Parenteral nutrition use in children with cancer

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EN	Enteral nutrition
HSCT	Haematopoietic stem cell transplant
PN	Parenteral nutrition

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ABSTRACT

Multiple disease and treatment-related factors contribute to intestinal insult and influence the nutritional status of children with cancer. Many children with cancer will experience intestinal dysfunction during their cancer journey and children with cancer are a common referral group for inpatient parenteral nutrition. Appropriate use of parenteral nutrition in children with cancer and intestinal failure may alleviate malnutrition and associated risks. However, proper selection of patients, correct parenteral nutrition prescription and close monitoring is important to avoid unnecessary intestinal failure or parenteral nutrition related complications, minimise long term nutritional sequelae or additional costs to health services and optimise intestinal rehabilitation.

INTRODUCTION

Despite advancement in survival outcomes for childhood cancer, [1, 2] the diagnosis and treatment of these conditions continues to be associated with significant nutritional burden. All children with cancer are at risk of inadequate nutritional state or malnutrition, which may manifest as 'under-nutrition' (weight loss, inadequate weight gain or decreased fat free mass), 'over-nutrition' (excessive weight gain or increased proportion of body fat) or specific nutritional insufficiency (e.g. micronutrient deficiency).

The reported prevalence of malnutrition in children with cancer is 5.2% - 48%[3-6] and this may present at any stage during a patient's cancer journey from the time of diagnosis, throughout treatment and into survivorship. The impact of malnutrition varies in severity between individuals and can include detrimental consequences for critical childhood processes of

growth, development and puberty. In children with cancer, malnutrition has been associated with poorer survival outcomes, increased morbidity, increased episodes of febrile neutropenia with bacteraemia and reduced physical, emotional and social functioning scores for health related quality of life.[5, 7-11] Further, increased risk of long term health complications and comorbidities has been associated with malnutrition in childhood cancer survivors.[12, 13]

Multiple disease and treatment-related factors may contribute to intestinal insult and influence the nutritional status of children with cancer. Chemotherapeutic agents and radiation therapy deplete the immunologically rich environment of the gastrointestinal tract and cause direct mucosal injury, which is further propagated by the production of reactive oxygen species and pro-inflammatory factors.[14] Mucositis is a complex inflammatory condition of the mucous membranes which can affect any portion of the gastrointestinal tract and is commonly classified as oral or gastrointestinal mucositis.[15] Chemotherapeutic agents may also directly alter absorptive and secretory functions of the intestinal villus-crypt unit and modify activity of brush border enzymes, which are essential to carbohydrate absorption pathways. Other layers of the intestinal wall may sustain damage from chemotherapeutic agents including cells of the lamina propria, musculature and enteric nervous system, resulting in intestinal dysmotility and predisposing to small intestinal bacterial overgrowth.[16] Chemotherapy-induced immunosuppression and loss of mucosal barrier integrity increases the risk of secondary gastrointestinal infections (viral, bacterial, fungal, parasitic) which may further augment mucosal damage and lead to associated complications (e.g. pseudomembranous colitis).

Many children with cancer will experience intestinal dysfunction during their cancer journey, which may manifest as gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal

pain) and be associated with feed intolerance. Regular assessment and early identification of nutritional risk is important to facilitate timely intervention with nutritional support when indicated. Reduction in gut absorptive function that does not require intravenous supplementation to maintain health and / or growth can be termed 'intestinal insufficiency or deficiency'.[17] These children often require optimisation of dietary calories, oral nutritional supplements or enteral nutrition (EN) support to meet their energy requirements. EN has been shown to be an effective and well-tolerated method of feeding in children with cancer and those undergoing Haematopoietic Stem Cell Transplant (HSCT).[18-22]

