PERSPECTIVE

The European Society for Blood and Marrow Transplantation (EBMT) roadmap and perspectives to improve nutritional care in patients undergoing hematopoietic stem cell transplantation on behalf of the Cellular Therapy and Immunobiology Working Party (CTIWP) and the Nurses Group (NG) of the EBMT

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Malnutrition is the most common comorbidity during the continuum of hematopoietic stem cell transplant (HSCT) and negatively impacts clinical outcomes, response to therapy, quality of life, and costs. The intensive conditioning regimen administered before transplant causes inflammatory damages to the gastrointestinal system, which themselves contribute to trigger graft versus host disease (GvHD) in the allogeneic setting. GvHD and other post-transplant complications such as infections adversely affect food intake and gut absorption of nutrients. Consequently, patients exhibit signs of malnutrition such as weight loss and muscle wasting, thus triggering a "vicious circle" that favours additional complications. Among HSCT centres, there is marked variability in nutritional care, from screening for malnutrition to nutritional intervention. The present paper, elaborated by the Cellular Therapy and Immunobiology Working Party and the Nurses Group of the European Society for Blood and Marrow Transplantation, aims at defining a roadmap that identifies the main nutritional critical issues in the field of HSCT. This document will be propaedeutic to the development of clinical algorithms to counteract risk factors of malnutrition, based on scientific evidence and shared among HSCT centres, and thus maximize transplant outcomes.

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INTRODUCTION

Hematopoietic stem cell transplant (HSCT) represents the main therapeutic option in treating several malignant and non-malignant diseases. The intravenous infusion of hematopoietic stem cells collected from the patient (autologous transplant) or a related/unrelated donor genetically non-identical donor (allogeneic transplant), aims to reset the defective immune system and help restore the blood-forming cells of the patient's bone marrow [1]. Before the transplant, a myeloablative or non-myeloablative conditioning regimen, including intensive chemotherapy and sometimes total body irradiation (TBI) is needed to eradicate damaged cells. In allogeneic transplant, potent immunosuppressive drugs are used to allow engraftment [1]. However, the conditioning program could result in serious complications like infections and GvHD, as well as a number of gastrointestinal side effects (such as mucositis, taste changes, loss of appetite, nausea, vomiting, and diarrhoea). Taken together, these factors affect oral food intake and promote gut malabsorption of nutrients, with consequent weight loss [2].

Indeed, malnutrition is the most common comorbidity during the continuum of HSCT [3] and has a detrimental impact on relapse, length of stay, engraftment, the incidence of infections, survival, and costs [3–5].

Nonetheless, in real-world clinical practice, both awareness and consideration of nutritional issues remain poor [6]. As a consequence, nutritional assessment is not performed

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Table 1. The main nutritional critical issues in the field of HSCT.

Priority topic	Key points
Nutritional status	Loss of appetite and GvHD are the most significant factors deteriorating nutritional status in the early period, especially in allogeneic HSCT.
Nutritional assessment	Nutritional risk screening should be performed during the first outpatient visit and within 48 hours since hospital admission. Patients at risk should then undergo an assessment to effectively diagnose malnutrition.
Nutritional intervention	The first approach should be nutritional counselling, to manage symptoms favouring the assumption of well-tolerated food. If oral food intake is inadequate, EN should be preferred as it is more physiological and with lower complications compared to PN.
Neutropenic diet	There is no evidence that neutropenic diet would reduce the infection rate. The only valid recommendation is safe food handling through strict hand hygiene. Caution is needed towards uncooked, undercooked, cold, and unpasteurized foods.
Specific nutrients	The use of glutamine, omega-3 fatty acids, and probiotics cannot be yet recommended to improve prognosis.
Physical exercise	Patients should be encouraged towards physical exercise before, during, and after HSCT to reduce fatigue and anxiety and to improve muscle strength and QoL.

EN enteral nutrition, *GvHD* graft versus host disease, *HSCT* hematopoietic stem cell transplant, *ONS* oral nutritional supplements, *PN* parenteral nutrition, *QoL* quality of life.

appropriately [7], and malnutrition remains under-recognized [8] in more than 70% of cancer patients. Among HSCT centres, a lack of standardized operating procedures in screening for malnutrition and management of complications such as GvHD has been observed, resulting in a marked variability in nutritional care [9]. It has been noted that there is a discrepancy between the prevalence of malnutrition for haematological cancer (between 30% and 40%) and the malnutrition diagnosis rate (lower than 20%) [8]. As a result, a wide heterogeneity of *modus operandi* has been highlighted, which is ethically unacceptable because all patients should have the right to adequate nutritional management in the context of simultaneous care [10].

