Nutritional Influences on Immunity and Infection

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Learning Objectives

- Impact of infection on health and disease
- Malnutrition, inflammation, and the infectious processes
- Chronic diseases, nutrition, microbiome, and infection

20.1 Introduction

The complex nutrition-immunity-microbiome-infection-genomic connection is presented in this chapter, bringing their relationship together in an integrated view with a focus on the role of nutrients in maintaining the integrity of the immune system. Infection has been a primary challenge to human health and disease throughout history. It is now recognized that an individual's vulnerability to infection is associated with nutritional status. Malnutrition increases the risk of infection and immune system compromise. The past century's renaissance of nutrition science has supplied the increasing evidence for the roles that essential nutrients, dietary intake, environmental exposures, and nutrigenomic influences play in the ability of the immune system to respond and resolve infectious insults. The recognition of the importance of nutrition within the scope of assessment and intervention, which is often overlooked in healthcare, is presented as having an overall impact on outcome. The current knowledge of the role of nutrients and their interrelationships with the immune system and chronic disease provides scientific support for the nutritionally trained practitioner. This chapter will describe some of the key mechanisms and nutrient influences on the immune response as well as dietary and lifestyle considerations for treatment.

Nutritional deficiencies and insufficiencies have known associations with increased susceptibility to infectious disease. Infection can also increase requirement for nutrients and produce further undernutrition, infection, and compromise of the immune system, setting up a vicious cycle between malnutrition and infection [1, 2]. Malnutrition is the primary global cause of immunodeficiency for all age groups, especially for infant mortality with poor nutrition promoting underweight, weak, and vulnerable children. Optimum nutrition status allows the metabolic function defense and repair mechanisms to increase immune integrity.

Optimal nutritional status contributes to health maintenance and the prevention of infection. The function of healthy cells is maintained by adequate nutrition, movement, and sleep routines. Primary and secondary malnutrition may occur when each individual lacks the available clean food, nutrients, and water that are required. The healthy immune system enables the body's ability to adapt, recover, and survive. When there is disruption in the nutrient intake, the malnutrition that ensues contributes to a cascade of adverse metabolic events leading to illness. The nutritionally trained practitioner assesses an individual to identify where malnutrition may be present and develops an intervention with early delivery of essential nutrients in an effective and comprehensive manner. Healthcare practitioners are often challenged to understand the importance of adequate nutritional support in the prevention and treatment of infection, multiple organ failure, and most life-threatening systemic sepsis [3].

The aim of this chapter is to provide the current science for and a description of the interaction between nutritional status of an individual and immunological susceptibility to infection, as well as integrative and functional approaches to interventions that may be considered to restore immune integrity and restore wellness. There will not be an in-depth review of immune function. Please refer to the excellent presentations of the immune system by Dr. Vodjani in ▶ Chaps. 19 and 49.

This chapter is divided into three sections.

1. Impact of infection on health and disease
2. Malnutrition, inflammation, and the infectious processes
3. Chronic diseases, nutrition, microbiome, and infection

20.2 Impact of Infection on Health and Disease

Until the beginning of the nineteenth century and the industrial revolution, illness was primarily impacted by physical injury and acute infections related to poor sanitation practices that allowed a higher prevalence of infection. Throughout thousands of years of history, the human body has survived through the strength of several defense mechanisms, including an alert immune system, the impermeable skin membrane, and gut barrier, and the more recently recognized microbiome that shields all body orifices. It has been well established, even by Hippocrates almost 3000 years ago, that these mechanisms are dependent on an optimal nutritional status in order to maintain health and to prevent infection.

> Illnesses do not come upon us out of the blue. They are developed from small daily sins against Nature. When enough sins have accumulated, illnesses will suddenly appear. –Hippocrates (c. 460 – c. 370 BC)

During the nineteenth century, outstanding scientific discoveries occurred and changes in philosophy took place regarding the biological functions within the human body, enabling greater appreciation of the fact that when the biochemical mechanisms of our defense system are disrupted, it increases vulnerability to infectious disease.

