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# Nutritional Aspects in Immunocompromised Patients

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***Abstract***

With the rise in life expectancy, there has been an increase in the population with immune deficiency. This necessitates the need to find ways to improve the quality of life and survival rate for these individuals. This review focuses on dietary modifications as a means to boost the immune system.

The abstract emphasizes the significance of nutrition and lifestyle changes in supporting immune function. A well-balanced diet, rich in essential nutrients and immune-boosting foods, is crucial. Addressing nutrient deficiencies, engaging in regular physical activity, and managing stress are also important for improving immune health. Individuals with immune deficiencies should seek guidance from healthcare professionals when making dietary changes.

Food safety is closely linked to immune health, especially for immunocompromised individuals who have a higher risk of foodborne diseases. Preventing foodborne infections involves implementing food safety management systems and following low microbial diets.

While diet is significant, other interventions are also important for individuals with compromised immune systems. Planning a healthy diet for these patients should consider adequacy, balance, calorie control, nutrient density, moderation, and variety.

In conclusion, enhancing the immune system and improving the quality of life for individuals with immune deficiencies requires a comprehensive approach that includes dietary modifications, food safety practices, and other lifestyle changes. By implementing these strategies, it is possible to strengthen the immune system and enhance health outcomes for individuals with compromised immune function.

***Key Words:*** Immune system, Immunodeficiency, Nutrition, Pediatrics.

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## 1- INTRODUCTION

The immune system is critical in defending against microorganisms and recognizing malignant cells (1). Impairment of the immune system can lead to a predisposition to infections. A variety of factors can cause acquired immune suppression, including protein-energy malnutrition, chronic renal or hepatic dysfunction, diabetes mellitus, and immunosuppressive drugs (2, 3).

Cancer is a prevalent chronic condition worldwide, affecting nearly 5% of the United States population (4). The use of chemotherapy agents and monoclonal antibodies may suppress the immune system in different ways. In some cases, this immunosuppression may last for years after treatment cessation (5).

For example, purine analogs can impair cell-mediated immunity and increase the likelihood of herpesvirus infections. This susceptibility might be prolonged for about 2 years. Other chemotherapy agents and monoclonal antibodies also impair the immune system (4, 5).

Therefore, considering patients' susceptibility to infections is important in those with a history of chemotherapy. It can help improve their quality of life and attenuate infection rates.

Primary immune deficiency can lead to severe or recurrent infection, autoimmunity, and malignancy. Despite being underestimated globally, primary immune deficiency populations are increasing due to new advancements in diagnostic methods. Better treatment modalities are now available, allowing for increased lifespan. As clinicians, we encounter several questions regarding types of physical activity, diet, supplement therapy, vaccination, and so on. This review discusses available evidence for immune deficiency nutrition protocols.

### 1-1. Nutrition in Primary Immune Deficiency Patients

Weight loss is more prevalent in children and adult patients with Primary Immune Deficiency (PID) disease. There are many factors related to malnutrition, including inflammatory or infectious gastrointestinal disorders (6).

Patients with Severe Combined Immune Deficiency (SCID) suffer from Failure to Thrive (FTT) caused by poor energy intake, malabsorption, and increased Resting Energy Expenditure (REE) due to hypermetabolism related to chronic infection (7). FTT has been observed in about 54% -88% of patients at diagnosis. Oropharyngeal Candidiasis and chronic infection in the gastrointestinal (GI) tract are related to poor feeding intake and malabsorption. Hypermetabolism occurs in about 93% of patients with FTT, and patients with significant weight loss have the highest metabolic rates. Infants are particularly susceptible to hypermetabolism status (8). Some studies have shown that measured REE, if being higher than 150% of Predicted REE, can help control hypermetabolism in these patients (7).

Severe MTHFD1 deficiency, severe disruption of folate absorption or vitamin B12 delivery by PCFT and TC mutations are associated with SCID. In these patients, folic acid and vitamin B12 supplementation, plus nucleoside supplementation in patients with severe MTHFD1 mutations, may be beneficial (9).

