Nutritional Support in Juvenile Cancer Patients under Hematopoietic Stem Cell Transplantation

doi: https://doi.org/10.32635/2176-9745.RBC.2018v64n3.43

Terapia Nutricional de Pacientes com Câncer Infantojuvenil submetidos a Transplante de Células-Tronco Hematopoiéticas

Terapia Nutricional de Pacientes con Cáncer Infantojuvenil sometidos a Transplante de Medula Òsea

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Abstract

Introduction: Nutritional status is influenced by hematopoietic stem cell transplantation (HTSC). Nutritional disorders in HSCT patients are common and are a consequence of the primary disease, cytoreduction therapy performed during the conditioning regimen and complications such as infections, neutropenic enterocolitis, graft versus host disease, among others. **Objective:** To carry out a narrative review based on the main studies and positioning of experts in literature, in addition to the experience of our group. **Method:** Bibliographical survey of the main studies and consensus on the nutritional therapy, oncology patient, pediatric oncology patient and transplantation HSCT. **Results:** Poor nutritional status and nutritional supply can negatively influence immune function during metabolic stress, increasing the risk of complications and disfavoring the prognosis. Nutritional intervention proposals and the main recommendations for oral, enteral and parenteral nutrition therapy were reviewed. Two algorithms were developed, based on the results of the review, discriminating the phases of HSCT, in order to facilitate the decision of nutritional therapy. **Conclusion:** There is little evidence to support nutritional recommendations and nutritional therapy for children and adolescents submitted to HSCT. Much information is based on studies with adults or pediatric population oncology in common antineoplastic treatment. There is a need for controlled clinical trials to evaluate the applicability and benefits of nutritional therapy in pediatric patients undergoing HSCT.

Key words: Diet Therapy; Neoplasms; Bone Marrow Transplantation; Enteral Nutrition; Parenteral Nutrition.

Resumo

Introdução: O estado nutricional é fortemente afetado pelo processo de transplante de células-tronco hematopoiéticas (TCTH). Os distúrbios nutricionais em pacientes TCTH são comuns e são consequência da doença primária, da terapia de citorredução realizada durante o regime de condicionamento e das suas complicações, como as infecções, enterocolite neutropênica, doença do enxerto contra o hospedeiro, entre outras. **Objetivo:** Realizar uma revisão narrativa com base nos principais estudos e posicionamento de experts na literatura, somado à experiência do nosso grupo. **Método:** Levantamento bibliográfico dos principais estudos e consensos sobre os temas terapia nutricional, paciente oncológico, paciente oncológico pediátrico e transplante TCTH. **Resultados:** O estado nutricional e a oferta nutricional deficientes podem influenciar negativamente a função imune durante o estresse metabólico, aumentando o risco de complicações e desfavorecendo o prognóstico. Propostas de intervenção nutricional e as principais recomendações para a terapia de nutrição oral, enteral e parenteral foram revisadas. Dois algoritmos foram desenvolvidos, baseados nos resultados da revisão, discriminando as fases do TCTH, com a finalidade de facilitar a decisão da terapia nutricional. **Conclusão:** Existem poucas evidências para embasar as recomendações nutricionais e a terapia nutricional para crianças e adolescentes submetidos ao TCTH. Muitas informações são baseadas em estudos com adultos ou população pediátrica oncológica em tratamento antineoplásico comum. Há necessidade de ensaios clínicos controlados para avaliar a aplicabilidade e os benefícios da terapia nutricional em pacientes pediátricos submetidos a TCTH.

Palavras-chave: Dietoterapia; Neoplasias; Transplante de Medula Óssea; Nutrição Enteral; Nutrição Parenteral.