20.3 Key Metabolic Mechanisms for Defense and Repair

- Enterohepatic circulation (see ▶ Chap. 16)
- Phase I and phase II biotransformation/detoxification (see ▶ Chap. 14)
- Gastrointestinal, lung and skin/barrier integrity/membrane integrity (see ▶ Chap. 12)
- Mitochondrial function
- Methylation (see ▶ Chap. 18)
- Hormonal function (see ▶ Chap. 32)
- Autophagy (see ▶ Chap. 51.2.6)
- Happiness (see ▶ Chaps. 6 and 30)

20.4 Insults to Our Defense and Repair Systems

20.4.1 Increased Toxin Load

As the industrial revolution evolved, increased toxin exposure accumulated from the discovery and use of petroleum which released petrochemicals and mercury into the air, the discovery of mercury (e.g., used in making the British top hat), the common use in dentistry of mercury (comprising about 50% of dental amalgam material), and pollution from industrial practices into rivers and the resulting contaminated water supply. The trend for increased environmental toxin exposure has continued to grow, so that at the time of this publication there have been more than 80,000 chemicals created with relatively few tested for safety. A most pervasive and hazardous pesticide toxin, glyphosate, is now used nearly universally in agriculture, thereby ending up in our water and food supplies.

20.5 Antimicrobial Resistance (AMR)

There has been continuous improvement in sanitation practices, perhaps too robustly going beyond the abilities of human and animal life to balance with the microbial world to avoid development of "superbugs" that have become resistance to antibiotics. The challenge of acute infections is of great concern to public health because of antimicrobial resistance (AMR) and the rise of "superbugs" that are considered the biggest threats to modern healthcare [4]. The primary driver of AMR is thought to be the overuse of antibiotics in humans and agricultural animals and overuse of antibacterial hand soaps and gels.

20.6 Gastrointestinal Dysbiosis: From Mouth to Anus

The two largest defense barriers to infection are the skin and the gastrointestinal tract (gut). The mouth and oral cavity provide the beginning of defense and repair by mastication, saliva digestives, and endocrine immune glands (parotid, tonsils, adenoids) preparing food that enters the gut for digestion and absorption. The next step is the pH 1–3 acid bath the bolus of food passes through in the stomach with antimicrobial action suppressing any pathogens traveling in with your food. The small intestine is the next pass, bathing the bolus in bile, pancreatic digestive enzymes, and bicarbonate, ready for the serious work of digestion. This is the location where the gut houses more than 70% of our body's immune tissue (lymphoid tissues) and, when compromised by insults, we become more vulnerable to infection weakening our immune integrity. Those lymphoid immune cells also depend on a healthy microbiota's symbiotic relationship to optimally function. The gut is frequently referred to as "the second brain" [5] because of its generous secretion of neurotransmitters and direct connections to and from the brain, the enteric nervous system. When insults like antibiotics, emotional upsets, stress, infection, chemicals, or toxic metals enter the gut, the gut barrier breaks down and suffers intestinal permeability ("leaky gut") that allows for non-desirable molecules to be absorbed and enter the blood and lymphatic systems, triggering an immune response of loss of self-tolerance, or an antigenic response against one's own tissue [6]. Once someone experiences a "leaky gut," a pro-inflammatory cascade initiates, adding a burden to the immune system and increasing vulnerability to infection.

20.7 Stressors

Stress can insult our defense and repair in several forms: biological, emotional, and energetic stressors. As stressors increase, there is a resulting biological stress, along with a concurrent increase in nutritional requirements. If the food intake cannot keep up with meeting the nutritional needs under stress, malnutrition ensues. Unfortunately, with the increased consumption of the standard American diet (S.A.D.), the population eats more calorie-dense, nutrient-depleted, processed, and high-sugar foods. A majority of the US population does not have the available nutrients to meet the essentials of a generally more stressed society [7]. One of the most prevalent nutrient deficiencies and insufficiencies in the USA from NHANES studies are "40% deficient in Vitamin A, C, D & E, calcium or magnesium deficient and >90% do not get enough choline, fiber & potassium." [6] (◘ Fig. 20.1).

About 65% of the population does not even meet the recommended daily allowance (RDA) for magnesium [8, 9]. More than two-thirds of the US population are either overweight or obese. This population subgroup has a higher risk of several chronic diseases.

Early in the twentieth century, great trust and hope were generated by Alexander Fleming's discovery of penicillin and the world of antibiotics [10], with the anticipation of ending uncontrolled bacterial infection. Now in the twenty-first century, as science looks back on the use of antibiotics, recognition is increasing that the overuse of antibiotics is enabling the development of what are now termed "superbugs."