In Common Variable Immune Deficiency (CVID) patients, enteropathy is found in rare cases, but gastrointestinal symptoms are more common (10). Acute infection with Giardia lamblia is frequent. Noninvasive colonization of the upper GI tract with Giardia lamblia causes chronic inflammation and damage to mucous membranes, leading to malabsorption and

triggering symptoms like diarrhea and weight loss (11). Additionally, micronutrient deficiencies such as vitamin A, B12, B1, folic acid, and iron are more prevalent in these patients. Vitamin A level (retinol) is low in CVID patients (12, 13) and has an important effect on mucosal immunity and regulates inflammation in the GI tract (12). Other fat-soluble vitamin deficiencies by vitamin D, E, and vitamin K are not common in CVID patients unless in those with severe malabsorption after duodenal villous atrophy. In this state, patients present with neurological disorders like progressive distal paresthesia and tremor, after vitamin E substitution, show improvement (14).

Zinc deficiency is also common in these patients due to malabsorption and chronic inflammation, which redistributes serum zinc by high consumption (15). Low levels of zinc can hurt vitamin A mobilization. Although assessment of zinc level with available biochemical markers may not be valid, supplementation is recommended if there is a deficiency of zinc or vitamin A serum level (15). Iron deficiency anemia may be seen in patients after being infected with chronic giardiasis (11). Also, other factors like bacterial overgrowth, autoimmune anemia, and chronic disease anemia caused by inflammation might explain this anemia (16). Finally, selenium deficiency has been shown to decrease significantly compared to the healthy group. Selenium suppresses the activation of pro-inflammatory pathways by chelating free radicals and blocking the nuclear transcription factor NF-kB activation. Bacterial infections are associated with a reduction in serum selenium concentrations. In this way, supplementation with selenium could improve deficiencies (17).

### 1-2. Nutritional Assessment

Anthropometric assessments, including weight, height (length for younger than 2 years), MUAC (Mid Upper Arm Circumference), and BMI, should be done. For younger patients (<2 years), weight for length should be done. All the results should be plotted on charts for children <2 years of age issued by World Health Organization (WHO) and charts for children ≥2 years of age suggested by growth and Centers for Disease Control growth (18).

Dietary assessment consists of dietary intake assessment with 24-hour food recall or a 3-day record of food. FFQs (Food Frequency Questionnaires) are used to estimate usual eating patterns but are time-consuming and usually implemented for research purposes (19). Other nutritional assessments include laboratory assessments for malnutrition like albumin and prealbumin, and micronutrient evaluations such as those of zinc, iron, vitamin A, vitamin D, vitamin B12, folic acid, selenium, copper, carnitine, and CRP serum levels (20). Body composition analysis with BIA (Bioelectrical impedance analysis) estimates fat mass, fat-free mass, and phase angle to detect disease outcomes after intervention. Bone health with a DEXA scan could detect bone densitometry and body composition. To determine the exact cause of malnutrition, a thorough medical history and physical examination should be conducted. This includes investigating food intake problems, disease comorbidities that increase hypermetabolic state, and any disease complications with increased intestinal loss such as gastrointestinal tract involvement (21).

### 1-3. Medical Nutritional Therapy (MNT)

In patients with primary immune deficiency, the oral route should be attempted first for nutritional support. However, this may not meet their increased metabolic needs, so concentrated formulas providing more energy per milliliter (about 0.8-1.0 kcal/mL) or standard formulas with 0.9-1.2 kcal/mL

may be better options. Hydrolyzed protein feeds are generally better tolerated, particularly in Omenn syndrome with marked gut inflammation, as they are better absorbed. If oral intake does not provide at least 70% of energy needs, enteral nutrition through NGT is recommended. A nasojejunal tube can be considered in infants where ongoing gastro-oesophageal reflux or delayed gastric emptying is preventing the establishment of oral or nasogastric feeding. For long-term nutritional support, gastrostomy may be needed (22). As a last resort, parenteral nutrition may be necessary to provide sufficient energy, particularly in patients with severe malabsorption and signs of intestinal failure (23). Measurement of Resting Energy Expenditure (REE) is mandatory to predict energy requirements (7). Predictive equations have poor correlations with accurate estimations, so the use of an indirect calorimeter may be helpful, though further research is needed in this respect (24). **Table 1** discusses energy, macronutrient, and micronutrient requirements.

