

A great number of infectious diseases exert a direct or indirect effect on nutrition and nutritional status. These effects are partly specific and partly unspecific.

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Interaction of Nutrition and Infections Globally: An Overview
by M.B. Krawinkel

Key insights

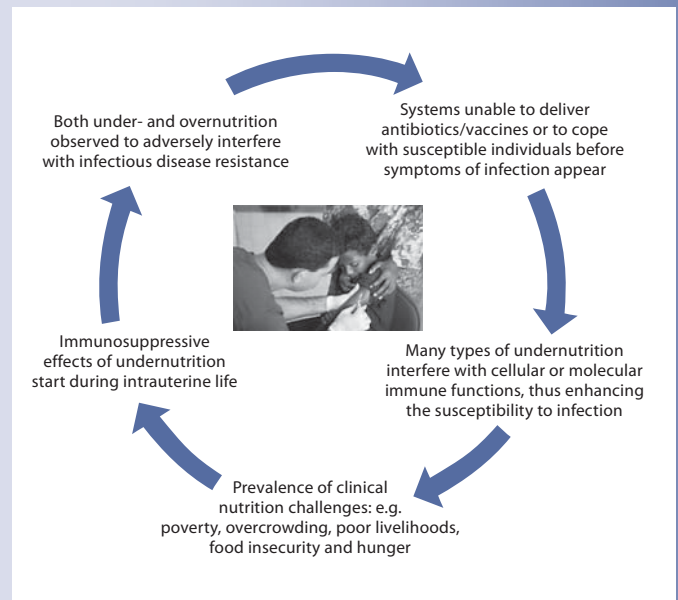
Undernutrition is an effective immunosuppressant, while infections often compromise nutritional status. The interactions between infections and malnutrition are manifold: improving nutritional status has great potential in preventing and managing infections.

Current knowledge

Associations between undernutrition and a higher risk of infections have been documented in different age groups in different countries, mostly in clinical settings. The immunosuppressive effect of undernutrition starts during intrauterine life. Pathophysiologically, many types of undernutrition interfere with immune functions and thus enhance the susceptibility to a number of infections. Recent research suggests that not only undernutrition but also caloric overnutrition impacts on immune response to infections and immunizations via neuroendocrine alterations.

Practical implications

Infectious diseases impact on the nutritional status, either specifically or through unspecific mechanisms such as anorexia, tachypnea, and vomiting. Infections in undernourished children are a common cause of death, and taking this finding into account helps to reduce the case fatality rate in severely malnourished patients.



Poor nutritional status makes individuals susceptible to infectious diseases. Undernutrition (and overnutrition) adversely affects the immune system; on the other hand, infections have a negative influence on nutritional status.

Recommended reading

Schlaudecker EP, Steinhoff MC, Moore SR: Interactions of diarrhea, pneumonia, and malnutrition in childhood: recent evidence from developing countries. *Curr Opin Infect Dis* 2011;24:496–502.

Interaction of Nutrition and Infections Globally: An Overview

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Key Messages

- **Undernutrition is an effective immunosuppressant.**
- **Infections often compromise the nutritional status.**
- **The interaction of nutrition and infections is often neglected.**

Key Words

AIDS · Immune response · Infections · Obesity · Pneumonia · Tuberculosis · Undernutrition

Abstract

The interaction of nutrition and infections is known by experience by generations of medical doctors. Before the era of antibiotics, diet was an integral part of the management of infections. Now, it is necessary to take a fresh look at this interaction as the understanding of immune response has expanded considerably. Comparatively little research has addressed the impact of nutrition interventions on the management of infectious diseases. Most observations of the interaction between nutrition and infections are epidemiological in character. This holds especially true for measles as well as for tuberculosis. In AIDS, the deterioration of the nutritional status is an indicator of disease progression. Infections in undernourished children are a common cause of death, and taking this finding into account helps to reduce

the case fatality rate in severely malnourished patients. Regarding the immune response, cellular as well as soluble components are affected by deficiencies of single nutrients or general undernutrition. The immunosuppressive effect of undernutrition starts during intrauterine life already: maternal nutrition status has been shown to impact on immune function in adult animals. Recent research suggests that not only undernutrition but also caloric overnutrition impacts on immune response to infections and immunization. This is partly due to the chronic inflammatory activity of the adipose tissue and partly due to neuroendocrine alterations. Infectious diseases also impact on the nutritional status, either specifically or through unspecific mechanisms, such as anorexia, tachypnea, and vomiting.