Resumen

Introducción: El estado nutricional es fuertemente afectado por el proceso de trasplante de médula ósea (TMO). Los trastornos nutricionales en los pacientes TMO son comunes y son consecuencia de la enfermedad primaria, de la terapia de citorreducción realizada durante el régimen de condicionamiento y de las complicaciones de éstas, como las infecciones, enterocolitis neutropénica, enfermedad del injerto contra el huésped, entre otras. **Objetivo:** Realizar una revisión narrativa con base en los principales estudios y posicionamiento de expertos en la literatura, sumado a la experiencia de nuestro grupo. **Método:** Levantamiento bibliográfico de los principales estudios y consensos sobre los temas terapia nutricional, paciente oncológico, paciente oncológico pediátrico y trasplante TCTH. **Resultados:** El estado nutricional y la oferta nutricional deficientes pueden influir negativamente en la función inmune durante el estrés metabólico, aumentando el riesgo de complicaciones y desfavorciendo el pronóstico. Las propuestas de intervención nutricional y las principales recomendaciones para la terapia de nutrición oral, enteral y parenteral se revisaron. Dos algoritmos fueron desarrollados, basados en los resultados de la revisión, discriminando las fases del TCTH, con la finalidad de facilitar la decisión de la terapia nutricional. **Conclusión:** Existen pocas evidencias para basar recomendaciones nutricionales y la terapia nutricional para niños y adolescentes sometidos al TCTH. Muchas informaciones se basan en estudios con adultos o población pediátrica oncológica en tratamiento antineoplásico común. Se necesitan ensayos clínicos controlados para evaluar la aplicabilidad y los beneficios de la terapia nutricional en pacientes pediátricos sometidos a TCTH.

Palabras clave: Dietoterapia; Neoplasias; Transplante de Médula Ósea; Nutrición Enteral; Nutrición Parenteral.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) involves the administration of chemotherapy, radiotherapy, and subsequent infusion of these cells. The indications for HSCT in pediatric cancer patients vary according to the cancer diagnosis, treatment resistance, relapse, and remission of the cancer[1].

These patients already present compromised nutritional status before HSCT, due to prior antineoplastic therapy for the underlying disease, which usually involves treatment resistance or relapse. Such processes trigger an inflammatory response, leading to metabolic alterations, anorexia, and loss of lean mass and other energy reserves[2,3]. In these cases, patients are already at nutritional risk before undergoing HSCT.

Complications from HSCT can be acute or chronic and depend on the underlying disease and its initial condition prior to the procedure, the type of transplant, chemotherapy, and the preparatory regime for radiotherapy.

The principal complications are bleeding, infections, organ failure, gastrointestinal toxicities, graft versus host disease (GVHD), graft failure or rejection, and recurrent disease.

Nutritional disorders in HSCT patients are also common and result from the primary disease and cytoreductive therapy during the conditioning regime and its complications, such as infections, GVHD, neutropenic enterocolitis, graft rejection, and liver disease, among others. Nutritional alterations occur due to these complications and situations of anorexia, nausea, and vomiting, altered taste, mucositis, diarrhea, and nutrient malabsorption, resulting in increased risk of malnutrition and nutritional deficiencies, electrolyte disorders, muscle catabolism, cachexia, and protein loss[4].

Thus, nutritional status is heavily affected by HSCT. Reduced protein intake, for example, can negatively influence immune function during metabolic stress, increasing the risk of complications and compromising the prognosis.

Malnutrition in non-oncological critical patients is known to be associated with increased infection rate, decreased healing capacity, increased length of hospital stay, and increased mortality. The situation is no different in cancer patients, who also present less tolerance to chemotherapy and radiotherapy[2,3]. According to the guidelines for nutritional support during HSCT, all patients undergoing this procedure with myeloablative conditioning regimes are at nutritional risk[5,6].

In patients with malnutrition, there is a dose reduction for administration of chemotherapy during the conditioning regimen for HSCT[7]. Drug pharmacokinetics and distribution are also known to vary according to the different tissues[8]. Patients with lean mass deficit and/or increased fat mass present altered drug metabolism.

Gastrointestinal complications such as diarrhea, severe mucositis, anorexia, intense vomiting, nutrient malabsorption, and GVHD are the principal factors responsible for a major portion of the indications for nutritional support: oral supplements, enteral nutrition, and parenteral nutrition.

