume: by gravity (leaving a collection bottle below the level of the stomach for 10 minutes) and suctioning with a 50 mL syringe.

**5. Prokinetic drugs:** ASPEN and ESPEN recommend intravenous metoclopramide and erythromycin for patients who are intolerant to enteral nutrition. CCPG recommends only metoclopramide, given the problems with erythromycin-induced bacterial resistance. In Brazil, domperidone and bromopride are also used; however, no specific trials have evaluated these drugs for this indication. Metoclopramide and bromopride are linked to the same D2 dopamine receptor; therefore, using them together has not proven effective and may increase side effects.

Oral naloxone has been used to increase enteral nutrition tolerance and reduced the incidence of mechanical ventilator-associated pneumonia during opiate analgesia.<sup>(48)</sup> The following doses are recommended:

- metoclopramide 10 mg IV every 6 hours;
- erythromycin 1 to 2 mg/Kg body weight IV every 8 hours;
- domperidone 10 mg PO every 6 hours; and
- bromopride 10 mg IV every 8 hours.

**6. Raised bed head:** ASPEN and CCPG strongly recommend raising the head of the bed when severely ill patient are receiving enteral nutrition. They recommend keeping the head of the bed elevated from 30 to 45° if it is not medically contraindicated.

**7. Blood glucose control:** There is evidence that intolerance to enteral nutrition during critical illness is associated with sub-optimal blood glucose control, suggesting that a more strict blood glucose control would both improve survival and potentially improve tolerance to enteral nutrition.<sup>(50)</sup> Hyperglycemia has adverse effects on the gastric emptying and promotes gastroparesis. ASPEN recommends maintaining blood glucose between 110 and 150mg/DL during nutrition

support because more strict control could lead to harmful hypoglycemia.<sup>(51)</sup>

## CLOSING REMARKS

Although controlled trials are lacking, there is little doubt that nutritional support and metabolic control are relevant considerations when managing acute severe head trauma patients.

Care should be devoted to the administration route and nutrition requirements. There should be frequent reassessments, recalculations and tailored adjustments for particular cases. Diet can even be used to modulate inflammatory responses.

The entire patient should always be considered, and a holistic and global approach to the patient's needs is desirable.

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## RESUMO

O objetivo do presente artigo é revisar a literatura e organizar os principais achados, gerando recomendações baseadas nas melhores evidências encontradas relativas à terapia nutricional nos casos de traumatismo cranioencefálico.

O traumatismo cranioencefálico permanece uma pato-

logia altamente letal, apesar dos avanços em seu diagnóstico e tratamento. Poucas intervenções terapêuticas tem se mostrado eficazes em melhorar este quadro.

Há múltiplas alterações metabólicas e hidroeletrólíticas decorrentes do traumatismo cranioencefálico, caracterizadas por um estado hipermetabólico associado a um intenso catabolismo, que levam a necessidades nutricionais específicas.

Na literatura atual não há diretrizes específicas para terapia nutricional em pacientes vítimas de traumatismo cranioencefálico grave, mas há muitos dados interessantes e questões que estão sendo melhores estudadas, possibilitando um melhor direcionamento da terapia nutricional neste cenário.

Além de avaliação e acompanhamento por uma equipe multiprofissional qualificada e treinada para estas questões, a introdução precoce do suporte nutricional, a utilização preferencial da via enteral com a infusão adequada de calorias, o uso de formulações adequadas e nutricionalmente equilibradas para cada caso específico, associadas a utilização de imunonutrientes específicos, melhor controle hidroeletrólítico e metabólico, além de melhor entendimento fisiopatológico e das consequências das próprias terapêuticas instituídas, parece modificar os desfechos destes casos.

**Descritores:** Traumatismos craniocerebrais; Traumatismos encefálicos; Terapia nutricional; Apoio nutricional; Nutrição enteral; Nutrição parenteral

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