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Impact of Nutritional Status on Infections

One of the oldest observations on the interaction between nutrition and infection is that malnutrition increases the susceptibility to tuberculosis. Still, as Cegielski and McMurray [1] state:

“The oral traditions of medicine and public health have it that malnutrition is an important risk factor for the development of tuberculosis (TB). Malnutrition profoundly affects cell-mediated immunity (CMI), and CMI is the principle host defense against TB. It makes biological sense. Although most health professionals readily accept this principle, much of this belief is based on un-

controlled observations such as disaster situations or on backwards logic from the cachexia common among TB patients. In fact, the evidence in humans is surprisingly thin from the perspective of scientific rigor. And few data, if any, quantify the extent of the relative or attributable risk of TB due to malnutrition' [1].

This 'experience without scientific evidence' holds also true for leprosy, which hardly affects people who have a nutritious and balanced diet. The clinical observation of temporary negativity of a former positive tine test in malnourished children who had been postnatally vaccinated against tuberculosis is in the same line: this observation did not find sufficient scientific interest to be investigated and proven. A recent review on research topics in tuberculosis does not mention one single study on the role of nutrition in primary prevention of tuberculosis [2], although – before effective tuberculostatic drugs became available – nutrition was a main tool for treating the condition in sanatoriums in Switzerland and elsewhere. The only limitation was that most people could not afford such treatment.

Epidemiological Aspects

Still, associations between undernutrition and a higher risk of infections have been documented in different age groups in different countries, and mostly in clinical settings. In France, for instance, the association between undernutrition and nosocomial infections in elderly patients has been demonstrated [3].

One study based on the National Family Health Survey 3 in India found the risk of infection in preschool children to be associated with a low body mass index for age and low weight-for-height. As low weight-for-height is determined by the actual deficit in food energy, the authors conclude that morbidity and the food energy deficit are associated [4].

The strong link between severe childhood malnutrition and infection has been frequently observed. In a Tanzanian hospital-based data analysis, septicemia was found to be the most common cause of death in these children [5]. The recommendation for prescribing an antibiotic before symptoms of infection appear is aimed at preventing morbidity and mortality.

As mentioned above, tuberculosis has empirically been associated with poverty, overcrowding, and malnutrition. During the wars of the 19th century, also typhus was clearly associated with poor livelihoods and expo-

sure to food insecurity and hunger. Due to the circumstances, most of the data are anecdotal and are not derived from well-designed studies [6]. In line with these observations, a case-control study in Bangladesh reported an association between the occurrence of leprosy and a period of food shortage [7].

The complexity of the association between infections and malnutrition has been illustrated by another study in

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Angola where an analysis of Demographic and Health Survey data led to the finding that malnutrition and anemia were linked to malaria and geohelminth infections [8].

Katona and Kotana-Apte [9] put it more generally: 'Malnutrition is the primary cause of immunodeficiency worldwide.'

Remarkably, not only undernutrition, but also caloric overnutrition has been found to adversely interfere with disease resistance. In the H1N1 epidemics of the year 2009, obesity was identified as a risk factor for a more severe course of the infection in several studies [10]. Apart from the observations on obesity in H1N1 infections, there are few papers reporting on an association between high body mass index and susceptibility to respiratory infections in general [11]. A reduced response to immunization with hepatitis B vaccine in obese persons has already been reported about 25 years ago [12].

Regarding malaria outcomes, there is some evidence that the morbidity and mortality of malaria attacks is higher in undernourished children. Deficiency of vitamin A, zinc, folate, and other micronutrients is also considered to cause severer disease [13].

Pathophysiological Aspects

The impact of the nutritional status on infections is mediated by the effect of nutritional deficiencies on the immune defense of the organism. Various deficiencies hamper cellular and humoral immune functions and, as illustrated in figure 1, this nutritional programming of immune functions starts before birth, i.e. the mother's nutritional status impacts on the immune defense of the offspring [14].

Many types of undernutrition interfere with immune functions and thereby enhance the susceptibility of patients to a number of infections. Table 1 gives a short overview of present knowledge of these interactions. The limitations of a review do not allow going into detail about each nutrient and its relevance for immune response. The most frequently addressed aspect is global

