The influence of nutrition on clinical outcomes in children with cancer

Ronald D. Barr1 | Michael C.G. Stevens2,3

1Department of Pediatrics, McMaster University, Hamilton, Canada
2Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, United Kingdom
3NIHR Cancer and Nutrition Collaboration, Southampton, United Kingdom

Abstract

Adequate and appropriate nutrition is essential for growth and development in children; all put at risk in those with cancer. Overnutrition and undernutrition at diagnosis raise the risk of increased morbidity and mortality during therapy and beyond. All treatment modalities can jeopardize nutritional status with potentially adverse effects on clinical outcomes. Accurate assessment of nutritional status and nutrient balance is essential, with remedial interventions delivered promptly when required. Children with cancer in low- and middle-income countries (LMICs) are especially disadvantaged with concomitant challenges in the provision of nutritional support. Cost-effective advances in the form of ready-to-use therapeutic foods (RUTF) may offer solutions. Studies in LMICs have defined a critical role for the gut microbiome in the causation of undernutrition in children and have demonstrated a beneficial effect of selected RUTF in redressing the imbalanced microbiota and improving nutritional status. Challenges in high-income countries relate both to concerns about the potential disadvantage of preexisting obesity in those newly diagnosed and to undernutrition identified at diagnosis and during treatment. Much remains to be understood but the prospects are bright for offsetting malnutrition in children with cancer, resulting in enhanced opportunity for healthy survival.

KEYWORDS

assessment, clinical outcomes, interventions, microbiome, nutrition

1 | BACKGROUND

More than 20 years have passed since the first international workshop on nutrition and cancer in children,1 held in Puebla, Mexico, under the auspices of UIICC (then called the International Union Against Cancer, now the Union for International Cancer Control). It was titled 'Nutritional Morbidity in Children with Cancer: Mechanisms, Measures and Management’ and had three objectives: to develop a consensus on the nature and magnitude of the challenges, to explore possible solutions, and to set goals and priorities in research. Almost a decade later, the second international workshop on nutrition and cancer in children was convened, again in Puebla2 (Figure 1). The output reflected the breadth of the issues that encompass consideration of nutrition in cancer and included position statements on nutritional status, measurements and outcomes, energy balance and body composition, bone morbidity, complementary and alternative medicines, dietary manipulation and vitamin supplementation, and experience in developing countries. Momentum has continued to grow in addressing the challenges of the “dynamic triangle” of children, cancer, and nutrition.3

The Children’s Oncology Group (COG) formed a nutrition committee that had its first publication in 2005,4 and the International Society of Pediatric Oncology (SIOP) held its first workshop on nutrition in 2013.5 Most recently, the COG committee has prepared an assessment of the state of the science.6 Meanwhile, the SIOP committee has evolved into a network with two streams: one focused on high-income countries (HICs) and the other on low- and middle-income countries (LMICs). The challenges are different in these two settings, but the network is united in its Terms of Reference that begin “Malnutrition in its...
broadest sense poses serious challenges in the management of children and adolescents throughout their cancer journey, from prior to diagnosis into long-term survivorship. Despite a significant increase in publications of work in this area over the past 20 years, the objectives of the first Puebla workshop remain relevant. The nature and magnitude of the impact of nutrition on outcomes for children with cancer are still unclear; optimal approaches to mitigation have yet to be defined with an agreed consensus; research is still needed to better understand the mechanisms by which nutritional status influences tolerance of, and response to treatment, and impacts the long-term health of survivors.

DEFINING NUTRITION

The definition of nutrition may sometimes be interpreted too narrowly by clinicians, limiting the insight necessary to understand the breadth of its role in both health and disease.

