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INVITED REVIEW

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The evolution of nutritional care in children and young people with acute lymphoblastic leukaemia: a narrative review

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Abstract

Background: Acute lymphoblastic leukaemia (ALL) is the most common paediatric malignancy in the world. Advances in treatment protocols have resulted in survival rates of >80% in most high-income countries (HIC); however, children and young people (CYP) with ALL continue to face significant nutrition-related challenges during treatment.

Methods: This narrative review outlines the changing landscape of treatment and survivorship for CYP with ALL and the advances in nutrition knowledge that call for changes to clinical nutrition practice.

Results: The incidence of ALL has remained stable in HIC; however, there have been significant advances in survival over the past 30 years. Overweight and obesity are increasingly prevalent in CYP with ALL at diagnosis, during treatment and in survivorship. Coupled with poor diet quality, high-energy and saturated fat intakes, altered eating behaviours and inactivity, this necessitates the need for a shift in nutrition intervention. Undernutrition remains a concern for CYP with high-risk treatment protocols where oral or enteral nutrition support remains a cornerstone of maintaining nutrition status.

Conclusions: With improved treatment protocols and high survival rates, a shift to focusing on diet quality, prevention of excessive weight gain and obesity during treatment and survivorship is necessary.

KEYWORDS

acute lymphoblastic leukaemia, childhood cancer, nutrition assessment, nutrition intervention, nutrition status

Key points

- A lack of practice guidelines continues to contribute to wide variation in nutrition practice in high-income countries.
- The prevalence of overweight and obesity at diagnosis has increased.
- Dietitians need to focus on diet quality rather than total calories for children and young people (CYP) with acute lymphoblastic leukaemia.
- Obesity prevention has become increasingly important for CYP in survivorship, where nutrition is a modifiable risk factor for metabolic syndrome.

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INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is the most common paediatric malignancy with incidence closely related to age and sex.[1,2] Worldwide, the age-standardised incidence rate has remained stable (0.89–0.85 per 100,000, 1990–2017), whereas this has decreased in high-income countries (HIC) from 0.89 to 0.55/100,000 (1990–2017).[1] Survival rates have significantly increased over the past 60 years, moving from a near-fatal condition to one where almost 90% of children and young people (CYP) with ALL are cured in HIC, such as the United Kingdom.[3–5] This significant improvement has been attributed to several factors, such as improved supportive care, robust clinical trials and international collaborations, treatment stratification and the development of minimal residual disease (MRD) testing,[6,7] which is fundamental to risk-directed therapy.[8,9]

Evidence for the optimisation of nutrition status during treatment and into survivorship has increased over the past 20 years[10]; however, considerable variation in practice between paediatric oncology centres in HIC continues to be documented across all areas of nutrition care, including screening, assessment, interventions and monitoring practices.[11–15] An absence of established, evidence-based guidelines for medical nutrition therapy plays a significant role in this lack of harmonisation and translation of research into clinical practice, with no consensus on the type and timing of nutrition assessment or duration of nutrition interventions.[16,17]

This narrative review outlines the changing landscape of ALL treatment and survivorship in CYP, and the accompanying nutrition challenges. We highlight how advances in nutrition research have resulted in a greater understanding of the role of nutrition and nutritional status on outcomes such as treatment tolerance, quality of life and overall survival (OS).[10,18,19] However, the translation of this knowledge into guidelines and changes to clinical practice remains to be achieved.[11–15,20] In HIC, there is a need to shift the nutritional care focus, from one of short-term health goals (weight gain and growth) to long-term outcome goals, to reduce the burden of non-communicable disease in survivors of ALL.[21]

PRESENTATION AND DIAGNOSIS

Over the past 30 years, overweight and obesity have increased significantly in CYP undergoing treatment for ALL across all stages of treatment.[22–27] Most strikingly, increases in obesity seen in the general population[28] are now reflected in CYP with ALL at presentation, with most studies reporting more than 15% overweight and/or obesity in newly diagnosed patients.[22–26,29] Obesity has been shown to influence outcomes such as treatment-related toxicity, response to treatment (persistent MRD), relapse rate and survival.[19] Our understanding of how being overweight or obese impacts outcomes is limited; however, potential mechanisms include overtreatment of chemotherapy (calculated by body surface area), increased fat mass (FM) altering drug pharmacokinetics or pharmacodynamics,[30,31] increased adiposity-associated chemotherapy resistance[22,24,29,30] and difficulties in physical and radiological assessments for obese CYP.[1,30] Furthermore, the risk of severe complications and toxicities, such as hyperglycaemia, abdominal complications (e.g., constipation and pancreatitis), bleeding, hyperlipidaemia, kidney dysfunction, liver dysfunction and serious adverse events, increases with increasing body mass index (BMI).[24] Despite the increasing trend of overweight and obesity at presentation, there remains a group of CYP with ALL that still present with malnutrition (underweight).[25,32,33] Studies have shown that being underweight is associated with a higher risk of relapse,[26,34] reduced survival[35,36] and severe adverse complications, such as thrombosis and fungal infections, compared to being well-nourished at diagnosis.[26]

