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Severe childhood malnutrition

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Abstract

The main forms of childhood malnutrition occur predominantly in children <5 years of age living in low-income and middle-income countries and include stunting, wasting and kwashiorkor, of which severe wasting and kwashiorkor are commonly referred to as severe acute malnutrition. Here, we use the term ‘severe malnutrition’ to describe these conditions to better reflect the contributions of chronic poverty, poor living conditions with pervasive deficits in sanitation and hygiene, a high prevalence of infectious diseases and environmental insults, food insecurity, poor maternal and fetal nutritional status and suboptimal nutritional intake in infancy and early childhood. Children with severe malnutrition have an increased risk of serious illness and death, primarily from acute infectious diseases. International growth standards are used for the diagnosis

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of severe malnutrition and provide therapeutic end points. The early detection of severe wasting and kwashiorkor and outpatient therapy for these conditions using ready-to-use therapeutic foods form the cornerstone of modern therapy, and only a small percentage of children require inpatient care. However, the normalization of physiological and metabolic functions in children with malnutrition is challenging, and children remain at high risk of relapse and death. Further research is urgently needed to improve our understanding of the pathophysiology of severe malnutrition, especially the mechanisms causing kwashiorkor, and to develop new interventions for prevention and treatment.

Tackling malnutrition is a major global health priority that is relevant to several of the United Nations' Sustainable Development Goals (SDGs) and is highlighted directly in Goal 2 ('Zero hunger'), which aims to "end hunger, achieve food security and improved nutrition and promote sustainable agriculture[1]". Several forms of malnutrition are recognized, including stunting, which is characterized by reduced linear growth, wasting (including moderate wasting and severe wasting, also known as marasmus), which is characterized by low body tissue mass and other physiological abnormalities (FIG. 1), and kwashiorkor, which is characterized by diffuse peripheral oedema. The current classification of malnutrition is based on body size or the presence of oedema, which does not indicate the aetiology or precise nutritional deficits in an individual. Accordingly, this classification can effectively screen and identify malnutrition, but it does not address each and every specific nutrient deficiency a child might have or the biological variability among children. Such differences have no effect on current empirical management strategies that aim to address the predominant macronutrient and micronutrient deficiencies and treat possible infections.

The term 'severe acute malnutrition' has replaced 'protein–energy malnutrition', which was used to describe children with severe wasting and kwashiorkor (also known as nutritional oedema). In this Primer, we focus on and use the composite term 'severe malnutrition' to refer to severe wasting and kwashiorkor and to better reflect the longstanding nature of the combined infectious and environmental insults that can occur in such cases. It is important to emphasize the multifactorial aetiology of severe malnutrition and its strong association with mortality[2], as well as the frequent coexistence of different types of malnutrition in the same child over time[3] and that such concurrence further exacerbates mortality[4]. Indeed, most children with severe wasting or kwashiorkor are also stunted[5–9]. In addition, we concentrate on the largest and most vulnerable group, children <5 years of age, reflecting SDGs Goal 2.2, which aims to "…by 2030 end all forms of malnutrition, including achieving by 2025 the internationally agreed targets on stunting and wasting in children under five years of age…1". Other populations can be malnourished, such as pregnant women (which has implications for fetal growth)[10], elderly individuals[11,12] and those with disabilities[13,14], but discussing these populations is beyond the scope of this Primer.

Epidemiology

Regions with a high prevalence of severe malnutrition often also have high childhood mortality, with underlying malnutrition having a major role in the risk of death. The global

estimates of the prevalence of severe malnutrition vary between agencies and according to the methodology used (BOX 1).

Commonly used figures are from the WHO, UNICEF and World Bank Group Interagency estimates, which provide both levels and trends for child growth and malnutrition[15] and are based on standard anthropometric indices. An estimated 155 million children <5 years of age were stunted in 2016, and 52 million were wasted, of whom 17 million were severely wasted[15]. The global burden of kwashiorkor remains uncertain due to its wide geographical variability and the failure to include assessments of oedema in most large nutritional surveys[16]; however some estimates from regions of southern and eastern Africa suggest that kwashiorkor accounts for 50–70% of cases of severe malnutrition[5]. Geographical variations in the prevalence of severe malnutrition have been observed (FIG. 2), which probably reflects differences in the distribution, causes and effects of multiple risk factors for malnutrition. These risk factors include social and environmental factors (such as poverty, poor education, limited health care access and contaminated environments)[17–20] and living in areas with a high burden of infectious diseases, such as respiratory tract infections, diarrhoeal diseases[21], HIV and turberculosis[19,22]. Other risks include dietary factors, such as acute and chronic food insecurity[23], as occurs during famines, as well as suboptimal breastfeeding and suboptimal complementary feeding practices[24].

The other major global metrics initiative, the Global Burden of Disease study, estimates the number of deaths and disabilities directly related to protein–energy malnutrition. The 2015 Global Burden of Disease Study reported a global decline in the prevalence of severe malnutrition from 25.4 million in 1990 to 22.4 million in 2015 (REF. 25). However, 1990 might have represented a peak compared with previous years, during which figures were uncertain and HIV was less prevalent. This influence is especially relevant for Sub-Saharan Africa, where HIV and severe malnutrition are strongly linked[22].

The 2015 Global Burden of Disease Study also reported that 174,000 deaths among children <5 years of age were directly due to protein–energy malnutrition[25]. Indeed, malnutrition, especially severe malnutrition, is associated with a high risk of death. The latest Lancet Nutrition series (published in 2013) estimated that 875,000 deaths were attributable to wasting (which was the cause of death of 12.6% of children <5 years of age), and 516,000 deaths were related to severe wasting (which was the cause of death of 7.4% of children <5 years of age)[2]. In ten longitudinal studies including ~54,000 child-years of follow-up and 1,300 deaths in children <5 years of age, all degrees of stunting, wasting and underweight were associated with an increased risk of death[4]. Mortality is higher in children with both wasting and stunting (who have a mortality hazard ratio (HR) of 12.3) than in those who have either wasting or stunting (a mortality HR of 2.3 for those with wasting only)[4]. The causes of death in individuals with malnutrition include infectious diseases (such as diarrhoeal diseases, pneumonia, measles and malaria) and metabolic disturbances (such as hypoglycaemia and refeeding syndrome (see Management))[26,27]. TABLE 1 summarizes the known HRs for deaths due to major childhood infectious diseases associated with various types of malnutrition[2].

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Mechanisms/pathophysiology

Determinants of severe malnutrition

The loss of muscle and fat tissue that characterizes wasting can be caused by inadequate protein and energy intake resulting from food insecurity, poor diet and disease. However, severe malnutrition is rarely caused by a single factor and generally arises from an interplay between social, political and economic factors, the presence of chronic infections and inflammation (both in the gut and systemically). In some circumstances, gender issues, such as a lack of female empowerment, are important drivers of malnutrition[28]. Children with severe malnutrition are common in conditions of population displacement, conflict and food shortage[29], which worsens the effects of many of the risk factors for malnutrition and are associated with ineffective remedial strategies.

Underlying mechanisms

Since the initial descriptions of severe malnutrition, studies aiming to understand the mechanisms and organ-specific and metabolic pathophysiology of severe weight deficits and oedema have been carried out. Historical comparisons are difficult given the changing definitions of malnutrition over time[30] and the wide range of clinical manifestations that reflects different pathologies.

Wasting—Our knowledge of the mechanisms and metabolic changes associated with wasting comes mainly from the literature on long-term starvation and cachexia (that is, wasting induced by a chronic illness)[31]. During short-term starvation (that is, up to several days of fasting), free fatty acids (FFAs) and ketone bodies are primarily oxidized using available fat stores from adipose tissue, and myofibrillar proteins can be broken down into amino acids, which can be converted into glucose (through gluconeogenesis). After several days of starvation (when body fat has been depleted), myofibrillar proteins are extensively broken down to maintain essential metabolic processes. The short-term regulation of macronutrient oxidation and synthesis depends on insulin and glucagon, whereas the long-term regulation of these processes is mediated by other hormones, such as growth hormone, thyroid hormones, catecholamines and corticosteroids.

In addition, cytokine release in cachexia, especially the release of tumour necrosis factor (TNF), IL-1 and IL-6, can negatively influence body composition through a reduction in appetite and food intake, and direct catabolic effects on skeletal muscle and adipose tissue[32,33]. Increased activation of the ubiquitin–proteasome pathway is the main process that degrades myofibrillar proteins in cachectic conditions[31,34]. Autophagy has also been implicated in muscle wasting[31] and ongoing autophagy can be detrimental for muscle cells by removing cellular components important for muscle metabolism and contraction, such as mitochondria. However, the specific roles of inflammation, proteasomes and autophagy in severe wasting in children in low-income and middle-income countries have not been studied in detail.

Kwashiorkor—Despite longstanding knowledge of kwashiorkor, the underlying pathophysiological mechanisms are poorly understood. In her earliest report, Cecily

Williams documented that children with kwashiorkor in Ghana were fed mostly a monotonous corn diet that was deficient in essential amino acids such as lysine and tryptophan[35]. However, few studies have identified any specific nutritional deficiencies associated with the development of kwashiorkor, and studies typically have not revealed major differences in food group intake between children who developed kwashiorkor compared with those who did not or with those who developed wasting[36,37]. Despite numerous hypotheses, the aetiology of oedema, which is the hallmark of kwashiorkor, remains undefined. In animal models, some features of kwashiorkor, such as hypoalbuminaemia, can be induced by a diet low in protein and high in monosaccharides and disaccharides[38,39], but oedema is rarely observed. In addition, the degree of hypoalbuminaemia and recovery upon nutritional management in children with kwashiorkor correlates poorly with the degree of oedema or the speed of its resolution[40]. Thus, controversy remains regarding the contribution of factors other than hypoalbuminaemia to the development of oedema in individuals with kwashiorkor[38,41].

Infections—Children with severe malnutrition are highly susceptible to life-threatening infections[2,42], which is a consequence of a secondary immunodeficiency. Indeed, the presentation of children with severe malnutrition to medical services might be due to a serious infection rather than the presence of malnutrition alone. Several potential mechanisms of immune dysfunction exist in individuals with malnutrition[43,44].