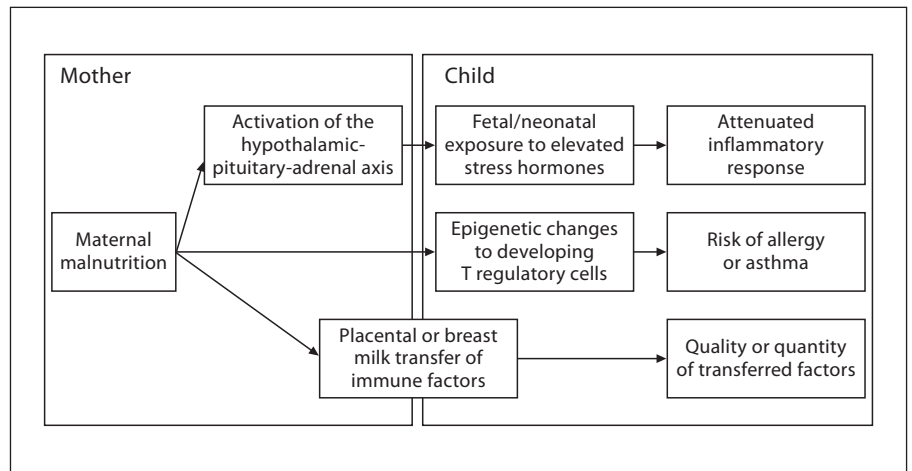


Fig. 1. MTCT of nutrition effects on immune functions. Based on Palmer [15].

Table 1. Some nutritional deficiencies affecting immune response

Nutrient deficit	Immune response	Ref.
All nutrients/energy	- IFN- γ release	18
	- Immune response to vaccine	19
	- Immature CD4 and CD8 cells, decrease in cell proliferation	20
Protein/amino acids	- Cytokine production	21
	- Regulatory angiotensin I converting enzyme 2 (Ace2)	22
Vitamin A	- Immune response to vaccine	23
	- Mucosal immunity	24
Iron, magnesium, zinc	- TNF- α , IL-1 β , and IL-10	25
Iron	- IL-4, T cell function	26
Zinc	- Immature CD4 and CD8 cells, decrease in cell proliferation	6
Vitamin D	- Toll-like receptor antimicrobial pathway in monocytes	27

undernutrition, which is not restricted to developing countries, but also extends to clinical nutrition challenges in industrial countries.

Regarding the association between general malnutrition and infection, the formerly used term ‘protein-energy malnutrition’ led to an underestimation of the global nutrient deficiency including macronutrients and micronutrients. With an increasing understanding of severe childhood malnutrition and the role of oxidative stress, the primary role formerly ascribed to protein is no longer accurate, neither concerning the condition in general nor concerning the impact of malnutrition on susceptibility to infections [16].

The interaction between nutritional status and various immune functions in the defense against infectious agents is complex and has up to now been insufficiently

addressed, mostly by a ‘one by one’ approach; however, a systems biology approach to this issue has been envisaged recently [17].

Regarding vitamin A deficiency, there has been a debate about the primary role of vitamin A in infectious diseases. For a long time, vitamin A deficiency itself was believed to contribute to high child mortality rates, and reductions in child mortality rates have been attributed to the vitamin’s supplementation until today [28]. As childhood mortality is an outcome of various variables (e.g. general livelihood, poverty, access to medical care, immunizations, and care practices including breastfeeding and others), the unique role of vitamin A supplementation has been questioned by the late Michael Latham [29]. Besides the discussion about optimal provision of the nutrient to populations in a sustainable manner, the

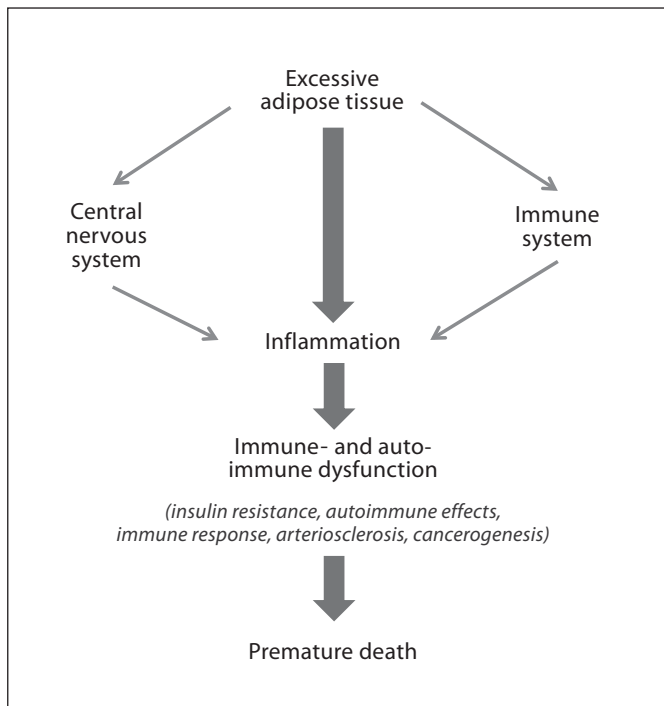


Fig. 2. Effects of obesity on the immune system. Modified after Dixit [34].

depressive effect of vitamin A deficiency on the immune system is beyond debate (table 1). Nevertheless, no study has proven that supplementation is the only way to provide the nutrient for prevention. Both β -carotene and preformed vitamin A contribute to the vitamin A status of individuals [30], but approaches to their integration into the normal family's diet are widely underresearched up to now.