MEDICAL TREATMENT

Prior to the 1970s, the prognosis for CYP with ALL was extremely poor. However, the development of combination therapies, many of which are still used, saw cure rates reach 70% by the end of that decade.[37] Large multicentre national and international trials in the 1980s and 1990s established the basis for treatment strategies that are effective for most children with leukaemia.[38] Over the past 30 years, medical treatment has become more tailored due to advances in our understanding of the pathophysiology of ALL[39] as well as risk-stratification based on age, sex, white cell count and MRD.[40] MRD has become a standard prognostic measure for evaluating response to treatment[41] and determines the treatment pathway, risk mitigation and stratification into treatment protocols.[42] Although there have been changes to antineoplastic combinations to achieve a reduction in tumour load, the basic approach to treatment has remained unchanged for more than 20 years (Figure 1). For most trials and treatment protocols, patients are allocated to treatment arms depending on MRD and other newer genomic measures and immunophenotyping which determine treatment intensity.[44] All aim to maximise the chance of cure for those with more challenging disease and to reduce 'over-treating' those with more responsive disease.[45] For patients with a poor response to initial *Induction* chemotherapy and those with relapsed or refractory ALL, new treatments such as nelarabine, blinatumomab and chimeric antigen receptor T-cell therapy (CAR-T) are currently being studied.[46–50]

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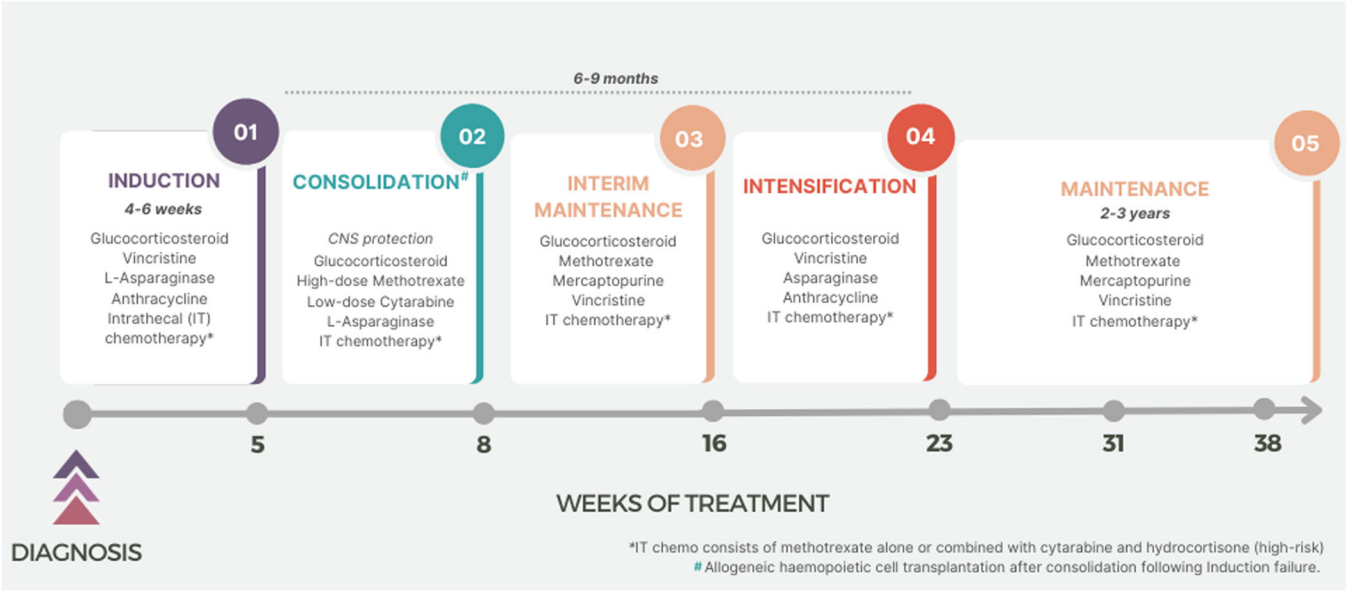

FIGURE 1 Overview of the phases of treatment for children and young people (CYP) with acute lymphoblastic leukaemia (ALL) adapted by the authors from Malard et al.[43]

Significant changes have also occurred in the *treatment and prevention of central nervous system (CNS)* disease. Earlier protocols included cranial or craniospinal radiotherapy. However, since the early 2000s protocols have utilised intrathecal treatment as an alternative for CNS-directed therapy to avoid the use of radiotherapy. The omission of cranial radiation following the UKALL 2003 study[51] resulted in a significant reduction in long-term complications such as poor growth, delayed pubertal development, endocrinopathies (hypothyroidism) and neurological impairment.[42] Glucocorticosteroids were one of the first drugs to be used to treat ALL, and they remain an essential part of treatment.[52] Glucocorticosteroids are given at a high dose for a prolonged period throughout *Induction* and then repeated at various intervals throughout treatment in short pulses. They are associated with significant side effects, including behavioural disruption and increased appetite, increased infection risk, cardiovascular disease, bone disease (rickets, osteopenia, osteoporosis, osteonecrosis), myopathy, endocrine dysfunction (steroid-induced diabetes and insulin resistance) and metabolic dysfunction (overweight/obesity).[43] Prednisone was initially the glucocorticosteroid of choice; however, it has been gradually replaced by dexamethasone due to its better CNS penetration, resulting in a reduction in CNS relapse and subsequent improvement in event-free survival.[43,53–55] The risk of side effects associated with glucocorticosteroids increases with increasing cumulative dose.[43] When used in combination with other treatment modalities, such as radiation or stem cell transplant, they are associated with increased insulin resistance.[56,57]

Improvements in diagnostic technologies, such as genome-wide analysis, immunophenotyping, cell morphology and cytogenetics, have resulted in the classification of more than 30 genetic subgroups of ALL (favourable vs. unfavourable genetics) that provide essential information for risk-stratified therapy (low- to high risk). Along with biologic features, this information guides clinicians in determining response to certain treatment protocols.[40,43] Despite these improvements, overall treatment-related toxicity remains high.[56,58,59] New (reduced intensity) treatment protocols are used for favourable prognoses, utilising new agents to improve survival and minimise toxicity.[60] Therapies such as molecular-targeted drugs and immunotherapy[40] have been incorporated into new international clinical trials, such as the European 'ALLTogether' study[45] and could result in changes to treatment and associated side effects for CYP with ALL.