Intestinal failure occurs when gut function falls below the minimum necessary for the absorption of macronutrients and / or water and electrolytes, and intravenous nutrition support may be required to meet energy, fluid and electrolyte requirements and prevent or correct malnutrition.[17] Parenteral nutrition (PN) is an intravenous solution containing macronutrients (protein, carbohydrate, fat) and micronutrients (vitamins and minerals), which is given through a catheter into a large vein to provide nutrition in children who cannot be fully fed by the oral or enteral route in order to sustain growth and prevent or correct malnutrition. PN should be reserved for children with significant gastrointestinal tract dysfunction and ongoing intolerance to advancement of enteral feeds or contraindication to oral or enteral feeding (e.g. gastrointestinal perforation or obstruction). For most patients, this period will be short-lived whilst the intestinal tract recovers from an insulting agent or event, however for some children with cancer, persistent intestinal failure may lead to requirement for long term inpatient PN, which in clinical practice generally refers to a period of use greater than 4 to 6 weeks.

This article provides a comprehensive critical review of current available literature on indications, use and management of short and long term PN in children with cancer. It highlights important considerations for all clinicians involved in managing children with cancer and intestinal failure to assist decision-making and facilitate appropriate patient selection, safe prescription and optimise monitoring practices and intestinal rehabilitation.

METHODS

A comprehensive literature review was performed in December 2018 of the following databases: Medline (Ovid) and Embase (Ovid). Thesaurus and/or keywords were used as follows: (exp "Neoplasm [MeSH term] AND "Parenteral nutrition"). Results were limited to English language and children 0-18 years of age. PubMed was searched using keywords only to retrieve E-publications and items not indexed in Medline. The Medline search strategy was adapted for use in other databases. Additional items were identified through hand-searching of reference lists of relevant retrieved articles.

INDICATIONS AND BENEFITS OF PARENTERAL NUTRITION

Children with cancer are a common referral group for inpatient PN with frequent indications including HSCT related secondary intestinal failure, cancer treatment induced feed intolerance and mucositis.[23]

Timing of initiation of PN depends on the age, size and situation of the child. The well-nourished human body can tolerate short periods of inadequate nutrition for up to 3 days in infants and 5 days in an older child / adolescent whilst enteral feeding or oral diet is established.[24] A large study of critically unwell children in intensive care showed superior clinical outcomes (acquisition of new infections, length of stay in intensive care) when PN

was withheld for 1 week compared with early PN.[25] In the presence of significant malnutrition or weight loss with gastrointestinal tract dysfunction limiting enteral tolerance, PN may be indicated earlier and further research is needed to define optimal time of PN commencement in children with cancer.[24]

Quality data on specific risks and benefits of PN use in children with cancer is limited. A 2015 Cochrane review found limited evidence from individual trials to suggest PN is more effective for weight gain than EN in well-nourished children with cancer undergoing chemotherapy. However, this was based on a small number of low quality studies and they concluded that further research is needed.[26] No conclusions were made regarding recommended mode of nutrition in children with cancer who are malnourished because of insufficient evidence and further studies are needed.[26]

A study of adults and children undergoing HSCT in 1984 reported engraftment three days earlier in patients given prophylactic PN compared with clinically indicated nutritional intervention however they concluded no overall clinical benefit based on other clinical outcomes.[27] Another study a few years later concluded PN use had no beneficial effect on the time course of marrow recovery but favourable effects on weight gain.[28] Nutritional innovation in recent decades including the development of elemental formulas and modern parenteral lipid formulations have changed nutritional management and hence results of earlier studies may not always be applicable to current practice. Further, clinical significance of weight gain post HSCT can be difficult to interpret due to the influence of other factors on fluid balance (e.g. medications and intravenous fluid therapy) and ideally, other nutritional parameters such as anthropometry should be performed and considered.