Nutrition is the balanced provision of the energy and nutrients needed for cellular life-sustaining biochemical reactions and protection against damage. These nutrients have to be provided on a continuing basis, although ultimately derived from intermittent consumption as the diet of the individual. There is the need to achieve a suitable mix at the cellular level, and there is also the need for that derived from the diet to be modulated. This modulation represents the regulated endogenous formation of critical nutrients in amounts appropriate for normal regulation of cell function. The mobilization of nutrients from structural and functional pools (bone, muscle, adipose tissue, liver) provides a buffer in times of need. A range of nutrients are also made available to the body as products of the metabolic activity of the microbiome in significant, but as yet undetermined, quantities. An inability to make available the energy and nutrients required to support healthy metabolism leads to abnormal body composition, especially when the buffers are drawn upon during periods of ill health but not repleted adequately during recovery. In summary, nutrition can be characterized as:

> the set of integrated processes by which cells, tissues, organs and the whole body acquire the energy and nutrients for normal structure and function, which is achieved at body level through dietary supply, and the capacity of the body to transform the substrates and cofactors necessary for metabolism.
All of these domains (diet, metabolic capacity, body composition and level of demand for energy and nutrients) are influenced by levels of physical activity and can vary according to different physiological and pathological or disease states.8

At different ages and stages of life, the needs for energy and any particular pattern of nutrients vary. The balance and amount of energy and nutrients needed depend on the range of experiences with which the healthy body has to cope. Health is identified as the ability to cope with a changing environment associated with the usual challenges of everyday life, unusual stresses from time to time, as well as the ability to recover. An inability to provide a balance of energy and nutrients that matches needs leads to altered body composition, most simply measured as changes in anthropometrics. The provision of a balance that makes good deficiencies and matches ongoing needs leads to restoration of altered body composition.

3 | UNDERSTANDING NUTRITIONAL STATUS

Nutritional status (or state) is the extent to which the body’s demands for energy and nutrients are met. Such demands are very variable and the supply of energy and nutrients from the diet also varies widely. When the demands are satisfied, cellular integrity is maintained, and the physiological and metabolic processes necessary to maintain structure and function, and secure linear growth, are ensured with an appropriate body composition; there is effective integration and control between organs and tissues, keeping intact the body’s defenses with appropriate inflammatory and immune responses. In growing children, the additional demands associated with growth must be met to maintain the expected pattern of linear growth and deposition of tissue appropriate for each stage of development. Taken together, this represents a satisfactory nutritional state in which optimal health is maintained.

If the dietary supply of energy and nutrients fails to meet the demands over an extended period, then ill health prevails. Cellular integrity is lost, physiological and metabolic processes are altered with associated changes in structure and function; there is dysregulation and perturbed control with altered inflammatory and immune responses. The period of time over which this becomes obvious varies depending on the nature and magnitude of the deficit, from minutes and hours to months or years. In practice, the imbalance will lead in due course to an alteration in the partitioning of nutrients to different tissues and/or functions, such that linear growth is impaired with a failure to either acquire an appropriate body composition or, if sufficiently severe or prolonged, result in a loss of structure (body mass) and function. Taken together, such changes represent a poor nutritional state and would be associated with poor growth and development, loss of resilience, and increased vulnerability. The functional consequences for all tissues and organs may not be apparent in the early stages, and, while at early ages these constraints are potentially reversible, such plasticity is lost progressively with increasing age.

At the other extreme, the consistent consumption of a diet that provides energy in excess of needs leads to an increase in weight and body mass. This not only is seen most obviously as increased adiposity, but also leads to metabolic dysregulation with changes in nutrient partitioning, blood pressure, and homeostatic responses. This process is reflected in the increased morbidity and mortality seen in overweight and obese members of the population.

