REVIEW ARTICLE

Nutritionally Acquired Immunodeficiency Syndrome: An Interaction of Nutrition, Infection, and Immunity

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Abstract

Nutritionally acquired immune deficiency syndrome (NAIDS) is a significant disadvantage to children with malnutrition. The role of nutrients in immunity and markers of inflammation in infections are highlighted. The complex interaction between malnutrition, infection, and immunity are elucidated. A brief note on the "ABCDEFG approach" for comprehensive assessment and nutrient supplementation for optimum intervention is included.

Keywords: Immunity, Infection, Malnutrition, Nutrition, Nutritionally acquired immune deficiency syndrome.

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Introduction and Background

Underweight and undernutrition, currently known as childhood malnutrition, is the most common cause of secondary immunodeficiency worldwide. However, it is not often considered or diagnosed.[1] It affects both innate and adaptive immunity, and the term, "nutritionally acquired immunodeficiency syndrome" (NAIDS) has been put forward.[2] Malnutrition worsens infection and infection worsens malnutrition,[3] producing a vicious cycle. Immunodeficiency related to malnutrition accounts for nearly 50% deaths from common infections among under-five children.[4] Directly or indirectly, 54% of the 10.8 million deaths per year among under-five children and every second death (53%) associated with infections in developing countries are related to malnutrition.[3] NAIDS refers to any degree or variety of adverse immunologic consequences of malnutrition. The immune system depends on the nutritional status to provide host resistance to infection. Both macronutrients and micronutrients deficiencies cause immune function impairment, most of which can be reversed by nutrient supplementation.

Malnutrition is a composite syndrome of multiple nutrient deficiencies, coupled with infection and metabolic derangements, and hence the earlier popular term, protein energy malnutrition (PEM), has been dropped. As per World Health Organization, malnutrition is the result of cellular imbalance between the supply of nutrients and energy and the body's demand for these to ensure growth, maintenance, and specific functions.

Although severe forms of malnutrition are on the decline, moderate wasting due to acute malnutrition and stunting due to chronic malnutrition are major contributors to childhood morbidity and mortality. It is prudent to understand NAIDS and the interaction of nutrition with infection and immunity, as these are modifiable risk factors.

Nutrition and Immunity

Nutrition is a critical determinant of immune response.[5] Malnutrition is associated with significant impairment of all phases of immunity.[6]

- Primary skin and mucous membrane barrier
- Cell-mediated immunity
- Phagocytic function.
- Complement system
- Humoral immunity-secretory immunoglobulin A concentration
- Cytokine production.

Multiple nutrient deficiencies or deficiency of a single nutrient can result in altered immune response.[7] Epidemiological and clinical data support the fact that nutritional deficiency alters immunocompetence. The situation is aggravated by socioeconomic disadvantages such as poor sanitation, poor personal hygiene, overcrowding, increased susceptibility to illnesses, contaminated food and water, inadequate nutrition knowledge, and varied dietary choices. Currently, most food choices are biased by TV and social media promotions and advertisements.

There is ample evidence to show that impaired immunity is a critical adjunct factor in malnutrition-related infection.[8,9] This applies not only to young children in developing countries but to all age-groups in all subsets of population like elderly and those with eating disorders and primary debilitating diseases.[10,11] However, the chance for reversibility is a ray of hope. The impairment of cell-mediated immunity among low birth weight infants have been shown to be restored partly by dietary supplementation of zinc. Among the elderly, impaired immunity has been shown to be enhanced by supplementation of multiple micronutrients.

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Current Insights into Nutrition and Immunity

There are at least five new insights in this regard, which can be applied for remedial intervention.

- Alteration in immune response occur early during reduction of micronutrient intake and not only in the chronic state.
- The extent of immunologic impairment depends on the type of nutrient involved, its interaction with other nutrients, severity of deficiency, concomitant infection, age, and comorbidities.
- Nutritional status and immunologic abnormalities predict overall outcome, risk of infection, and mortality, irrespective of the corrective interventions.
- Many micronutrients, if taken in excessive, can impair immune response. Nutritional modulations that regulate both sides of pro/anti-inflammatory equation hold greater promise in treatment, rather than one-sided immune boosting.
- Tests of immunocompetence are useful in titration of physiologic needs, assessment of safe lower and upper limits of micronutrients.