RISKS AND COMPLICATIONS OF PARENTERAL NUTRITION

Complications associated with PN use in children with cancer can be classified as mechanical, metabolic or infection related and are summarised in Table 1. Cancer treatments may independently affect immune function, lipid and glucose metabolism and further increase risk of metabolic and infective complications when compared with children on PN without cancer. [29, 30] PN has been identified as an independent risk factor for increased infection rate in children with cancer with a central venous access device.[31] The precise mechanism for this association is unclear but is likely multifactorial (e.g. treatment associated mucosal barrier injury, immunosuppression, frequent use of central venous access device) rather than an isolated direct effect from PN alone. PN use has been associated with loss of appetite and may delay resumption of oral diet in children post HSCT.[30]

Refeeding syndrome is a constellation of metabolic disturbances and physiological changes related to administration of a caloric load (EN or PN) or rapid feeding in the presence of severe malnutrition or starvation. Insulin is secreted in response to glucose administration, which drives glucose entry into cells as well as potassium, phosphate and magnesium, leading to intravascular depletion of these electrolytes. Risk factors for refeeding syndrome include prolonged fasting (>5 days), minimal nutritional intake for >7 days, weight loss > 10% body weight and underlying eating disorder.[24] Patients who require PN and are at risk of refeeding syndrome should have all electrolyte abnormalities corrected prior to commencement of PN and close monitoring including increased frequency of monitoring bloods (Table 2). Nutritional support should be graded up with caution and if significant electrolyte abnormalities develop, PN should be paused, intravenous fluids commenced

(containing 5% dextrose) and electrolyte abnormalities corrected prior to PN recommencement.[24]

PARENTERAL NUTRITION MONITORING AND OTHER INVESTIGATIONS

All children with cancer receiving PN should have routine monitoring to assess for tolerance and identify complications (Table 2).[24] Results should be used to provide individual patient recommendations and modifications to the PN prescription as indicated.

Children with cancer with protracted intestinal failure requiring long term inpatient PN require additional monitoring and assessment of nutritional status. This may include assessment of micronutrient status such as fat soluble vitamins (e.g. Vitamin A, Vitamin D, and Vitamin E), water soluble vitamins (e.g. Vitamin B12, folate) and trace elements (e.g. iron, zinc, copper, selenium). Accurate assessment of some micronutrients may be hindered by the presence of acute inflammation or frequent blood transfusions and individual patient circumstances should be considered when ordering and interpreting these tests.

Various biomarkers for intestinal function have been proposed for use in children with cancer undergoing chemotherapy to aid clinical assessment of degree of intestinal dysfunction and monitor stages of repair. Although biomarkers hold promise for early identification of intestinal mucositis and possible intervention (e.g. timely placement of nasogastric tube prior to onset of severe mucositis or cytopenias), none of these tests are without limitation. They remain largely research based and inaccessible to most clinicians in clinical practice and are summarised briefly below.[16, 32]

Sugar permeability tests (D-Xylose, lactulose/rhamnose and lactulose/mannitol ratio) have been used as markers for loss of barrier function but are complicated to perform and thus not practical in the clinical setting especially for children.[32] Plasma citrulline is a non-essential amino acid produced from glutamine in enterocytes which can be used as a marker of functional small intestinal mucosal mass to reflect absorptive capacity. Low levels have been shown to correspond with severe mucosal barrier injury in patients undergoing HSCT.[14, 32, 33] Isolated citrulline levels may have a role in differentiating site of gastrointestinal inflammation (small versus large bowel) in the absence of endoscopy and serial measurements can be used to monitor trends of cumulative small intestinal damage and progressive intestinal recovery / adaptation.[14] Breath tests such as the ^{13}C sucrose test measure expired breath 13CO2 to reflect enterocyte absorptive digestive enzyme function, following ingestion of a sucrose load that is digested in the intestine and metabolised in the liver. A decreased amount of expired 13CO2 occurs in the presence of gastrointestinal tract damage.[32] Other proteins such as intestinal fatty acid binding protein (I-FABP) and ileal bile acid binding protein (I-BABP) have been proposed as biomarkers but require further research to determine their exact role and practicality for clinical use.[16, 32]

PRINCIPLES OF MANAGEMENT IN CHILDREN WITH CANCER AND INTESTINAL FAILURE

Management of children with cancer and intestinal failure who require inpatient PN should address three key areas: (1) removal of factors precipitating or contributing to intestinal dysfunction where possible, (2) supportive care for gastrointestinal symptoms and (3) nutritional assessment and support as indicated to alleviate malnutrition, with close monitoring to avoid intestinal failure or PN related complications.