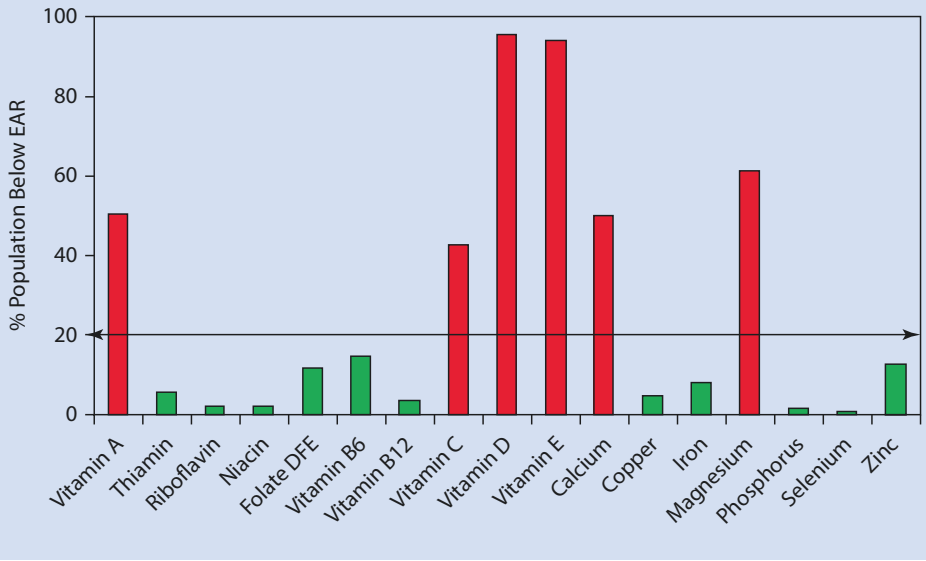

Fig. 20.1 NHANES 2001–2008 micronutrient deficits. Percentage of the adult population (aged 19 years) with vitamin and mineral intakes below the EAR for individuals (data from NHANES 2001–2008). Usual intakes from foods were estimated by using the National Cancer Institute (NCI) method [8]. (Reprinted from Agarwal et al. [8]. With permission from Taylor & Francis)

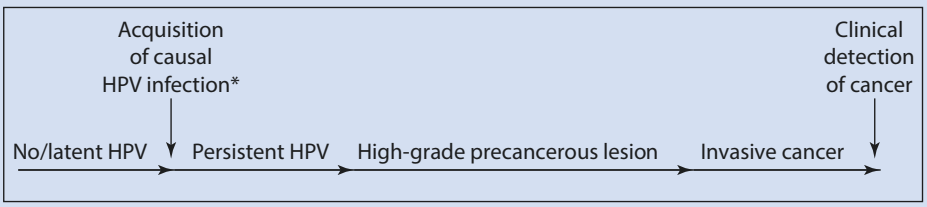

Fig. 20.2 HPV lifespan spectrum [12]. (Reprinted from Burger et al. [12]. With permission from Oxford University Press)

Superbugs are beginning to threaten the success of medicine and pharmacology. The antibiotics have weakened the defense mechanisms of the microbiome shield that humans have depended on throughout history. Public health concerns are increasing that the overuse of antibiotics in humans and animal husbandry, along with antimicrobial antiseptics, has become a health threat through the weakening of the microbiome protection of the population.

The discovery of subclinical unresolving infections that are associated with many of the chronic diseases is beginning to be appreciated by the global medical community. Infection increases infection-related morbidity and mortality [11]. Subclinical-level long-latency infections often go unnoticed while they alter and sometimes mutate tissue cells over time, leading to an acute disease. Examples of infection connections to chronic disease are:

- HPV virus causal of cervical cancer and neck/head cancers [12] (Fig. 20.2)
- *H. pylori* increased risk of gastric cancer [13] (Fig. 20.3)
- HSV-1 increasing risk of Alzheimer's disease [14]
- *Klebsiella pneumoniae* association with rheumatoid arthritis [15, 16]
- EBV and CMV combo-viral increasing risk of various cancers [17]
- *Chlamydia pneumonia* and atherosclerotic plaque formation [18]

With nutritional status being a major factor affecting host resistance to infection, this chapter focuses on how to assess a chronic disease sufferer's "infection load" or "infection status" using an integrative and functional lens, searching for the disease etiology and impaired resolution of inflammation (resolution biology) [19]. This assessment of infection status should become part of the nutritional and metabolic assessment differential. It rules out, or identifies, if infection is part of the etiology and pathophysiology of a disease condition. Once identified, targeted intervention proceeds to improve successful outcomes of restoring wellness (Fig. 20.4).

