Nutritional status in children and adolescents with leukemia: An emphasis on clinical outcomes in low and middle income countries

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Objective: The purpose of this narrative review is to examine the information available on the nutritional status of children with leukemia in low and middle income countries (LMICs), where the great majority of them live and malnutrition is prevalent, in order to identify best practices and remaining deficits in knowledge.

Methods: Literature relevant to measurement of nutritional status and the impact of nutritional status on important clinical outcomes in this population, and others of relevance, was reviewed.

Results: Arm anthropometry provides more accurate information on nutritional status than measures based on body weight in children with cancer. Both over- and under-nutrition are important determinants of tolerance of chemotherapy, compliance with treatment, relapse of disease, and survival. These relationships are subject to change with nutritional intervention. There are valuable roles for educational tools and ‘ready-to-use-therapeutic-foods’.

Discussion: Assessment of nutritional status is mandatory in this population and accomplishable at various levels of sophistication according to available resources. Recognition of the fundamental role of nutritional status in affecting outcomes in children with leukemia is expanding, but knowledge gaps remain. An apparently counter-intuitive strategy of caloric restriction may be worthy of exploration. There is a particular need to establish normative data, including measures of body composition, in children in LMICs.

Conclusions: Developing adaptive clinical practice guidelines for the measurement of nutritional status and for nutritional interventions, incorporating assessment of health-related quality of life, are evident priorities in the care of children with leukemia in LMICs.

Keywords: Nutrition, Children, Leukemia, Outcomes, Developing countries

Malnutrition (over- and under-nutrition) is mainly a problem of overweight and obesity in the populations of high income countries (HICs), those with an annual gross national income per capita of more than US $12,746 in 2013.¹ Over-nutrition is prevalent in young people with cancer in HICs; before, during, and after treatment.² Indeed, the majority of reports on the association between nutritional status and clinical outcomes in children with cancer originate in HICs and address the poorer prognosis of those who are obese, notably in the context of acute lymphoblastic leukemia (ALL)³ and acute myeloid leukemia (AML)⁴. In an otherwise comprehensive contribution, the review of malnutrition (under-nutrition) by Brinksma et al.⁵ was ‘restricted to studies in industrialized countries so as to exclude other influencing factors such as poverty and lack of health care facilities’.

Yet, more than 80% of children and adolescents with cancer reside in low and middle income countries (LMICs) where under-nutrition is the predominant perturbation of nutritional status.⁶ This has been described as ‘a state of nutrition in which a deficiency of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form and function, and clinical outcome’.⁷ The prevalence of under-nutrition at diagnosis in children with cancer, using a combination of measures, was almost 90% in a small sample (n = 25) in Chandigarh, India.⁸ Consequently, the greater challenge to be addressed is the relationship between under-nutrition and clinical outcomes in young people with cancer in LMICs, especially those with ALL that remains the commonest form of malignant disease in this age group (0–19 years) worldwide.⁹
From a survey undertaken by the Nutrition Working Group of the International Society of Paediatric Oncology (SIOP) it was determined that priorities for improving the nutritional care of children with cancer in LMICs are increased availability of nutritional educational resources for patients and families; enhanced education and nutritional assessment tools for physicians and nurses; and determining the role of complementary and alternative therapies in closing gaps in symptom management. In response to the first of these, an educational initiative has been undertaken successfully in Central America. The second priority provides the basis for the following report.

**Measurement of nutritional status and risk of under-nutrition**

The initial step in this process is screening for aberrations of nutritional status. This is based on determinations of height, weight, weight change, primary diagnosis, and co-morbidities, and is accomplishable by any health care professional. Formal nutritional assessment should be undertaken by a registered dietician using a validated tool, such as the Subjective Global Nutritional Assessment (SGNA). A simplified tool (SCAN) has been developed by the SIOP Working Group, validated against the SGNA, and used particularly in children with cancer.