Therefore, nutritional status can be defined as the extent to which the demands for energy and nutrients are satisfied by the dietary supply. Body shape, size (growth), and composition ("what you are") are the simplest way to define the adequacy of the diet to meet the body’s needs over extended periods and serve as the most readily accessible markers of the nutritional status. Other markers include the quantity and quality of the diet ("what you eat") together with physiological and metabolic markers of function, such as physical capacity or performance and micronutrient status ("what you can do"). No single measure marks the nutritional state and it is characterized best by considering all three domains—"what you eat, what you are, and what you (can) do."9

There is increasing interest in exploring the clinical utility of different physiological or metabolic measures, often termed biomarkers,9 that can be used as prognostic indicators of the risk of increased morbidity or mortality associated with differences in nutritional status. The most obvious example is body mass index (BMI). Equally, other biomarkers have been proposed to mark differences in the dietary pattern, the gut microbiome or the metabolome. Each offers something different and, while they may change with diet or activity, there is a need to better determine their sensitivity and specificity with respect to serving as biomarkers of nutritional status. A striking example of the use of biomarkers, of relevance to malnourished children with cancer in LMICs, is provided in a study of 20 Zambian children with severe acute malnutrition (SAM).10 Serum insulin growth factor-1 levels correlated with mid upper arm circumference (MUAC), while reduction in urinary metabolic signatures was associated with the reduction in intestinal villus height which characterizes the most severe (diarrheal) forms of SAM.

4 | CHALLENGES TO UNDERSTANDING THE IMPACT OF NUTRITION ON CHILDREN WITH CANCER

Most commonly, both in clinical practice and in research settings, BMI or another measure based on body weight is used to determine nutritional status in children with cancer. Yet BMI may be misleading as it does not distinguish muscle from adipose tissue,11,12 and body weight may be influenced considerably by tumor mass, so underestimating undernutrition.13 Among the numerous techniques used to determine body composition,14 dual-energy X-ray absorptiometry (DXA) has found favor as a clinical gold standard.15,16 However, DXA has limited availability in LMICs and even in many HICs, availability is
not sufficiently immediate to allow its frequent use in routine clinical settings where there is a need to assess change in body composition in response to treatment and to nutritional intervention.

In LMICs, assessment based on the use of arm anthropometry is much more common. The close relationship of MUAC to lean body mass (LBM, very similar to fat-free mass) and of triceps skin fold thickness (TSFT) to fat mass have been described in a study of newly diagnosed children with cancer in Canada comparing DXA with arm anthropometry. The advantage of using the MUAC and TSFT over weight-for-height (WFH), the measure of acute malnutrition recommended by WHO,18 was recognized more than 25 years ago in children with cancer in the United Kingdom13 with a threefold increase in the definition of undernutrition among children newly diagnosed with cancer when assessed by arm anthropometry compared with WFH. The same study also highlighted the increased risk of undernutrition in younger children and those with intra-abdominal tumors.

These methodological issues almost certainly underlie much of the variability reported in the prevalence of undernutrition in children with cancer in HICs. A review "restricted to studies in industrialized countries so as to exclude other influencing factors such as poverty and lack of health care facilities" noted prevalence rates at diagnosis ranging from 5% in children with leukemia to 50% in those with neuroblastoma19 and rates were higher with arm anthropometry than with BMI and WFH.

A systematic review published more recently identified 46 reports containing information from both "developed" and "developing" countries, but with especially limited information from the latter, and highlighted the lack of longitudinal data tracking nutritional status during or at the end of treatment; arm anthropometry was associated with higher prevalence rates of undernutrition than BMI. However, the authors were critical of the quality of evidence overall and concluded that "these limitations made it impossible to perform a meta-analysis of the associations between malnutrition and clinical outcomes."

It is clear that consistency in the assessment of nutritional status, and its repeated reassessment during and after treatment is a prerequisite for effective measurement of its impact on outcomes, and of the benefits of interventions designed to address identified malnutrition.