Skin, respiratory and gastrointestinal mucosal barrier integrity are often impaired in children with malnutrition, and the effects of this impairment are compounded by chronic subclinical enteric dysfunction in close association with alterations to gut microbiota[45,46]. Children with severe malnutrition have increased levels of markers of systemic immune activation, such as the pro-inflammatory cytokines TNF, IL-1, IL-6 and IL-12, which alter the growth hormone–insulin-like growth factor 1 (IGF1) axis and result in wasting and linear growth failure. Alterations in this axis are also observed in other childhood inflammatory conditions, such as juvenile arthritis and inflammatory bowel disease[47]. Systemic immune activation in severe malnutrition can be caused by acute and chronic infection, inflammatory enteropathy, translocation of microbial components from the gut lumen or mucosa into the circulation[48,49] and dysregulated immune responses[50].

Other alterations in the immune system in severe malnutrition include T cell dysfunction and reductions in neutrophil microbicidal activity[51], the number of dendritic cells, antigen priming and presentation[52] and protein levels in the complement cascade[44]. Thymic atrophy, T cell hyporesponsiveness and impaired T cell proliferation could result from chronic immune activation and/or the metabolic demands of T cells for glucose, amino acids and nutritionally mediated regulatory hormones, such as leptin[50,53,54]. Although some abnormalities in the immune system can resolve with nutritional rehabilitation[55], the reversal of susceptibility to infection and reduction in immune activation have not been well characterized.

Altered metabolism—Severe malnutrition can also affect many aspects of macronutrient metabolism and endocrine function[56,57] (FIG. 3). In contrast to severe wasting, which is associated with a starvation-induced response of subcutaneous fat loss and muscle wasting,

kwashiorkor has been speculated to be associated with a maladaptive metabolic response; a high-carbohydrate, low-protein diet is thought to lead to a continuous glycolytic response and protein catabolism that is inadequate to meet the amino acid requirements necessary to maintain essential protein synthesis pathways[58]. Indeed, protein breakdown has been shown to be lower in children with kwashiorkor than in children with severe wasting and in those in a recovered state[59,60]. In addition, reduced concentrations of essential and some nonessential amino acids have been reported, and these deficits were even more pronounced in children with kwashiorkor[61].

Lipid metabolism is also differentially affected in kwashiorkor and severe wasting. Adipocyte lipolysis is a tightly regulated process, with a central role for insulin in inhibiting hormone-sensitive lipase. Lipolysis is stimulated during starvation (that is, when insulin levels are low)[62,63], and lipolysis has been shown to be increased in a small cohort of children with severe malnutrition compared with a control cohort[62]. However, another study did not show elevated lipolysis in children with severe malnutrition at hospital admission compared with those in a state of nutritional recovery, although reduced FFA (palmitate) flux and oxidation were noted in children with kwashiorkor compared with children with severe wasting[63]. One caveat of this study is that lipolysis was assessed when children were in the semifasted state, when insulin levels were likely low and lipolysis was stimulated. Thus, how lipolysis is altered in the postprandial state is unknown. A recent study identified high acylcarnitine levels in the early period of hospital admission for severe malnutrition regardless of the presence of oedema, suggesting preferential fatty acid oxidation[64].

Glucose homeostasis is also disrupted in children with severe malnutrition; hypoglycaemia is common, although frequent or continuous glucose measurement studies have not yet been carried out to characterize this fully[56,65]. Kwashiorkor is associated with reduced endogenous glucose production compared with production in children with severe wasting or in healthy children, likely contributing to the development of hypoglycaemia[66]. This finding is consistent with the hypothesis that kwashiorkor is associated with a maladaptive metabolic response[58]. In addition, glucose clearance from the blood and uptake by tissues, which is regulated by insulin, are affected; several studies have reported impaired glucose clearance in both kwashiorkor and severe wasting[67–69]. A striking feature that seems to contribute to impaired glucose clearance is the blunted pancreatic endocrine response, with insulin sensitivity likely unaffected[67]. However, despite the reports of impaired glucose clearance in metabolic studies, hyperglycaemia has not been specifically reported in children with severe malnutrition (likely due to glucose levels usually being checked only when patients are symptomatic for hypoglycaemia), and its prevalence is unknown.

The mechanisms of impaired pancreatic function in children with severe malnutrition are poorly understood, but studies in preclinical models have implicated a more-polarized membrane potential, changes in cAMP-dependent protein kinase catalytic subunit-α protein levels and a reduced ability to increase intracellular Ca^{2+} levels in response to glucose[70–72]. In addition, no clear data are available regarding the pancreatic glucagon response (which is responsible for stimulating glucose production) in children with severe malnutrition. Glucagon concentrations have been reported to be either mildly reduced during the acute phase of malnutrition compared with levels at recovery or elevated in children with severe

wasting compared with controls[66,73], but stimulation tests or systematic glucagon response measurements during hypoglycaemia have not been carried out.

In general, cortisol levels in children with severe malnutrition are similar to levels in children without malnutrition or are increased, which is likely related to stress and indicates that the hypothalamic–pituitary–adrenal axis is preserved in children with severe malnutrition and is probably not responsible for the development of hypoglycaemia[64,74,75]. Most studies have shown a reduction in thyroid function in children with severe malnutrition, but the clinical relevance of this remains unclear[76,77]. In addition, leptin concentrations are low in children with severe malnutrition, reflecting the extent of adipose tissue loss. Leptin has a direct role in immune function, metabolism and appetite regulation, and its levels are inversely associated with mortality[64].

Oxidative stress—Oxidative stress has also been associated with severe malnutrition and, in particular, with kwashiorkor. Indeed, children with severe malnutrition have reduced levels of antioxidants, including vitamin E and glutathione, compared with children without malnutrition, and this reduction is more-pronounced in children with kwashiorkor[78–82]. Although a reduced intake of antioxidants likely contributes to the lower levels observed in children with malnutrition, this is also likely, in part, related to a reduced synthesis of certain antioxidants, such as glutathione[59]. An imbalance between levels of reactive oxygen species and antioxidants has been postulated to have a role in the pathophysiology of kwashiorkor[80], although a large randomized trial of an antioxidant mixture (containing riboflavin, vitamin E, selenium and *N*-acetylcysteine) in Malawi failed to show decreased rates of kwashiorkor[83], despite a pilot study suggesting a potential beneficial treatment effect[78]. An imbalance between reactive oxygen species production and detoxification by peroxisomes results in mitochondrial damage, which ultimately reduces ATP production and impairs cellular function in the liver. Mitochondrial dysfunction and ATP depletion together with specific nutrient deficiencies might influence the response to an intercurrent infection and contribute to the development of multi-organ failure[84–87]; this process needs further characterization.

Cardiac function and haemodynamics—Cohort studies of small numbers of children with severe malnutrition have reported cardiac muscle atrophy and decreased cardiac output[88], especially in children with kwashiorkor[89]. However, other studies have reported a normal cardiac output when corrected for body surface area[90,91], with impairments observed only in the most severely ill children, which was probably related to sepsis. The largest study to date excluded severely ill children and showed no major differences in cardiac function between hospitalized children with severe malnutrition and children without malnutrition at an average of 4 days after admission[91]. The mechanisms leading to cardiac atrophy have not been well studied, although one study used a mouse model of calorie restriction to show that this was related to a proportional decrease in different subcellular components of cardiomyocytes[92].

Hepatic function—Severe malnutrition, in particular kwashiorkor, is associated with changes in hepatic metabolic function. A striking feature of kwashiorkor is the presence of hepatic steatosis (that is, fatty liver)[35]. One study suggested that the hepatic steatosis in

kwashiorkor is not related to the impaired secretion of lipids (in the form of very low-density lipoproteins) by the liver[93]. In addition, an increase in fatty acid release from adipose tissue that could be taken up by the liver has been observed in children with kwashiorkor in some[62,94], but not all[63], studies, which might be related to whether the analyses were performed when the participants were in the fasted state. Impaired hepatic lipid oxidation might also explain the hepatic steatosis observed in children with kwashiorkor[63]. This lipid oxidation is difficult to assess in children, but some data from post-mortem samples and animal models suggest that mitochondrial function, which is mainly responsible for hepatic lipid oxidation, is impaired[66,84,95,96]. Indeed, impaired mitochondrial function would be expected to affect hepatic synthetic pathways, and reduced glucose synthesis in children with kwashiorkor was shown to be correlated with mitochondrial activity[66]. Other alterations in the livers of children with kwashiorkor include reduced albumin synthesis[97], although whether other hepatic synthetic processes (such as the production of coagulation factors) are altered has not been studied.

Enteropathy—Although much interest surrounds the potential association of stunting with enteropathy[98], intestinal dysfunction also accompanies severe malnutrition. Indeed, diarrhoea is common in children with malnutrition and is associated with poor clinical outcomes[99–101]. Several factors might contribute to secretory and osmotic diarrhoea in individuals with malnutrition, including intestinal infections and inflammation[102]. In addition, poor nutrient digestion resulting from impaired hepatobiliary and pancreatic exocrine function could contribute to nutrient malabsorption and diarrhoea[103–106]. Malnutrition leads to small intestinal villous blunting, thereby reducing intestinal absorptive capacity, including impaired monosaccharide and disaccharide absorption, which could contribute to osmotic diarrhoea[107].

Children with severe malnutrition have distinct alterations in their intestinal microbiota that can affect intestinal inflammation and function, as well as the growth of the child[108]. In addition, the faecal microbiota of children with kwashiorkor in Malawi was immature, with a reduced diversity, compared with the microbiota of their twins without malnutrition[109]. Interestingly, mice that received transplantation of the faecal microbiota from children with kwashiorkor had a more profound weight loss than mice transplanted with microbiota from the twin without malnutrition, and this weight loss was associated with signs of disturbed metabolic pathways. In a separate birth cohort in Bangladesh, the presence of an immature faecal microbiota was linked with wasting[110]. Another study comparing the microbiomes between children with kwashiorkor and children with wasting found a more-modest difference in microbiome composition[111]. A potential limitation of studying the microbiota in children with severe malnutrition is the use of antibiotic treatment before stool collection, which profoundly affects microbiota composition. Interest is growing regarding the interaction between the bacterial microbiome, the virome[112] and eukaryotic organisms, but the functional consequences of microbiota alterations in children with severe malnutrition have yet to be well characterized.

Renal function—Studies assessing renal function (determined by glomerular filtration rate) in children with severe malnutrition have been limited. Given the frequency of

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diarrhoea and dehydration in these children, the pre-renal contribution to reduced glomerular filtration might have a substantial role. Low glomerular filtration rates in children with malnutrition and dehydration have been reported[76], and subsequent studies have reported impaired glomerular filtration rates and signs of tubular dysfunction with reduced urine osmolality, but the clinical relevance of low glomerular filtration remains unclear[113].