20.8 Malnutrition, Inflammation, and the Infectious Processes

Infection, as well as trauma or excessive visceral fat, appropriately perturbs the immune system into secretion of inflammatory molecules like cytokines, acute phase reactants, and others [11]. It is not possible to cover the scope of the physiology of the immune system and inflammation in this space; the focus of this chapter is to describe how malnutrition and insufficiencies of specific nutrient groups can perpetuate compromising the immune system and the microenvironment, so the natural immune mechanisms of defense and repair from infection are weakened (see ▶ Chaps.

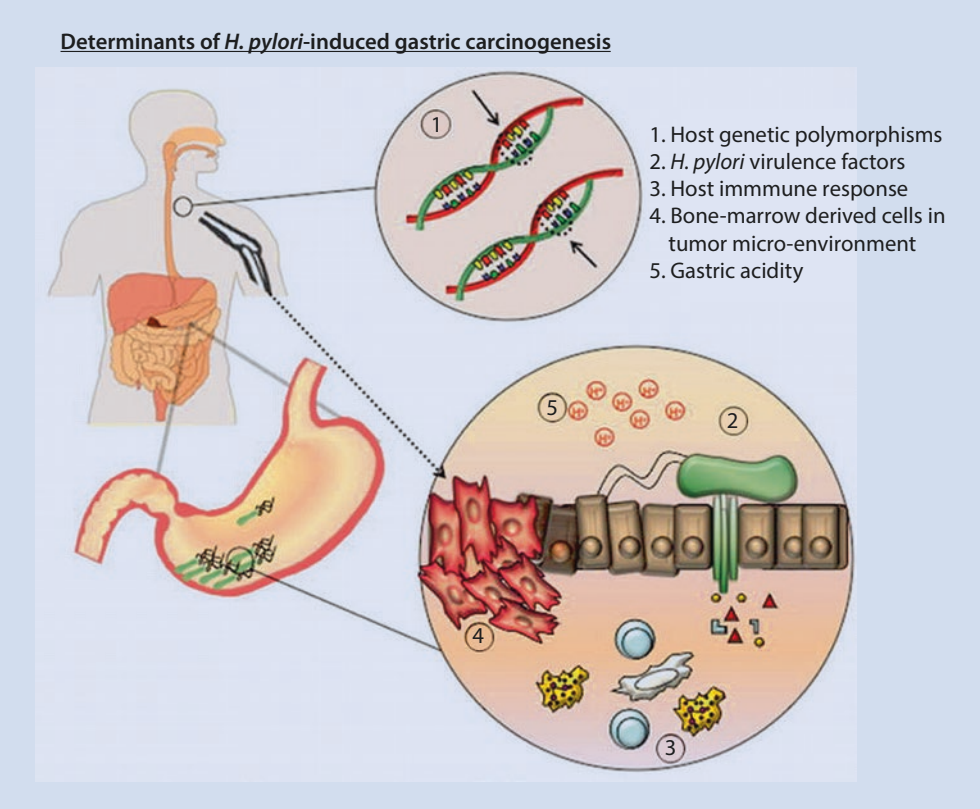

Fig. 20.3 *H. pylori* increased risk of gastric cancer [13]. (Reprinted from Kim et al. [13]. With permission from Elsevier)