**Table-1:** Management of macronutrients and micronutrients in PID (Primary Immune Deficiency)

| Variable | Value |
|---|---|
| Energy | 120-150% EER |
| Protein | 1.2-1.5 gr/kg/day |
| Fat | Total fat:30%<br>W3 and W6 based on the median intake of the population and AI |
| Iron | 1-3 mg/kg/day(prophylaxis)<br>3-6 mg/kg/day (Treatment) |
| Vitamin A | Deficiency:5000-15000 unit/day (1500 to 4500 RAE/day)<br>(Specific dose should be based on serum markers and clinical condition) |
| Vitamin D | Deficiency: Infants:2000 units/daily for 6 weeks then 400-1000 units/daily<br>Children and adolescents: 2000 units/daily for 6 to 8 weeks then 600 to 1000 units/daily. |
| Vitamin K | Deficiency:0.3-0.5 mg/daily |
| Vitamin E | Infants, children, and adolescents:25-50 unit/kg/day |
| Selenium | Prevention for parenteral nutrition:1-3 mcg/kg/day<br>Deficiency: up to 100 mcg/kg/day |
| Vitamin B12 | Infant, children, and adolescents (IM):250 to 1000 mcg daily or every other day for 1 week, then weekly for 4 to 8 weeks, then monthly for life |
| Folic Acid | Infants, children, and adolescents (oral, IM, IV): Initial dose 0.5 to 1 mg for 3 to 4 weeks then 0.1 to 0.3 mg daily maintenance dose. |

Abbreviations

EER (Estimated Energy Requirement), AI (Adequate intake), W3 (omega3), W6 (omega6), mcg (Microgram), RAE (retinol activity equivalents)

### 1-4. Nutrition in Secondary immune deficiency (SIDD)

Nutrition plays a crucial role in the management of Secondary Immune Deficiency (SIDD). Various factors can compromise the immune system, leading to acquired immune suppression, affecting one or a combination of humoral immunity, cellular immune system, complement system, or even innate

immunity. The most common causes of acquired immune deficiencies are aging, prematurity, malignancies, infective diseases, or chronic diseases (25).

Secondary antibody deficiency is an important acquired immune deficiency that might be caused by various factors, including hematologic malignancies, protein-losing states due to renal, gastrointestinal, or cutaneous loss, side effects of therapies that target B cell or Non-B cell, and conventional immunosuppressive therapies (3). Patients with secondary antibody deficiency are at a higher risk of infections, including complicated infections. The nutritional requirements for patients with SIDD should be based on general recommendations and specific medical nutrition for the underlying disease. In other immunocompromised states, nutritional support and management will depend on the immune dysregulation phenotypes. It is essential to maintain adequate nutrient intake to support the immune system's function and improve clinical outcomes. A registered dietitian can provide individualized nutrition care to optimize dietary intake and reduce the risk of malnutrition in patients with SIDD.

**1-5. Foodborne infectious diseases**

Nutrition and food safety are closely linked. Foodborne diseases and undernourishment create a vicious cycle of worsening health, especially among immunocompromised individuals (26). Studies have shown that patients with weakened immune systems (primary or secondary immune deficiencies) due to disease processes or medication are more susceptible to food-borne pathogens, and the prevalence of foodborne diseases among them is reported to be about 20% higher than in the general population. Other factors such as age, particularly younger than 5 years or older than 60 years, nutritional deficiency due to poor absorption or poor intake of food, and consumption of antacids, especially PPIs (proton pump inhibitors), could also increase the risk of food-borne diseases (27).

Preventing foodborne infections in immunocompromised patients can be achieved in several ways, the most crucial one includes implementing food safety management systems in hospitals, nursing homes, elderly-care homes, and childcare centers (27). Management systems, for example, identify potential hazards before problems occur and ensure that products are free from microbiological, chemical, and physical contamination (28). And special requirements for food establishments serving highly susceptible populations are available in the U.S. Food Code (29).

The second important issue is low microbial diets, which means avoiding consuming foods that are more likely to contain pathogenic microorganisms. Such diets are recommended by some hospitals for high-risk patients (30, 31). Based on the American Cancer Society (32), an Absolute Neutrophil Count (ANC) of <1000/μL indicates a weak immune system, an ANC <500/μL for a few days results in a high risk of infection, and an ANC of 100/μL or fewer means that the risk of infection is extremely high. Different groups of patients, such as Human Stem Cell Transplant (HST) patients before engraftment, are candidates for a Low Microbial Diet (LMD) and are advised to follow this diet for 3 months (31-33).