Removal of precipitating or contributing factors

Precipitating factors should be removed and differential causes for intestinal dysfunction identified and treated where possible e.g. secondary gastrointestinal infections, cessation or dose reduction of implicated drugs. In patients undergoing HSCT, specific inflammatory and immunological processes within the gastrointestinal tract should be considered and are summarised in Table 3.[34]

Supportive care for symptoms

Accurate assessment and documentation of fluid balance in the medical record is essential to guide decision making on appropriateness of PN indication and monitoring ongoing progress. Information recorded should include daily weight, frequency and size and nature of all gastrointestinal losses (stool, vomit, other), urine output and all intake volumes (oral / enteral / parenteral).

Management of diarrhoea and vomiting requires careful attention to fluid balance to monitor for dehydration and electrolyte imbalances. Literature on therapeutic options in children with chemotherapy induced diarrhoea is very limited. There is literature to support the use of loperamide or octreotide for management of persistent diarrhoea in adults with cancer (once infectious causes have been excluded) [15, 35] and oral antibiotics are recommended for adults with cancer with greater than 24 hours of chemotherapy induced diarrhoea to prevent septic complications.[36] The relevance of these findings to management of diarrhoea in children is unclear and there is a need for future research.

Management of other common gastrointestinal symptoms including abdominal pain, nausea and vomiting should follow specific management guidelines of the treating unit and aim to

minimise the impact of these symptoms on the patient and optimise their capacity for oral and enteral nutritional intake.

Nutritional assessment

Traditional anthropometric measures (weight, height and body mass index) in children with cancer may not differ from healthy age matched controls despite significant loss of body cell mass and increase in fat mass, potentially leading to inaccurate nutritional assessment.[6, 37] Weight may be affected by multiple factors including tumour growth or shrinkage, changes in fluid status (hyper hydration or dehydration) or medication use (e.g. steroid induced fluid retention or diuretic use) and evolving malnutrition may be masked. Optimal techniques for routine nutritional assessment in children with cancer are unclear, however use of alternative anthropometry measurements (e.g. triceps skin fold, mid upper arm circumference) are recommended when possible in conjunction with traditional measures.[11]

Nutritional support

EN is recommended as the nutritional strategy of choice in all patients with a functional gastrointestinal tract.[32, 38-41] It provides essential trophic factors to maintain gastrointestinal mucosa[31, 42] and when compared to PN, has been shown to have lower infection rates, less requirement for monitoring bloods, less cost and can be easily administered as an outpatient.[29, 38, 40, 43- 45] Animal models of gastrointestinal mucositis show glucose and amino acids are still absorbed during active inflammation when administered continuously, however lactose and fatty acids are not and use of an elementary, lactose free formula with reduced long chain triglycerides given continuously via enteral feeding tube may maximise chances of absorption and enteral tolerance in children with cancer.[15] In clinical practice, peptide based or semi-elemental formulas are commonly recommended as initial feed choice when enteral

feeding is indicated and the patient tolerance is assessed by close nutritional follow up. A recent Cochrane systematic review found no statistically significant evidence to support reduction in severity of mucositis or infection with glutamine supplementation, however only 2 studies were included.[26]

When appropriately indicated, PN prescription in children with cancer should involve an experienced dietitian to determine specific targets for energy and protein requirements. Macronutrient requirements differ depending on age, baseline nutritional state and clinical situation and whilst an age-appropriate balance of carbohydrate, protein and fat should be maintained where possible, metabolic changes in children with cancer may alter the way substrates are utilised and influence individual needs. Further, accessibility of individualised rather than standard hospital solutions of PN may differ between individual centres and influence ability and duration to meet target macronutrient requirements.