A third compartment of body composition that is affected adversely by cancer and its treatment in children is bone mineral content.21 This is especially important because approximately 40% of bone mass is accumulated in childhood and adolescence. In this age group, osteopenia and osteoporosis have been defined as bone mineral density (BMD) Z scores of −1.0 to −2.0 and less than −2.0, respectively. This definition has been updated to recognize that fragility and fracture can occur at "better" BMD values.22 Most of the studies in children with cancer have been performed in those with acute lymphoblastic leukemia (ALL). These patients exhibit osteopenia at diagnosis,24 and this becomes more pronounced with the onset of treatment.25 It is associated with prevalent vertebral fractures, which are often unrecognized clinically.26 Such loss of bone mineral has been examined in detail by Orgel et al,27 using both quantitative computed tomography (QCT) and DXA. QCT has the advantages of distinguishing compact/cortical bone from the trabecular/cancellous counterpart, which is much more active metabolically, and determining volumetric (v) BMD instead of areal BMD available from DXA. A dramatic loss of vBMD, more than 6% on average, occurred during remission induction, a much higher proportion than was demonstrable by DXA. The impact on compact/cortical bone mass was much less, but this revealed thinning associated with expansion of the medullary cavity. Others have shown that surrogate measures of bone modeling in such children reveal a pattern of bone resorption exceeding bone formation.28 It is likely that this imbalance, resulting in loss of bone mineral, is due mainly to corticosteroids and methotrexate in children with ALL.21

Osteopenia in children with cancer is not limited to those with ALL. It has been described in association with solid tumors and is a common feature in children with brain tumors in whom it has been associated with an added adverse effect on health-related quality of life.30

5 NUTRITION AND OUTCOMES OF CANCER IN CHILDREN IN LMICs

In LMICs, where the great majority of children with cancer reside, malnutrition is prevalent in the young members of the general population and undernutrition is all too common in those diagnosed with cancer.32 As demonstrated in large studies in Central America, this reflects, in considerable measure, the influence of socioeconomic disadvantage33 and it portends poorer prospects for survival, as well as a higher rate of treatment abandonment and a trend toward a greater risk of relapse (Table 1).

The disproportionate burdens of prevalence, morbidity, and mortality in children with cancer in LMICs, compounded by the prevalence and severity of undernutrition, has prompted the SIOP PODC Nutrition Working Group to devote attention to the resultant challenges. An early initiative was to examine the nutritional practices in LMICs as these relate to the care of children with cancer.35 This highlighted the need for improved education of health care professionals on nutrition and adoption of tools for assessing nutritional status by physicians and nurses as well as dieticians. In turn, this led to the development of a framework for adapted nutritional therapy,36 which formed the basis of a determination of the capacity to provide nutritional care in pediatric oncology units in India.37 There then followed the application of the algorithm for delivery of nutritional support in a single center in India. This demonstrated a proof of principle; using the algorithm produced better nutritional outcomes than the institutional standard of care.39

The need for a structured approach to nutritional supplementation is exemplified in Malawi where one report suggested that almost all children with cancer (95%) are severely malnourished at diagnosis when assessed by arm anthropometry.40 This may be exacerbated by comorbidities such as TB, HIV, and parasitic infection for which patients should be screened. In a further study of patients with Wilms tumor, malnutrition was associated with a decreased vincristine clearance rate, implying that dose modification may be required to avoid excessive toxicity.41
### TABLE 1  Distribution of children by category of nutritional status using 3 (TSFT, MUAC, albumin) indicators and clinical outcomes