Brain function—Severe malnutrition is associated with acutely altered cerebral function and behavioural changes; children with kwashiorkor have cerebral atrophy[114,115] and irritability, and children with severe wasting are often apathetic, with slowed movements and impaired speech. However, the underlying mechanisms of these behavioural changes are poorly understood. Although the association of severe malnutrition and growth in early life and development has been well documented, few studies have focused on long-term developmental effects. Impaired development after an episode of severe malnutrition has been reported in children[116], and psychosocial interventions have been shown to improve their development[117]. However, differing case definitions and treatment strategies make it challenging to disentangle the direct effects of severe malnutrition from the effects of other risk factors and adversities that these children typically experience. Additional studies are needed, particularly to understand the long-term effects on different domains of development. In contrast to severe malnutrition, the cognitive deficits associated with stunting are well described. Indeed, for every 10% increase in the prevalence of stunting, the proportion of children reaching the end of primary school has been estimated to drop by 7.9%[118,119].

Other pathophysiological alterations—Cellular Na^+/K^+-ATPase pumps that maintain fluid, electrolyte and substrate levels might be impaired in children with severe malnutrition. An increased membrane permeability was found in leukocytes from children with kwashiorkor, and reduced Na^+/K^+-ATPase activity has been observed in children with severe wasting, potentially as part of an adaptation to reduce energy expenditure[120,121].

Diagnosis, screening and prevention

Diagnosis

Although case definitions of severe malnutrition for epidemiological, biological and clinical purposes focus on anthropometry[122] (BOX 2), malnutrition is a functional problem and has been defined as a state resulting from lack of uptake or intake of nutrition leading to altered body composition, decreased body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease[123]. Anthropometry is used to assess severe malnutrition because the functional deficits are difficult to measure directly. Anthropometry is therefore a proxy and not a direct measure of malnutrition. Importantly, no ‘gold standard’ measurement for the diagnosis of severe malnutrition exists. Different anthropometric measures assess different aspects and durations of the underlying functional deficit, and some relate more closely to body composition and clinical outcomes than others.

Anthropometry—The accepted diagnostic criteria for severe malnutrition have changed over time. Initially, the measurement of weight-for-age (that is, comparing the weight of the

child with the weight of age-matched children in a reference population) was used, and severe malnutrition was defined as <60% of the reference weight[124]. This definition was later refined with the addition of oedema as an additional criterion to diagnose kwashiorkor[30]. To focus on the highest risk group of the most acutely malnourished children rather than on those with a low weight-for-age who were mainly stunted, weight-for-height was later used. Weight-for-height compares the weight of the child to the weight of well-nourished children of the same height (length is used if children are <2 years old). The WHO recommended expressing measurements as weight-for-height Z-scores (WHZs), that is, the number of standard deviations below or above the reference median value[125]. The main growth references that are used for the diagnosis of severe malnutrition are those derived from the 2006 WHO Multi-Country Growth Reference Study, which describes how children 'should' grow under optimal health, environmental and nutritional conditions[126]. Severe acute malnutrition is defined by the WHO as a WHZ of >3 standard deviations below the reference value for median weight-for-height or the presence of bilateral pitting oedema[127].

Interestingly, a review of all studies on the relationship between anthropometric indices and mortality concluded that WHZs are the least effective predictor of mortality[128] and that unadjusted mid-upper arm circumference (MUAC) was more-discriminatory for assessing mortality in several countries in Africa and Asia[129]. The association between MUAC and mortality might be due to the preferential selection of children who are younger, have both stunting and wasting and are particularly at risk[130]. A MUAC of <115 mm was introduced as an independent diagnostic criterion for severe acute malnutrition in children aged 6–59 months by the WHO in 2013 (REF. 131) (BOX 2). Although the use of MUAC for diagnosis is limited as this measurement does not identify the same children with malnutrition as WHZs[122], following the development of community-based management programmes that are effective in preventing malnutrition-associated deaths, MUAC has been used more frequently. An alternative is to increase the MUAC cut-off value up to 120 mm to pragmatically define severe malnutrition. Although the additional children diagnosed with severe malnutrition on the basis of an increased MUAC value are not the same as those identified by WHZs, this approach can better identify children with a higher risk of death than an approach using both MUAC and a WHZ[132].

Identification of oedema—Oedema is a sign of kwashiorkor and is assessed by pressing firmly down on the third to fourth tarsal bones on the dorsal aspect of the child's foot for 3–5 seconds and then looking for pitting oedema for 2–3 seconds. Oedema is graded according to the location on the body; grade 1+ indicates oedema limited to the feet and lower legs, 2+ indicates oedema that is present in the arms and grade 3+ indicates oedema of the face. The presence of symmetric, bilateral oedema of the feet in a vulnerable child in a high-risk population, regardless of the child's anthropometric measurements, is generally sufficient to diagnose kwashiorkor.

Infants <6 months of age—The diagnosis of severe malnutrition in infants <6 months of age presents special challenges. These include the practical difficulties of undertaking anthropometric measurements on small infants[133] and that many individuals assume

malnutrition is rare at this age and so do not take measurements at all[134]. However, the burden of malnutrition in this age group is high[135]. The WHO currently recommends using a weight-for-length Z-score (WLZ) of <−3 to identify infants with severe malnutrition, but only because of the paucity of evidence for other criteria. Few prospective studies have examined the discriminatory performance of different anthropometric measures against the risk of death, but both weight-for-age and MUAC have been suggested for infants >60 days old[136]. Similar to what has been found in older children, MUAC identifies a slightly different group of infants but has superior performance for predicting mortality than WLZs for populations in Gambia and Kenya[137,138]. A MUAC of <110 mm for infants >60 days of age has been proposed based on a clinical trial in Kenya, which confirms that this measurement can identify infants with a very high risk of death[6,138].

Screening

In practice, given the challenges of measuring WHZs frequently or at a large scale in a community, screening programmes tend to use a MUAC of <115 mm to assess severe malnutrition in children 6 months to 5 years of age, and the assessment of oedema is used to diagnose kwashiorkor (FIG. 4). Indeed, the best approach for screening for severe malnutrition is to measure MUAC frequently, ideally every month or every time a child is unwell. All anthropometric indices are better at identifying high-risk children in the short term, that is, in the month following the measure[128], and this applies to MUAC as well[139]. A promising approach to screening for severe malnutrition is to provide mothers with MUAC tapes that have a cut-off value of 115 mm and show them how to detect malnutrition using this measurement[6,140]. This technique is simple enough to be taught rapidly[140] and enables malnutrition to be detected early (before the onset of complications), hence reducing the need for initial inpatient treatment[6]. However, the use of MUAC tapes to screen for severe malnutrition still has substantial room for global expansion, which has been delayed owing to the lack of guidelines, until recently, by normative bodies such as the WHO and UNICEF. This delay has contributed to the poor uptake of this practice by local practitioners and professional bodies.

Prevention

Given the high morbidity and mortality associated with severe malnutrition, preventing it is one of the most important goals in global health. Nevertheless, prevention remains elusive in most impoverished and humanitarian settings, and it requires programmes that address maternal and child malnutrition holistically. Many countries have reduced the overall prevalence of severe malnutrition and stunting through the reduction of inequities[141–143]. In most instances, this achievement has required a combination of economic growth, the use of public sector programmes focused on reducing inequities and investments in nutrition-sensitive (those that directly affect nutrition, such as breastfeeding and complementary feeding support programmes) and nutrition-specific (those that indirectly affect nutrition, such as improved agriculture and social safety nets) interventions. Indeed, no single intervention has effectively reduced the rates of severe malnutrition or stunting for individual children[144,145], and packages of public health approaches are needed. These packages should include improved access to clean water, sanitation and hygiene, improved agricultural productivity to minimize food insecurity, timely universal vaccinations, early and efficient

access to primary health facilities and care for acute illnesses (for example, pneumonia, diarrhoea, measles and malaria), an emphasis on exclusive and continued breastfeeding and attention to effective complementary feeding. Each approach is likely to affect malnutrition generally and, in turn, affect the rates of severe malnutrition[146].

Despite several countries reducing the rates of malnutrition in general, inconsistent effects of vertical programmes on childhood malnutrition have been reported. Indeed, the largest and most comprehensive multicentre trial testing the use of small quantities of lipid-containing nutrient supplements did not show significant benefits regarding stunting or wasting in Malawi[147] and showed only modest benefits in Ghana[148,149]. The same intervention did have a better effect on stunting and wasting in Burkina Faso[150], but notably, this trial also included treatment for diarrhoea and malaria. These data emphasize the importance of interventions beyond nutritional therapy alone in at-risk populations.

At the level of the individual, a comprehensive prevention package should begin with teenage girls and young women before pregnancy and should include comprehensive health education and the use of nutritional interventions aimed at optimizing their overall physical health, nutritional status and psychosocial readiness for pregnancy and childbirth[151]. During pregnancy, women should be provided with evidence-based prenatal and perinatal support, including micronutrient and macronutrient supplementation, treatment for infectious diseases (including prophylaxis and treatment for acute infections) and early and frequent education regarding neonatal nutrition and care[152]; this strategy is believed to improve the health status of both the mother and the infant.

Optimizing macronutrient intake during infancy to prevent the development of severe malnutrition begins with the prompt initiation of breastfeeding, followed by exclusive breastfeeding for the first six months of life and the subsequent progressive introduction of nutritious and diverse complementary foods, with continued breastfeeding for ≥2 years[153]. In addition, context-specific micronutrient programmes can be used and might include vitamin A, iron, multiple micronutrient powders or small quantities of lipid-containing nutrient supplements. Additionally, zinc supplements can be used in children with acute diarrhoea. All children <5 years of age living in at-risk communities should undergo frequent growth monitoring, with the commencement of treatment for acute malnutrition when necessary. They should also receive all recommended immunizations and have ready access to essential interventions and therapeutics when required (including oral rehydration salts for diarrhoea, antibiotics for pneumonia and antimalarials, as well as antiretroviral therapy and opportunistic infection prophylaxis for children who have or have been exposed to HIV infection)[154]. Early and comprehensive intervention for children with moderate malnutrition is important for limiting the incidence of severe malnutrition as these children are assumed to have an increased risk of progression to severe malnutrition[155].