Excessive provision of calories should be avoided. Adequate protein is critical to counteract catabolic effects of cancer on muscle and immune function. Hyperglycemia may be encountered and is commonly multifactorial, related not only to PN use, but steroids, transient insulin resistance and other factors. The glucose content of PN may require modification and consideration should be given to the role for insulin therapy if hyperglycemia persists despite changes to modifiable factors. Children with cancer on long term PN may have periods where they are prescribed fat-free PN in the context of high triglyceride levels. When this occurs alongside minimal oral intake, there may be risk of essential fatty acid deficiency. Abnormal essential fatty acid profiles have been documented in patients undergoing HSCT.[46] Fat intake should be independently assessed to ensure the minimum recommended dosage is administered to prevent essential fatty acid deficiency (0.1g/kg/day).[47]

Measures should be taken to minimise risk of intestinal failure associated liver disease (IFALD). These include avoiding excessive PN caloric intake, consideration of PN cycling (providing hours off infusion) and administration of trophic feeds, which are small volumes of feed provided continuously into the gastrointestinal tract by enteral feeding tube to help maintain the integrity of the gastrointestinal tract.[42] When a patient does not have a nasogastric tube in place to provide trophic EN and they are safe to receive small volumes of feed, the benefits should be discussed with the patient and family and nasogastric tube insertion considered at the first suitable opportunity.

Carnitine is a micronutrient with an important role in fatty acid metabolism and energy production in muscle. Children with cancer have risk factors for carnitine deficiency (decreased oral intake, increased metabolic requirements, interference with metabolism / excretion by certain chemotherapy agents (cisplatin, ifosfamide, doxorubicin)) and carnitine deficiency has been studied as a potential contributor to cancer-related fatigue however the role of supplementation remains unclear and there are few studies in children.[48-49]

The role of the microbiome in intestinal damage and dysfunction in children with cancer is an emerging area of research. Alterations in the microbiome have been documented in patients undergoing HSCT and associated with adverse transplant outcomes.[50] Multiple influencing factors have been proposed including use of prophylactic antibiotics, neutropenic diet and PN. Future research in children undergoing HSCT will help to elucidate the role of microbiome assessment and management.

DISCUSSION

The challenges inherent to performing quality research in paediatric nutrition are present in many of the existing published studies related to PN use in children with cancer. Many studies are retrospective and assess heterogeneous populations with different diagnoses at variable times during treatment or diagnosis with variation evident in methods of nutritional assessment and diagnostic criteria for malnutrition. These limitations influence the capacity to compare studies and extrapolate findings to clinical settings. This review provides a summary of current literature on PN use in children with cancer but demonstrates the need for future large prospective studies assessing nutritional management in children with different types of cancer. Future research is needed to help define the role and outcomes for different forms of nutrition support in this high nutritional risk population and to develop clinical tools to aid clinician and patient decision making.

Children with cancer have multiple risk factors for gastrointestinal insult and nutritional compromise is common. In clinical practice, determining the degree of intestinal dysfunction can be challenging for clinicians and there may uncertainty about which patients are appropriate for PN use and when to refer. This paper highlights the paucity of current literature or published indications to guide clinicians in decision making and the clear need for further research in this area. Use of PN in children with cancer should be judicious and PN should be reserved for children with significant gastrointestinal tract dysfunction and ongoing intolerance to advancement of enteral feeds or contraindication to oral or enteral feeding. With supportive intestinal rehabilitation, most children with cancer will successfully be able to grade up on oral diet or EN and wean PN within a few weeks. Regular reassessment of enteral tolerance and capacity to wean and cease PN is important to avoid

unnecessary delay in PN wean and cessation and undue burden of prolonged hospitalisation (for patients and families), PN associated complications (for patients) or cost (for hospitals).

All children with cancer who require long term inpatient PN should have a trained paediatric nutrition support team actively involved in their ongoing care and have unique management considerations (Fig. 1). An active approach towards intestinal rehabilitation is important and emerging areas of research such as the role of the microbiome in intestinal dysfunction may provide future avenues for targeted treatment. Home PN for children with cancer is institution dependent and is uncommon. When available, it requires careful assessment of the family and child's suitability for the service, including consideration of the significant burden of care and availability of appropriate home nursing support services.