<table>
<thead>
<tr>
<th>Nutritional status by disease classification</th>
<th>First event N (%)</th>
<th>No. of patients</th>
<th>% 2-year EFS (SE)</th>
<th>Log-rank test P value</th>
<th>Log-likelihood test P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Death</td>
<td>Relapse</td>
<td>Abandonment</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALL</strong></td>
<td>17 (8.9)</td>
<td>28 (14.7)</td>
<td>11 (5.8)</td>
<td>191 (24.1)</td>
<td>68.7 (3.9)</td>
</tr>
<tr>
<td>Adequate</td>
<td>19 (12.8)</td>
<td>15 (10.1)</td>
<td>17 (11.5)</td>
<td>148 (18.7)</td>
<td>67.1 (4.1)</td>
</tr>
<tr>
<td>Moderately depleted</td>
<td>46 (10.1)</td>
<td>72 (15.9)</td>
<td>56 (12.8)</td>
<td>454 (57.2)</td>
<td>60.8 (2.5)</td>
</tr>
<tr>
<td>Severely depleted</td>
<td>82 (10.3)</td>
<td>115 (14.5)</td>
<td>86 (10.8)</td>
<td>793</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trend test</td>
<td>P = 0.802</td>
<td>P = 0.481</td>
<td>P = 0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other leukemias + MDS</strong></td>
<td>8 (38.1)</td>
<td>4 (19.0)</td>
<td>0 (0.0)</td>
<td>21 (14.3)</td>
<td>45.8 (11.3)</td>
</tr>
<tr>
<td>Adequate</td>
<td>10 (40.0)</td>
<td>10 (40.0)</td>
<td>2 (8.0)</td>
<td>25 (17.0)</td>
<td>12.0 (6.5)</td>
</tr>
<tr>
<td>Moderately depleted</td>
<td>34 (33.7)</td>
<td>30 (29.7)</td>
<td>10 (9.9)</td>
<td>101 (68.7)</td>
<td>25.6 (4.5)</td>
</tr>
<tr>
<td>Severely depleted</td>
<td>52 (35.4)</td>
<td>44 (29.9)</td>
<td>12 (8.2)</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trend test</td>
<td>P = 0.587</td>
<td>P = 0.613</td>
<td>P = 0.153</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lymphomas</strong></td>
<td>3 (10.0)</td>
<td>2 (6.7)</td>
<td>3 (10.0)</td>
<td>30 (14.8)</td>
<td>72.3 (8.4)</td>
</tr>
<tr>
<td>Adequate</td>
<td>1 (2.6)</td>
<td>2 (5.3)</td>
<td>4 (10.5)</td>
<td>38 (18.7)</td>
<td>79.1 (7.1)</td>
</tr>
<tr>
<td>Moderately depleted</td>
<td>22 (16.3)</td>
<td>9 (6.7)</td>
<td>24 (17.8)</td>
<td>135 (66.5)</td>
<td>57.5 (4.5)</td>
</tr>
<tr>
<td>Severely depleted</td>
<td>26 (12.8)</td>
<td>13 (6.4)</td>
<td>31 (15.3)</td>
<td>203</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trend test</td>
<td>P = 0.114</td>
<td>P = 0.915</td>
<td>P = 0.190</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Solid tumors</strong></td>
<td>20 (19.6)</td>
<td>11 (10.8)</td>
<td>7 (6.9)</td>
<td>102 (5.6)</td>
<td>59.4 (5.6)</td>
</tr>
<tr>
<td>Adequate</td>
<td>16 (25.8)</td>
<td>9 (14.5)</td>
<td>11 (17.7)</td>
<td>62 (16.7)</td>
<td>40.6 (6.8)</td>
</tr>
<tr>
<td>Moderately depleted</td>
<td>82 (41.4)</td>
<td>21 (10.6)</td>
<td>33 (16.7)</td>
<td>198 (55.7)</td>
<td>25.8 (3.6)</td>
</tr>
<tr>
<td>Severely depleted</td>
<td>118 (31.9)</td>
<td>41 (11.1)</td>
<td>51 (13.8)</td>
<td>370</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trend test</td>
<td>P &lt; 0.001</td>
<td>P = 0.771</td>
<td>P = 0.043</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>48 (14.0)</td>
<td>45 (13.1)</td>
<td>21 (6.1)</td>
<td>344 (22.7)</td>
<td>65.0 (2.9)</td>
</tr>
<tr>
<td>Adequate</td>
<td>46 (16.8)</td>
<td>36 (13.2)</td>
<td>34 (12.5)</td>
<td>273 (18.1)</td>
<td>57.3 (3.2)</td>
</tr>
<tr>
<td>Moderately depleted</td>
<td>184 (20.5)</td>
<td>132 (14.7)</td>
<td>125 (14.0)</td>
<td>896 (59.2)</td>
<td>48.4 (1.8)</td>
</tr>
<tr>
<td>Severely depleted</td>
<td>278 (18.4)</td>
<td>213 (14.1)</td>
<td>180 (11.9)</td>
<td>1513</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trend test</td>
<td>P = 0.006</td>
<td>P = 0.407</td>
<td>P &lt; 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*There was one second malignant neoplasm.

bThere were two second malignant neoplasms.