NUTRITION CHALLENGES ASSOCIATED WITH MEDICAL TREATMENTS

Historically, nutrition interventions in paediatric oncology have focused on the prevention and treatment of undernutrition (mainly manifesting as weight loss) while promoting healthy growth by optimising energy intake. However, new challenges have become apparent driven by changes in medical treatments and with rising rates of overweight and obesity during childhood (Figure 2).[61,62] There is growing evidence of early weight gain in treatment which persists into survivorship in up to 40%–50% of patients.[63,64] With survival rates for CYP with ALL at 80%–90% in HIC,[65,66] there is a need to shift the focus to optimising nutrition status for longevity to reduce the burden of noncommunicable diseases.[21]

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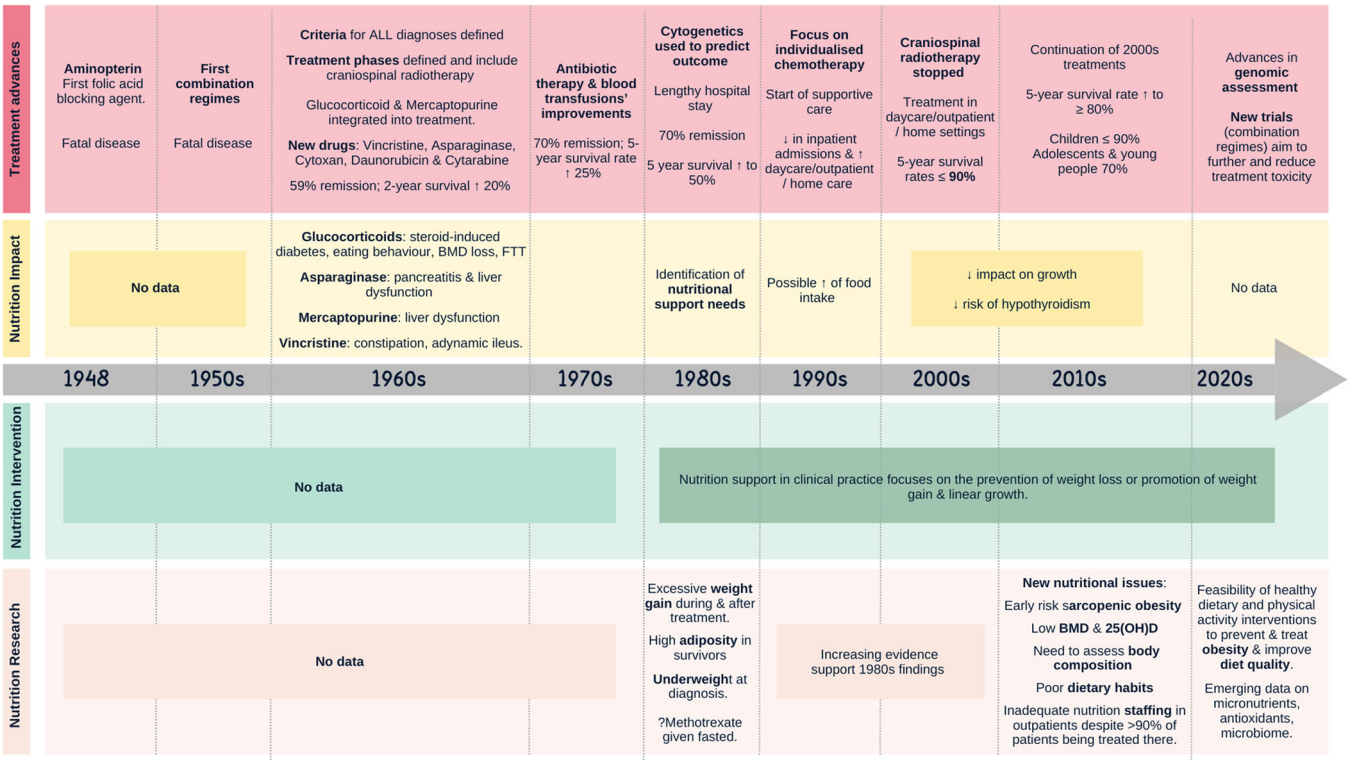

FIGURE 2 Historical perspective of treatment changes, possible impacts on nutritional status/intake, evidence for nutrition interventions and nutrition research.