Nutritional follow-up is extremely important in all phases of the treatment. These patients thus need to be assessed continuously, and algorithms to determine the nutritional support should be applied to ensure the best decision. This process ensures adequate identification of nutritional risk and early indication of nutritional support, considering the diagnosis, type of transplant, and treatment and its adverse effects, increasing the benefits of this support and avoiding the risks of inadequate indication[5,6].

With the objective of discussing proposals for nutritional intervention, the main guidelines for oral, enteral, and parenteral nutritional support were reviewed, and two algorithms were developed, discriminating the phases of HSCT, with the purpose of facilitating the decision on nutritional support.

Nutritional support

The goals of nutritional support can be separated according to the treatment phase. During the pre-HSCT phase, the goals are to correct or maintain adequate nutritional status, adjusting the reserves of macro and micronutrients to improve the patient's tolerance to the antineoplastic therapy, decrease the risk of infection, and improve immune status and response to inflammation during treatment. During hospitalization for HSCT, the nutritional goals are to minimize nutritional injury, control gastrointestinal symptoms, improve the response to antineoplastic therapy, decrease overall complications, minimize the deficit in growth and development, control the proinflammatory response, and shorten the length of hospital stay [9]. Anabolism rarely occurs during the metabolic-nutritional therapy, since the inflammatory response leads to the production of catabolic hormones, which are associated with the process of stress in diverting the metabolic pathway for proteins, which are then used as an important source of energy in this phase[2].

In the post-HSCT period, the goals are to maintain an adequate growth and development curve, correct the patient's nutritional status, and control the nutritional and metabolic repercussions of the cancer therapies[8,9].

The overall objective of nutritional support is to improve the treatment response, decrease the risks of complications, and improve survival and quality of life.

Despite major discussion on the preferred route for nutritional support in these patients during HSCT[10-13], enteral nutrition should be prioritized as long as the gastrointestinal tract is functional. The indications for each nutritional support route, such as oral supplementation, enteral nutrition via tube feeding, and parenteral nutrition, will be discussed next, considering the available data in the literature and our group's experience.

Enteral nutrition – the gastrointestinal tract

To perform enteral nutritional support (oral, via tubes, or via ostomies), the team should assess the gastrointestinal tract's functional capacity. Situations that modify the digestive and absorptive systems, such as mucositis, infections, and GVHD, among others, can compromise the adequate processing of nutrients and be inefficient if they are poorly indicated[14].

Based on the premise that prolonged fasting causes atrophy of the intestinal mucosa, breaching the immunological integrity of the gastrointestinal tract and increasing the risk of bacterial translocation, food constitutes an important stimulus for maintaining the intestinal mucosa's function and structure, releasing pancreatic and biliary secretions and hormonal factors[14].

Oral and tube feeding should be prioritized in patients with a functional or partially functional gastrointestinal tract, before indicating parenteral nutrition, since they preserve the intestinal mucosa's trophism[12].

A breached integrity of the gastrointestinal tract's cell membrane, with alterations in the intestinal barrier, may be associated with the conditioning regimes used for HSCT, besides the prophylactic use of antibiotics, destroying the intestinal flora. Jointly, these aspects can increase the risk of microbial translocation and infections. This can all be further exacerbated by atrophy of the intestinal villi due to the nutrient deficiencies in the lumen (low food intake) and malnutrition, leading to the depletion of macro- and micronutrients[15,16].

Oral nutritional support

According to Duggan *et al.*, nutritional support by the oral route should be considered in these patients[10] to meet their nutritional requirement. Meanwhile, Bechard *et al.* & Tavil *et al.* did not find the same results[17,18]. Therefore, the indication of oral nutritional support should be assessed on a case-by-case basis and should occur when food intake is less than 70-80% of the nutritional recommendations for three to five consecutive days, considering the nutritional status at risk, expected time for the improvement of food intake, and predicted timing of the HSCT, the gastrointestinal tract, and conditioning[19,20]. The suggestion is thus to perform daily food intake calculations.