Management

The goals of management of severe malnutrition are to prevent short-term mortality, achieve sustained nutritional recovery to reduce susceptibility to life-threatening infections and to support neurocognitive development. Despite their striking clinical differences, the treatment

recommendations for kwashiorkor and severe wasting have several common elements (BOX 3).

The current management of severe malnutrition has evolved over several decades and is mostly based on expert opinion and a few observational studies and not on data from modern randomized clinical trials[156,157]. Management is based on a series of WHO guidelines and training programmes, which are practical and have been widely adopted. Indeed, the management guidelines have become so engrained in clinical practice that it might be considered unethical to carry out randomized controlled trials except to show equivalence or superiority to the current standard of care. Notably, many of the principles of management have emerged from emergencies, and translating these to low-income and middle-income countries, in which severe malnutrition is a daily burden on health systems, remains a challenge[158]. In general, management includes the use of therapeutic foods along with antibiotics to treat any underlying infections. Management can be undertaken in communities for children with uncomplicated severe malnutrition (that is, children who are clinically stable and do not display clinical features of complications, especially coincidental infections).

Therapeutic foods

Therapeutic foods, such as ready-to-use therapeutic foods (RUTFs) and F-75 and F-100 milks, were designed for nutritional and metabolic stabilization and rehabilitation, and their use aims to address anticipated calorific needs and treatment stage-appropriate protein, electrolyte and micronutrient requirements, in addition to initially limiting exposure to nutrients that could be harmful to metabolically unstable children or those with infections, such as sodium and iron. However, the precise nutrient requirements of children with severe malnutrition and the bioavailability of these therapeutic foods are not well established and might vary by setting and the presence of comorbidities in some patients.

The formulations of F-75 and F-100 were derived and optimized based on metabolic studies of hospitalized children with severe malnutrition, with the aim of providing the micronutrients and macronutrients that are likely to be deficient in a child with severe malnutrition. F-75 is used for initial refeeding and F-100 is effective in facilitating rapid catch-up weight gain but might not correct all of the metabolic disturbances in children with severe malnutrition.

RUTFs were developed to contain the same nutritional content as the F-100 therapeutic milk formula but in a dehydrated form that can be administered in the home environment with no preparation or cooking required and minimal risk of contamination[159]. RUTFs have no mandatory formulation but do have minimum micronutrient and macronutrient concentrations and quality control and microbiological safety standards, which are outlined by WHO and UNICEF[160]. The predominant formulation of RUTFs consists of peanut paste, milk powder, sugar, oil and micronutrients. The high cost of RUTFs is largely due to their milk powder component, which might be only partially overcome by using local production methods as this is also associated with high costs, including the costs of constructing and maintaining appropriate production facilities and importing ingredients, as well as high local taxes. Trials investigating the use of RUTFs without milk powder have suggested an inferior

effect on child growth[161,162]. The essential polyunsaturated fatty acid (PUFA) composition of RUTFs is not optimal[8,163], but a more-favourable composition, such as a reduced ω-6 PUFA content or increased long-chain ω-3 PUFA content, presents challenges for shelf life; the effects of these compositions on growth and neurodevelopment are uncertain.

As RUTFs provide individuals with nutrients at levels that are nearly impossible to reach without supplementation[164], the direct assessment of the effect of RUTFs on weight gain compared with the effect of a local diet alone has not been carried out. However, children treated with RUTFs have a higher proportion of recovery and weight gain than children who received a local diet supplemented with additional vitamins and minerals[7,165].

Despite the benefits associated with use of therapeutics foods, a rapid increase in macronutrient and micronutrient intake can lead to some negative health consequences, including diarrhoea (due to carbohydrate malabsorption)[166,167] and refeeding syndrome (BOX 4). The risk of refeeding syndrome might be reduced when children consume therapeutic foods on demand based on their appetite rather than being force-fed using a nasogastric tube[168,169]. However, no randomized trials testing the formulations, amounts or durations of feeding of F-75 or F-100 have been published.

Antibiotics

Current guidelines recommend empiric antibiotics for all children with severe malnutrition because of concerns that although some children might not initially present with signs of infection, they might deteriorate suddenly without fever or other warning signs[170,171]. No prospective clinical trials showing the need for antibiotics in children with complicated severe malnutrition have been published. However, there are reports of *in vitro* nonsusceptibility to β-lactam antibiotics and gentamicin, the recommended first-line agents, although the implications of these findings in terms of outcomes have yet to be tested in clinical trials. Interpreting the results of these studies is challenging owing to biases; these studies are usually conducted in tertiary centres and/or do not distinguish community-acquired from hospital-acquired infections[172].

For outpatient management of children with uncomplicated, severe malnutrition, the use of routine antibiotic therapy has been questioned because of the cost and the risk of enhancing antimicrobial resistance. In one study in Malawi, children with severe malnutrition receiving amoxicillin or cefdinir had 36% and 44% reductions in mortality, respectively, and they had faster recoveries than children who received placebo[5]. Of note, this area had a high prevalence of kwashiorkor compared with other centres. In another study in Niger, mortality was unchanged in children with uncomplicated severe wasting who had not been previously treated for malnutrition and who were given oral amoxicillin compared with placebo in an outpatient feeding programme attached to a referral hospital[173]. However, amoxicillin treatment was associated with a faster recovery and a 14% reduction in the proportion of children who were referred to hospital in another study[173]. Collectively, evidence from these trials supports the use of empiric antibiotics in outpatient management[172,174], although further research on other types and severities of malnutrition, other care settings, the effects on antimicrobial resistance, the potential use of point-of-care biomarkers and costs are needed.

Other interventions

Profuse watery diarrhoea, hypovolaemia and shock are common in children with severe malnutrition and are associated with high mortality, despite current management guidelines[99,175]. The optimal composition and rate of administration of intravenous or oral fluid therapy, or other supportive therapies, in settings that do not have access to advanced paediatric intensive care is unclear and controversial[176] as only two small trials have been conducted to study individuals with severe malnutrition[177,178]. Another large trial indicated that aggressive fluid management in children without severe malnutrition and diarrhoea, but with some signs of shock, is harmful[179], which is likely to be the case in children with malnutrition. Studies that distinguish shock caused by sepsis from hypovolaemia caused by diarrhoea in children with severe malnutrition have not been carried out, but they are needed to inform management strategies that could be implemented in hospital settings.

Other features of severe malnutrition include chronic systemic and intestinal inflammation, infection and environmental enteric dysfunction (that is, inflammation, reduced absorption and reduced barrier function in the small intestine)[49]. Mortality risk is more closely related to markers of systemic rather than intestinal inflammation[102], although bacterial intestinal translocation and aberrant immune function might contribute to both systemic and intestinal inflammation. Trials assessing the use of oral prebiotics or probiotics among children with severe malnutrition have not shown effects on inpatient mortality outcomes, but they do suggest subsequent benefits for growth[9,180], and in the future, the use of prebiotics and probiotics are likely to be better directed by improved knowledge of microbiota ontogeny and function[112,181]. Gut-protective therapies targeting inflammation, microbial translocation, malabsorption, intraluminal nutrient processing and normalization of the intestinal microbiota might yield novel and effective interventions. Other potential strategies for reducing malnutrition-associated mortality and improving growth include the use of anti-inflammatory agents[182] and gut-trophic nutrients, including alanyl-glutamine[176,183] and other dipeptides.

Uncomplicated severe malnutrition

Until the 2000s, all children with severe malnutrition were usually managed as inpatients with milk-based therapeutic foods and empiric broad-spectrum parenteral antibiotics, which assumed that these patients always had nutritional and metabolic complications and serious, sub-patent infections[127]. However, management has been revolutionized by the detection of children with uncomplicated malnutrition, who can be safely treated in the community via a proactive, public health-based approach to care. This is made possible by community screening that uses MUAC assessments and by feeding children a RUTF at a dose of 175 kcal/kg per day[129,184].

The effectiveness of RUTFs in decreasing the mortality of children with severe malnutrition cannot be overstated. Early RUTF trials reported a lower mortality for children treated with RUTFs in their community than for those previously treated in hospitals. Following these trials, community treatment programmes rapidly expanded, which dramatically improved treatment coverage to reach previously untreated children. Following from this, many community-based programmes have shown lower mortality rates compared with historical

data for hospital-based treatment outcomes. Accordingly, the development of community-based programmes has largely occurred in the absence of formal randomized controlled trials (comparing children treated with RUTFs with untreated children), as carrying out these trials would be unethical. For the same reasons, the effectiveness of hospital-based treatment in reducing mortality has never been formally established.

Decentralized services closer to patients' homes can avoid the costs and risks of inpatient care, including nosocomial infections[185,186], and has enabled uncomplicated severe malnutrition (generally >90% of all children with severe malnutrition) to be treated in the community[184] (FIG. 5). Outcomes of children with uncomplicated severe malnutrition treated in their community are markedly better than of children with complicated malnutrition of similar anthropometric status[187,188].

Complicated severe malnutrition

Children with complicated severe malnutrition (that is, children with a more-severe disease who are sick) are managed as inpatients so that life-threatening complications (such as infections) can be addressed along with nutritional and metabolic deficits. The aim of nutritional management is to address disturbed carbohydrate and energy metabolism, which affects blood glucose levels and body temperature regulation[67,189], as well as the distribution of fluid and electrolytes. Regular feeding with, initially, less energy-dense food aims to prevent and treat hypoglycaemia, reduce sodium levels, and increase potassium and phosphate levels. The administration of hyperosmolar and intravenous fluids is avoided whenever possible[190].

Therapeutic feeding is cautiously started with milk-based food (specifically, 130 ml/kg per day of F-75, which provides 97.5 kcal/kg per day) that initially contain low levels of protein and sodium and high levels of potassium, which is designed to match the child's reduced metabolic capacity. Initial feeding aims to improve metabolism, gut motility and nutrient absorption, and clinical improvements during this phase manifest as improved appetite and reduced oedema (if present). When appetite is restored and the signs of infectious complications improve, children transition to RUTFs or milk-based foods with higher energy and protein levels (such as F-100 at 130–200 ml/kg per day which provides 130–200 kcal/kg per day) to gain weight. No other food should be given, with the exception of breast milk, which should be given before therapeutic foods are administered to keep stimulating the maternal milk supply. Additional micronutrients (such as zinc for diarrhoea) beyond what are included in the therapeutic food are generally unnecessary without specific signs of a deficiency[190].