The *prevalence of obesity* in CYP with ALL increases over time from 15% at diagnosis to 40% during and after treatment in HIC.[23,67,68] Poor dietary choices, increased sedentary behaviours and high and prolonged use of glucocorticosteroids during treatment are potential predictors of overweight and obesity development in CYP with ALL, especially in those on low- to medium-risk protocols.[69,70] Increases in obesity have also been documented in CYP treated with high-risk protocols at the end of treatment.[71,72] Initial reports of obesity in survivors of childhood leukaemia dates back to the 1980s.[73] Studies evaluating the impact of overweight and obesity have increased over the past few decades, with a particular focus on the relationship between increased adiposity and OS, event-free survival and the increased burden of chronic treatment-related conditions such as metabolic syndrome and cardiovascular disease.[22,25,56,74–79] Other factors identified as influencing obesity risk include socio-economic factors, geographical location and ethnicity.[80,81] These determinants are known to influence physical activity and dietary intake and are also seen in the general population.[82–84] For CYP with ALL, targeted nutrition and physical activity interventions that start during treatment are needed. Areas of focus should include growth trajectories, reducing excessive weight gain during treatment, preserving muscle function through minimising losses of lean muscle mass (LMM) and supporting health-promoting behaviours.[80,81]

Despite the increase in overweight and obesity both at presentation and during treatment, *undernutrition* remains an area of concern for CYP on more intensive, high-risk treatment protocols.[34,72,85] In the 1990s, the median prevalence of undernutrition at diagnosis and during treatment was 10% and 54%, respectively.[23,32] Importantly, in recent years, we have seen a decrease in the prevalence of undernutrition in CYP treated with standard- or intermediate-risk protocols (3.2% in *Maintenance* and *Consolidation*), whereas undernutrition, defined as >10% weight loss, remains high in those treated with high-risk protocols (10.3%).[25,72] Early and rapid weight loss may reflect loss of LMM, which negatively impacts survival and infection risk, and could result in rebound weight gain and development of sarcopenic obesity later on.[36,86] Predictors of weight loss (>5%) during *Induction* include high-risk protocols, being ≥10 years of age, having trisomy 21, being overweight/obese at diagnosis and having hyperglycaemia.[85] Finally, CYP who lose >5% weight in the first 3 months have a higher risk of treatment-related complications such as bacteraemia and episodes of febrile neutropenia,[36] thrombosis and fungal infections.[24] Interestingly, normalisation of weight (between the end of *Induction* and the start of *Maintenance*) has been shown to mitigate some of the risks, suggesting that a shift in focus towards correcting early changes in nutritional status might improve outcomes, including survival.[35]

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Glucocorticosteroids can cause resistance to leptin (the satiety hormone), suppress the secretion of growth hormone and increase triglyceride synthesis, contributing to the dysregulation of food intake appropriate for energy requirements, altered dietary patterns[87] and risk of cardiovascular disease.[88] When paired with *asparaginase*, as is the case in ALL treatment protocols, glucocorticosteroids can cause acute hypertriglyceridaemia due to the inhibition of lipoprotein lipase and reduced triglyceride clearance.[89] Although many of the late effects of cancer treatments are not modifiable for survivors, factors such as consumption of excess energy, saturated fat and sodium, along with inadequate micronutrient intakes,[90] lack of physical activity and long-term sedentary behaviours due to chemotherapy-induced fatigue or gait impairments,[91] are important considerations across all treatment stratifications. Particular attention should be paid to dietary habits, with a focus on diet quality and physical activity.

CYP undergoing treatment for ALL commonly report *gastrointestinal symptoms such as constipation* secondary to antineoplastics, particularly vinca alkaloids (due to neuropathy, which can result in paralytic ileus), environmental changes (e.g., long hospital admissions, altered dietary intake, low dietary fibre [DF] and reduced physical activity) and opioid use (an essential component of pain management).[92] No literature exists comparing the dose and frequency of laxative use with DF or dietary patterns in CYP with ALL. In practice, children experiencing constipation should receive a comprehensive assessment of dietary intake, including total fluid intake and optimal sources of both bulking and fermentable fibres, which are known to be beneficial.[93]

Despite being integral to the successful management of ALL,[94,95] exposure to high doses of dexamethasone increases the risk of early sarcopenia, characterised by progressive muscle atrophy (loss of LMM and function), loss of muscle strength and increased musculoskeletal morbidity with incomplete recovery.[86,96,97] These losses have been identified to occur early in treatment (i.e., during *Induction*) and are associated with prolonged hospital admissions,[97] severe adverse events, invasive fungal infections[96] and reducing health-related quality of life.[19,86,98–100] The morbidity of sarcopenic obesity is of particular concern for CYP with ALL due to the combined effect of excess FM on health (i.e., increasing the risk of metabolic syndrome) and low LMM on frailty risk.[101,102] Body composition is rarely measured in standard practice, and anthropometric measures such as BMI percentile have been shown to correlate poorly with changes in body composition.[103] Further research is required to increase our understanding of the mechanisms of sarcopenia and its associations with treatment complications to allow the development of early nutrition and physical activity interventions that can be adopted into clinical practice.[96] More direct measures of body composition such as ultrasonography[104] would provide greater insights and inform interventions aimed at preserving LMM and reducing excess fat gains.[105]

EVOLUTION OF NUTRITION SCREENING AND ASSESSMENT

Nutrition screening

Nutritional screening is important to identify those at risk of developing malnutrition (both under- or over-nutrition) and implement timely assessments and interventions.[106,107] Several paediatric malnutrition screening tools have been developed and validated for general hospitalised populations and are used in CYP with cancer[108–112]; however, they are limited in their application due to the impact of disease, treatment intensity and nutrition-impact symptoms.[113] Furthermore, there is no consistency in the *type* of screening tool or frequency of use internationally.[11–16] For CYP with cancer, two screening tools have recently been developed. The screening tool for childhood cancer (SCAN) was developed and validated in 2016 to identify malnutrition risk in CYP with cancer,[114] but it does not identify the risk of overnutrition (overweight and obesity).[114] More recently, the nutrition risk screening for paediatric cancer (NRS-PC) has been used to identify muscle mass status in CYP with a high BMI.[115] Although these tools offer some support in determining the risk of malnutrition (under/overnutrition) in CYP with cancer, larger studies are needed to validate these tools in specific populations, including CYP with ALL, and develop more accurate screening algorithms for prioritising nutrition interventions in clinical practice.