Infection and Inflammation

There are several inflammatory markers that are useful in clinical practice in the setting of infection.[12] The inflammatory responses to various infections and diseases warrant regulation and a balancing equation. Otherwise, the cytokine and other immune responses can do more harm than good. The cytokine storm and antibody-dependent enhancement are now thought to be key factors for adverse outcome in fatal infections such as severe dengue and COVID-19. This state may be devastating in a malnourished child fighting life amid several handicaps.

Cytokines are the key inflammatory mediators. Cytokines also play a role in the pathogenesis of edema in Kwashiorkor. Cytokines also affect linear growth and bone remodeling. The cytokines belong to two classes: pro-inflammatory and anti-inflammatory. The proinflammatory cytokines are essential to initiate defense against pathogens. Overproduction may cause counterproductive effects by causing tissue damage. Proinflammatory cytokines include IL1beta, IL2, IL6, IL8, and TNF α. The anti-inflammatory cytokines downregulate inflammation. Excess anti-inflammatory cytokines also cause deleterious effects by flaring up of infection. Anti-inflammatory cytokines include IL1 receptor antagonist, IL 4, IL 10 and IL13.

Cytokines also autoregulate; IL 10 and IL4 suppress pro-inflammatory cytokines. Excessive response of cytokines leads to systemic inflammatory response syndrome (SIRS), which must be balanced by compensatory anti-inflammatory response syndrome (CARS). An uncontrolled inflammatory response result in imbalance between pro-mediators such as free radicals and anti-inflammatory mediators such as zinc, selenium, etc. These interactions are important in the complex pathophysiology of certain infections, life-threatening conditions, and in the clinical syndrome of malnutrition. It is also important to note that changes in hormones modulate cytokine response, but it is now understood that these hormonal changes are more likely to be secondary to cytokine response itself. Adequate regulation of immune responses is important in balancing infection and inflammation.

Malnutrition and Immunity

The malnourished child is at a disadvantage with respect to both innate and adaptive immunities (Table 1). Among LBW babies, the preterm usually gains adequate immune response by 3 months, but SGA may continue to be deficient for several months.

Starting from the skin and mucous membrane barrier, protective secretions, complements, cytokines, killer cells to the T- and B cell-mediated immunity are deranged and suboptimum in malnutrition (Table 2). Features of NAIDS closely resemble that of HIV-AIDS, and the common morbidities are due to fungal, viral, bacterial, mycobacterial, and opportunistic infections. There are several clinical and laboratory markers of immunity and nutritional status.[13]

- Malnutrition affects skin barrier → "small black patches" over pressure points, extensor surfaces of the ankles, knees, and above the wrist, elbows. Gradually spreads to the legs, forearms, knees, and elbows "crazy pavement epidermis." Cracking along skin lines (shins) produces "mosaic skin" or "cracked skin". The older hyperpigmented patches mature and become sharply demarcated, which strip off very readily, leaving a pink raw surface exposed underneath (elbows, knees, ankles, diaper area)—"enamel paint spots", "flaky paint", or "peeling paint". Currently, the classic lesions are less seen, but a variety of skin changes are noted, which are collectively known as 'nutritional dermatosis'.
- Undernourished children show high mortality due to opportunistic infections. Morbidity due to various infections such as pneumonia, diarrhea, and measles is increased.
- Lymphoid tissues show atrophy especially thymus, spleen, peripheral lymph nodes.

Reduced cell-mediated immunity is evidenced by a smaller number of mature, fully differentiated T lymphocytes, especially T4 type. Delayed cutaneous hypersensitivity responses to both recall and new antigens is reduced. Low thymic hormone activity may be the major trigger for reduced T-cell response.