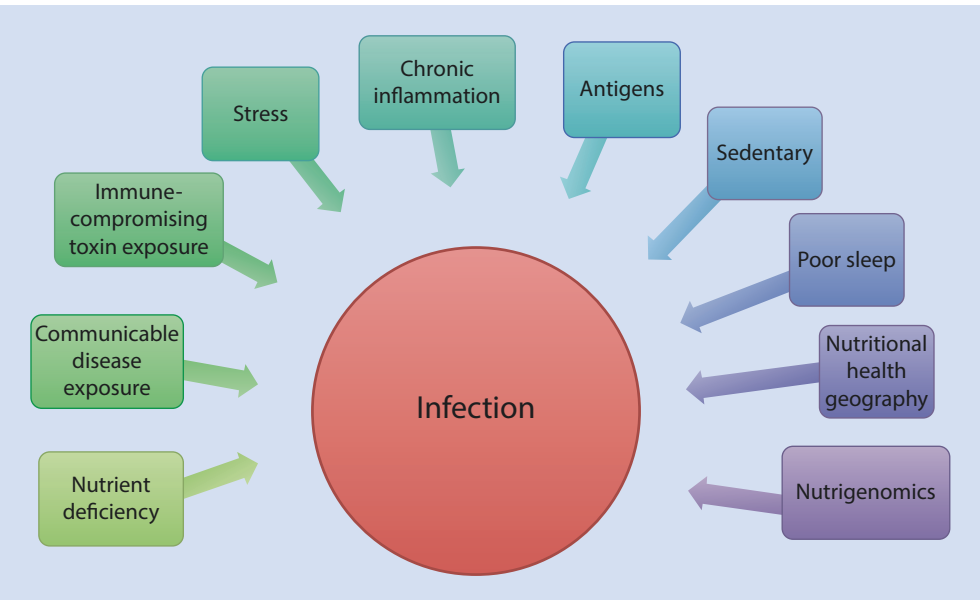

Fig. 20.4 Key nutritional, lifestyle, and environmental influences on infection

19 and 50). Inflammation almost always accompanies infection and, when prolonged, sets up susceptibility for all chronic diseases.

For acute infections, this inflammatory response is a critical part of tissue healing, with increased blood flow and heat. Increased heat can involve local tissue or produce systemic natural hyperthermia with fever. If infection continues to be unresolved, it can produce a prolonged state of inflammation with continuing subclinical infection(s) that over time can result in a loss of self-tolerance and perturb metabolic mechanisms toward diseased tissue that can lead to any of the chronic diseases. The inflammatory load of an individual should be assessed for each chronic disease and infection ruled out as a potential contributor to total body inflammation [20].

Tuberculosis (TB) is a leading cause of death worldwide, despite being preventable and often curable [21, 22]. It is prevalent in malnourished populations with poor sanitation [20].

Schwenk states that TB, also called "consumption," is predisposed by a state of macro- and micronutrient deficiencies.

There is a complex relationship between tuberculosis and malnutrition, in that TB can increase nutrient requirements and lead to a worsening of nutritional status. In high-TB rate countries, vitamin A, carotenoids, and vitamin D levels are found to be low and deficient. Nutritional correction of malnutrition factors is considered part of the best approach to the treatment of tuberculosis [20, 21].

20.9 Diagnosis of Nutrition Status and Infection-Related Diseases

There is much evidence for association or causal nutritional insufficiencies or deficiencies increasing the risk of someone becoming infected. Once infected, levels of tissue inflammation increase until clinically observable (see ◘ Fig. 20.2) and may linger long term unless resolved back to wellness. If the infection continues even at a subclinical level, it can continue to weaken the host integrity of the immune system [11].

Inflammation is the body's normal response and protects the body from infection from pathogens like bacteria or viruses, as well as injury. Inflammation can be acute, which should be short-lived as the body resolves an infection or injury, or chronic and long term and can be destructive, leading to chronic diseases. Examples of chronic diseases that can develop from a long-latency infection are periodontitis, asthma, inflammatory arthritis, and inflammatory bowel disease.

Conventional therapies for chronic inflammation use anti-inflammatories primarily from two categories of pharmaceuticals: steroids and nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs counteract enzymes and prostaglandins. NSAID use of more than 10 days is not desirable, due to increased risk of stomach ulcers and gastrointestinal bleeding and sometimes adverse effects like worsening of asthma or kidney problems.

