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Revisión

Enteral nutrition therapy for critically ill adult patients; critical review and algorithm creation

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Abstract

Introduction: Undernutrition directly affects critically ill patient’s clinical outcome and mortality rates.

Objective: Interdisciplinary algorithm creation aiming to optimize the enteral nutrition therapy for critically ill adult patients.

Data source: Pubmed, SciELO, Scholar Google, Web of Science, Scopus, with research of these key words: protocols, enteral nutrition, nutritional support, critical care, undernutrition, fasting.

Setting: Intensive Care Unit, Hospital de Clínicas, Federal University of Uberlândia, MG, Brazil.

Measurements and main results: Were established in the algorithm a following sequential steps: After a clinical-surgical diagnosis, including the assessment of hemodynamic stability, were requested passage of a feeding tube in post-pyloric position and a drainage tube in gastric position. After hemodynamic stability it should be done the nutritional status diagnosis, calculated nutritional requirements, as well as chosen formulation of enteral feeding. Unless contraindicated, aiming to increase tolerance was started infusion with small volumes (15 ml/h) of a semi-elemental diet, normocaloric, hypolipidic (also hyperproteic, with addition of glutamine). To ensure infusion of the diet, as well as the progressive increase of infusion rates, the patient was monitored for moderate or severe intestinal intolerance. The schedule and infusion rates were respected and diet was not routinely suspended for procedures and diagnostic tests, unless indicated by the medical team.

Conclusions: For nutrition therapy success it is essential routine monitoring and extensive interaction between the professionals involved. Nutritional conducts should be reevaluated and improved, seeking complete and specialized care to the critically ill patients. Adherence to new practices is challenging, though instruments such as protocols and algorithms help making information more accessible and comprehensible.

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Key words: Protocols, Enteral nutrition, Critical care. Undernutrition, Fasting.

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Terapia nutricional enteral para pacientes adultos en estado crítico: análisis crítico de la literatura y la creación de algoritmo

Resumen

Introducción: La hiponutrición afecta directamente al pronóstico clínico y las tasas de mortalidad del paciente crítico.

Objetivo: Creación de un algoritmo interdisciplinar cuyo objetivo es optimizar la terapia con nutrición enteral para los pacientes adultos críticos.

Fuente de datos: Pubmed, SciELO, Scholar Google, Web of Science, Scopus, con la búsqueda de estas palabras clave: protocolos, nutrición enteral, soporte nutricional, atención crítica, hiponutrición, ayuno.

Contexto: Unidad de Cuidados Intensivos, Hospital de Clínicas, Universidad Federal de Uberlândia, MG, Brasil.

Medidas y principales resultados: Se establecieron en el algoritmo los siguientes pasos secuenciales: tras un diagnóstico clínico-quirúrgico, que incluía la evaluación de la estabilidad hemodinámica, se solicitaba la colocación de una sonda de alimentación en la posición post-pilórica y un tubo de drenaje en la posición gástrica. Tras la consecución de la estabilidad nutricional se realizaba el diagnóstico del estado nutricional, se calculaban las demandas nutricionales y se escogía la formulación de la nutrición enteral. A no ser que estuviese contraindicado, se iniciaba la tolerancia con la infusión de volúmenes pequeños (15 ml/h) de una dieta semielemental, normocalórica, hipolipídica (también hipoproteica con la adición de glutamina). Para asegurar la infusión de la dieta, así como el aumento progresivo de las tasas de infusión, se monitorizaba al paciente con respecto a la intolerancia intestinal moderada o grave. Se respetó el régimen y las tasas de infusión y la dieta no se interrumpió de forma rutinaria para los procedimientos y las pruebas diagnósticas, a no ser que el equipo médico lo indicase.

Conclusiones: Para el éxito de la terapia nutricional, es esencial monitorizar de forma rutinaria y extensiva la interacción entre los profesionales implicados. Las conductas nutritivas deberían reevaluarse y mejorarse, buscando la atención completa y especializada de los pacientes críticos. La adherencia a las nuevas prácticas es un reto, si bien los instrumentos como los protocolos y los algoritmos ayudan a hacer la información más accesible y comprensible.