- Altered T-cell response, impair activation of B lymphocytes, and thereby humoral immunity to certain antigens.
- Secretory IgA levels decrease with a paradoxical increase in concentration of IgG due to the greater number of infections
- Complement levels and activity, particularly C3 decreased.
- Macrophage—antigen presentation, destruction of bacteria in phagocytes are reduced
- Production of cytokine—interleukin-1—is reduced
- Protein synthesis is decreased.
- Altered reciprocal relationships between nutrition and the intestinal microbiota result in altered immune function, intestinal dysbiosis, chronic inflammation, and immune dysregulation.

Thus, in clinical practice, a malnourished child may not develop the clinical features like fever or features of inflammation, fast breathing, etc., even in the setting of a serious infection. For e.g., with minimal signs and symptoms, the child may be having military tuberculosis, with a false-negative tuberculin skin test, features of pneumonia. Hence, clinical suspicion and anticipatory approach are recommended.

Key Nutrients for Immunity

Several nutrients are identified to play a key role in immunity and thereby survival and quality of survival. The role of each one of the following is summarized in Table 3.

- Vitamin A
- Vitamin B complex-B2, B6
- Vitamin C

Table 1: Various types of immunity and various handicaps in malnutrition

Innate immunity (non-specific defense mechanisms)		*Adaptive immunity specific defense mechanisms)*	
Timeline: 0–12 hours		*Timeline: 1–7 days*	*Cell-mediated immunity*
1st line of defense	2nd line of defense	3rd line of defense	**Reduction:**
Skin Mucous membranes Secretions of skin Secretions of mucous membranes	Macrophages Other phagocytes (i.e., neutrophils, NK cells) Antimicrobial proteins The inflammatory response (e.g., redness, fever)	Lymphocytes (B and T cells) Antigen specific Antibodies Memory	Delayed cutaneous hypersensitivity responses (recall, new antigens) Skin homograph injection Thymic size Thymic hormone activity Thymic T cell and T cell-dependent zones in lymph nodes and spleen Lymphocyte proliferation and DNA synthesis Circulating CD3 subsets Circulating CD4 subsets Mixed lymphocyte reaction (MLR) IFNγ, IL_1, IL_2 and IL_2 R generation
The first line of defense includes the skin, mucous membranes, hair within the nose, cilia in the upper respiratory tract, urine, perspiration, saliva, stomach gastric juice, and sebum The second line of defense includes an inflammatory response and white blood cells called phagocytes that ingest pathogens.			**Moreover:** Increased relative proportion of TdT immature T cells potential increase of suppressor T cells and/or circulating suppressor factors Anergy Response to mitogens (PHA, Con-A) **Humoral immunity:** Decreased: Immunoglobulin production S. IgA T cell-independent antibody production bactericidal power **Nonspecific immune function** Decreased: Complement components phagocytosis metabolic activation and destruction of bacteria Macrophages and neutrophils, neutrophil chemotaxis lysozyme levels in secretions **Moreover:** Skin and mucosal dysfunctions Alteration of intestinal flora Rise in gastric pH

- Vitamin D
- Vitamin E
- Zinc
- Selenium
- Copper
- Iron, especially protein bound iron
- Other immuno-nutrients—glutamine, arginine (conditionally essential amino acids), valine, leucine and isoleucine, S. IgA, lactoferrin, human milk oligosaccharides, pro and prebiotics, nucleotides, EFA and others-iodine, cobalt, magnesium, calcium.

Clinical Evaluation

Clinical evaluation of a child warrants a comprehensive assessment using the ABCDEFG check list.[18] This includes the following:

- Anthropometry: the gold standard for nutritional status to identify stunting, wasting, and combination states—e.g., wasting and stunting.
- Biochemical and labs: supportive and confirmatory data—sugar, electrolytes, CBC, total lymphocyte count (cell/mm^3)—