NUTRITION ASSESSMENT

Nutrition assessment in childhood cancer is a dynamic process, with re-evaluation required at each phase of treatment.[116] There is no single 'gold standard' to assess nutritional status in CYP with ALL,[117,118] and disruptions to body measurements caused by oedema, fluid shifts and changes in body composition (i.e., loss of LMM and accrual of FM) have been widely documented and make it more complex.[23,29,32,117–119] Recent research has focused on better understanding of 'what children are' by assessing body composition, 'what children eat' by assessing diet quality, including nutrient requirements, and 'what children can do' by assessing changes in physical function, all of which are necessary to improve patient outcomes.[118] Here, we will address the evolution of nutritional care in the context of 'what children are' and 'what children eat'. A narrative on 'what children can do' is beyond the scope of this review.

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What children are (body composition)

Traditional measures of nutritional status (weight, height and BMI) are used in practice to assess whether a child is growing optimally, particularly during treatment.[78,118,120] However, BMI, age- and sex-adjusted BMI percentiles and *Z*-scores have their limitations. Gains in FM have been shown to correlate poorly with BMI during treatment for ALL[121–123] and can result in the misclassification of nutritional status if weight, height and BMI are used in isolation.[23,29,32,117–119] This is due to the high prevalence of sarcopenic obesity that develops during treatment.[123,124] Mid-upper arm circumference (MUAC) is a quick and sensitive method of measuring LMM independent of temporary gains in fluid, ethnicity or tumour mass.[119,125–127] Despite being recommended as part of the minimum gamut of nutrition assessment measures, centres do not regularly record arm anthropometry.[14,15] There remains utility in using BMI Z-score at diagnosis as a proxy for body fat percentage, but any longitudinal monitoring should use additional measures such as MUAC, triceps skinfold or bioelectrical impedance.[67,103,117] Monitoring body composition in survivorship is not routinely performed, despite the significant impact of overweight and obesity in perpetuating the burden of treatment-related chronic diseases, such as metabolic syndrome and frailty[86] in cancer survivors.[80]

What children eat (diet quality)

Evidence describing nutrient intakes of CYP with ALL during treatment is scarce and often combined with heterogeneous diagnoses.[90,128–139] However, the evidence is consistent regarding excessive intakes of energy, saturated fat, refined carbohydrates and sodium in CYP with ALL across all age groups and treatment phases when compared to dietary reference intakes (DRIs),[137,139–141] with poor adherence to dietary guidelines also reported after treatment.[142–144] Recent insights into dietary intakes from the Diet and Acute Lymphoblastic Leukaemia Treatment (DALLT) study ($N = 640$) found that *energy intake* decreased during treatment for most age and sex groups, regardless of exposure to glucocorticosteroids and disease risk; however, energy still exceeded DRIs in 75% of patients.[139] In contrast, increases in energy intake with each consecutive day of dexamethasone pulses during *Maintenance* were reported in a Dutch cohort.[145] However, the authors did not determine whether energy intakes remained elevated for more than 4 days post-dexamethasone treatment. The Dutch cohort[145] and DALLT[90,139] both reported *saturated fat intakes* exceeding DRIs, with seven times higher odds of over-consuming fat across all age groups.[139] They reported that having a higher BMI at diagnosis and during *Maintenance* was a predictor for higher saturated fat intake (adjusted-carbohydrate intake).[139] Therefore, healthcare professionals, especially dietitians working with CYP with ALL, need to consider the total energy and saturated fat content of their diets for early intervention.

Micronutrient status (apart from 25-hydroxyvitamin D [25(OH)D]) is not routinely measured in CYP with ALL in HIC, likely due to limited research[129–131,133,146,147] and difficulties in interpreting the data.[148] Emerging evidence suggests that micronutrient abnormalities (deficiencies and excess) are prevalent.[117,131] For instance, across heterogeneous diagnoses, a low plasma selenium concentration was associated with increased risk of an adverse event, including relapse, developing noncurative disease or death by 2%.[131] Additionally, low selenium and low magnesium concentrations predicted complication rates.[131] Interestingly, deficiencies were most common in normally nourished and over-nourished CYP with cancer, where high intakes of energy-dense and micronutrient-poor foods are consumed.[149–152] Data reporting *micronutrient intakes* are inconsistent due to different dietary assessment methods used. Nevertheless, it appears that intakes either exceed recommendations (vitamins A, E) or fall short of recommendations (vitamin B_{12}, folate, vitamin D, calcium, magnesium, selenium, zinc, copper and omega-3 fatty acids).[129–133,147] Diet-based antioxidant intake was associated with decreased infection rates and mucositis after *Induction*.[153] These data indicate that patient-centred dietary interventions are needed from the time of diagnosis, and consideration should not only be given to energy and saturated fat intakes but also to the micronutrient quality of the diet for all CYP with ALL.