Under current WHO recommendations, children are discharged from inpatient care when their serious complications have resolved rather than after they have met specific anthropometric targets, and they continue therapeutic feeding and supplementary feeding (for moderate malnutrition) as outpatients[151] (FIG. 6). The transition of patients from the hospital setting to home requires ensuring that the parent or caregiver understands the treatment phases and what is expected from them in addition to enrolling them in available nutritional, medical and social services.

Children with complicated severe malnutrition are usually admitted to hospital because of severe infections and typically have a fatality rate of 12% to >20%[168,191]. HIV infection is present in 15–29% of children hospitalized with severe malnutrition in Sub-Saharan Africa and is associated with a threefold increased risk of inpatient mortality[168,192,193]. Studies aiming to reduce mortality in children with complicated severe malnutrition have included increased nursing support, systematic feeding or reductions in intravenous fluid administration and have been met with limited success[194–196], presenting a clear need for research to improve care[22,176].

Infants <6 months of age

Infants <6 months of age with severe malnutrition are fed with breast milk and infant formula, or diluted F-100 milk, often by using a technique called ‘supplementary suckling’. A key aim of treatment is to establish or reestablish effective exclusive breastfeeding wherever possible. These infants also receive empiric antibiotics[134]. Further research is needed to determine the efficacy of this strategy and other components of the management of these infants[197].

Quality of life

Children with severe malnutrition typically live in settings of pervasive poverty, low female literacy, food insecurity, inadequate water and sanitation and overstretched health systems[198]. Acute management interventions for the treatment of severe malnutrition do not fundamentally alter these underlying risks. Most children with acute malnutrition are also severely stunted at presentation[7,173], which indicates that they have chronic ill health and malnutrition. Several studies in Malawi, Kenya, Gambia and Bangladesh have shown that anthropometric recovery is not sufficient as children have a high rate of death following discharge from inpatient care for severe malnutrition, predominantly from pneumonia and diarrhoea[6,199]. In addition, mortality is increased in children following treatment in community-based nutrition programmes[184,200]. The reasons for this likely contains a home environment that includes risk factors for malnutrition, an undiagnosed chronic illness and that attending health care visits for episodes of illness or ongoing therapeutic feeding might be limited in certain areas[200,201]. In addition, some children with severe malnutrition might have a pre-existing vulnerability (such as a mild immune deficit that would cause minimal health problems in a resource-rich setting with a low prevalence of infectious diseases) that results in a cycle of illness and malnutrition and a high degree of vulnerability to infection[202]. Certainly, not all siblings who grow up in the same family are equally affected by the same home environment[203].

During treatment and recovery from severe malnutrition, weight and MUAC usually increase rapidly, but height does not, and growth is typically sufficient only to reach the baseline height-for-age Z-score[173,203]. Children who have been treated for severe malnutrition typically have less lean mass (that is, fat-free mass) than children without malnutrition in the same community[162,204,205]. Indeed, children in Malawi had lower lean tissue and were more severely stunted at an average of 7 years after hospitalization for severe malnutrition, than controls, but had a similar head circumference and respiratory and cardiometabolic

function[204]. In addition, children with prior severe malnutrition have weaker hand grip and lower exercise tolerance than children who have not had malnutrition[204,206]. This 'thrifty' growth pattern indicates that severe malnutrition in early childhood might predispose an individual to noncommunicable diseases later in life. However, this predisposition is difficult to assess as stunting and other insults might have been present before severe malnutrition developed in the children enrolled in these studies. Although the effect of *in utero* exposure to malnutrition and its risk factors leading to a wide range of noncommunicable diseases later in life is established[207,208], the critical window or risk for these effects and the consequent effect of infant and child malnutrition on noncommunicable diseases later in life is still unclear[209].

Severe malnutrition and stunting are associated with delayed child neurodevelopment, behavioural problems, lower school achievement and reduced adult earning potential[2,210]. The use of psychosocial stimulation, such as play and giving positive feedback training to mothers or prolonged home visiting programmes after infants or young children with severe wasting or kwashiorkor have been discharged from the hospital, has been shown to significantly improve infant development scores in the short term, as well as educational achievement and IQ into adolescence[116,211,212]. Several micronutrients are potentially essential for cognitive development, including PUFAs, thiamine, choline, vitamin D, folate, iron, copper, selenium and iodine[213], and deficiencies in these might vary among children with severe malnutrition according to the child's age, location and the cause of malnutrition. However, supplementation with these micronutrients has not undergone clinical trials with neurodevelopmental end points in the context of severe malnutrition.

Further studies are needed to assess the optimal duration of treatment with therapeutic foods, factors limiting lean (muscle, organ and connective) tissue synthesis (including the role of high-quality dietary protein), how zinc and other micronutrients can modulate lean tissue deposition, the benefits of psychosocial stimulation and physical activity and the long-term effects of malnutrition on health risks in adolescence and adulthood[204].

Outlook

Although this Primer has highlighted many of the negative consequences of severe malnutrition, it is important to note that our understanding of the epidemiology and management of severe malnutrition has improved. Indeed, community-based management of severe malnutrition has revolutionized treatment programmes and has enabled large numbers of children to receive effective nutritional and clinical care in various settings. Children with severe malnutrition and a high risk of death can be easily identified, and many of them can be successfully treated at the community level by parents with assistance from community health workers, in addition to outreach services.

The use of appropriate prevention and management interventions for severe malnutrition could prevent 61% of cases of wasting and almost 350,000 child deaths annually[214], and several major international initiatives, such as No Wasted Lives[215], are working towards ambitious targets to achieve this. Although progress towards lowering childhood mortality is ongoing, more work is still required. Indeed, as more children survive episodes of severe

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malnutrition, and as poverty decreases in many countries, new challenges will emerge. For example, helping children to survive an episode of severe malnutrition is no longer enough. Following the Global Strategy for Women's, Children's and Adolescents' Health (2016–2030), we must also help these children to thrive[214]. To do this, curative and preventive services must be transformed. More effort is needed in previously neglected populations, such as infants <6 months of age[216] and children with underlying disabilities[217] and other identified vulnerabilities. In addition, focus is needed on the prevention of relapse and readmission, although how this can be achieved is uncertain. One large trial investigating the use of prophylactic co-trimoxazole for high-risk children following discharge from hospital in Kenya showed negative results for reducing the risk of relapse and death[6]. However, other broad-spectrum antibiotics or other therapies that could support a prolonged period of immune system recovery might be beneficial. In addition, improved social support and social safety nets to address food security are other areas to explore. Other research gaps regarding severe malnutrition are described in BOX 5 (REFS 218,219).

An improved understanding of several areas of the pathophysiology of severe malnutrition and the efficacy of potential interventions might be able to save the lives of these high-risk children. For example, understanding the pathophysiology of kwashiorkor could lead to phenotype-specific therapeutic interventions; this requires research that uses modern tools for assessing metabolism and other physiological functions. In addition, although much of the previous research on the pathophysiology of severe malnutrition has been informative and hypothesis-generating, the research does not commonly meet today's standards for quality in terms of participant selection, the avoidance of bias and sample size. Going forward, the testing of well-founded hypotheses in appropriately designed randomized trials with the use of biomarkers, information on mechanisms and sound clinical measures is required.

The overarching priority is to make severe malnutrition a thing of the past in countries in Africa and Asia, as is the case in Europe and North America today. Achieving the SDGs for health and nutrition will be possible only through addressing severe malnutrition, and to do this, we must recognize that reducing the burden of morbidity and mortality associated with severe childhood malnutrition is a global moral imperative. To eradicate severe malnutrition will require political will, investment in peace building and reducing man-made and natural disasters, which are issues that should unite the world.

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Box 1

Estimating the epidemiology of malnutrition

Global data regarding the epidemiology of malnutrition must be understood with reference to methodological challenges and contextual factors. For example, wasting is often highly seasonal, and the number of cases peaks around the time of pre-harvest rains, when food is scarce and the burden of infectious diseases increases (for example, a higher prevalence of malaria and diarrhoeal diseases). In many instances, the interface of food insecurity (that is, a lack of access to a sufficient quantity of affordable, nutritious food), population displacement and drought also produce the conditions leading to famine.

In addition, although prevalence estimates from cross-sectional surveys are suitable for slowly changing conditions such as stunting, they are not suitable for capturing the rapidly changing nature of severe and moderate malnutrition, which have a fairly acute onset and rapid resolution. Malnutrition can also recur, which can be unrecorded or without contact with health services at each episode. Accordingly, incidence is the most informative epidemiological measure of acute malnutrition[220], but it is rarely well documented owing to difficulties in ascertainment[221]. Addressing this limitation, prevalence-to-incidence conversion factors are sometimes used to determine the incidence of malnutrition, especially to estimate caseloads to plan treatment services[222]. Efforts are underway to improve surveillance systems for severe malnutrition.

The problems with the measurements used to diagnose malnutrition in surveys can also affect epidemiological estimates. For example, mid-upper arm circumference (MUAC) and the presence of oedema, which are both case-defining criteria, are not measured in many field surveys, resulting in underestimates of prevalence as these criteria do not necessarily overlap with those of wasting, which is defined on the basis of low weight-for-length measures[223,224]. Even when included, the presence of oedema might be missed in rapid surveys undertaken by poorly trained surveyors[16].

Finally, infants <6 months of age with malnutrition might be missed in epidemiological surveys, either by design or because MUAC standards for this age group have not been established. Whether surveys of malnutrition in children <5 years of age include infants <6 months of age is not always clear.

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Box 2

Anthropometric criteria for nonmicronutrient malnutrition in children 6–59 months of age*

Global acute malnutrition[‡]

Any of the following:

- Weight-for-height Z-score <−2
- Mid-upper arm circumference (MUAC) <125 mm
- The presence of nutritional oedema

Moderate acute malnutrition[‡,§]

Either of the following:

- Weight-for-height Z-score ≥−3 to <−2
- MUAC ≥115 mm to <125 mm in the absence of nutritional oedema

Severe wasting[‡,‖]

Either of:

- Weight-for-height Z-score <−3
- MUAC <115 mm in the absence of nutritional oedema

Kwashiorkor[‡]

- Any weight-for-height Z-score
- Any MUAC
- The presence of nutritional oedema

Severe acute malnutrition

- Severe wasting and/or kwashiorkor

Moderate underweight[¶]

- Weight-for-age Z-score ≥−3 to <−2

Severe underweight[¶]

- Weight-for-age Z-score <−3

Moderate stunting[¶]

- Height-for-age Z-score ≥−3 to <−2

Severe stunting[¶]

- Height-for-age Z-score <−3

For younger children, typically those <2 years age, length is commonly measured instead of height, giving weight-for-length or length-for-age values. Z-scores refer to the number

of standard deviations away from a reference population median. For example, a Z-score of −1 equates to 1 standard deviation below the 2006 WHO Growth Standard (http://www.who.int/childgrowth/en). *See REF. 131. ‡Acute conditions. §Diagnosed according to weight-for-length or weight-for-height and/or MUAC criteria; also referred to as ‘moderate wasting.’ ‖Diagnosed according to weight-for-length or weight-for-height and/or MUAC criteria. ¶Chronic conditions.