Table 2: Features of nutritionally acquired immunodeficiency syndrome

Immunity and severe malnutrition	
Immunity	*Features in severe malnutrition*
Gross	Lymphoid atrophy, involution of thymus and tonsil, size and weight are reduced.
Histology	Fewer lymphoid cells, Hassal's bodies enlarged degenerated and calcified, loss of lymphoid cells around blood vessels in spleen and lymph nodes, paracortical areas show depletion of lymphocytes
Delayed type hypersensitivity	Depressed to new and recall antigens complete anergy to battery of antigens
Qantity and quality of T lymphocytes	Reduction in the number of T lymphocytes, increased number of immature and undifferentiated lymphocytes (null cells)
CD4+ cells	Number and proportion reduced
CD8+ cells	Moderate reduction in suppressor cells.
Ratio of CD4+ to CD8+	Decreased
Immunity	*Causative factors in malnutrition*
Reduced T lymphocytes	Reduced thymic hormone and thymic factors like ubiquitin, thymosine, thymique humoral factor, lymphokines, lymphocytotoxic factors
Reduced B lymphocytes	Due to decreased T lymphocytes failure to activate B lymphocytes to produce immunoglobulin
Increased cytokine response-IL 1 1L6, TNF alpha, INF gamma	Altered SIRS/CARS ratio, due to reduced Vit A, glutathione, compromised capacity to neutralize free radicals.
Cytokine response to LPS	ILI, IL6, TNF alpha diminished, so cannot protect against toxins
Interleukin 10 (anti-inflammatory)	Increased leading to deficient immune response.
Lymphoid atrophy, decreased delayed hypersensitivity, low thymic hormone, reduced T helper cells, low NADPH activity	Micronutrient deficiency-zinc, vitamin A, iron
Immunity	*Severe malnutrition*
Complement system	Reduced C3 C5, factor B, total hemolytic activity
Opsonic activity of plasma	Decreased
Phagocytosis	Affected, metabolic activation and inactivation of bacteria decreased.
Lyzozyme	Concentration decreased due to decreased production by neutrophils, monocytes, increased excretion in urine
Quality of mucus, integrity of physical barrier	Affected and causes adherence of bacteria to the epithelial cells increased
Cytokines	ILG, CRP, soluble receptors of TNF increased,
Lipoprotein	Decreased, inability to bind LPS in tackling bacterial endotoxins

<1,500 cells (immunosuppression) and <800 (nutritional depletion), hemoglobin, ferritin, serum proteins—albumin, prealbumin, retinol binding protein, transferrin, LFT, RFT, Ca, P, Mg, Specific nutrient assays are done in relevant cases—serum 25 OH vitamin D3, retinol, ascorbic acid, delayed hypersensitivity skin testing for T cell function—Tuberculin skin test

- Clinical features of wasting, stunting, edema, overt, or subclinical micronutrient deficiency states
- Dietary evaluation: this includes dietary history starting from nutrition *in utero*, IYCF practices, family pot feeding, current intake and diet during illness and convalescence.
- Environmental/ecological background: factors like poverty, illiteracy, ignorance, and overcrowding
- Functional evaluation: immunity, susceptibility to infections, bone health, endurance, survival, and quality of life
- Growth pattern: type and time of growth faltering

Nutritional Management and Immunomodulation

The immediate goal is managing medical complications such as infection, dehydration, shock, stabilizing sugars, electrolytes, and correction of overt deficiencies like anemia. Various locally available and natural therapeutic foods are widely used for immunomodulation in children with severe malnutrition.[19] The long-term goal of therapy is to achieve 90% of weight for height using adequate nutrient supply and achieving optimum immunity.

Optimal intake of all nutrients ideally would be achieved through consumption of a well-balanced and diverse diet with micronutrient supplementation, if needed.[20] The dose of various nutrients within upper safety limits are given in Table 4. Anticipatory nutrition guidance and nutrition education that result in a behavioral change communication (BCC) are recommended for a crusade against malnutrition.[21] Only this can aim survival and quality of survival among the vulnerable children.