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Introduction

According to the specialized literature, the prevalence of undernutrition among hospitalized individuals ranges from 18.2% to 40%.1,2,4,3 Due to the increase in the metabolic basal rate6,7 and the presence of numerous situations that make the administration of enteral diets8,9,10 difficult, there is an expectation that undernutrition prevalence among critically ill patients will be even higher.11,12 The presence of malnutrition among critically ill patients is alarming13 due to its association with a higher susceptibility to infections;14,15 lean body mass reduction; predisposition to respiratory insufficiency/failure;7,16 impairment of wound and anastomosis healing;17,18 development of pressure ulcers;19,20 increase of cost and length of hospitalization;21,22 and higher mortality rates.14

Nutritional therapy plays an important role in the treatment of critically ill patients, because it allows the tailored administration of energy and nutrients, prevents/reduces the installation of undernutrition, or corrects nutritional alterations already installed in undernourished patients.23,24 In addition, it has been recently demonstrated that nutritional therapy plays a primary therapy role, intervening directly in the pathophysiological alterations of diseases and hence, in the clinical moment.25 However, the guarantee of nutritional care that meets the specific requirements of each critically ill patient, is still a challenge for nutrition professionals worldwide.8,12,25

Factors such as gastrointestinal disorders, use of vasoactive drugs, problems related to the feeding tube and the indication of fasting for procedures, have been shown to be the major causes for the reduction/suspension of enteral diet infusion, particularly in the first days following severe injury.26,27,31 In clinical practice the presence of these interference factors is associated with considerable differences between the caloric goal, the prescribed diet and the one effectively infused.9,25,30 According to McClave et al.28 some interference factors in diet administration can be classified as avoidable, and can be controlled or even solved in the clinical practice, assuring a better infusion of the calculated and prescribed diet. However, some interference factors are classified as unavoidable, i.e., they are inherent to the clinical status of the critically ill patients or to the therapeutic planning. This means that, even recognizing the direct or indirect interference of the factor in the installation of protein-energy malnutrition (PEM), it is not possible to control or solve it.29

In the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition guidelines,32 it is indicated that the use of protocols provides better infusion of the enteral nutrition therapy suggested, ensuring a more appropriate supply of energy and nutrients to the critically ill patient. Adam and Batson33 report four main areas in which the use of a protocol can benefit the care of a critically ill patient: i) in patient selection, ensuring the administration of diet exclusively for patients with a formal indication of nutritional therapy; ii) in the programming of nutritional therapy, ensuring that the diet is initiated and conducted at the correct moments; iii) in the supply of energy and nutrients, ensuring that the critically ill patient receives the appropriate amount and ratio of nutrients; and iv) in the diet composition, ensuring that the formulation has an optimal composition that meets the specific requirements for nutrients according to the clinical moment of each patient.

Objectives

Considering the potential importance associated with the implementation of protocols/algorithm, this study aimed to conduct a critical review in order to create an algorithm in an attempt to optimize enteral nutrition therapy for critically ill patients, hospitalized in the Adult Intensive Care Unit (ICU), Hospital de Clínicas, Federal University of Uberlândia, Uberlândia, MG, Brazil.

Methods

For the algorithm creation, between September and November 2009, a review of specialized literature was conducted, with the selection of guidelines and recently published articles in outstanding scientific periodicals in the areas of nutrition and intensive care. Moreover, some protocols found in the literature, as well as the experiences of researchers in the area, were used as the basis for creating the algorithm presented in this study.

The studies analyzed were originally published in English, with reference to the databases: PubMed, SciELO, Google Scholar, Web of Science and Scopus. The following keywords and their combinations were used as a search strategy: protocols, enteral nutrition, nutritional support, critical care, undernutrition and fasting.

The study was approved by the Research Ethics Committee of the Federal University of Uberlândia (Protocol Registration CEP/UFU 367/08).

Results and discussion

A prominent principle adopted for the algorithm creation was the inclusion of the various professional
categories that act directly or indirectly in the provision of enteral nutrition. The proposed actions in the algorithm functions were distributed among medical, nursing, nutrition, and pharmacy staff, as well as the whole multiprofessional enteral nutrition team. To highlight the specific actions of each team, each group was represented by boxes with different shapes and colors in the algorithm.