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Box 3

Management of severe acute malnutrition

The management of children with severe malnutrition has several components:

- Therapeutic feeding with macronutrients and micronutrients to achieve homeostasis and overcome the nutrient deficits
- The immediate identification and management of life-threatening infections and complications such as sepsis and metabolic derangements
- The treatment of subclinical infections and underlying conditions, such as HIV or tuberculosis
- The cognitive stimulation and emotional support of the child and psychosocial support for their parents or caregivers
- Linkage to medical, nutritional and social services during therapy and recovery

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Box 4

Refeeding syndrome

Refeeding syndrome can contribute to poor clinical outcomes in children with severe malnutrition. Rapidly increased nutrient intake can cause a switch from a catabolic to an anabolic state, which can lead to a surge in insulin secretion, acute hypoglycaemia and the transport of extracellular electrolytes into cells. This electrolyte flux can lead to dangerously low blood concentrations of potassium, magnesium and phosphate, which can result in lethargy, seizures, muscle weakness, impaired cardiac function and respiratory failure[225].

The precise incidence of refeeding syndrome is unknown, which is related to the lack of a precise definition and the fact that, in most settings, the accurate measurement of electrolytes and other biomarkers cannot be carried out. In addition, insufficient intake of electrolytes and their loss through the gastrointestinal and renal systems can affect electrolyte concentrations, making it challenging to relate abnormal plasma levels to refeeding syndrome. A recent study in Uganda reported hypophosphataemia in 76% of children with severe malnutrition 2 days after admission, which was associated with mortality[168].

Interestingly, refeeding syndrome influenced the development of the main milk-based refeeding formulation used for the stabilization of patients (F-75), which is characterized by a low protein content and reduced energy content (mostly from carbohydrates) compared with F-100, and contains phosphate, potassium, magnesium, vitamin A and zinc, among other micronutrients. However, as F-75 provides individuals with an energy source that is mostly from carbohydrates, this leads to increased glucose levels and, potentially, a surge in insulin secretion and a high demand for phosphorylated glycolytic intermediates, which could precipitate severe hypophosphataemia. Whether reducing calorie intake or energy from carbohydrates during the initial hospitalization of patients with severe malnutrition would reduce the incidence and severity of refeeding syndrome is currently unknown.

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Box 5

Selected research priorities in severe malnutrition

- Determining the burden of severe malnutrition based on its incidence
- Determining the causes of death associated with malnutrition, including infection and impaired energy metabolism
- Determining the pathophysiology of kwashiorkor and its implications for management
- Determining the mechanisms of functional immune impairment and the association with nutritional rehabilitation
- Determining the long-term effect on body composition, metabolism and neurodevelopment of severe malnutrition and its treatment, with or without preterm and/or low birth rates
- Devising preventive strategies that work on a large scale and are low in cost
- Developing strategies for the integration of protocols to prevent severe malnutrition in fragile and humanitarian settings
- Improving the management of acute malnutrition in infants <6 months of age[197]
- Improving risk stratification to help identify which patients need inpatient care and those that need empiric antimicrobials, and determining which antimicrobials should be used
- Simplifying treatment protocols and developing protocols that can be used at the community level with minimal supervision
- Developing new formulations of ready-to-use therapeutic foods that optimize several nutritional parameters to maximize patient survival, weight gain, correction of metabolic perturbations, and long-term cognitive, physical and immunological development

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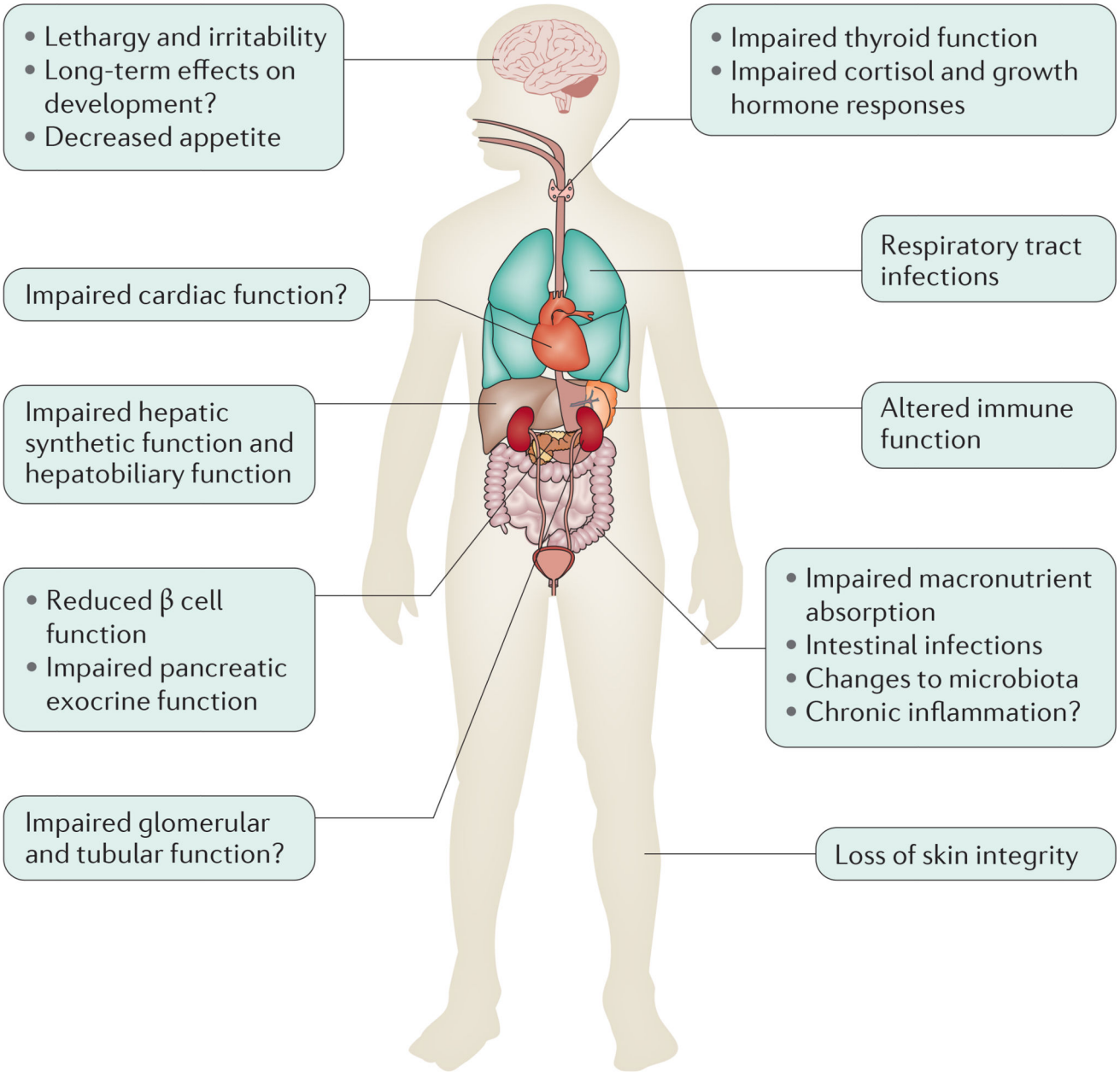

Figure 1. Organ system involvement in severe malnutrition.

Severe malnutrition can affect several organ systems. The functional impairments in these systems have been characterized, but the underlying mechanisms have not been fully elucidated.

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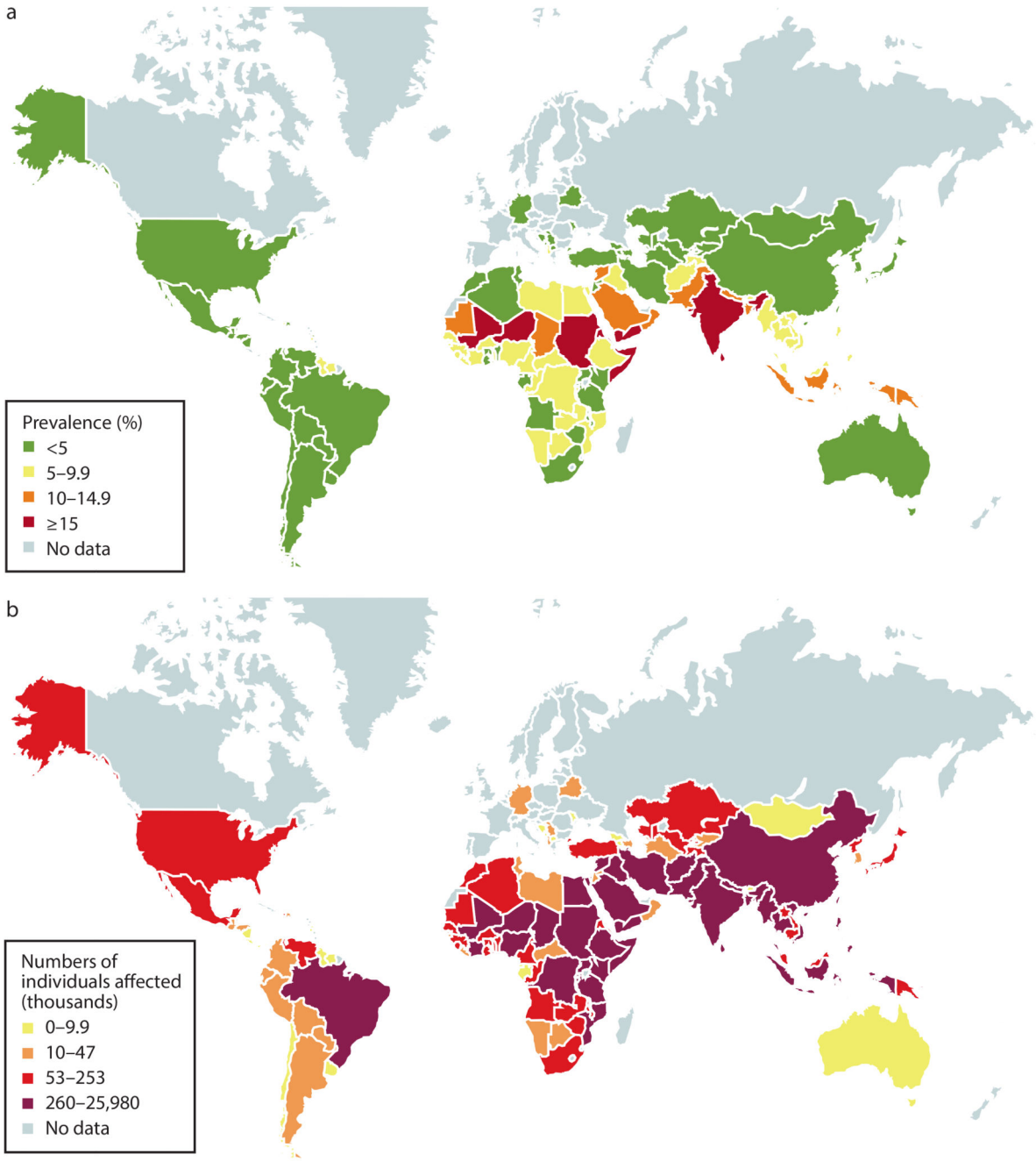

Figure 2. Prevalence of wasting.