Oral supplements have been tested in children and adolescents with cancer undergoing transplantation. Since the conditioning treatment is highly aggressive, the oral route for traditional diet is compromised in most patients. Reinforcement via complete oral supplements becomes an interesting strategy. However, only a small portion of children and adolescents can be maintained with this therapy from the nutritional point of view. In our study, follow-up data on 89 patients showed that 29% remained on exclusive oral feeding throughout the period, which contributed to their reaching approximately 90% of their baseline energy requirement and 76% of their total requirement. Of all the patients in the study, 46% used industrial oral supplements (24 were autologous and 17 allogenic transplant patients)[21].

According to a study in pediatric cancer patients, oral supplements prescribed in amounts less than 35% of energy requirement will rarely produce benefits in the maintenance or recovery of nutritional status for patients with higher degrees of depletion. This same study found that 60-70% of patients with severe and mild malnutrition, respectively, managed to reach at most 45% of their requirement with the supplements provided. Approximately 30% in the two groups reached 100% of their requirement[22]. These data illustrate the difficulty in nutritional support by the oral route.

Programmed withdrawal of the oral supplement can be done starting with improvement in the food intake (≥ 70-80% of energy requirement, calculated for two or three days), conditioned on reaching 100% of requirement without the oral supplement. It is necessary to consider the treatment phase, presence of gastrointestinal toxicity, and the patient's current clinical and nutritional status[20].

Nutritional support via tube feeding or ostomies

Severe malnutrition is characterized by a system depleted of energy and muscle tissue, deficient nutritient reserves, compromised cell function, and breached cell membrane integrity, which affects the majority of the host's organ systems and explains the favorable results of parenteral nutrition, especially in malnourished patients with cancer[6].

This group observed that tube feeding in children and adolescents with cancer during HSCT is feasible, not presenting severe complications associated with the therapy. Less severe complications occurred in 55% of patients: intensification of episodes of vomiting or diarrhea with progression of the diet's volume (16%), dislodgement of the tube (19%), fungal infection in the oral cavity (9.7%), and tube obstruction (6.5%)[21].

Enteral nutrition has been widely recommended for adults and children during cancer treatment. Various

studies have found it feasible in cancer patients undergoing HSCT, with favorable evolution in nutritional status obtained via tube feeding[23-30].

Some trials have considered enteral nutrition as effective as parenteral nutrition, with lower complication rates. Enteral nutrition has also been associated with better survival, lower incidence of acute and chronic GVHD, faster recovery of neutrophils, and lower risk of infection[12,24-27].

Data from another study suggest that nutritional support in the pre-HSCT phase and during HSCT was associated with better nutritional recovery after HSCT[25].

Current studies show an inverse correlation between malnutrition and clinical outcomes, such as: lower risk of bacterial and fungal infection and shorter length of hospital stay. In patients with acute myeloid leukemia, malnutrition at diagnosis and more pronounced weight loss during HSCT were important prognostic factors associated with lower survival and worse disease outcome[26].

Enteral nutritional support has thus been widely recommended for pediatric patients undergoing HSCT, and enteral nutrition via tube feeding is the preferred route in the absence of severe toxicity to the gastrointestinal tract[23,28,29]. Taking into account the risks and benefits, the most adequate timing and method for the cancer patient's nutritional support during this process can be a difficult decision, and algorithms should be used to orient these decisions (Figures 1 and 2).

There are several benefits of enteral feeding over parenteral nutrition, such as fewer complications (which include bloodstream infections and metabolic complications), less catheter manipulation, greater ease in the supply of macronutrients, protection of the intestinal mucosal barrier, and better control of metabolic stress. There is also the advantage of lower cost with the use of the gastrointestinal route[30].

Therefore, routine use of parenteral nutrition is not indicated, and this route is reserved for cases in which the toxicity or severe complications of the gastrointestinal tract preclude the use of total enteral nutrition[31-34].