In this scenario, standardized clinical algorithms, based on available scientific evidence and shared among HSCT centres, need to be developed to counteract risk factors of malnutrition and thus maximize transplant outcomes. On the basis of this purpose, the Cellular Therapy and Immunobiology Working Party (CTIWP) and the Nurses Group (NG) of the European Society for Blood and Marrow Transplantation (EBMT) have elaborated the present paper, with the aim of defining a roadmap that identifies the main nutritional critical issues in the field HSCT to improve nutritional care in HSCT patients. The following issues, summarized in Table 1, were identified as priority fields of improvement or development.

NUTRITIONAL STATUS IN THE CONTEXT OF HSCT

Impaired pre-transplant nutritional status increases the risk of long-term malnutrition [11]. In this regard, more than 20% of patients undergoing HSCT experience an involuntary weight loss greater than 10% before the transplant, often due to reduced oral food intake [12].

During the continuum of HSCT, patients are continuously exposed to the risk of malnutrition, as shown in Fig. 1. Side effects of the conditioning regimen contribute to reducing oral food intake and by promoting gut malabsorption, leading to weight loss and altered body composition, especially in terms of enhanced muscle catabolism. In addition, during chemotherapy, there is a further decrease in oral intake. The first forty days following transplant (early period) reflect the period with the highest risk for nutritional status deterioration, particularly in patients who receive allogeneic HSCT. In this regard, loss of appetite and GvHD are the most significant factors influencing nutritional status [12]. Allogeneic HSCT entails using donor-derived stem cells, which increases the risk of both short-term and long-term complications [3]. In the early phase, glucose control is very important as hyperglycaemia impairs immune function, diabetes mellitus (DM) increases the risk of infections, and glucocorticosteroids use in the treatment of GvHD increases the risk of dysglycemia. Noteworthy, this population is already susceptible to infections, as conditioning regimens and prior therapies lead to recurrent and long-lasting neutropenia. Moreover, in patients treated with allogeneic HSCT, hyperglycaemia causes elevation of pro-inflammatory cytokines and enhances muscle catabolism [2, 13].

In the context of HSCT, prolonged hospitalization contributes to malnutrition as decreased physical activity induces muscle wasting and reduced physical function [14]. Body composition analysis may allow us to better understand nutritional status, as it reflects nutritional intakes, losses, and needs over time. Accordingly, most malnourished patients have low muscle mass or sarcopenia; nevertheless, these conditions are often hidden and overlooked, especially in patients with normal weight or excess adiposity [15]. Muscle wasting is a nutritional feature which has been related to decreased survival, worse clinical outcomes and quality of life (QoL), as well as increased therapy toxicity [16] in cancer patients. Reduction of skeletal muscle frequently occurs after a conditioning regimen [17], and it has been reported that more than 50% of patients experience sarcopenia before HSCT with an adverse effect on physical function and QoL [18]. Sarcopenia is also caused by decreased oral caloric intake during the conditioning regimen and after the transplant [19]. Even after discharge, many patients continue to experience weight loss due to insufficient oral intake, especially those treated by allogeneic HSCT and affected by chronic GvHD [20].

Obesity, DM, and liver dysfunction are prognostic factors in the nutritional status assessment prior to HSCT [21]. Moreover, these metabolic disorders have been highly detected in survivors after allogeneic HSCT [22].

Personalized nutritional support during hospital stays aimed to prevent deterioration of nutritional status can reduce mortality and improve the physical status and QoL [23]. In addition, adequate nutrition during the early period to engraftment after allogeneic HSCT is associated with reduced non-relapse mortality and improved survival as well as GvHD-free survival at 5 years [24].

Nutritional status tends to decline over time. To better manage clinical nutrition in HSCT, systematic and comprehensive monitoring of nutritional status before and after HSCT, with adequate early nutritional support when needed, is imperative [25].