When indicated, the use of PN in children with cancer and intestinal failure may alleviate malnutrition and associated risks. However, appropriate selection of patients, correct PN prescription and close monitoring is important to avoid unnecessary complications associated with intestinal failure or PN, optimise intestinal rehabilitation, minimise long term nutritional sequelae and additional costs to health services.

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Legend of Figures

Figure 1	Summary of important considerations for clinicians involved in management of children with cancer requiring long term inpatient parenteral nutrition.

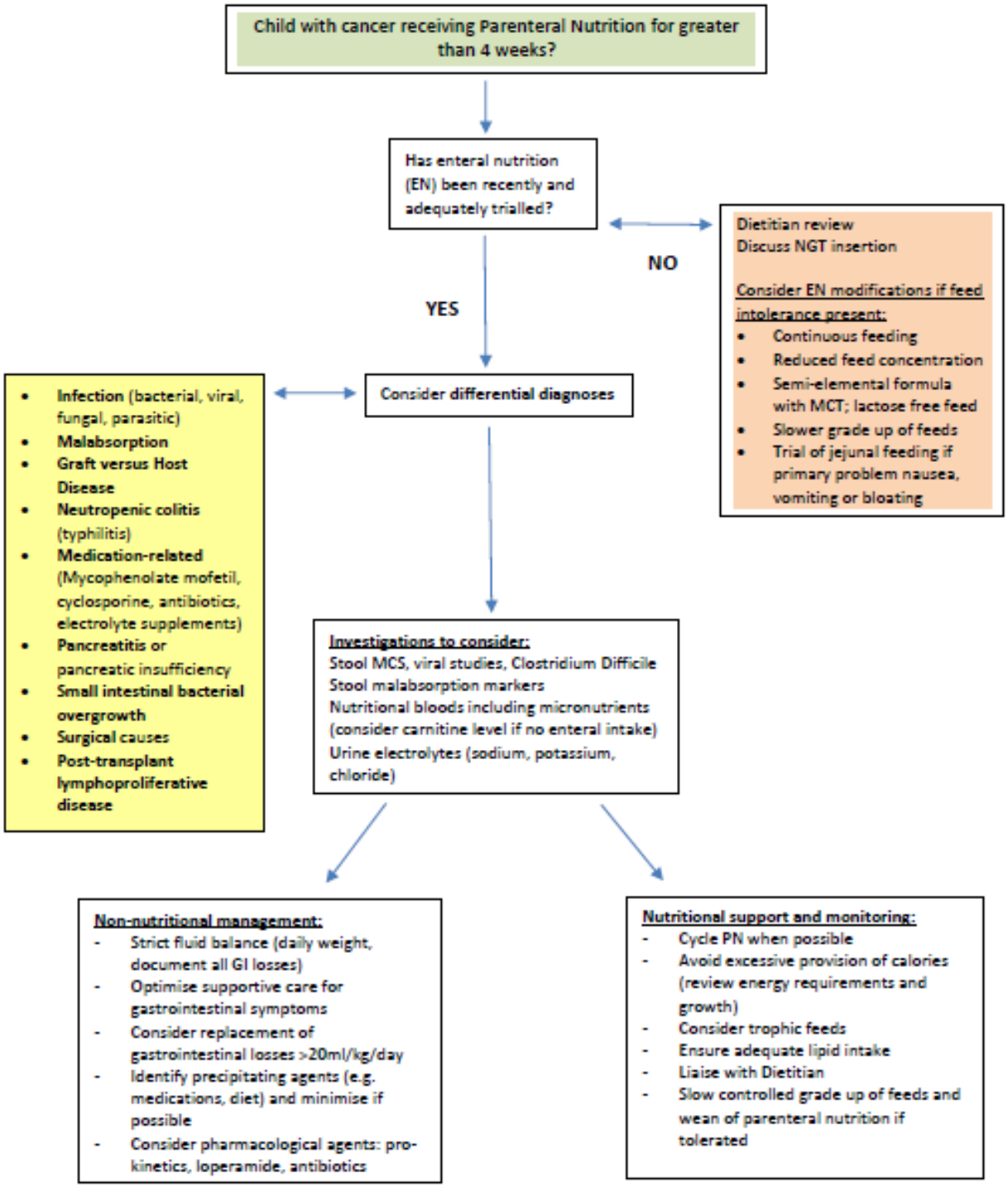

TABLE 1 Parenteral nutrition related complications.