The prevalence of wasting as a percentage of the population (part **a**) and the number of individuals (thousands; part **b**). Data from the Global Targets Tracking tool, version 3 (http://www.who.int/nutrition/trackingtool/en/; May 2017).

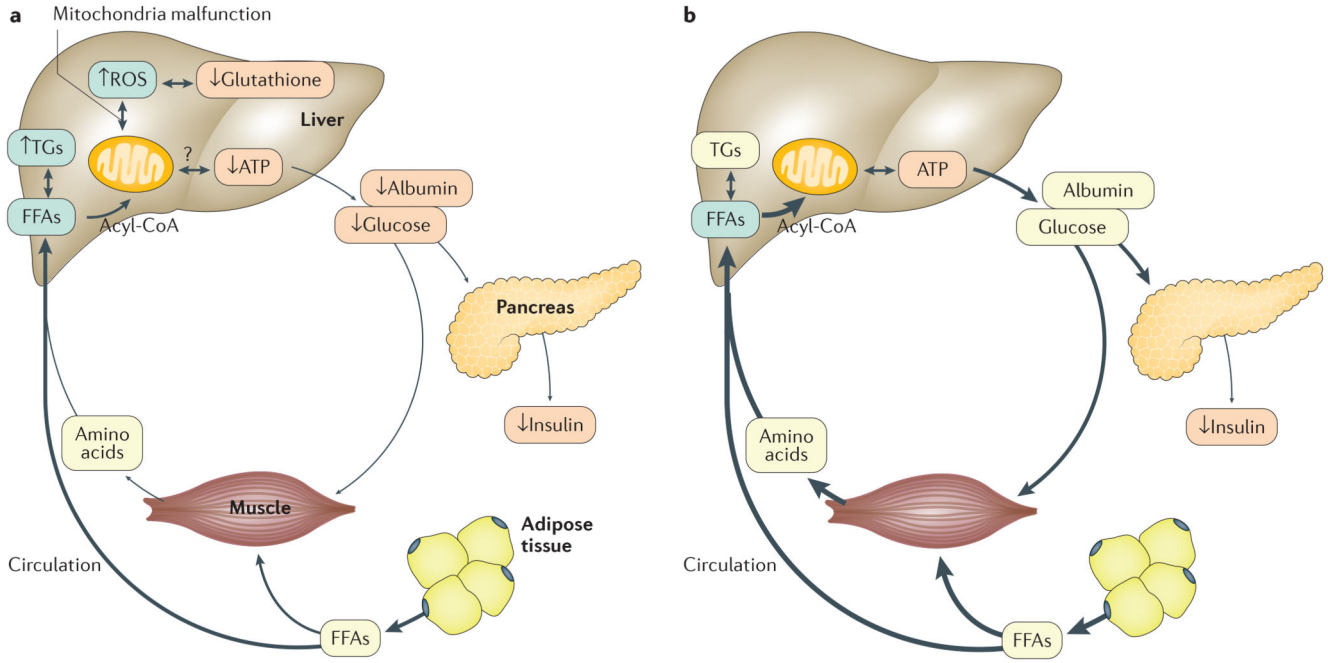

Figure 3. Metabolic changes in severe malnutrition.

Reduced secretion of insulin contributes to a catabolic state in both kwashiorkor (part **a**) and severe wasting (part **b**). In severe wasting, the reduced secretion of insulin leads to a lipolytic and proteolytic response and the release of free fatty acids (FFAs) and amino acids into the bloodstream. FFAs are taken up by muscle tissue for oxidation. Both FFAs and amino acids are also partially taken up by the liver and are used for ATP production and the synthesis of essential proteins and glucose. In kwashiorkor, this adaptive response is disturbed, which causes a reduced release of FFAs from adipose tissue and amino acids from muscle tissue. Mitochondrial damage in the liver is associated with increased reactive oxygen species (ROS) production and reduced glutathione. Arrow thickness represents the amount of metabolites in that pathway. TGs, triglycerides.

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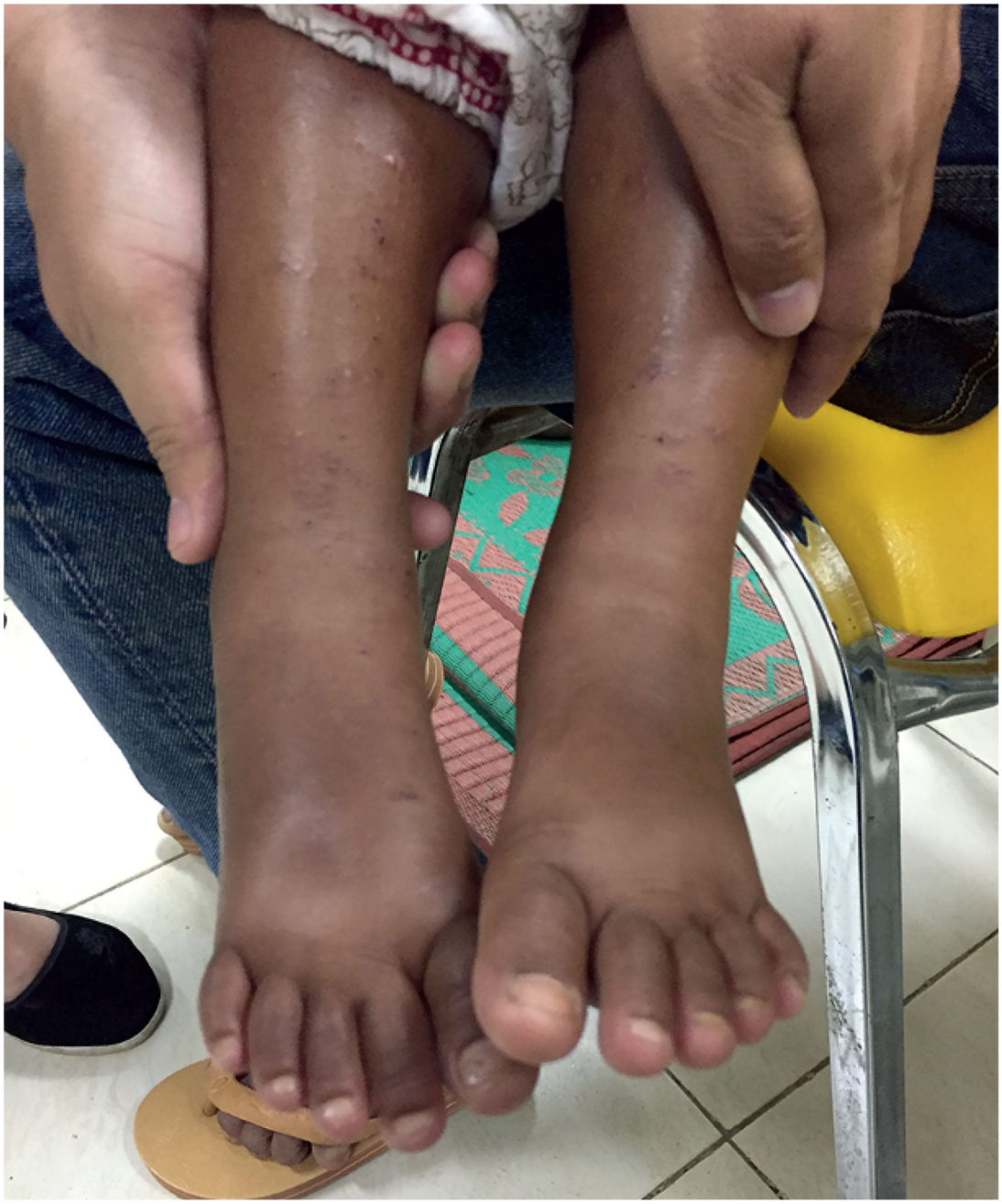

Figure 4. Assessment of oedema.

Oedematous swelling of the lower extremities with skin changes in a child with kwashiorkor.