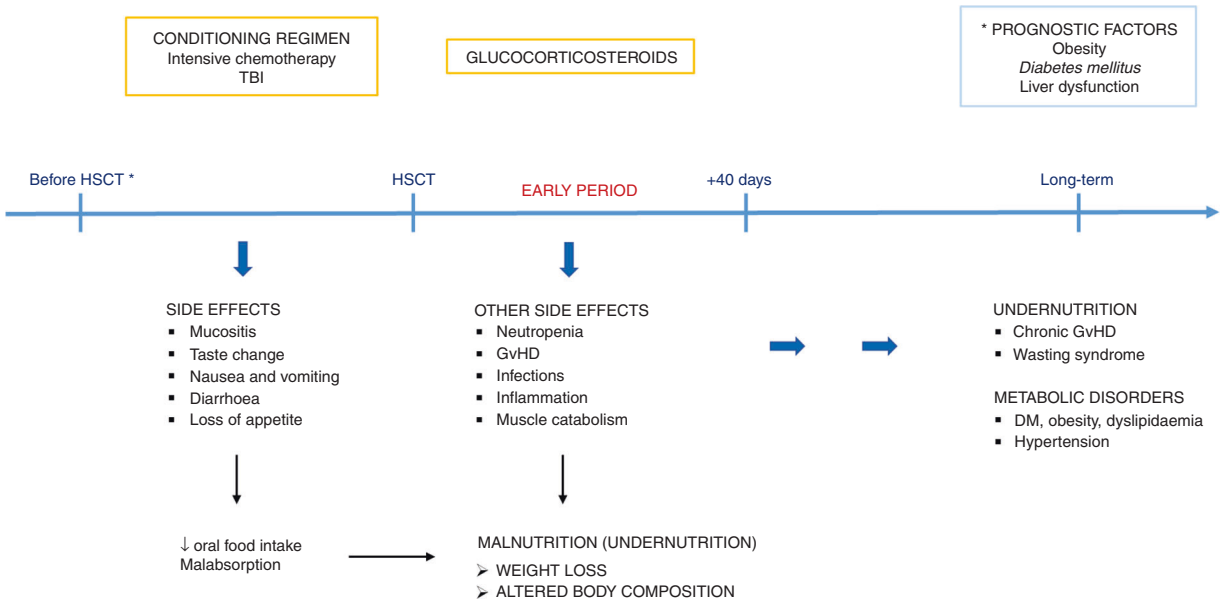

Fig. 1 Risk factors of malnutrition during all the continuum of HSCT. DM diabetes mellitus, GvHD graft versus host disease, HSCT hematopoietic stem cell transplant, TBI total body irradiation, ↓ reduction.