A special clinical role has been attributed to vitamin A supplements in measles. Based on research in South Africa [31], the World Health Organization has established a guideline requiring that measles patients in developing countries should be provided with one dose of vitamin A at the time of diagnosis in order to prevent complications of the disease [32]. Up to now, an effect of similar strength has not been shown for any vitamin A intervention in any acute infectious disease.

Besides the impact of nutrient deficiencies and general malnutrition, a view of the association between nutrition and infections also needs to take the effect of caloric overnutrition on the risk of infections into account. Kanneganti and Dixit [33] state in a recent review: 'respiratory infections, including influenza, bronchitis, pneu-

Table 2. Immunological aspects of obesity (based on Kanneganti and Dixit [33])

Thymus	involution/immune dysfunction
Immune system	vaccination failure
Adipose tissue	inflammasome activation, insulin resistance
Blood vessels	inflammatory processes in veins and arteries
Respiratory tract	acute and chronic respiratory tract infections (pneumonia), asthma
Various organs	cancer (breast, uterus, colon, esophagus, pancreas, kidney, prostate)
Bones/joints	arthritis, gout
Liver	fatty liver disease (NAFLD), cirrhosis

monia, tuberculosis, septicemia, and nosocomial infections, also contribute to substantial morbidity and mortality in obese patients.'

As illustrated in figure 2, fat tissue exerts effects through its hormones ghrelin and leptin which result in neuroendocrine changes. These alterations impact on the immune system and induce inflammatory responses, e.g. in the endothelium of blood vessels and in the pancreas [34].

A recent review reported several interactions between the immune and the metabolic system in obesity (table 2). There is an expansion of aberrant immune cell populations (T and B cells, macrophages, eosinophil and neutrophil granulocytes, and mast cells) in adipose tissue inducing chronic inflammatory processes. On the other hand, there is an ectopic lipid deposition in lymphoid organs probably negatively affecting immune response and alertness [33].

Whereas these data suggest a higher susceptibility to infections, a recent study on the functions of peripheral blood mononuclear neutrophil granulocytes found normal chemotaxis, phagocytosis, and superoxide production in the cells of obese patients [35].

Food and Infections

Infections associated with food production and food processing require a different perspective; they are primarily biological, but also social and environmental in character. A number of specific infections is associated with agricultural food production, i.e. bacterial (e.g. tetanus), viral (e.g. rabies), and parasitic infections (e.g. schistosomiasis). These are typically acquired during labor in

the fields and through irrigation. Animal husbandry was found to be associated with toxoplasmosis [36].

Regarding food-borne infections, the numbers of persons affected are widely different depending on the food safety standards of each country and their implementation. As an illustration, table 3 presents data from the Centers of Disease Control in the USA for the year 2009. The figures illustrate that even with high food safety standards, an annual number of >17,000 cases occurred, and an overall case fatality rate of about 2.10% indicates that the diseases can take a serious course and are not just a light indisposition. In many, especially developing, countries food safety is a major concern and great efforts are made to reduce the incidence of food-borne infections. Yet, even in industrialized countries, there is room for improvement of surveillance and epidemiological investigation of outbreaks [37].

Impact of Infections on Nutrition

A great number of infectious diseases exert a direct or indirect effect on nutrition and nutritional status. These effects are partly specific and partly unspecific. Both types can be light and minor or serious and life-threatening. One example is AIDS, which specifically causes the 'wasting syndrome', a marasmic status. As another example, normal nutrition is compromised by fast breathing caused by dyspnea due to pneumonia or bronchiolitis.

In hyperendemic areas of HIV, malnutrition may be found in children as the first clinical sign of the infection.

Epidemiological Aspects

In hyperendemic areas of HIV, malnutrition may be found in children as the first clinical sign of the infection. An investigation of the nutritional status of children in areas with high HIV prevalence indicates that even maternal HIV infection is associated with a significantly higher relative risk of 1.28 (1.16–1.42) for stunting, 1.26 (1.02–1.55) for wasting, and 1.2 (1.11–1.43) for underweight in children [39].