In the algorithm organization, the establishing of appropriate actions was sought in order to solve various problems related to the enteral nutrition of critically ill patients, such as: i) to reduce periods of total or partial fasting, to which patients are submitted during the period in the ICU, ii) to improve tolerance to enteral nutrition, and iii) to enable a faster diet improvement, optimizing the administration of enteral nutrition according to individual responses and tolerances, always attempting to reduce the incidence and severity of PEM among critically ill patients.

**Hemodynamic stability and tube positioning**

The first proposed action is to establish the clinical and surgical diagnosis of the patient, which must be performed by the medical team responsible. Immediately after this diagnosis three procedures should be performed, as a rule, simultaneously: i) to identify whether the patient presents hemodynamic stability, according to internal protocols and specific ICU procedures (medical staff); ii) to insert and confirm the post-pyloric positioning of the feeding tube (nursing staff), and iii) to insert and position the gastric drainage tube (nursing staff) (fig. 1). Therapeutic action should be taken until the patient’s hemodynamic stability is achieved. From the moment the patient is hemodynamically stable, and the feeding and drainage tubes are properly positioned, the procedures are initiated for the selection of the route of diet administration. Once the enteral route is indicated as preferable to the parenteral route for feeding a patient who is expected to be nil per os, the insertion of a feeding tube, before being certain of using this route, aims to shorten the delay in starting the enteral nutrition due to tube feeding positioning.

In enteral nutrition practice, it is common that the suspicion of gastroparesis and/or the absence/decrease in small bowel sounds, lead to a delay in the initiation of enteral diet administration of five to seven days. However, due to the high possibility of critically ill patients developing PEM, with the consequent increases in morbidity and mortality, this action must be reevaluated. In the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition guidelines it is indicated that “in the patients in ICU, neither the presence nor absence of small bowel sounds nor the evidence of the passage of flatus and stool are required to star the enteral nutrition.” Thus, the initiation of enteral nutrition should be considered as soon as the patient acquires hemodynamic stability or requires only low doses of vasoactive catecholaminergic drugs (norepinephrine < 0.3 µ/kg/min).

It has been shown in the literature that both gastric and post-pyloric positioning of feeding tubes are acceptable for the enteral nutrition of critically ill patients. However, in those cases that it is necessary to suspend the diet due to repeated high residual gastric volume, the post-pyloric positioning of the feeding tube should be considered. Thus, in the algorithm it is recommended to confirm the post-pyloric positioning of the feeding tube, by simple X-ray of the chest with visualization of the diaphragm, before starting the infusion of enteral nutrition. The post-pyloric feeding tube positioning is also indicated due to the requirement of a gastric drainage tube, to prevent bronchial aspiration and to optimize the evolution of the patient, allowing the administration of appropriate amounts of energy and nutrients.

**Nutritional status diagnosis**

After hemodynamic stability and before the diet infusion, the nutritional status diagnosis is necessary, which may be performed by any member of the multiprofessional nutritional therapy team (fig. 1). Although in clinical practice, the assessment of the nutritional status of critically ill patients is not an easy task, according to the specialized literature the use of the multi-frequency bioelectrical impedance analysis instrument has been recommended. This instrument can be used for the assessment of the nutritional status of patients that present alterations in the total body, extracellular and intracellular water distribution due to the presence of diseases (as occurs in critically ill patients). However, there is no consensus related to this conduct. Scheunemann et al. have demonstrated that mean standardized phase angle, obtained by Bioelectrical Impedance Analysis, presented weak agreement with other methods of nutritional assessment, as well as low specificity, and could not be recommended as a marker of nutritional status. In this way, observations and information provided by the staff, such as: lean body mass reduction; respiratory weakness; development of decubitus ulcers; frequency of bowel movements and stool characteristics; development or worsening of swelling; among others, may assist the team in nutritional assessment evaluation.