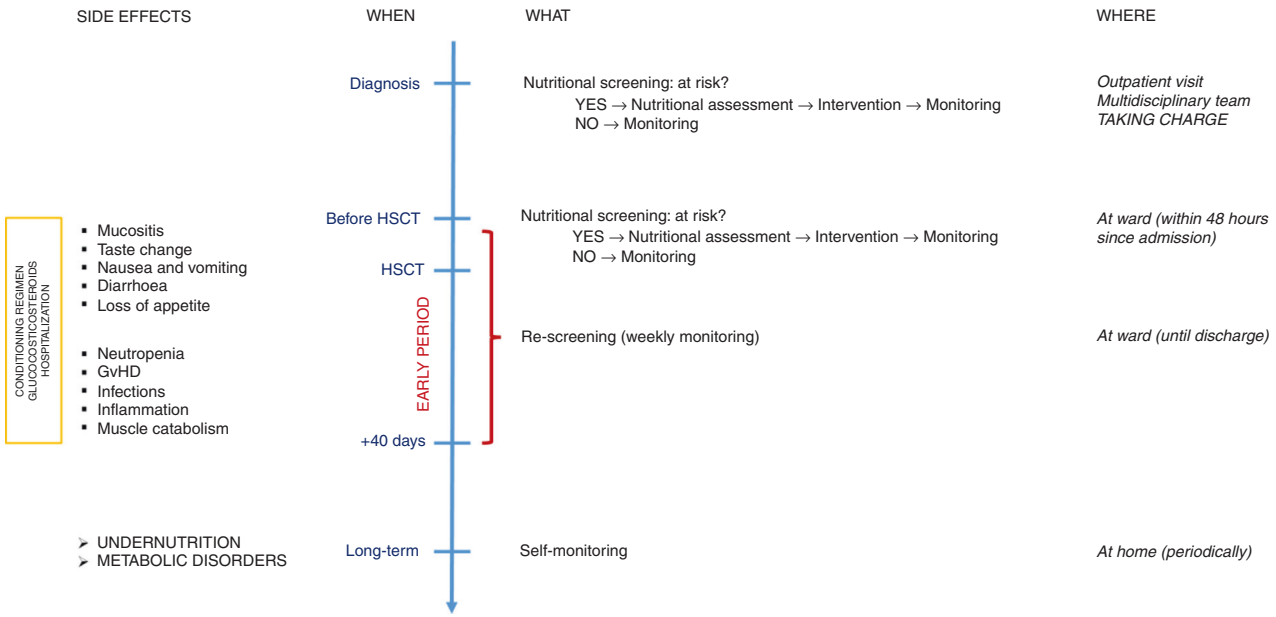

Fig. 2 Flow-chart for the ideal timing of different interventions. GvHD graft versus host disease, HSCT hematopoietic stem cell transplant.

SYSTEMIC NUTRITIONAL ASSESSMENT: HOW

A systematic nutritional assessment during the continuum of HSCT is necessary to preserve nutritional status. Figure 2 represents a flowchart for the ideal timing of different interventions: nutritional screening and assessment, nutritional intervention, and monitoring.

Every patient who is a candidate for HSCT is at risk of having a poor nutritional status and thus should be referred to the nutritional support team to establish a rigorous monitoring program [25]. To raise knowledge of dietary problems among oncologists, haematologists, nurses, and other specialists, it is preferrable that nutritional evaluation take place as part of a shared multidisciplinary outpatient appointment coordinated by a dietitian. According to the Global Leadership Initiative on Malnutrition (GLIM) criteria [26], during the first visit, a screening for determining the risk of malnutrition should be performed using validated tools (i.e., MUST, MNA, NRS-2002, PG-SGA). Patients at nutritional risk should then undergo an evaluation to effectively diagnose malnutrition, through the assessment of phenotypic (unintentional weight loss, low body mass index and reduced muscle mass) and etiologic (reduced food intake or assimilation, and inflammatory status) criteria [26].

Currently, there are several available techniques to evaluate body composition. In the oncological setting, bioelectrical impedance analysis (BIA) is widely used to estimate muscle mass. Phase angle (PhA) provided by BIA is a marker of abnormal body composition and is calculated from measured values of resistance (R) and reactance (Xc). Moreover, BIA is an emergent approach alternative to blood biomarkers in evaluating oxidative stress levels [27]. As BIA results are influenced by all conditions affecting

the ratio between extracellular and intracellular water, the vectorial method to analyse bioelectrical impedance (BIVA) has been proposed to overcome this obstacle. BIVA allows monitoring of nutritional status and nutritional interventions during therapies [28].

Both in oncology clinical and research settings, the use of computed tomography (CT) is spreading extensively. Analysis of CT slices extrapolated from diagnostic CT images allows for the distinction between adipose (subcutaneous, visceral, and intramuscular) and skeletal muscle tissues through the segmentation of cross-sectional areas at the third lumbar vertebra level [27].

Within 48 hours of hospital admission for HSCT, screening for malnutrition should be performed. Because of treatment and possible related side effects, patients should be monitored continuously during hospitalization. In this regard, nutritional screening and assessment should be repeated weekly on the ward until discharge.

Before discharge, patients should be instructed to periodically self-monitor their nutrition status and to promptly report to the healthcare professional any changes in body weight as well as in appetite, oral food intake, and health status.

NUTRITIONAL INTERVENTION: TYPE AND TIMING

Nutritional intervention aimed to maintain or recover appropriate nutritional status should be initiated and tailored according to current nutritional status, clinical condition, planned treatment, and expected outcome [29]. Preferably, nutritional intervention should be started before severe impairment of nutritional status occurs.