Cardinal signs and physiology of inflammation

Rubor (redness): increased blood flow
Tumor (swelling): exudation of fluid
Calor (heat): exudation of fluid, increased blood flow, release of inflammatory mediators
Dolor (pain): chemical mediators; inflammatory exudates stretching pain receptors and nerves
Functio laesa (loss of function): pain, fibroplasia, metaplasia, disruption of structure

For the IFMNT practitioner, changing the patient's dietary intake and use of dietary or herbal supplements to correct nutrient deficits or excesses can support the underlying systems promoting the inflammation. For instance, NSAIDs act on suppressing eicosanoid and prostaglandin metabolites. Assessment of blood RBC fatty acids (linoleic (LA) and alpha-linolenic acid (ALA) and their metabolites, gamma-linolenic acid (GLA), di-homo-gamma-linolenic (DGLA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) reveals where there may be an underlying imbalance directly related to what they eat. Developing a diet plan to *rid* intake of inflammatory foods and *get* foods that are anti-inflammatory is a desirable goal. (see ▶ Chap. 43). Key foods include therapeutic use of food oils that can modulate a person's fatty acid status and provide ability to control inflammation. Phytonutrients rich in the variety of colorful fruits and vegetables have powerful anti-inflammatory action. Some herbs have excellent evidence of anti-inflammatory support with successful practice-based experience.

Anti-inflammatory foods, herbs, and dietary supplements targeted recommendations based on patient assessment

Foods

Whole-foods, pesticide-free, vegetable, and fruit variety of color, adequate protein, healthy fats and oils, foods-rich in herbal components, and hydration; minimize or avoid processed and high-sugar foods and beverages; avoidance of identified antigenic foods. (see ▶ Chap. 43)

Herbs

- Turmeric/curcumin
- Resveratrol
- Boswellia
- Artemisinin
- Garlic
- Quercetin (suppresses mast cells)
- Proteolytic enzymes: bromelain, papain, trypsin, etc. (contraindicated for alpha-1-antitrypsin deficiency+ genetics)

Dietary supplements

- Vitamin C (contraindicated for hemochromatosis+ genetics)
- Adequate methyl nutrients
- Vitamin D3 (if indicated per personalized assessment)
- Vitamin A (if indicated per personalized assessment)

Infectious processes are biological stressors that alter the requirement of an individual metabolism beyond the RDA/RDI recommendations. Recognition of this principle drove the emergence of the field of orthomolecular nutritional therapy early in the twentieth century, leading to provision of the right nutrients at a molecular and cellular level. Under high-stress conditions, micronutrient requirements are altered [23]. For example, vitamin C requirements as a primary cellular antioxidant vary for an individual depending on the stress load, diet, gastrointestinal function, and genomics [24] as stated by Dr. Tim Spector, "there is a lot of variability in the ways in which healthy people react to food (and nutrients)" [25]. With the recognition of how unique and diverse individual physiologic immune responses are to food and lifestyle, the inclusion of a per-