Of special interest regarding the interaction of infection and nutrition is the mother-to-child transmission (MTCT) of the virus through breast milk. The risk of transmission by breast milk seems to be highest with mixed feeding and breastfeeding beyond 6 months of age [40]. Whilst these findings seem to suggest that breastfeeding by an HIV-infected mother is dangerous for the

Table 3. Foodborne infections: numbers of cases, deaths and case fatality ratio [38]

Pathogen	Deaths	Unknown	Total	CFR
<i>Campylobacter</i>	9	720	6,058	0.15%
<i>Listeria</i>	21	0	157	13.38%
<i>Salmonella</i>	24	344	7,023	0.34%
<i>Shigella</i>	1	128	1,854	0.05%
STEC O157	2	6	461	0.43%
STEC non-O157	1	2	286	0.35%
<i>Vibrio</i>	7	6	160	4.38%
<i>Yersinia</i>	2	14	152	1.32%
<i>Cryptosporidium</i>	8	62	1,345	0.59%
<i>Cyclospora</i>	0	0	32	0.00%
Total	75	1,282	17,528	2.10%

CFR = Case fatality ratio; STEC = Shiga toxin-producing *Escherichia coli*.

non-infected infant, there is growing evidence that breastfed infants have better chances of survival and may even be protected against HIV by lactic acid bacteria in breast milk [41].

A Cochrane review from 2009 concluded:

'Complete avoidance of breastfeeding is efficacious in preventing MTCT of HIV, but this intervention has significant associated morbidity (e.g., diarrheal morbidity if formula is prepared without clean water). If breastfeeding is initiated, two interventions are efficacious in preventing transmission: 1) exclusive breastfeeding during the first few months of life; and 2) chronic antiretroviral prophylaxis to the infant (nevirapine alone, or nevirapine with zidovudine)' [42].

In earlier studies, the timing of breastfeeding was given the highest attention in order to assure maximum benefit from breastfeeding for the child and to avoid excess risks compared to children fed breast milk substitutes. Nowadays, as the authors of the Cochrane review conclude, antiretroviral drugs play an increasing role also for prevention of MTCT.

Another specific infection with a high impact on nutritional status is tuberculosis. As already known in the European literature of the 19th century, tuberculosis is a major causal factor in malnutrition. Since then, improving the nutritional status of patients has been one element in tuberculosis case management; however, in spite of the experience of many clinicians, the scientific evidence for nutrition interventions in tuberculosis is rather weak, and more research is needed to confirm this evidence [43].

The effect of AIDS on the nutritional status of affected patients is dramatic: as mentioned above, in young chil-

dren, malnutrition is regarded as a key sign of AIDS in hyper-endemic areas; in adults, 'slim disease' is a common term when AIDS develops in the HIV-infected patient. Besides the immediate effect on the patient, a survey in Kenya found that children in HIV-affected households had a higher rate of stunting compared to children from non-HIV-affected families [44]. A review of 18 countries of sub-Saharan Africa confirmed this finding for the years 2003–2008 [45]. This is one of the tragic aspects of the HIV pandemic: even non-infected children are endangered and often die early.

Another well-known association exists between diarrhea and malnutrition: without an early feeding regimen to prevent it, diarrhea causes a catabolic state, and the acetone in the blood exerts an anorectic effect on its own. Therefore, clinicians speak of the vicious circle of diarrhea and malnutrition. As demonstrated quite recently in a study in Libya, diarrhea episodes are predictors of chronic malnutrition in children presenting with 'stunting' [46]. This observation holds true for various causes of chronic and recurrent diarrhea, i.e. intestinal infections with bacteria and parasites.

Besides general malnutrition, various intestinal parasites and parasites affecting the urinary tract cause iron deficiency anemia through blood loss in a great number of people worldwide. Therefore, effective programs for the prevention of iron deficiency anemia need to be accompanied by deworming medication and measures to improve general hygiene [47].

Besides general malnutrition, various intestinal parasites and parasites affecting the urinary tract cause iron deficiency anemia through blood loss in a great number of people worldwide.

The specific effects of infections on nutritional status are an area which still deserves much research to better understand and include nutrition interventions into the case management of a given infection. However, not only a specific effect of a specific cause can be responsible

for deterioration in nutritional status. Again, according to experience and corroborated by some evidence, unspecific aspects of infections cause nutritional problems, e.g. tachypnea in pneumonia, frequent vomiting in whooping cough, and anorexia in various infectious diseases [48].

Conclusions

Undernutrition and caloric overnutrition interact with infections, whilst infections exert a mostly negative effect on food intake and the nutritional status. The specific mechanisms include hormonal as well as cytokine effects. Besides single nutrient deficiencies, global undernutrition is a major contributing factor to the more severe if not fatal course of various infections. The interactions between infections and malnutrition are manifold and improving the nutritional status has a great potential in preventing and managing infections.

Disclosure Statement

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