In case patients develop symptoms that limit oral food intake without completely compromising it, the first approach should be nutritional counselling (NC), which aims to manage symptoms favouring the consumption of well-tolerated, and carbohydrate- and protein-rich food and beverages. Consequently, the most effective way to maintain or enhance nutritional status is through a diet rich in calories and proteins [16]. A Lebanese randomized controlled trial done by Jabbour et al. (2018) demonstrated the promising effect of NC on food intake among 46 adults receiving HSCT and an improvement in nutritional status among autologous HSCT patients only [30]. From the same trial, NC resulted associated with a trend of improved vitamins and minerals intake [31]. Interestingly, a correlation was found between the number of days without oral intake following allogeneic HSCT and the incidence of serious acute GvHD: more than 9 days with no oral intake was associated with acute GvHD grades III-IV [32].

If oral food intake is inadequate, artificial nutrition (AN), which includes the use of oral nutritional supplements (ONS), enteral (EN), and parenteral nutrition (PN) is required [16]. Specifically, guidelines of European Society for Clinical Nutrition and Metabolism (ESPEN) suggest preferring EN as the first choice for nutritional support, as it is associated with a lower incidence of infective complications [25].

EN is more physiological than PN as it follows the natural passage of the alimentary bolus along the GI tract and contributes to preserving the gut mucosal integrity and function. Indeed, a state of "*eubiosis*" (i.e., an interspecies balance of intestinal microbiota community) is characterized by elevated microbial diversity and is associated with lower acute GvHD incidence [33, 34]. Moreover, EN has been also associated with greater overall survival and neutrophil engraftment [35]. On the other hand, prolonged PN has been associated with a reduction in microbial diversity and worse outcomes [3].

A limitation in the choice of EN is represented by the difficult positioning of EN devices (i.e., nasogastric (NG) tube or stoma) in patients with severe mucositis, nausea, or vomiting. These conditions may also cause the premature interruption of enteral nutritional support and a consequent shift towards PN. Furthermore, a greater infective risk in positioning an EN access is present in immunocompromised patients [36]. Besides, patients' tolerability of EN via NG tube remains an issue that requires further research [37].

PN should be initiated only in the case the GI tract is severely compromised (i.e., severe mucositis, intractable vomiting, paralytic ileus, severe diarrhoea, symptomatic GvHD), a condition more frequent following allogeneic HSCT [25]. In clinical practice, PN is often preferred to EN [38]. A possible strategy to enhance EN tolerability in HSCT patients could be to maximize the pharmacological control of chemotherapy-induced nausea and vomiting, a clinically significant side effect in patients treated with emetogenic chemotherapy regimens. In this regard, a recent survey revealed scarce compliance with anti-emetic guidelines [39]. The alteration of glucose metabolism, specifically hyperglycaemia, which is a complication of PN, has been associated with unfavourable outcomes and increased incidence of DM after transplant [40, 41]. The augmented rate of infections in patients treated with PN is thought to be due to bacterial translocation, which is a consequence of both the lack of intestinal stimulation by food and the augmented mucosal permeability [42].

Several studies comparing EN and PN in HSCT patients have demonstrated the beneficial protective effects of EN. Among these are a better global survival, a shorter time for platelet engraftment, a decreased incidence of acute severe GVHD, and fewer catheter-related infections [42, 43].

IS THERE A REAL NEED FOR A NEUTROPENIC DIET?

After myeloablative therapy and HSCT, all patients experience a prolonged period of neutropenia that increases the risk of infections. Historically, a "low bacterial diet" or "neutropenic diet" (ND) was introduced as a theoretical strategy to reduce the risk of acquiring systemic infection in immunocompromised patients, by restricting the intake of foods with potential pathogenic microbes. ND is defined as "any diet intended to reduce the ingestion of bacterial and fungal contaminants by the exclusion of foods such as uncooked fruits and vegetables, cold cuts, undercooked eggs and meat, unsterilized water as well as unpasteurized milk products and soft cheeses" [44].