In a report from Guatemala, children with ALL who were severely malnourished at diagnosis and remained so at six months of chemotherapy had a five-year overall survival (OS) rate of 56.9%, in part related to a high rate of treatment abandonment. The OS of children who were adequately nourished throughout was 79.8%. For those who were severely depleted nutritionally at diagnosis but became adequately nourished by six months with nutritional supplementation the five year OS was 77.5%. This appears to be the first report of the efficacy of nutritional intervention in restoring survival prospects for children with cancer who were undernourished at diagnosis. A subsequent report from the COG provided comparable evidence.43

The prices of commercial nutritional supplements are such that these products are unaffordable in many LMICs, and although the engagement of nongovernmental organizations (NGOs) such as Childhood Cancer International (CCI https://www.childhoodcancerinternational.org) can help to fill this gap, the remaining deficit has stimulated interest in ready-to-use local therapeutic foods (RUTF). An early report of the beneficial impact of a peanut-based RUTF (chiponde) was published a decade ago.44 Children with Wilms tumor in Malawi showed weight gain during preoperative chemotherapy with evidence of better response to treatment. At the SIOP meeting in Kyoto in 2018 colleagues from the Tata Memorial Hospital in Mumbai presented the results of a randomized clinical trial of RUTF in undernourished children with cancer.45 Those in the experimental arm had significantly greater weight gain and improvements in body composition with fewer episodes of febrile neutropenia.
6 | NUTRITION AND OUTCOMES OF CANCER IN CHILDREN IN HICs

Much of the attention focused on nutrition in children with cancer in HICs has been toward the impact of obesity in children with malignant disease, particularly on clinical outcomes in children with acute leukemia. In 2005, Lange et al first described a higher rate of treatment-related mortality in children with acute myeloid leukemia (AML) who were obese at diagnosis.46 Soon thereafter, Butturini et al reported that event-free survival (EFS) and OS rates were compromised in children with ALL who were obese at diagnosis,47 observations supported by subsequent studies.48 A systematic review undertaken by Orgel et al demonstrated that a higher BMI was associated with a significantly increased mortality rate, poorer EFS, and a statistically nonsignificant trend toward greater risk of relapse in children with ALL (Figure 2a) but no studies showed an increased risk of infection in overweight or obese children as an explanation for this finding.49 There is now convincing evidence that obesity during induction is an independent predictor of persistent minimal residual disease (MRD).50,51 The nature of this relationship is complex, as obesity appears to convey continuing long-term risk to EFS even after accounting for end-of-induction MRD status.50 The duration of obesity during the initial, intensive months of chemotherapy predicts EFS independently.43 There are also other associations between high BMI and treatment-related toxicities in children with ALL,51 including osteonecrosis (especially in females), hepatotoxicity, and pancreatitis,53 and the incidence of adverse events during premaintenance chemotherapy.54

Data on children with AML are less numerous, although a higher BMI at diagnosis has also been associated with poorer EFS and OS (Figure 2b), and a link has been suggested between obesity and high rates of fatal infection.55,56

Studies of children with solid tumors are scarce, but one systematic review has addressed this area,57 and, despite a paucity of good data, the authors identified evidence for an influence of BMI on both survival and treatment toxicity in some diagnostic subgroups. Other studies have confirmed the variable prevalence of undernutrition at diagnosis and a relatively high risk of significant deterioration in nutritional status in the early months of treatment, but did not link this with outcome.58,59