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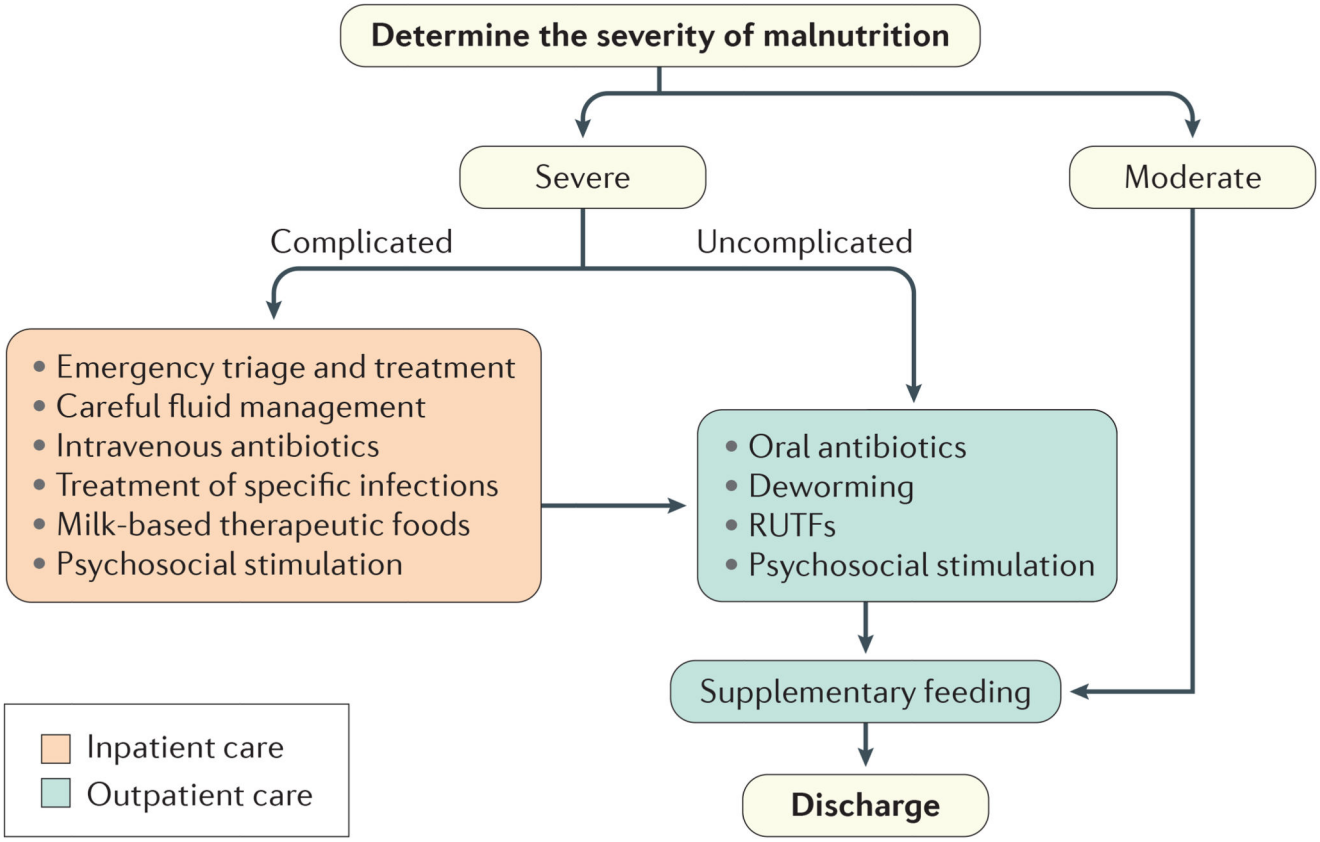

Figure 5. Overview of management of severe and moderate malnutrition.

The first step in the treatment of malnutrition is to determine the severity. Moderate malnutrition is typically treated with the use of supplementary foods, which are administered in addition to the child's normal diet. Uncomplicated severe malnutrition is usually treated with ready-to-use therapeutic foods (RUTFs), which are given instead of the child's normal diet, in addition to a course of oral antibiotics and along with other treatments, such as deworming and treatment for other non-life-threatening infections. The management of complicated severe malnutrition requires admission to an inpatient facility with adequate paediatric emergency care facilities and a nutritional rehabilitation care programme. Children with complicated malnutrition can be discharged from inpatient facilities when serious complications have resolved, and subsequently entered into outpatient management programmes. Management includes the use of therapeutic foods and antibiotics and the treatment of other infections. After the completion of treatment for severe malnutrition, children are transitioned from RUTFs to their home diet, which is a potential point of faltering. However, aside from standardized supplementary feeding, strategies to decrease this risk have not been assessed in trials.

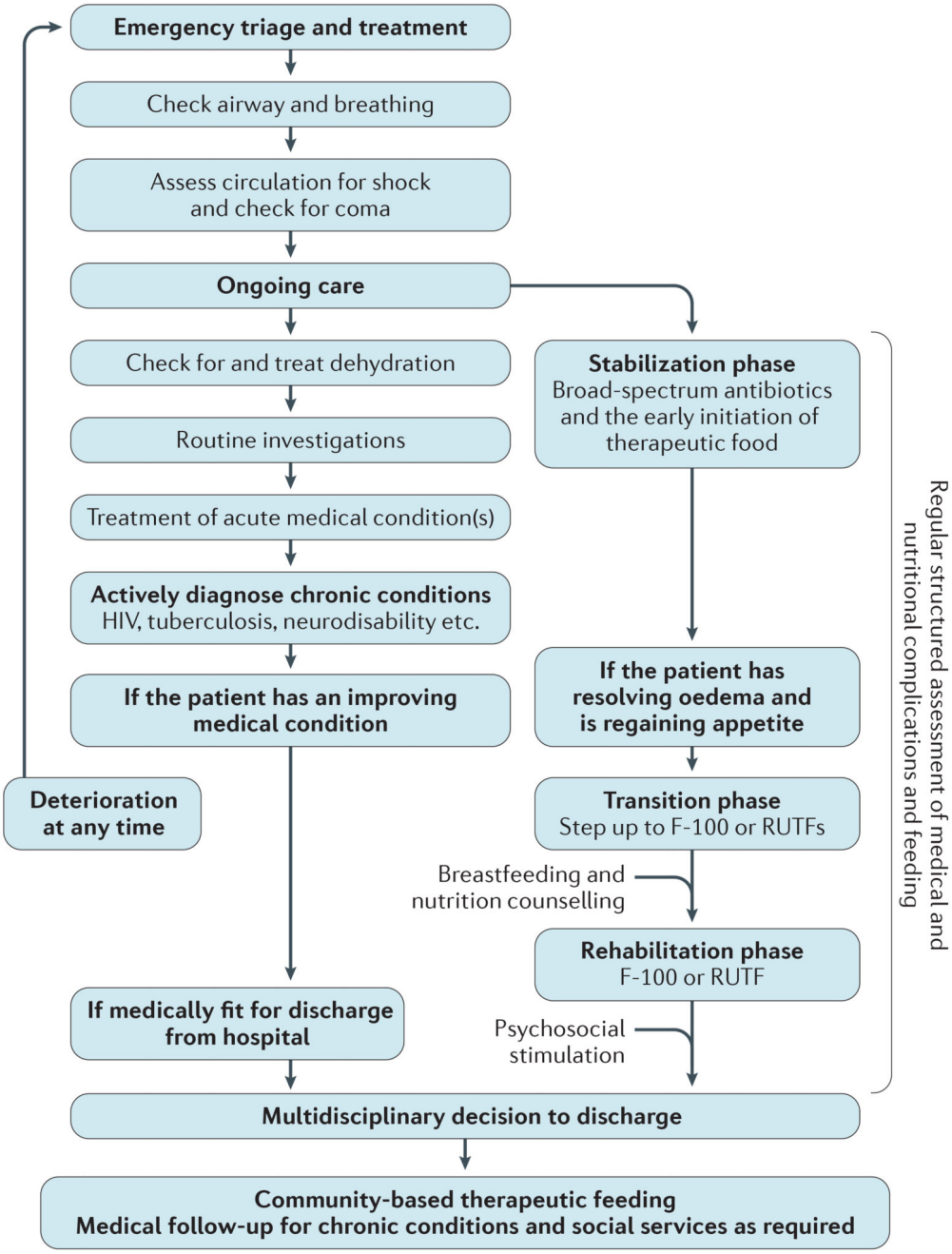

Figure 6. Detailed management of complicated severe malnutrition.

The challenges associated with the management of children with complicated severe malnutrition require the integration of structured, high-quality paediatric care and nutritional support, which must happen in parallel and in a multidisciplinary manner. Paediatric care focuses on the identification and treatment of the most immediately life-threatening problems, as laid out in the WHO Emergency Triage and Treatment guidelines. Nutritional support focuses first on helping to restore physiological processes to a normal state and then on achieving rehabilitation. Initially, use of the ‘ABCD’ mnemonic can help focus attention

on the assessment and maintenance of the airway (A) and breathing (B), circulation (C) and disability (coma, convulsion and dehydration (D)). Children with complicated severe malnutrition remain exceptionally vulnerable during treatment and can deteriorate rapidly without clear prior warning signs. Accordingly, monitoring and frequent re-evaluation are essential. When prevalent, comorbidities such as tuberculosis and HIV should be actively tested for. If community-based management of uncomplicated severe malnutrition is available, the decision to discharge children from hospital is based on their appetite and the resolution of complications rather than on anthropometric parameters, and should be decided by nutritional and clinical staff. The treatment process in hospital and after discharge should be explained to parents and caregivers, and they should know what help is available to them and what is expected of them. RUTFs, ready-to-use therapeutic foods.

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Table 1

Anthropometric measures and risk of death in children <5 years of age

	All deaths HR (95% CI)	Pneumonia deaths HR (95% CI)	Diarrhoeal deaths HR (95% CI)	Measles deaths HR (95% CI)	Deaths due to other infectious diseases HR (95% CI)
Height-for-age or length-for-age Z-score					
<–3	5.5 (4.6, 6.5)	6.4 (4.2, 9.8)	6.3 (4.6, 8.7)	6.0 (3.0, 12.0)	3.0 (1.6, 5.8)
–3 to <–2	2.3 (1.9, 2.7)	2.2 (1.4, 3.4)	2.4 (1.7, 3.3)	2.8 (1.4, 5.6)	1.9 (1.0, 3.6)
–2 to <–1	1.5 (1.2, 1.7)	1.6 (1.0, 2.4)	1.7 (1.2, 2.3)	1.3 (0.6, 2.6)	0.9 (0.5, 1.9)
≥–1 (control)	1.0	1.0	1.0	1.0	1.0
Weight-for-length Z-score					
<–3	11.6 (9.8, 13.8)	9.7 (6.1, 15.4)	12.3 (9.2, 16.6)	9.6 (5.1, 18.0)	11.2 (5.9, 21.3)
–3 to <–2	3.4 (2.9, 4.0)	4.7 (3.1, 7.1)	3.4 (2.5, 4.6)	2.6 (1.3, 5.1)	2.7 (1.4, 5.5)
–2 to <–1	1.6 (1.4, 1.9)	1.9 (1.3, 2.8)	1.6 (1.2, 2.1)	1.0 (0.6, 1.9)	1.7 (1.0, 2.8)
≥–1 (control)	1.0	1.0	1.0	1.0	1.0

Adapted from Black *et al.*[2]. CI, confidence interval; HR, hazard ratio.