Direct measurement of nutritional status is the next step. The first matter to be addressed is the most appropriate measure. In HICs there are numerous sophisticated measures, such as body cell mass calculated from total body potassium, that even in this setting have limited availability and applicability. Dual energy X-ray absorptiometry (DEXA) is often cited as the most useful measure of body composition in clinical practice but is seldom accessible in LMICs. Bioelectrical impedance analysis is less expensive than DEXA and has the advantage of portability. Its use has been reported in children in an LMIC, although the technique is less accurate in subjects who have an abnormal hydration status and is challenging to accomplish in children less than 5 years of age.

Simple anthropometric techniques offer the best approach to the measurement of nutritional status in LMICs that is inexpensive, adequately accurate, and uniformly available. The measure used most commonly is body mass index (BMI, weight in kilogram per height in centimeter squared). However, like other measures based on weight, such as weight-for-height (WFH) and percent ideal body weight, BMI is not an accurate measure of body composition in children who have large tumor volumes; a circumstance all too common in LMICs. As a result, the use of arm anthropometry, including triceps skin fold thickness (TSFT) and mid-upper arm circumference (MUAC), has found favor. These measures offer the additional advantage of being independent of ethnicity and valid in populations that are constitutively relatively short, such as the Maya of Guatemala.

In a study of more than 8000 pre-school aged children admitted to a hospital in Kilifi, Kenya over a 3-year period, simple arm anthropometry was as accurate as the World Health Organization’s recommendation of a WFH Z score of ≤3 in predicting death. Oguz et al., in a study from Turkey, reported that WFH was normal in a series of 62 children with cancer at diagnosis but 27% of them were malnourished as defined by MUAC and TSFT values less than the fifth percentile. In a group of Mexican children with solid tumors, Sosa-Ruiz et al. reported a frequency of under-nutrition at diagnosis more than twice as high by arm anthropometry (more than 50%) as by WFH (less than 25%). Likewise, in a study involving more than 1000 children and adolescents with acute leukemia in Guatemala, less than 15% with ALL and 20% with AML were under-nourished at diagnosis as defined by a BMI less than the fifth percentile. Corresponding proportions were 57 and 69% when severe nutritional depletion was defined on the basis of MUAC and TSFT. Despite such a body of evidence, a recent review on nutrition in children with cancer makes no mention of arm anthropometry.

**Impact of nutritional status on clinical outcomes**

At first glance it may appear that the clinical practice guidelines developed by the American Society of Clinical Oncology (ASCO), for dosing of chemotherapy in obese adults with cancer, provide a useful starting point. Indeed, the ASCO guidelines include two important statements – doses of chemotherapy calculated on the basis of body surface area (BSA) should use actual and not ideal body weight, and there is no evidence for increased toxicity or reduced efficacy of such chemotherapy. However, these guidelines are of uncertain relevance to children and adolescents who are obese or overweight; there is no consideration of underweight patients; the impact of sarcopenic obesity is unresolved; and the effect of change in weight over time is not addressed. As emphasized by Tolbert and Kearns body size is an important variable in drug disposition, linked to volume of distribution and plasma clearance. The use of total body weight to calculate drug doses may be supra-therapeutic, leading to more toxicity, or sub-therapeutic, leading to reduced efficacy, according to the tissue distribution of individual drugs. While some practitioners use ideal body weight or lean body weight in adults to calculate doses of IV opiates and anesthetic agents, there are no randomized...
controlled trials to demonstrate increased safety and efficacy with this approach.29

The importance of dose intensity of chemotherapy is widely recognized in pediatric oncology, as exemplified in the successful treatment of Ewing sarcoma by ‘interval compression’.30 The related concept of pharmacokinetic mass is also of importance,29 as in the cases of the fat-soluble agents propofol and fentanyl. Again, it must be acknowledged that height, weight, and age are related to organ development (e.g. of kidney and liver) in pre-pubescent children, so these variables are important determinants of drug clearance in growing patients.29

In this context, among the most pertinent considerations are tolerance of chemotherapy, co-morbidities (especially infection), abandonment of treatment, relapse of disease, and death. Although there are abundant studies of the influence of under-nutrition on health-related quality of life (HRQL) in adults with cancer, the literature is largely silent on this association in children and adolescents.