Although in the clinical practice traditional methods for the assessment of nutritional status (albumin, prealbumin and anthropometry) are widely employed, in accordance with the Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition guidelines, these methods have not been validated in critical care. Nevertheless, before starting nutritional therapy the evaluation of weight loss/gain (swelling), food intake prior to the injury that led to ICU admission, severity of current illness and presence
of co-morbidities, and gastrointestinal tract function, are recommended in an attempt to detect possible prior and/or current alterations in the nutritional status of the patient.32

Choice of diet infusion route

After the nutritional status diagnosis, the choice of diet infusion route must be performed (fig. 2). For all patients with an indication of nutritional therapy, the choice of the enteral route rather than the parenteral route is recommended.32,45 Thus, for a well nourished patient, there should be an evaluation of whether there is an expectation of initiating enteral nutrition within seven days. If the response is positive, the placement of the feeding tube should be confirmed and enteral feeding should be initiated as soon as possible. However, if during the seven days, for any reason, enteral nutrition is not started, only after this period total parenteral nutrition should be installed.46 For patients with a diagnosis of PEM, the possibility of immediate initiation of enteral feeding must be considered. For unnourished patients, in situations where the administration of enteral feeding is impossible, the immediate initiation of total parenteral nutrition is...
recommended with a daily assessment of the possibility of initiating any volume, even if reduced, of enteral feeding (for example < 15 ml/h).

**Choice of dietary formulation**

At this point, the choice of dietary formulation should be made, calculating the energy and nutrients requirements and the enteral diet prescription (fig. 1). The dietary formulation suggested in the algorithm is semi-elemental, normocaloric and hypolipidic. In addition, the diet should be hyperproteic and should have pharmacological amounts of glutamine22 in its composition. Despite the higher cost, the decision to indicate a predigested chemically specialized diet is based on the higher tolerance of the patient for this type of formulation, which can benefit the early initiation of enteral feeding, even in those patients with intestinal failure. Thus, it is possible to minimize discontinuance in the diet evolution due to gastrointestinal intolerance, and consequently to reduce the frequency of PEM among critically ill patients.

It is necessary to emphasize that there is no consensus in the literature to indicate the semi-elemental diet as an initial dietary formulation for critically ill patients. Although, in some situations, such as: previous intolerance to other commercial enteral diets; fasting for a period longer than seven days; severe pancreatitis; or short bowel syndrome, the use of a
enteral nutrition is safe and effective\textsuperscript{54} and benefits the diet.\textsuperscript{45} If the issue is analyzed in a more extensive way, it can be argued that the recovery of tropism and intestinal absorption capacity, i.e. the intestinal sufficiency, is directly related to reducing the frequency and severity of infectious and non-infectious complications, length and costs of ICU and in hospital stay, and mortality rate. Thus, it seems that the indication of polymeric diets as the initial prescription for patients in a critical condition, only due to its lower cost,\textsuperscript{39} should be reevaluated.

The outstanding characteristics of the dietary formulation suggested in this study are essential for the recovery of intestinal sufficiency and for the clinical outcome of the patient. Although there are other semi-elemental diets on the market, which are also hyperproteinic and contain protein presented in the hydrolyzed form, it is essential to analyze the complete dietary formulation composition. Since most of the other semi-elemental diets available on the market are normolipidic, patient tolerance is usually lower to this kind of diet. In addition, other diets with hydrolyzed protein do not have glutamine in their composition. Although there is no consensus regarding the absorption of glutamine administered by the digestive route, it is noteworthy that glutamine is the preferential nutrient for enterocytes, contributing to the restoration of the intestinal mucosa tropism.\textsuperscript{49} An additional feature is the fact that critically ill patients usually present an increased intestinal permeability. Several researchers have demonstrated that enteral administration of dipeptide alanine-glutamine\textsuperscript{48} or glutamine “granules”\textsuperscript{50} is effective in preventing the increase of intestinal permeability in patients in a critical condition, especially those exposed to burns.\textsuperscript{49} This effect is directly associated with a decrease in the frequency of systemic infection,\textsuperscript{51} in the hospitalization period\textsuperscript{46} and in the mortality rate.\textsuperscript{50,49,52}

Start enteral nutritional therapy

The entire process shown in the algorithm up to the moment of initiating the diet infusion must be performed in the shortest time possible, enabling enteral nutrition to be initiated within the first 24 to 48 hours of ICU admission.\textsuperscript{47} This recommendation is due to the numerous benefits of early enteral nutrition (in the first 24-48 hours of hospitalization).\textsuperscript{37,33} Early enteral nutrition is safe and effective\textsuperscript{48} and benefits the critically ill patient\textsuperscript{48} by reducing the hypercatabolic response to trauma,\textsuperscript{50,57} by allowing a faster achievement of a positive nitrogen balance,\textsuperscript{50,38} by performing an effective prophylaxis for reducing gastrointestinal stress ulcers,\textsuperscript{50,61} and by providing improved wound healing.\textsuperscript{52,63}