Still, due to the alterations in the gastrointestinal tract, disorders in intestinal absorption and permeability, adjustment to the enteral diet may be necessary. Special formulations with extensively hydrolyzed diets may be necessary in some cases. In the experience of the GRAACC group, oligomeric diet was necessary in approximately 68% of patients during HSCT who used tube feeding during the study period[21].

Various research groups have defended the use of percutaneous endoscopic gastrostomy (PEG) in cancer patients, especially when prolonged nutritional support is necessary[35-37]. Although this method has not been tested in patients with HSCT, it may be useful and feasible for patients undergoing more prolonged therapy (> 4 weeks). In order to avoid complications such as greater injury and/or bleeding when introducing the tube, this procedure is not recommended in the presence of lesions in the oral mucosa and/or gastrointestinal tract, along with periods of immunosuppression and thrombocytopenia[19].

Finally, nutrition via nasoenteral tube feeding is feasible in children and adolescents undergoing HSCT and should be encouraged. The main difficulty is gastrointestinal toxicity. Controlled clinical trials are important to assess the applicability and benefits of nutritional support and particularly the applicability of nasoenteral tube feeding and PEG, including studies on early indication.

Delay in the indication of nutritional support can hinder the use of tube feeding and increase the risk of complications. Thus, early indication of tube feeding can benefit more patients, reducing the need for parenteral nutrition or at least decreasing the time of its use and the related risks[19,31-34].

Good practices are recommended in enteral nutritional support, as discussed by Aspen[38]. Silicone or polyurethane tubes are recommended, with the smallest possible diameter and preferably with a weighted tip to reduce extrusion, especially after episodes of vomiting. Administration can be performed at the start of conditioning until the first week post-transplantation, the period in which oral diet is compromised. Infusion of the enteral diet should always be performed by controlled drip to improve tolerance, where an enteral diet infusion pump is recommended[23,39].

Difficulties in introducing the tube can occur due to the risk of trauma, as in the presence of grade 3 and 4 mucositis, sinusitis depending on the degree of involvement of the nasal sinuses and possible difficulty in draining the nasal sinuses in the tube's presence, infection, and bleeding. The suggestion is thus to introduce the tube with a platelet count of 30 thousand/mm³ (or 20 thousand/mm³ after platelet infusion)[19].

One contraindication to enteral nutritional support is a non-functional gastrointestinal tract, which occurs more frequently in these patients due to paralytic ileum and neutropenic enterocolitis[9].

As with other therapies, programmed withdrawal of nutritional support via tube feeding can begin when oral intake reaches ≥70-80% of energy requirement for two or three days. Progression aims to reach nearly 100% of requirement with the aid of oral supplements. It is necessary to consider the treatment phase, presence of gastrointestinal toxicity, and current clinical and nutritional status[19,20,32].

Principal difficulties in the indication of enteral nutrition

Parenteral nutrition will be necessary in some

circumstances to guarantee some nutritional supply. The main situations are: (1) intestinal obstruction syndromes, pseudo-obstruction, and dysmotility; (2) after a conditioning regime with the following symptoms: nausea, intractable vomiting, diarrhea or output ostomy (diarrhea ≥500 ml or ≥ three evacuations per day for two days), or severe mucositis; (3) high-output ostomy (≥1,000 ml/day); (4) ischemic intestine; (5) massive gastrointestinal hemorrhage; or (6) GVHD in severe initial conditions[19,20,32].

Parenteral nutrition

Parenteral nutrition in cancer patients has sparked great discussion, since these individuals can present severe restrictions in the gastrointestinal tract.

Historically, total parenteral nutrition was the most frequently used method to furnish nutrients during HSCT. The importance of nutrition, especially parenteral nutrition, was well-evidenced after publication of the results of a randomized trial by Weidsdorf *et al.*, showing that administration of prophylactic parenteral nutrition during HSCT increased survival in the group that received it, after three years of follow-up[40].

However, parenteral nutrition is also associated with increased risk of complications (especially infectious and metabolic), particularly in patients with severe immunosuppression, as is the case of patients undergoing HSCT.