Nutrition interventions

All CYP with cancer should have access to nutrition care across the cancer continuum that is provided by trained nutrition experts; however, many centres are only able to provide care for inpatients.[12–14,16,154–158] Alongside, a lack of evidence-based guidelines, staffing, workload and a lack of protected clinical time for quality improvement projects and research are significant barriers to providing optimal nutrition care and interventions for CYP with cancer.[14–16] In an effort to address the lack of guidelines, a series of 21 consensus statements were published in 2022[159] and included issues relevant to CYP with ALL, including overweight/obesity at diagnosis and during treatment and the increased risk of sarcopenic obesity with exposure to long courses of glucocorticosteroids.[159]

Estimating energy requirements

Given the risk of over- and undernutrition on clinical outcomes, accurately determining energy and protein

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requirements for CYP with ALL is necessary to inform nutrition interventions. Although indirect calorimetry is deemed 'gold standard', its use in the everyday clinical environment is impractical.[160,161] Predictive equations developed as far back as the 1980s[162] are universally used to estimate energy and nutrient requirements in clinical practice.[163,164] These equations may include the addition of a physical activity factor or illness factor that may not be representative of CYP with ALL, resulting in overestimation of requirements.[67,117] No predictive equations specific to paediatric cancer are available.[165]

Goals of nutrition interventions

Nutrition interventions should be proactive, begin at diagnosis and include baseline nutrition status (including growth trajectories), energy and nutrient intakes, treatment intensity, risk stratification and the nutritional risk of the diagnosis.[166–168] For CYP with ALL, interventions to promote healthy body composition should begin early to mitigate the physical and psychosocial morbidities associated with treatment.[72] Broadly, nutrition interventions should aim to maintain growth and development *during treatment* while ensuring quality of life.[169] A tiered approach has long been recommended in the literature, beginning with education on optimising diet/nutrient intake through food, escalating to parenteral nutrition (PN) in the context of malnutrition and compromised gut function (Table 1).[167,168,175] To prevent weight loss and treatment-associated malnutrition, it was common practice for health professionals to recommend a high-energy, high-protein intake.[175] However, with increased overweight and obesity at diagnosis, early in treatment and in survivorship, this approach may no longer be appropriate, particularly for CYP on standard risk protocols.

It is important to note that CYP with ALL are less likely to require or receive enteral tube feeding (ETF) compared to other high-risk cancers such as acute myeloid leukaemia, solid and CNS tumours.[176] However, in the presence of undernutrition, nutrition support through dietary counselling, oral supplements (ONS) or ETF may be necessary. Where indicated, ONS may be an effective strategy; however, compliance and poor palatability, as well as the severity of the nutrition impact symptoms, may necessitate more intensive supports such as ETF, and possibly PN.[166,170,177] Once the nutrition goal has been achieved, advice should focus on healthy eating to promote normal growth while avoiding excess weight gain or FM accumulation.[178–180] This is especially important for CYP with ALL due to glucocorticosteroids.[100,181]

The development of obesity after treatment for ALL has received the most *research* attention (Supporting Information S1: Table 1). Over the past 5–10 years, studies have been designed to reduce the overall risk of developing obesity or cardiometabolic complications after treatment and are targeted during *Maintenance* or survivorship.[182–186] Pilot[29] and feasibility studies[187,188] have demonstrated success in achieving energy deficits,[29] reduced glycaemic load,[29,187] improved intakes of nutrients, such as calcium,[21,189] DF, simple sugars[187] and sodium,[188] and address food-based behaviours, and physical activity.[182–185,190–192] Several interventions have been initiated earlier in treatment[29,182,184,185,188,192] in an attempt to attenuate the increase in BMI *Z*-scores that begin during *Induction*.[193,194]

In *survivorship*, nutrition interventions should be tailored to enhancing dietary quality by focusing on eating behaviours and increasing intakes of fruits, vegetables and wholegrains to improve health outcomes.[87,99,195] Dietitians and nutritionists are not often routinely part of survivorship.[12,14,15,196,197] Nonetheless, they have the potential to facilitate obesity prevention as well as other important dietary considerations required for optimal health during survival. This necessitates appropriate levels of staffing across the cancer continuum. Looking forward, dietitians must consider tailoring diet and physical activity recommendations and behavioural interventions to the cancer diagnosis and its treatments, with greater consideration of diet *quality* or *composition* of the energy-providing macronutrients and less of a focus on total calories or BMI.[198]

Enhancing bone health

Bone demineralisation in CYP with ALL has been extensively reported,[199,200] with up to a six-fold increased risk of developing fragility fractures compared to healthy subjects[201] and impairment of optimal bone mineral acquisition during periods of growth.[202] The aetiology of bone morbidity is multifactorial and includes bone marrow leukaemic infiltration leading to decreased bone formation, osteoclast stimulation induced by cytokines,[200] deterioration of the bone microarchitecture secondary to chemotherapy and glucocorticosteroids,[202,203] inadequate dietary intake and physical inactivity.[204–206] Glucocorticosteroid-induced growth failure has been documented in CYP with ALL due to the impact of high-dose glucocorticosteroids attenuating the secretion of growth hormone.[207] Risk factors for impaired bone health include younger age, lower body weight and bone loss documented after cessation of treatment.[207]

Studies aimed at correcting bone mineral losses using bisphosphonates are reported.[200,202,208] At present, there is not enough evidence or resources to perform bone mineral density (BMD) surveillance on all ALL survivors or those treated with glucocorticosteroids.[209] Further research is needed to establish the best therapeutic interventions to restore BMD, as are long-term studies for evaluating the recovery of BMD after treatment and the impact of interventions, such as bisphosphonates, on long-term fracture risk.[202,210]

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TABLE 1 Consolidation of proposed nutrition interventions according to ALL risk stratification and known nutritional risks for CYP.