**Tolerance of chemotherapy**

There is considerable information on compromised tolerance in under-nourished children with cancer in HICs, including perturbations of drug metabolism,31 with resulting delays in chemotherapy, increased toxicity, and compromised survival.12 Good examples are provided by the retrospective studies of Lange et al.4 in children with AML and Butturini et al.3 in children with ALL. In the former, both underweight and overweight patients were much more likely ($P = 0.003$ and <0.001, respectively) to have treatment-related mortality, especially in the first two courses of chemotherapy. In the latter study, obese children dosed on the basis of BSA received lower doses of drugs per kilogram than non-obese patients and had no greater short-term toxicity than those of healthy weight. In a more recent study from the Children’s Oncology Group,32 it was demonstrated that being overweight at diagnosis or during treatment, in children with ALL, was associated with higher rates of hepatic and pancreatic toxicity in the overweight group, and fungal infections and pulmonary toxicity in those who were underweight.

Comparable data from LMICs are scarce. However, important early contributions were made by colleagues in Mexico, especially the group in Puebla, as summarized by Barr.33 These investigators demonstrated associations between nutritional status and tolerance of chemotherapy, treatment-related mortality, and overall survival. In particular, Lobato-Mendizabal et al.34 reported a 5-year survival rate, in children with ALL, of 83% in well-nourished patients and 26% in those with under-nutrition. In a study of children with Burkitt lymphoma in Malawi, those who were under-nourished were more likely to have profound and prolonged neutropenia, Gram-negative septicemia, and treatment-related mortality.35 Investigators in Malawi also demonstrated that, in patients with Wilms’ tumor, the clearance rate of vincristine was decreased compared to patients in the United Kingdom (AUC values almost twice as great in the Malawian children), and that this difference was explained by nutritional status.36

**Compliance with and abandonment of therapy**

Compromised prospects for survival of children with ALL have been related to poor compliance with chemotherapy in Mexico37 and Brazil.38 At its nexus non-compliance is manifest as abandonment of therapy, which has been described as the commonest cause of treatment failure in children and adolescents with ALL in Central America39 where the phenomenon of abandonment has been minimized with the provision of social support.40 Under-nutrition is linked to abandonment of therapy and, in turn, to socio-economic disadvantage.25 The development of a measure for determination of socio-economic status in Guatemala41 was stimulated by the need to identify families at risk of abandoning treatment and to focus appropriate interventions on them and on their under-nourished children with cancer.

**Remission-induction death, relapse of disease, and survival**

Studies in HICs have been decidedly informative on these associations with nutritional status. Children with AML who are underweight or overweight/obese are less likely to survive ($P = 0.006$ and $P = 0.002$, respectively).4 Obese children with ALL, especially those 10 years of age and older, are also more likely to relapse and less likely to survive.3 In fact the higher the BMI and body weight the greater are the risks of both outcomes. Orgel et al.42 observed that children with ALL who were obese or overweight at diagnosis had higher rates of minimal residual disease (MRD) at the end of induction therapy than children of healthy weight, and they had poorer event-free survival independent of MRD status.

Results from studies performed by the Center for International Blood and Marrow Transplant Research are especially instructive. Children ($n = 3687$) who underwent cyclophosphamide-based conditioning regimens in the treatment of leukemias were categorized according to nutritional status. This revealed that those who were underweight or at risk of underweight were less likely to experience treatment-related mortality than those in the other nutritional categories, but had a higher relapse rate by 3 years from transplant (Table 1).43 By contrast, in children who had allogeneic transplants for aplastic
leukemia (n = 1281), those who were under-nourished had the lowest rates of acute graft-versus-host disease (stages III and IV) and 100-day mortality, and 5-year overall survival rates higher than in obese children (Table 2).44

Reports from LMICs are less definitive. As described by Mejia-Arangure et al.45 in Mexico, under-nourished children with ALL are at particular risk of death during remission induction. However, the relationship of nutritional status to relapse rate is much less clear. In the large study from Central America there was no such correlation.25 Nevertheless, there is almost, but not quite,46 unanimity of study results pointing to the poorer prospects for survival of under-nourished children with ALL in LMICs.25