Newman *et al.* observed that parenteral nutrition has presented more adequate indications, although 13% of cases still present duration less than five day, when they could have been treated by the enteral route. Prolonged periods of parenteral nutrition, for more than 28 days, were not common[41].

Despite evidence of positive nutritional outcomes with the supply of total parenteral nutrition in children and adolescents during HSCT[42], there are few studies in this context, and information is scare on the effects of total parenteral nutrition in this population. The recommendations are thus based on the results of the studies discussed previously, including data in adults, which also provide the basis for the principles of nutritional support in children and adolescents with cancer.

In pediatric oncology, some diagnoses and some antineoplastic agents, such as chemotherapy with methotrexate, thiotepa, fluorouracil, melphalan, cisplatin, and abdominopelvic and whole-body radiotherapy leave the patient much more prone to severe gastrointestinal toxicities and nutritional risk. Parenteral nutritional support may thus be necessary[19-21,42,43].

Important aspects in the use of parenteral nutrition are monitoring and metabolic control of the supply and the type of catheter used. Since there is a major risk of metabolic alterations due to the patient's inflammatory state and infections from manipulation of the catheters, special attention should be given to this therapy's management[19,21].

The main indications for parenteral nutrition are the impossibility of total or partial use of the gastrointestinal tract; severe thrombocytopenia not resolved by platelet infusion in patients receiving enteral therapy; and difficulty in meeting nutritional requirement with full enteral nutrition therapy in five days, considering the patient's nutritional status and the predicted time for grafting[43].

Therefore, it is essential for treatment planning in these patients to determine the criteria for decisions on nutritional support, improving the processes and guaranteeing that the therapy will bring more benefits than complications. Chart 1 lists some guidelines.

Finally, the routine use of parenteral nutrition is not recommended unless the toxicity or severe complications in the gastrointestinal tract prevent the full supply by the enteral route. Good practices in enteral nutritional support are recommended, as specified in Aspen, 2002.

Algorithms for nutritional support

Algorithms are important for orienting decisions on interventions. Algorithms for children and adolescents with cancer should consider several factors, such as food intake, nutritional risk of the disease and of the antineoplastic therapy, gastrointestinal toxicities, time on therapy, and in certain situations the prognosis of cure[19].

St. Jude Children's Research Hospital developed the first algorithm, which became a milestone in this process. Following the creation of a metabolic support team in 1988, the instrument was developed and tested from 1991 to 1996. At the end of the study, the researchers succeeded in demonstrating that the algorithm's implementation improved the indications for nutritional support, with an overall increase in the therapy's use, especially via tube feeding and gastrostomy, reducing the excessive indications of parenteral nutrition[20].

In 2002, the group developed the first algorithm for indication of enteral nutrition, which was tested up to 2004[22]. Based on this study, the authors concluded that oral supplements can be used to prevent nutritional depletion in patients at risk, but that they are not effective in patients with moderate to severe depletion, in whom early tube feeding is necessary.

At a meeting in 2004, the Children's Oncology Group (COG) proposed a new algorithm, based on the same premises as the one developed by St Jude[44].

Some other publications emerged, showing similar

Chart 1. Guidelines for nutritional support during HSCT

Summary of guidelines and recommendations	Level of evidence
Implement nutritional support in patients undergoing HSCT that are malnourished and are not able to swallow and/or absorb nutrients adequately for a prolonged period. When parenteral nutritional support is necessary, it should be used, but suspended as soon as the toxicities have resolved.	Level B
Enteral nutrition is the preferred route and should be used in patients with a functional gastrointestinal tract when oral intake is inadequate to meet nutritional requirement.	Level C
Specialized nutritional support should be offered to patients undergoing HSCT who develop moderate to severe forms of GVHD, since they may present inadequate oral intake and/or significant intestinal malabsorption.	Level C
It is recommended to discontinue support therapy via parenteral nutrition when 50% of requirement has been met by the enteral route in adults. However, there are no guidelines for children, so 70-80% is suggested.	Level C

Source: Adapted from Garófolo[19], Huhmann[5], Aspen[38], Bozzetti et al.[34], Arends et al.[6].
Key: HSCT: hematopoietic stem cell transplantation; GVHD: graft versus host disease.

results with the use of algorithms in the pediatric cancer population. Figures 1 and 2 suggest the algorithms for early nutritional support, according to the treatment phase in HSCT. They were developed by our group, based on algorithms proposed in the literature and others tested in cancer patients by various groups, including ours at GRAACC[20,22,44-46].