ALL risk stratification	Considerations	Nutrition intervention
Standard risk	No evidence of malnutrition or weight loss at diagnosis.	Optimise dietary (nutrient) intake and nutrient density, focusing on healthy eating according to country-specific dietary guidelines for age and sex.[170] Manipulate meal size and frequency based on symptoms.
Goal: maintain weight status, prevent obesity and avoid protein-energy malnutrition during treatment.		Preservation of muscle mass and bone mineral density (vitamin D and calcium intake).
	Difficulty maintaining baseline weight status.	Food fortification: optimise intake when possible and boost energy and protein composition (if appropriate) when able to eat with minimal difficulty.[99]
		Oral nutrition support: determine current intake and percentage contribution of ONS to energy and protein intakes.[99]
	Evidence of treatment-induced malnutrition or high nutritional risk therapy.	Oral nutrition support: determine current intake and percentage contribution of ONS to energy and protein intakes.[99]
		EN: if oral intake insufficient to meet growth demands or nutrition repletion insufficient.[170] ETF should be considered *before* nutrition status has deteriorated.[170]
		Consider patient requirements, gastrointestinal function and quality of life when determining feeding regime.
	Evidence of gastrointestinal toxicity or severe mucositis secondary to therapy	EN: consider patient requirements, gastrointestinal function and quality of life when determining feeding regime.[62] Consider continuous feeds.
		PN: consider in chronic malnutrition and patients unable to tolerate continuous EN.[170] Monitor for refeeding syndrome.
	Pancreatitis secondary to therapy.	If oral intake not tolerated or appropriate, EN (consider continuous NG feeds). Replace with nasojejunal (NJ) enteral feeds if NG not tolerated.[171,172]
		PN if NJ feeds not tolerated. Supplement with maximum tolerated rate of EN.[170–172] Monitor for refeeding syndrome.
High risk	Difficulty maintaining baseline weight status.	Oral nutrition support: determine current intake and percentage contribution of ONS to energy and protein intakes.[99]
Goal: prevent protein-energy malnutrition during treatment.		EN: consider patient requirements, gastrointestinal function and quality of life when determining feeding regime.
	Evidence of treatment-induced malnutrition or high nutritional risk therapy.	EN: consider patient requirements, gastrointestinal function and quality of life when determining feeding regime.[62] ETF should be considered *before* nutrition status has deteriorated.[170] Consider continuous feeds.
		PN: consider in chronic malnutrition and patient unable to tolerate continuous EN[170] or to increase total caloric intake.[62] Monitor for refeeding syndrome.
	Evidence of gastrointestinal toxicity or severe mucositis secondary to therapy.	EN: consider patient requirements, gastrointestinal function and quality of life when determining feeding regime. Consider continuous feeds.
		PN: consider when gastrointestinal tract not functioning or cannot be accessed (inadequate oral or EN).[62,170] Monitor for refeeding syndrome.
	Pancreatitis secondary to therapy.	If oral intake not tolerated or appropriate, EN (consider continuous NG feeds). Replace with NJ enteral feeds if NG not[173,174] tolerated.[171,172]
		PN if NJ feeds not tolerated. Supplement with maximum tolerated rate of EN.[170–172] Monitor for refeeding syndrome.
Survivorship	Evidence of treatment-induced overweight and obesity.	Optimise dietary (nutrient) intake and nutrient density, focusing on healthy eating according to country-specific dietary guidelines for age and sex.[99]
Goal: reduce risk of obesity, chronic disease and metabolic syndrome.		

Abbreviations: ALL, acute lymphoblastic leukaemia; CYP, children and young people; EN, enteral nutrition; ETF, enteral tube feeding; NG, nasogastric; ONS, oral supplements; PN, parenteral nutrition.

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Vitamin D deficiency (VDD) increases the risk of low BMD by more than three-fold.[211,212] VDD (<50 nmol/L) occurs in approximately 30%–40% of CYP with ALL at diagnosis, which is similar to VDD reported in healthy children.[129,130,134,135] Interestingly, VDD is more prevalent in older children (12–18 years), over-nourished children or children having higher skin pigmentation.[129,130,134–136] Furthermore, reduced sun exposure and vitamin D intake (diet/supplementation), impaired nutrient absorption (mucositis) and altered metabolism (glucocorticosteroids) increase the risk of VDD.[90]

In the absence of specific guidelines for all CYP with cancer, advice on improving diet (calcium) and physical activity should be given irrespective of BMD to achieve optimal bone mineral accrual.[202,210] When there is no known VDD, supplementation in accordance with national guidance is recommended.[210] Where there is VDD, supplementation ≥600 IU/day has been shown to increase concentration to >75 nmol/L in observational studies across all diagnoses.[129] Further interventions should focus on identifying optimal vitamin D doses and optimal 25(OH)D concentration parameters for CYP with ALL.