Impact of nutritional interventions
One of the earliest efforts to reverse under-nutrition and its adverse clinical consequences was undertaken 20 years ago in children with ALL in Mexico. Administration of a fortified snack was reported to improve nutritional status and tolerance of chemotherapy.47 While this study was subject to challenge on the basis of methodology, it paved the way for others. In Malawi the use of ‘chiponde’, a ready-to-use-therapeutic food (RUTF), appeared to enhance the pre-operative nutritional status of children with Wilms’ tumor during neo-adjuvant chemotherapy and seemed to improve tumor response significantly.48 Meanwhile, in Guatemala, the poor prognosis of children with ALL, who were severely depleted nutritionally at diagnosis, was reversed if they improved their nutritional status, as measured by arm anthropometry, in the first 6 months of treatment.49 Some of this improvement was effected by the use of ‘incaparina’, an RUTF based on a mixture of maize and soy flours.41

A particularly important objective of nutritional intervention is the restoration of lean body mass, most of which is composed of skeletal muscle. While urinary and serum creatinine may be surrogate measures of skeletal muscle mass,50 on the basis of existing metabolism, this is determined more accurately by DEXA.51 In children and adolescents with ALL there is early sarcopenia with the initiation of chemotherapy.52 The administration of creatine attenuates the accumulation of body fat in such children during continuation chemotherapy,53 and is worthy of exploration as a nutritional supplement in further clinical trials.

A different and provocative perspective
Under-nutrition may have not only a negative impact on the treatment of children with cancer, it may also decrease the incidence of these diseases. One of the factors involved in under-nutrition is caloric restriction, defined as the reduction of estimated caloric needs by 15% or more. Caloric restriction may be one of many reasons why cancer profiles in LMICs differ from those in HICs.54,55 For example, there appears to be a significantly lower incidence of leukemia in children in LMICs.56 By what mechanism can caloric restriction decrease the incidence of cancer? Chronic exposure to a low-calorie diet results in reduced circulating levels of several hormones and growth factors, such as insulin and insulin-like growth factor, leptin and adiponectin, and vascular endothelial growth factor. This leads to decreased growth factor signaling, improved stability of vascular endothelium, reduced inflammation, improved cellular and systemic energy homeostasis, and a more physiological cellular micro-environment. Together these responses to long-term caloric restriction result in decreased risks of cancer and progression of established disease, although there may be a threshold below which the reverse is true.57,58

Caloric restriction was reported to produce better results in patients receiving radiotherapy,59 and short-term starvation was associated with improved

### Table 1 Nutritional status and outcomes from allogeneic HSCT in children with leukemias

| Weight group (BMI\(^{\text{†}}\) percentiles) | Three-year relapse rate (%) | Cumulative TRM\(^{\text{‡}}\) rate (%) |
|---------------------------------------------|-----------------------------|----------------------------------|
| UW (less than fifth)                        | 33                          | 18                               |
| RUW (5th–24th)                              | 33                          | 19                               |
| Normal (25th–85th)                          | 29                          | 21                               |
| OW (86th–95th)                              | 25                          | 22                               |
| OB (more than 95th)                         | 21                          | 28                               |

| Weight group (BMI\(^{\text{†}}\) percentile) | Acute GVHD\(^{\text{§}}\) (grade III/IV) (%) | Mortality at 100 days (%) | Five-year OS\(^{\text{‡}}\) (%) |
|---------------------------------------------|-----------------------------------------------|---------------------------|-------------------------------|
| UW (less than fifth)                        | 8                                            | 13                         | 76                            |
| RUW (5th–24th)                              | 8                                            | 15                         | 69                            |
| Normal (25th–85th)                          | 11                                           | 12                         | 75                            |
| OW (86th–95th)                              | 15                                           | 17                         | 71                            |
| OB (more than 95th)                         | 24                                           | 29                         | 65                            |

\(^{\text{†}}\)Hematopoietic stem cell transplantation.  
\(^{\text{‡}}\)Body mass index.  
\(^{\text{§}}\)Graft-versus-host disease.  
\(^{\text{‡}}\)Overall survival.  