Relatively few studies have examined specifically the relationship of undernutrition to outcome in children with cancer in HICs. One report from the Netherlands identified undernutrition, defined by BMI, in 5% of children at diagnosis and reported an association with a lower survival rate.60 This was a heterogeneous population of patients, half of whom had hematological malignancies. The association with lower survival was also linked to nutritional status three months after diagnosis, confirming the continuing impact of nutrition as treatment progresses—an observation supported by another more recent study with similar findings.61

Changes reflecting alterations in body composition, perhaps without significant change in BMI, may also occur during and after treatment. Loss of muscle mass (sarcopenia) has been reported, particularly in children with ALL.14,62–64 It may occur early in therapy and without restoration by the end of treatment.63 Sarcopenic obesity is well described in survivors of hematopoietic stem cell transplantation (HSCT) with total body irradiation (TBI).65 but is now recognized increasingly in long-term survivors of ALL treated without HSCT.66 The consequence is double jeopardy from excess visceral (“bad”) fat and inadequate skeletal muscle mass resulting in metabolic dysfunction and frailty.68 The European Working Group on Sarcopenia in Older People has included a functional component in the definition and diagnosis.69 Efforts to redress the disorder in children with cancer have focused on improving physical activity.70

7 | MECHANISMS BY WHICH MALNUTRITION IMPACTS OUTCOME

There are data to suggest that both over and undernutrition can affect cancer outcomes, but the mechanisms by which these effects are mediated may not be the same.

Obesity (overnutrition) is associated with substantial metabolic and endocrine abnormalities, including alterations in sex hormone metabolism, insulin and insulin-like growth factor (IGF) signaling, adipokines, and inflammatory pathways. There is strong evidence for its association with cancer risk,71 and it is possible that some of the same factors may also affect tumor biology and response to treatment.

In childhood cancer, most work to explore mechanistic reasons for adverse outcome is based on studies in ALL. Although high insulin and insulin growth factor-1 (IGF-1) are likely to contribute to the incidence of ALL,72 they have not been linked directly to ALL outcome but may nevertheless be important influences, via signaling pathways, on survival.73 Experiments in murine leukemia models suggest that obesity affects treatment outcome directly,74 and there are data to suggest that adipocyte absorption and metabolism of chemotherapeutic agents can reduce cytotoxicity in cancer microenvironments, contributing potentially to poorer survival outcomes.75 At a clinical level, obesity raises challenges for optimal dosing of chemotherapy, and increased adiposity may affect pharmacokinetics/dynamics of individual drugs depending on their lipophilic properties.76

The hope remains that antiobesity interventions may yet be able to reverse the disadvantage imposed; this has been demonstrated in a mouse leukemia study77 but will need to be explored in a clinical setting.

There is no published work elucidating mechanisms for the disadvantage of undernutrition specifically in children with cancer, but reduced weight and abnormal body composition, together with impaired micronutrient status, may impact resilience to the disease process as well as to treatment directly. Mechanistic themes involved may include altered immune function, modified cellular bioenergetics and redox state, and changes to epigenetic influences on cellular control. The association of cachexia with a cancer diagnosis is well known, and its multiorgan impact has been elucidated (Figure 3).78

The role of micronutrient deficiency and supplementation is uncertain.79 There is good evidence that adequate micronutrient
FIGURE 2  Impact of BMI on survival in ALL (a) and AML (b). Data from Orgel et al48 showing meta-analysis of EFS and OS. The filled diamonds represent study-specific relative risks (RR), the open diamonds the summary RRs, and the horizontal lines the 95th CI. A statistically significant correlation was shown between poorer EFS and OS with higher BMI. Further analysis of data for ALL (not shown here) suggested that the effect may be slightly greater in preadolescents/adolescents (> 10 years). Reprinted by permission from Oxford University Press: American Journal of Clinical Nutrition. Association of BMI and survival in pediatric acute leukemia: a meta-analysis. Orgel et al.48
status is required to support, among other cellular processes, normal immune function. Micronutrient deficiency is likely to be more common in LMICs and may therefore contribute to adverse treatment outcome by accentuating morbidity from infection and/or treatment tolerance. Robust trials are needed, but some data suggest that, for example, vitamin A insufficiency accentuates treatment-related morbidity and that folate insufficiency may impact both treatment morbidity and outcome in ALL. The literature on vitamin D deficiency in childhood cancer is complicated by increasing reports of insufficiency in normal childhood populations but it appears more common in adult survivors, although specific therapeutic causation is uncertain and the benefits of supplementation are also unclear.