Consideration of eating behaviours

Lifelong eating behaviours develop during childhood.[113,213] Approximately 50% of ALL diagnoses occur in children aged <5 years, and the impact of the disease and its lengthy treatment (up to 3 years) on food intake and feeding behaviours can be significant,[152,214] with most survivors reporting a lack of awareness of their increased risk of later health problems.[196,215–217] Many children with ALL experience *at least one nutritional problem* during treatment and beyond, which can include low diet quality,[142–144,149] consumption of energy-dense processed foods, low intakes of fruits and vegetables,[118,150,218] increased pressure from parents to eat,[218] permissive parenting,[192] food cravings[219] and learned food aversions.[220]

Relative to healthy peer controls, ALL survivors exhibit poor diet quality secondary to picky eating (i.e., strong preference for a small number of foods and resistance to trying new foods) and poor self-regulation of dietary intake (i.e., difficulty starting and stopping eating based on internal hunger cues), whereby some aspects of ALL treatment may unintentionally support their development.[87,99,150,218,221] With improvements in survival rates and lack of holistic nutrition support during treatment, these behaviours persist into adulthood and likely influence the development of overweight and obesity.[80] Difficulties in managing cravings, preference for high-energy foods, urgency to eat, selective eating and parenting behaviours are all considerations when planning interventions.[222,223]

AREAS OF INCREASING RESEARCH INTEREST

Micronutrient supplementation

Antioxidant supplementation or targeted intakes above the upper reference values are not part of conventional treatment in CYP with ALL and are considered complementary/alternative.[224] The rationale has been that they may interfere with the effectiveness of chemotherapy and radiotherapy due to their action on free radicals (FR).[153] FR at low/moderate concentrations are essential for normal body functions.[140] However, excess FR can damage cancer cells and healthy tissues, increasing the risk of treatment complications.[137] Some authors[133,137,138,146,225] have reported that higher total antioxidant status and antioxidant capacity (the cumulative action of the antioxidants in plasma) may counteract some of the toxic effects of FR, by reducing treatment-related side effects and improving clinical outcomes in CYP with ALL.[138] Interestingly, a recent study showed reduced toxicities and no harm in CYP with ALL receiving antioxidants (vitamins A, C, E and Zn) in dosages below the recommended upper limit during *Induction*.[153]

The microbiome

Our understanding of the role of the gut microbiome (GM) during treatment for ALL and beyond is in its infancy.[226,227] Recent studies have shown associations between dysbiotic changes[228,229] and outcomes such as toxicities,[230] infectious complications,[231,232] chemotherapy-induced pneumonia,[233] immune dysregulation[234] and depletion of certain species compared to healthy controls,[235] impacting morbidity and mortality.[230] These changes have led researchers to hypothesise that dysbiosis may persist long after treatment and predispose survivors to chronic disease.[234–237]

Modulating the GM through targeted interventions (pro-, syn- and prebiotics) to support microbial stability is of growing interest; however, rigorously designed safety and efficacy trials are lacking for any change to current recommendations in practice. DF may be an important strategy in nutritional management (e.g., treatment-induced constipation), as diets high in DF confer a variety of health benefits by stimulating the growth of healthy gastrointestinal bacteria[238] and promoting the production of short-chain fatty acids.[226,239,240] However, healthy children rarely meet their DF recommendations.[173,174,241,242] There are no documented contraindications to consuming the recommended amount of DF and a gradual increase should be considered.[93] Further randomised controlled trials (RCTs) are required to identify the optimal probiotic (s), dose and prebiotics/DF that influence the composition and function of the GM in this setting.

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Calorie restriction

An increase in our understanding of the role of adiposity in chemoresistance has led to the hypothesis that caloric restriction could improve chemosensitivity and response to treatment at the end of *Induction*.[22,41,243] This approach is contrary to historical weigh-focused, high-energy, high-protein interventions for all cancer diagnoses, often failing to differentiate between the nutritional needs of different diagnoses.[175] These newer, more targeted approaches provide insights into the impacts of diet and lifestyle modifications early in treatment. They have proven that supportive care interventions (nutrition and physical activity) can be implemented early.[29,187,188,244,245] Given the advances in ALL treatments and the potential reduction in treatment-related toxicities, ongoing research is needed to monitor the impact of new protocols on nutrition-related outcomes across multiple centres.

CONCLUSION

The evolution of antineoplastic therapies, treatment protocols and supportive cares has led to significant improvements in survival for CYP with ALL in HIC. The development of overweight and obesity after treatment has long been documented; however, pre-existing overweight and obesity at diagnosis have increased significantly, necessitating a shift towards attenuating further treatment-associated weight increases during treatment and into survivorship. Nutrition interventions need to reflect these changes, with less of a focus on high-energy, high-protein foods and greater emphasis on diet quality and changes in eating behaviours associated with treatment. Establishing clinical guidelines to guide nutrition interventions based on risk stratification remains the most important consideration for standardising practice and optimising nutrition as a modifiable risk factor for CYP with ALL. Given the advances in ALL treatments and the potential reduction in treatment-related toxicities, ongoing research is needed to monitor the impact of new ALL protocols on nutrition-related outcomes and replicated in larger sample sizes across multiple centres.

AUTHOR CONTRIBUTIONS

Jessica M. Bate and Mark F.H. Brougham contributed to the section on medical treatment; Breeana Gardiner contributed to sections on bone health, the microbiome, undernutrition and complications associated with treatment; Raquel Revuelta Iniesta contributed to sections on malnutrition, nutrition assessment, dietary intake and micronutrient assessment. Louise Henry contributed to the evolution of nutrition challenges and nutrition interventions. Amy L. Lovell contributed to all sections and drafted the full manuscript. Breeana Gardiner, Louise Henry and Raquel Revuelta Iniesta critically revised the full manuscript. All authors provided review of the final draft and have read and approved the final version of the manuscript submitted for publication.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

TRANSPARENCY STATEMENT

The lead author confirms that the manuscript is an honest, accurate and transparent summary of the literature base.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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