Based on different low microbial diets introduced for patients with a low white blood cell count, high-risk foods include raw and processed meats (bacon, sausage, and raw smoked meats), raw eggs, unpasteurized dairy products (milk, cheese, butter, yogurt), raw tofu, fruit juices and raw fruits, raw vegetables, unpasteurized honey, raw cereals, tap water or raw water, contaminant-free ice,

and fast-foods. Studies have indicated that high-risk foods may be contaminated by common food-borne pathogens, especially enteric bacteria, Salmonella, Campylobacter, Shigella, and Escherichia coli, which are responsible for the high mortality rate in immune-suppressed patients (34). For example, patients with HIV are 20 times more susceptible to Salmonellosis than healthy individuals (35). Major food-borne pathogens reported in immunocompromised patients and some specific susceptibilities are discussed in **Table 2**.

**Table-2:** Major food-borne pathogens reported in immunocompromised patients

| Subgroup | Microorganism | Symptoms | Source of Contamination |
|---|---|---|---|
| Bacteria | Salmonella (39)<br>Listeria (40)<br>E.coli, (41)<br>Campylobacter (42) | persistent diarrhea in immunocompromised children in developing countries (Okhuysen and Dupont 2010),<br>patients with hematological malignancies(27) | uncooked foods contaminated |
| Virus | Cytomegalovirus,<br>Norovirus (NoV) (43),<br>Hepatitis E (44) | Norovirus (NoV) infection, which is often foodborne or waterborne, poses a higher risk of severe consequences in immunosuppressed patients, causing chronic gastroenteritis Hepatitis E infection in immunocompromised organ transplant patients, chronic hepatitis | consumption of insufficiently cooked game or pork meat, |
| Fungi | Aspergillus,<br>Candida, (45)<br>Saccharomyces cerevisiae,<br>S.(46)boulardii, (47) | invasive infections in transplant patients | Nearby construction sites or environmental sources like plants or vegetables.<br>Person-to-person spread does not occur |
| Parasite | Cryptosporidium (48)<br>,Giardia duodenalis,<br>Toxoplasma (49, 50) | heart/lung, hematopoietic stem cell (HST), and solid organ transplants (SOT | Raw or unpasteurized milk.<br>Shared water pool, resistant to alcohol-based hand sanitizer and chlorination of water<br>If immunocompromised, avoid contact with farm animals(51)<br>Shared water pool, resistant to alcohol-based hand sanitizer and chlorination of water |

Since immunosuppressed people are susceptible to infection from many sources, other interventions have also been used in their nutrition advice besides a low microbial diet (36). Therefore, it is important to focus not only on the selection of allowed food items and cooking methods used in LMD, but also on

the type of food management service and compliance with food safety protocols, which could play an important role in providing safe food for immune-compromised patients.

The most critical aspect of nutrition in immunosuppressive patients is planning a healthy diet. It should ensure that an eating pattern considers these items: adequacy, balance, calorie control, nutrient density, moderation, and variety (37).

Adequacy reflects a diet that provides sufficient energy and nutrients to meet the needs of healthy people. Balance in the diet helps to ensure the adequacy of different types of foods in proportion to one another. Calorie control requires careful planning to design an adequate diet within a reasonable calorie allowance. Nutrient density promotes adequacy and calorie control. Moderation contributes to adequacy, balance, and calorie control. Variety improves nutrient adequacy. In general, a healthy diet emphasizes a variety of fruits, vegetables, whole grains, and fat-free or low-fat milk products; includes lean meats, poultry, seafood, legumes, eggs, seeds, and nuts; is low in saturated and Tran’s fats, cholesterol, salt (sodium), and added sugars (38).

## 2- CONCLUSION

As the population affected by immune deficiencies continues to grow, it becomes increasingly important to explore strategies that can enhance their quality of life and survival rate. This review emphasizes the significant role of nutrition and lifestyle modifications in boosting the immune system of individuals with immune deficiencies. By adopting a well-balanced diet, incorporating immune-boosting foods, addressing nutrient deficiencies, and embracing a healthy lifestyle, patients can potentially strengthen their immune function and improve overall health outcomes.

## 3- ACKNOWLEDGMENT

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