Regarding the infusion of enteral nutrition, the algorithm proposes that the evolution of the volume and rate of infusion should be conducted every 12 hours, only after evaluating the tolerance of the patient to the previously infused volume. In the absence of moderate or severe signs and symptoms, such as, pain or bloating, diarrhea, vomiting, constipation or metabolic abnormalities, it is suggested that the diet evolution should be effective and progressive. The proposal of this study is an initial infusion pump volume of 15 ml/h, continued for 12 hours.\textsuperscript{37,64} After this initial period the infusion speed should be increased by 15 ml/h every 12 hours until the patient receives the volume of nutrition corresponding to the infusion rate of 60 ml/h. At this moment, aiming to confirm and guarantee the tolerance of the patient to the diet, the infusion rate should be continued for 36 hours.\textsuperscript{37} After this period, the continuation of the diet evolution by 15 ml/h every 12 hours (as previously performed) is indicated, until the volume of diet corresponding to the calculated caloric goal is achieved and infused (fig. 1). After this period of evolution and the confirmation of the tolerance of the patient, the transition from semi-elemental diet to another type of specialized or standard diet, preferably polymeric, can be started. The diet transition should be performed gradually to ensure the maintenance of the tolerance of the patient to the new dietary formulation.

Patient monitoring

At all times, when any member of the multidisciplinary team identifies that the patient has moderate or severe intolerance during the period of evolution, prior to the suspension of the diet, it is recommended to reduce the infusion rate to the one previously tolerated. After this procedure, the patient should be reevaluated every six hours. As soon as the reduction of signs and symptoms of intolerance is identified, the diet infusion rate should return to the values previously indicated (fig. 1).

The actions proposed by the algorithm indicate other solutions rather than the suspension of the diet in the presence of interference factors. In the current literature, the importance is highlighted of procedures that seek to reduce the influence of these factors on the real administered diet volume.\textsuperscript{5,29} This suggests that, in practice, the administered volume should be as close as possible to the volume calculated/prescribed for all patients, thus ensuring the benefits of the enteral nutrition institution.

Supplemental parenteral nutrition

In some situations, the presence of moderate or severe intestinal intolerance can lead to delays in the evolution of the diet and the administration of the
volume corresponding to the calculated caloric goal within the time estimated by the algorithm (five to six days) becomes impossible. In situations where the amount corresponding to the caloric goal is not reached (within a period of seven to ten days), a supplemental parenteral nutrition should be considered.62,67

Monitoring residual gastric volume

Another way to evaluate the tolerance of the patient to the diet and also to prevent bronchial aspiration, is the daily record, of the nursing staff, regarding the appearance and the volume of fluid eliminated through the gastric drainage tube, which is also suggested in the algorithm created. The maximum tolerable level of residual gastric volume (RGV) indicated by the literature is quite variable, i.e. at the present moment it is not possible to define a RGV value above which the diet should be suspended.68 Some other procedures are also important in the prevention of bronchial aspiration, such as: head of the bed raised 30º to 45º, the aspiration of upper respiratory tract secretions, post-pyloric placement of feeding tube and simultaneous decompression of the stomach with the gastric drainage tube open.65

In the algorithm presented in this study, it is suggested that when identifying the presence of fluid stasis and/or when the volume of gastric secretion drained is higher than 1,200 ml/12 h,69 it is necessary to keep the gastric drainage tube open, and to reevaluate every 6 hours. The suggestion of this volume limit was derived from results reported in the literature, indicating that stipulating a higher RGV cutoff may contribute to a faster evolution of the programmed diet.69,70 Reevaluation is important, as only one episode of high RGV does not indicate the need for immediate diet suspension.69 For the care of the patient who is presenting a high RGV, before suspension of the diet, the administration of prokinetic agents, the investigation of signs and symptoms of sepsis, a decrease in the dose of drugs used for sedation, and the elevation of the head of the patient’s bed are recommended.49 In situations where the volume is less than 1,200 ml/12 h, and the drained material does not have the appearance of fluid stasis, the gastric drainage tube can remain closed. However, it is suggested that the appearance and volume of fluid drained should be reevaluated every six hours, until the possibility of gastric stasis can be excluded and thus, the drainage tube can be withdrawn.