Regardless of medical outcome, quality of life is important for children receiving treatment for cancer. Studies have reported that nutritional status (both undernutrition and overnutrition) adversely impacts domains of health-related quality of life (HRQOL). Evaluation of parental concerns also highlights anxieties about eating and nutrition during treatment and may significantly influence the success of interventions utilized to address nutritional problems.

8 | A VIEW TO THE FUTURE

As stated in a recent Lancet Commission report, “Malnutrition in all its forms, including obesity, undernutrition, and other dietary risks, is the leading cause of poor health globally.” Where lie the opportunities for further progress within the discrete realm of nutrition in children with cancer? Building on success is an obvious way forward and will include

- Continuing and expanding the education of families and health care professionals.
- Promoting routine assessment and surveillance of nutritional status, consistent with local resources, by established methods.
- Increased availability of nutritional supplements that are affordable and culturally appropriate, such as ready-to-use therapeutic foods.
- Utilization of algorithms for nutritional interventions, commensurate with local realities.
- Maintenance of a registry with standardized elements to record nutritional care and provide a platform for clinical research.
- Basic science research as to how bioactive substances (phytochemicals) in the diet may affect the biology of childhood cancer and response to therapy.

While much is yet to be done at the clinical level to assess nutritional status consistently and to measure the impact of interventions, prospects for truly innovative research are exemplified by studies of the intestinal microbiome. The natural experiment provided by twins in Malawi has revealed the importance of the microbiome in the pathogenesis of Kwashiorkor, and a recent review confirms evidence for disruption of the normal microbiome in children with cancer.
this be “turned on its head” with the use of healthy fecal microbiota transplants as has been accomplished with Clostridium difficile infection,89,90 which is so common in children with cancer during periods of prolonged neutropenia? Preliminary trials have also suggested a role in the treatment of metabolic syndrome,91 an evolving concern in childhood cancer survivors,67 particularly those treated with HSCT.92 Experience of fecal microbiota transplantation in children is yet limited, a recent study from Jeffrey Gordon et al points to the ability to modify the gut microbiome by simple dietary manipulation.93 Initiatives based on a growing understanding of dysbiosis and the role of the microbiome are priorities in advancing the care of children with cancer, especially in LMICs.94

Such avenues of enquiry must be subject to the rigors of randomized clinical trials, as should studies of interventions to minimize sarcopenia during and after treatment. The latter could involve nutritional supplementation with creatine95,96 of value in the treatment of muscular dystrophy96 and well tolerated by children with cancer.97 In all of the endeavors, it is essential to incorporate important clinical outcomes such as tolerance of chemotherapy, infections, relapse of disease, survival, HRQOL, and nutritional end points such as obesity.

Increasing awareness of the challenges and opportunities in the nutritional care of children with cancer is a high priority. This demands engagement with the clinical community via national and international collaborative trial groups and with a wide variety of stakeholders at the policy level—WHO, SIOP, IARC (International Agency for Research on Cancer), CCI and other NGOs, and multiple levels of government—among them. Utilization of publications, presentations, social media, and conventional news outlets affords obvious mechanisms.

Finally, it must be emphasized that nutrition in children with cancer, notably in LMICs, is encompassed in United Nations Sustainable Development Goals, particularly numbers 2 (zero hunger), 10 (reduced Inequalities), and 17 (partnerships for the goals). The charge to our community of interested parties is to take advantage of this framework in striving to achieve real progress in the nutritional care of children with cancer worldwide.

**ORCID**

Ronald D. Barr https://orcid.org/0000-0002-5711-7440

**REFERENCES**