CONCLUSION

There is little available evidence to base the nutritional and nutritional support recommendations for children and adolescents undergoing HSCT. Much of the existing information is based on studies in adults or in the pediatric cancer population undergoing ordinary antineoplastic treatment.

Parenteral nutrition still appears to be the first choice in many centers that provide treatment with HSCT. However, according to the previous discussion and our experience, enteral nutrition is a feasible procedure in patients undergoing HSCT and should be encouraged. The principal difficulties for patients with tube feeding are thrombocytopenia and gastrointestinal complications, which can be managed as long as the support is programmed early.

Treatment protocols are thus important for guiding these decisions. There are currently no algorithms proposed to orient decisions on nutritional support for pediatric cancer patients undergoing HSCT.

Controlled clinical trials are thus essential for assessing the applicability and benefits of these interventions, whether through protocols or algorithms, and particularly assessing the applicability of early tube feeding and PEG.

CONFLICT OF INTEREST

None.

FUNDING SOURCES

None.

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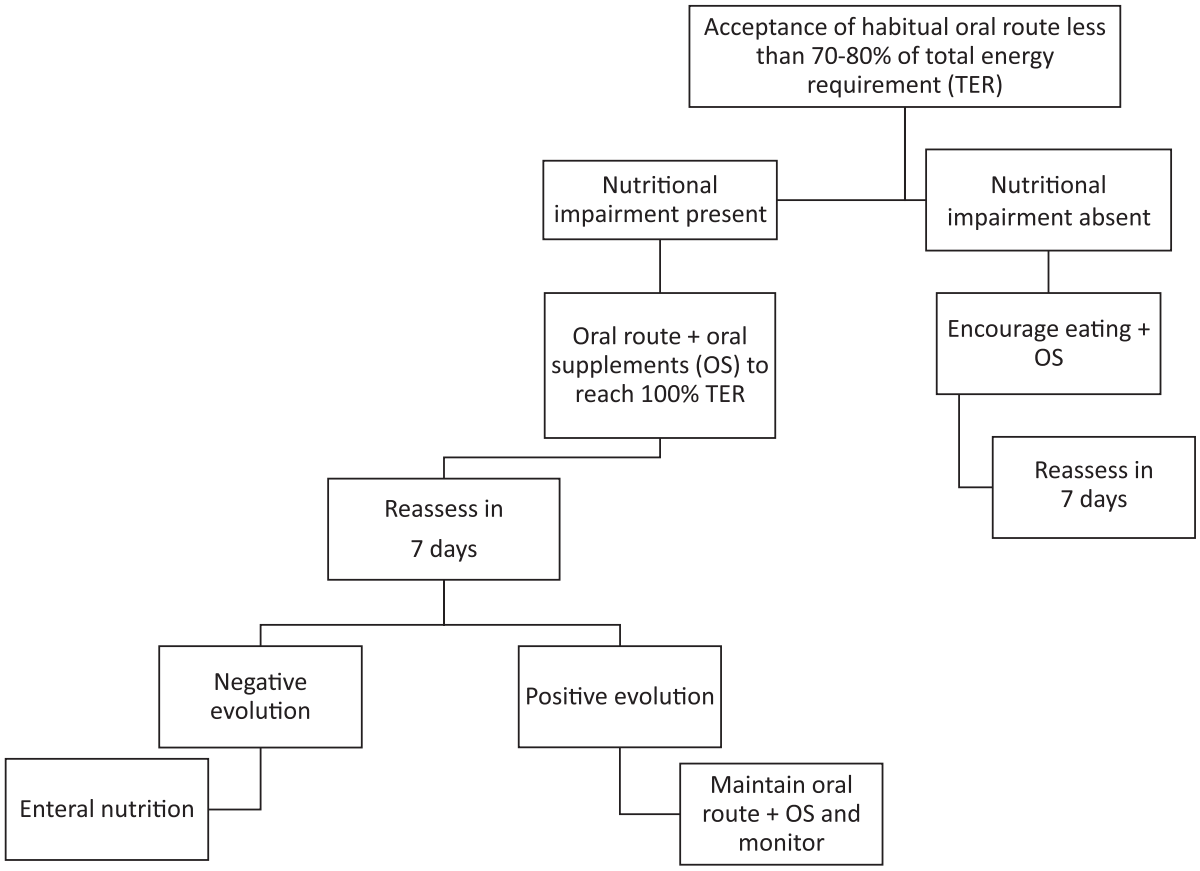