Mechanical or equipment	Infective	Metabolic
• CVAD thrombosis • CVAD break • CVAD occlusion • Accidental dislodgement CVAD • Parenteral nutrition pump malfunction	• CVAD associated bloodstream infection • CVAD site infection • CVAD tunnel infection	• Deficiency or excess of individual parenteral nutrition components e.g. hypertriglyceridemia, hyperglycaemia • Acid-base imbalance • Electrolyte derangement • Drug interaction or compatibility problems • Intestinal failure associated liver disease • Refeeding syndrome • Bone disease

CVAD; central venous access device

TABLE 2 Suggested monitoring tests for children with cancer on inpatient parenteral nutrition.[24]

Timing of investigation	Monitoring test		
	Blood	Urine	Other
Baseline (prior to PN commencement)	Serum electrolytes, urea, creatinine, glucose, calcium, phosphate, magnesium, triglyceride level, full blood count, venous blood gas. Consider micronutrient deficiencies if clinically indicated.	Urinalysis	Weight Height Head circumference (for children less than 2 years old)
Daily for first 3-5 days on PN or until stable on full PN	Serum electrolytes, urea, creatinine, glucose, calcium, phosphate, magnesium, triglyceride level. Note- patients at high risk of refeeding syndrome may require 6-8 hourly serum electrolytes, urea, creatinine, glucose, calcium, phosphate and magnesium in addition to standard monitoring bloods (for 24-72 hours or as recommended by local nutrition support team).	Urinalysis	Daily weight

Weekly monitoring once stable on short term PN (or as clinically indicated)	Serum electrolytes, urea, creatinine, glucose, calcium, phosphate, magnesium, triglyceride level, full blood count, venous blood gas. Consider micronutrient deficiencies if clinically indicated.	Urinalysis Urine electrolytes (sodium, potassium, chloride)	Regular weight (at least twice weekly)

PN; parenteral nutrition

TABLE 3 Mechanisms of intestinal injury and differential diagnoses to consider in children following Haematopoietic stem cell transplant.[34]

Feature of intestinal injury	Timing Post HSCT		
	Pre-engraftment phase (usually between day 0 to day 14-30 post HSCT)	Early post-engraftment phase (day 30-100 post HSCT)	Late post-engraftment phase (>day 100 post HSCT)
Mechanisms	• Immunosuppression • Marrow aplasia (neutropenia) • Cancer treatment related gastrotoxicity (chemotherapy, radiotherapy) • Medication side effects • Gastrointestinal dysbiosis	• Immunosuppression • Cellular and humoral immunodeficiency (lymphocytes) • Graft versus Host disease • Medication side effects • Gastrointestinal dysbiosis	• Immunosuppression • Presence of Epstein Barr Virus infection • Graft versus Host disease
Differential diagnoses	• Infection (viral, bacterial, fungal, parasitic) • Neutropenic colitis (typhilitis) • Pseudomembranous colitis (Clostridium difficile) • Small intestinal bacterial overgrowth	• Viral enteritis (Cytomegalovirus gastroenteritis) • Other infection (bacterial, fungal, parasitic) • Graft versus Host disease (acute) • Pneumatosis Intestinalis • Thrombotic microangiopathy after Transplantation • Megacolon • Cord colitis • Small intestinal bacterial overgrowth	• Infection (viral, bacterial, fungal, parasitic) • Post-Transplantation Lymphoproliferative Disease • Graft versus Host disease (chronic)

HSCT; Haematopoietic Stem Cell Transplant