Some original studies have investigated the advantages of ND to reduce the infection rate among HSCT patients. However, they are all in agreement with the finding that there is no evidence that ND would lower the infection rate in HSCT patients [45] or neutropenic cancer patients [46, 47] and advise following safe food handling guidelines in both adults and paediatric oncology patients undergoing myelosuppressive chemotherapy [48]. A study done by Taggart et al. (2019) showed no significant differences in food craving, nausea, diet limitation or QoL when comparing ND to a food safety-based diet in 102 American paediatric patients (mean age 11.7 ± 9.3 years) undergoing HSCT [49]. No evidence of effect, is not the same as evidence of no effect," was the adage used in a Cochrane systematic review [44] comparing a low-bacterial diet to a control diet to prevent infection in cancer patients with neutropenia brought on by chemotherapy. This is because the small number of patients included in the studies could account for the lack of a significant difference between treatment groups. The results of other recent systematic reviews are consistent with this finding [35, 50, 51]. Recently, ESPEN guidelines on clinical nutrition in cancer stated that there is no evidence to support the use of a "low bacterial diet" to prevent infections and related outcomes [25]. All dietary recommendations are based on physiological considerations and results of mainly observational trials. The only recommendation should be safe food handling through strict hand hygiene [52].

Despite the lack of evidence and references, ND is still often implemented to prevent food-medicated infections, usually from start of conditioning therapy until neutrophil recovery [53].

Moreover, ND continues to be recommended on 35% of the websites of the 20 top US cancer centres, despite strong evidence against its use [54].

A survey performed about nutritional practices showed that the majority of EBMT centres (93%) used ND alone or ND with food fortification (addition of high-energy ingredients) and oral nutrition supplements, even if evidence is lacking [9, 36]. Both from a medical and nursing perspective, there is a need to focus on replacing ND by safe food handling.

A newly performed survey among German, Austrian, and Swiss HSCT centres [55] showed that having nutritional guidelines for patients undergoing allo-HSCT was the current practice in all 28 participating centres, whereby 86% of them provided a low-microbial diet during the neutropenic phase. Only 5 (18%) centres ever observed a food-associated infection during hospitalization, whereas food-associated infections were reported to occur more often in the outpatient setting (64%). The authors point out the need for nutritional guidelines for patients undergoing allo-HSCT. However, the nutritional treatment in clinical practice as well as the use of food supplements was very heterogeneous. In line with current general recommendations, the centres seemed to focus on safe food handling practices rather than providing a strict ND.

It is worth mentioning the studies currently carried out in low- and middle-income countries since ND is advised to patients receiving treatment for acute leukaemia to reduce infections despite evidence to the contrary from high-income countries. The studies presently being conducted in low- and middle-income countries are noteworthy because, contrary to evidence from high-income countries, ND is still recommended to patients getting treatment for acute leukaemia in order to reduce infections [56]. An ongoing study in Iran aims to compare the effects of food safety guidelines in comparison to the ND on infection rates in patients with acute myeloid leukaemia [57]. On the other hand, a pilot study in paediatric oncology patients in India showed that ND was not effective in reducing febrile neutropenia and was associated with a higher rate of neutropenic enterocolitis when compared to the standard diet [58].

There is a heterogeneous use of nutritional therapies and low adherence to current practice guidelines [9, 59–62]. Most dietary recommendations are based on physiological considerations and results of mainly observational trials. Although most studies have important limitations, nowadays there is no proof of efficacy in preventing infections or death by ND [52].

Currently, there is no evidence to support the use of ND for the prevention of infection and related outcomes [25]. More high-quality data are required to provide evidence-based nutrition to patients during and after allo-HSCT.

RESEARCH ON SPECIFIC NUTRIENTS

Immunonutrition refers to the ability of specific nutrients to modulate immune system activity. The aim is not only to provide energy and protein but also to modify inflammatory or immune responses. Some immunonutrients may have a role in reducing HSCT complications [63].

Glutamine is an essential nutrient for enterocytes and lymphocytes. Several studies have demonstrated beneficial effects after glutamine administration in patients treated with HSCT, specifically a reduction in the incidence of mucositis, GvHD, and infections were observed. Moreover, omega-3 fatty acids have an immunomodulator role and might mitigate the effects of pro-inflammatory cytokines reducing post-transplant complications [2].

A systematic literature review has highlighted how the use of immunonutrition is associated with a reduced risk of GvHD after HSCT, potentially as a result of better immune function and of a scavenger effect on free radicals [64].

Nonetheless, clinical data are scanty, due to both sizes and heterogeneity of available studies [35]. Since there are currently no data from randomized clinical studies on the beneficial effects of glutamine and omega-3 used in patients receiving HSCT, existing recommendations do not advocate their routine use in this subset of patients in order to improve prognosis [25].