Figure 1. Algorithm for nutritional support in pediatric patients in the pre-HSCT phase

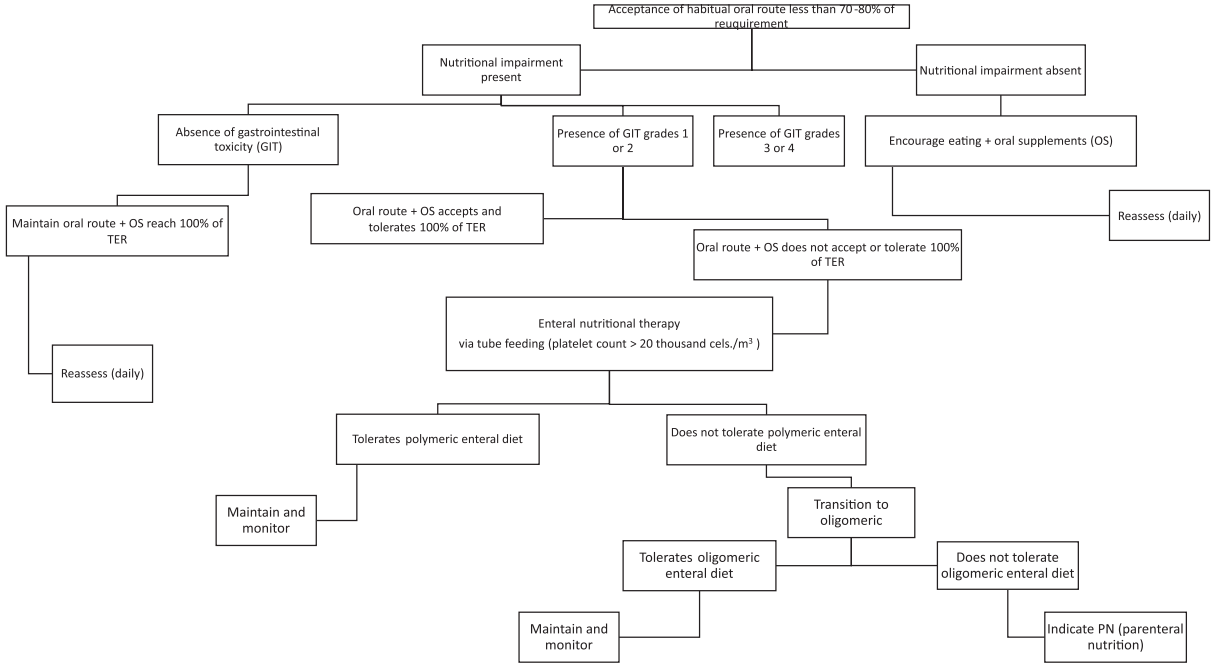

Figure 2. Algorithm for nutritional support in pediatric patients during HSCT

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Recebido em 30/8/2018
Aprovado em 1/11/2018