Despite all these considerations, some researchers have suggested that gastric residual volume values from 50-150 ml to 250-500 ml every four hours represent the same risk of regurgitation, bronchial aspiration and/or pneumonia for critically ill patients.62,67 These remarks indicate that the resolution of this issue is far from a consensus, which suggests the necessity for further clinical studies to be carried out with appropriate experimental designs.

Nursing procedures

Throughout the period of enteral nutrition, some actions of major importance, which are restricted to the nursing staff, should be undertaken:

– Aiming to reduce the risk of bronchial aspiration, it is recommended in the algorithm that the head of the bed should be raised between 30º and 45º. Aspiration of gastric secretions is a major complication of enteral feeding.22 Different factors may identify a patient with high risk of bronchial aspiration, such as: decrease of level of consciousness,22 infusion of intermittent diet in bolus,22 high doses of sedation and catecholamines,69 among others.

– In the algorithm the confirmation of feeding tube positioning every 3 days is recommended, or according to the procedures of each ICU.70 Various daily procedures performed in the ICU may lead to displacement of the feeding tube, such as aspiration of airway secretions, position change, examinations and surgical procedures, and displacement by the patient, among others. Moreover, the bedside placement of feeding tubes can lead to misplacement and higher risk of pleuropulmonary complication, for example.71

– The administration schedules of enteral diets and infusion rates prescribed should be respected, avoiding delay and interruption in the administration of the programmed diet. During the quotidian routine, medical and nursing teams are responsible for various functions that require dedication and time for their accomplishment. The daily assessments and emergency care of critically ill patients, medical prescription, as well as bathing, medication administration and the monitoring of different parameters, occupy most of the time and attention of these two teams. However, even faced with several other complex therapies, of high technology and extreme necessity, the attention to nutritional therapy cannot be disregarded. The administration of the recommended amounts of energy and nutrients and the nutritional interventions, can directly contribute to the resolution of the disease process, having a great impact on the prognosis of the critically ill patient.77

– Flush the feeding tube with water at each change of diet bottle (suggested 50 ml).70 This practice seeks to avoid clogging and the need to replace the feeding tube, which can lead to diet discontinuation for long periods of time.

– During diagnostic procedures or examinations, the diet infusion should not be suspended, unless specifically indicated. In the study developed by Mcclave et al.29 it was shown that discontinuation of the infusion of diet occurs in more than 85% of patients for an average of 20% of the infusion period, and in more than 65% of cases the suspension of the diet could have been avoided. The intolerance of the patient to the diet may represent a third of the suspen-
sions, but in this study only half of the patients presented real intolerance. Another third of the suspensions were due to an indication of total fasting for procedures or diagnostic tests and the remaining suspensions were due to high volumes of residual gastric secretions.

Conclusion

The first step toward enteral nutrition success is the recognition, by the whole multiprofessional healthcare team, of the role that nutrition plays as a primary therapy, contributing to the clinical development and a better prognosis for hospitalized patients, particularly critically ill patients. Thus, the commitment of the whole multiprofessional healthcare team is necessary in order to offer specialized and appropriate care in nutritional therapy for the clinical moment of the critically ill patient. Several actions should be discussed by the team and carried out in due time, enabling the enteral nutrition to be instituted for all indicated patients, and aiming to start the diet administration as early as possible. Even from the moment that the administration of the prescribed diet is started, a constant monitoring of nutritional therapy is required, with the recording of any factor that might interfere in the effective evolution of the volume of the prescribed diet which, if not properly controlled/solved, may evolve into the suspension of the diet.

The interaction between the teams may be particularly difficult in University Hospitals, where the turnover of the patients is very high. For this reason, interdisciplinary communication should be well established, and each team should be required to seek improvement and integration with the work developed by the other teams. Patients require integral and individualized care and need to receive the nutritional therapy appropriate to their requirements and characteristics.

The adherence of the multiprofessional team to new practices is a goal which is often difficult to achieve, but one which should be encouraged. Instruments such as protocols and algorithms can assist in this process of changing behavior, especially by making information easily available and more comprehensive. Efforts to incorporate new practices that will benefit patient care must be taken daily and may result in the reduction of morbidity and mortality of patients in critical conditions.

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References