UW, underweight; RUW, risk of underweight; OW, overweight; OB, obese.

### Table 2 Nutritional status and outcomes from allogeneic HSCT in children with aplastic anemia

| Weight group (BMI\(^{\text{†}}\) percentile) | Acute GVHD\(^{\text{§}}\) (grade III/IV) (%) | Mortality at 100 days (%) | Five-year OS\(^{\text{‡}}\) (%) |
|---------------------------------------------|-----------------------------------------------|---------------------------|-------------------------------|
| UW (less than fifth)                        | 8                                            | 13                         | 76                            |
| RUW (5th–24th)                              | 8                                            | 15                         | 69                            |
| Normal (25th–85th)                          | 11                                           | 12                         | 75                            |
| OW (86th–95th)                              | 15                                           | 17                         | 71                            |
| OB (more than 95th)                         | 24                                           | 29                         | 65                            |

\(^{\text{†}}\)Hematopoietic stem cell transplantation.  
\(^{\text{‡}}\)Body mass index.  
\(^{\text{§}}\)Graft-versus-host disease.  
\(^{\text{‡}}\)Overall survival.  

UW, underweight; RUW, risk of underweight; OW, overweight; OB, obese.
effectiveness and reduced side effects of chemotherapy in animal models.60 Short-term starvation alone has decreased tumor cell growth in vitro to the same extent as treatment with cyclophosphamide.61 These studies show how starvation-based differential stress resistance can be used as a strategy to alter the efficacy of chemotherapy and have the potential to maximize the differential toxicity to normal and cancer cells.61 The first randomized clinical trial, focused on the effectiveness of caloric restriction as part of treatment for breast cancer, is underway.62

The effects of caloric restriction on the incidence and treatment of cancers in childhood have not been studied sufficiently and may have limited clinical applicability. Nevertheless, adult-attained height is correlated strongly with cancer risk.63,64 Short stature in populations living in LMICs is determined, to some degree, by a low protein intake among other dietary factors. The WHO multicenter growth reference study found that children around the world, who were fed an adequate diet, showed a strikingly similar pattern of growth.65 This may explain why the second generation of immigrants to the United States attains a stature that is similar to the rest of the US population, but also has an equivalent risk of cancer.66,67 Perhaps with improvement in the diets of children in LMICs, especially with increased protein intake, we may see an increase in the incidence of malignant diseases, including leukemias.

Further considerations
There is a need to enhance awareness of this challenge among colleagues in HICs as a stimulus to fostering initiatives in nutrition in pediatric oncology in LMICs, especially through ‘twinning’ partnerships.68 Workshops, such as those held in Puebla, Mexico,69,70 and the formation of a working group on nutrition in the SIOP71,102 were driven by that intent. The SIOP working group has held events in Mumbai, India (September 2014) and Amman, Jordan (April 2015) with another planned for Sao Paolo, Brazil (November 2015).

A notable gap in knowledge is robust normative data on nutritional status and body composition in children in LMICs, especially anchored to accepted standards in clinical practice like DEXA. Such information would provide a solid foundation for studies of nutritional morbidity and structured interventions as envisaged, for example, in Central America.72 Nutritional interventions should be based on local resources but could be designed to test the effect of an additional supplement, e.g. creatine in a randomized trial. Outcome measures should include clinically important metrics, such as dose intensity of chemotherapy achieved in ALL, in addition to improvements in nutritional status and body composition.

Complementing such endeavors there is an opportunity to determine the HRQL of children and adolescents with cancer in LMICs73 as a function of their nutritional status, and to examine the impact of nutritional interventions on HRQL. These are but a few of the ways forward that will address an important component of the care of young people with cancer in less advantaged societies. Models of such sustainable advances have been described.74

Disclaimer statements
Contributors The authors contributed equally.

Funding None.

Conflicts of interest The authors have no conflicts of interest to report.

Ethics approval None.

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