Table 3: Key nutrients and their role in immune regulation and modulation

Key nutrients and their role	*Key nutrients and their role*
Iron—improve oxygen carrying capacity, reduce lactic acid production, reduce morbidity, mortality, help in oxidative reactions, phagocytosis, antibody levels, T cell response and IL2 production	Copper—WBC proliferation and function, IL2 response, co-factor for ferroxidase, Cytochrome C, Superoxide dismutase
Vitamin A—enhance T cell, CD4 Count, NK cell, T helper cell and mucosal health, cell division,	Selenium—antioxidant, Selenoproteins enhance immunity, cytokine production, immunoregulation
Vitamin C—relieve common cold, improve immune response, enhance antimicrobicidal and NK cell tasks, chemotaxis, lymphocytes	Zinc—catalytic, structural and regulatory ion, CD3, CD4, CD4/CD8 ratio, speedy recovery from virus, wound healing, increase antibody
Vitamin B complex	Cobalt and manganese—increases the movement and phagocytic activity of neutrophils
Riboflavin (B2)—antioxidant, anti-inflammatory, immune function	Others—arginine enhances T-cell number and function by increasing responsiveness, anti-tumor properties.
Pyridoxin (B6)—promote antibody and cell mediated immunity	Glutamine seems to increase intestinal enterocyte activity, gut mucosal growth, lymphocyte proliferation.
Vitamin E—antioxidant, modulate cytokines and macrophage activation, stimulate T cell	Valine, leucine, isoleucine—increase protein synthesis
Vitamin D—effects on B cells, macrophages, monocytes, antimicrobicidal effects, T cell tolerogenic response	S IgA—offers surface tract protection against diarrhea and pneumonia, the most important killer disease in children.
Immunomodulation, blood vessel regeneration	EFA—dry, scaly and leathery skin, with underlying erythema and loss of skin barrier
Magnesium—required for properdin in the alternate complement pathway	Probiotics and prebiotics—Main gut flora and healthy symbiosis with host and regulate immune function
Activates components of the complement and coagulation systems	Ratio of Omega 6: Omega 3 LCPUFAs (Adrenic and arachidonic acid: EPA and DHA- 5-10:1) for balancing pro and anti-inflammatory responses
Required for oxygen radical generation, and degranulation in activated human neutrophils.	Omega-6 polyunsaturated fatty acids (PUFAs)—proinflammatory, changes composition of the cell membrane phospholipids. Impair cell division, hormonal signal transduction
Calcium ions bound to calmodulin, involved in the production of the prostaglandins and other eicosanoids	Omega-3 fatty acids—anti-inflammatory, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—at the site of inflammation are enzymatically converted to specialized pro-resolving mediators (SPMs) like resolvins, protectins, and maresins. which aid in reducing inflammation
Iodine—role in antibody production.	

Table 4: Recommended dosages of macro- and micronutrients

Nutrient	*Dosage*
Protein	1.5–2.0 g of protein per kg of body weight per day as per age
Omega 3 fatty acid	250 mg/day
Vitamin A	50,000 IU <6 months, 100,000 IU 6–12 months or 200,000 IU >1 year and weight >8 kg. Dose can be repeated on day 2 and day 14 in overt deficiency
Vitamin C	200–300 mg/day
Vitamin D	2000 IU in infants and 6000 IU daily >1 year. X 3 months in Rickets, For others 400–600 IU daily
Vitamin E	50–100 mg/day
Vitamin B6	5–15 mg/day
Zinc	2 mg/kg/day
Iron	3 mg/kg/day
Magnesium	Day 1—0.3 mL/kg/day deep IM (50% magnesium sulfate IM) once, followed by same oral dose up to 2 weeks
Calcium	600–800 mg daily for 3 months
Copper	0.3 mg/kg/day

Summary

- Nutrition is crucial for growth, immunological response, survival, and quality of life.
- All types of body defense get impaired in NAIDS and is an important cause of morbidity and mortality in children.
- Children with malnutrition may have serious infections, without manifesting the usual clinical features like fever, features of inflammation, fast breathing etc.
- Micronutrient sufficiency plays a major role in determining immune response and immune modulation.
- Optimizing immunity is desirable than boosting as a perfect balance is needed, nothing low and nothing in excess.
- A well-balanced diet is essential for growth, development, and well-being.

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