Patients undergoing HSCT often experience clinically significant diarrhoea, which alters the ecosystem of gut microbiota. Moreover, prolonged use of total PN reduces intestinal tropism [65]. Probiotics may increase the diversity of the gut microbiota, but there are no studies on their effects in HSCT recipients, making it impossible to make any definite conclusions [35].

INTEGRATION OF PHYSICAL EXERCISE

Ageing, malnutrition, and sedentarism are accelerators for muscle loss and lead to poor physical function [27]. Consequently, some patients may already have a compromised ability to perform daily tasks before HSCT [66]. Additionally, several common side effects of treatment, such as nausea, loss of appetite, GvHD, and hospitalization in an isolation room, cause physical changes (loss of muscle mass and strength, physical pain), as well as behavioural changes (reduced physical activity, depression, and anxiety), which worsen physical function and QoL [18].

Patients should be encouraged towards physical exercise before, during, and after HSCT. In fact, physical exercise has been associated with reduced fatigue, anxiety and improved muscle strength as well as QoL in cancer patients [67]. Furthermore, it has been associated with increased survival after discharge in allogeneic HSCT patients [68–70]. Thus, the multidisciplinary team must include specialized physiotherapists because personalized exercise programs should always be incorporated into nutritional support plans in order to fully support the maintenance of muscle mass [29].

PERSPECTIVES AND CONCLUSIONS

The adequate nutritional status allows a better response to therapy and an improved QoL of patients undergoing HSCT. It is of pivotal importance in the management of this subset of patients in the presence of a nutritional team, both in the pre-and in post-transplant phases.

Whatever nutritional support modality is chosen, it is strongly advised to provide constant monitoring of the patient, aiming to evaluate the effectiveness of the intervention and to prevent and/or treat any possible complication.

In order to implement a successful nutritional support program and maintain the compliance of patients treated with HSCT, it is fundamental to improve the communication between patients/caregivers and healthcare providers, starting from the initial discussion of treatment pathways and nutritional intervention options.

Currently, the *modus operandi* in clinical practice is not standardized and this reflects the heterogeneous methodology of the available literature which does not support a robust consensus regarding the timing for starting nutritional support. However, like in the oncologic setting, it seems reasonable to anticipate the deterioration of nutritional status, implementing strict nutritional monitoring and early support from the initial disease occurrence. Furthermore, the criteria for choosing artificial support, in particular PN, should be more specifically detailed and then shared among HSCT centres.

In the paediatric setting, specific guidelines are not available, highlighting the urgent need to define shared nutritional management protocols. Furthermore, it is important to consider deficient and excessive nutritional status. Indeed, it has been demonstrated that overweight children undergoing autologous

and allogeneic HSCT have a reduced survival rate as compared with their normal-weight counterparts [71].

A personalized nutritional intervention that accounts for nutritional counselling and or artificial nutrition addresses the maintenance of stature and weight growth and prevents a further worsening of nutritional status. The goal must be to prevent and maintain overall nutritional status derangement during oncological therapies in order to improve outcomes and mitigate the impact of endocrine disorders, which frequently develop during and after treatment.

Survival after childhood cancer has significantly improved over the last decades. Nevertheless, oncological therapies can cause long-term complications. Childhood cancer survivors have a high risk of developing chronic cardio-metabolic diseases in later life, as late complications may manifest months to years after treatments [72]. Both disease and treatment can damage the hypothalamus and pituitary gland or other organs (e.g., pancreas, kidneys, liver) leading to several disorders, which are related to metabolic syndrome or its components such as obesity, hypertension, dyslipidaemia, and insulin resistance [73]. In particular, the conditioning regimen before HSCT was associated with metabolic dysfunction and abnormal body composition in childhood cancer survivors [74]. A multidisciplinary approach is mandatory both to prevent and treat cardio-metabolic disorders during the continuum of oncological disease starting at diagnosis and continuing to survivorship.

Nutritional support plays a central role in multimodal cancer care. Signs of malnutrition are not always visible in the early stage but nutritional status deterioration occurs rapidly in the context of HSCT. All efforts should be made to ensure nutritional support for patients from early phases of the transplantation process.

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The authors declare no competing interests.

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