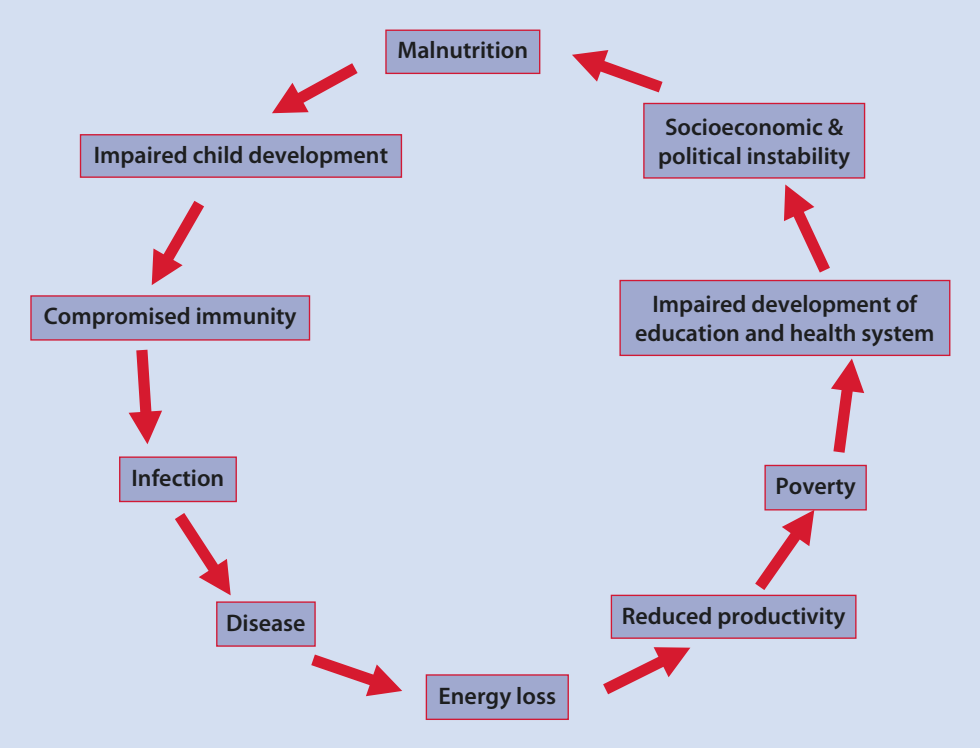

Fig. 20.5 Protein energy malnutrition increases prevalence of infection, leading to energy loss for the individual [2]. (Reprinted from Schaible and Kaufmann [2]. With permission from Creative Commons License)

son's nutrition status as part of their differential exam for development of a comprehensive treatment plan is of utmost importance.

Over human history, many cultures have evolved food traditions to meet specific health needs such as pregnancy, or infection, or child development. Records from Hippocrates describe specific foods to treat various disease conditions. In the Middle Ages, eggs were soaked in vinegar to dissolve the eggshell, rich in calcium and minerals, to be given to a pregnant woman. Various herbal teas were given for various types of infections and many other conditions. Besides food being a source of nutrients, herbal and nutraceutical oral supplementation became prevalent in the eighteenth century. In 1831, the first intravenous (IV) technology was attempted for treatment of cholera by a Scottish doctor, Dr. Thomas Latta. It took another 100 years for further development of intravenous therapies and only became commonly available clinically by licensed practitioners in the 1960s. Once determined safe and clinically feasible, it was embraced by many medical specialties where patients were impacted by compromised gastrointestinal function and malnutrition [26]. Today, many hospital and clinic infusion centers administer IV vitamins, mineral and nutrient cocktails, and intramuscular (IM) nutrients to support nutritional status of individuals seeking prevention, or as prescribed due to compromised oral dietary intake. IV treatments can provide nutrients for individuals with increased nutrient requirements, especially with the biological stressors presented by acute or chronic infections.

One of the most life-threatening infectious conditions is severe sepsis [27] with no effective treatment options. In 2014, the results of one of the first clinical trials for IV ascorbic acid at Division of Pulmonary Disease and Critical Care Medicine, Department of Internal Medicine, School of Medicine, Virginia Commonwealth University were published.

The conclusion of the $n = 26$ human trials with severe sepsis and a variety of diagnoses of cancer, respiratory failure, and others was that infusion of intravenous ascorbic acid was safe and may positively influence patients when challenged with severe sepsis with multi-organ failure. The study showed improved lower biomarkers of inflammation, C-reactive protein (CRP), and procalcitonin (PCT) that correlate with the overall extent of infection. Higher levels of both have been biomarkers linked to higher incidences of organ injury and death in the critically ill. These two biomarkers proved accurate to assess effectiveness of the IV ascorbic acid. Thrombomodulin (TM) was the biomarker used to measure endothelial injury status and showed similar improvement Fig. 20.5.

20.10 Differential for Nutritional Infection Risk

20.10.1 Look for Evidence of Infections

Toolbox to identify infectious relationship with nutrition status:

- Nutrition physical exam (see ▶ Chap. 40)
- Medical history: diagnosis, medical event history, infectious history, residential location

- Signs and symptoms: medical symptoms questionnaire (MSQ)
- Laboratory and procedural testing (basic nutrition-related and, if applicable, for disease-specific and sometimes patient-specific markers)
- Bioelectrical impedance analysis (if available)
- Laboratory nutrition status and infection-related biomarkers (Table 20.1 and Fig. 20.6).

The nutrients most studied regarding immunonutrition that should be considered in the assessment are listed in Table 20.2 and will be discussed below.

20.11 Chronic Diseases, Nutrition, Microbiome, and Infection

All chronic diseases have associations with acute or subclinical infections as potential etiologies for a chronic disease individual. Infections are caused by the exposure to such pathogens as virus, bacteria, parasites, fungi, or prion. Many chronic diseases have known nutrient-microbiome-infection interactions [57]. When completing an initial assessment differential consideration of an infectious component of any patient presenting with a chronic disease, it should be part of an initial assessment differential to identify if infection could be part of the pathophysiology.

Malnutrition, altered microbiome, and infection interact to influence health and disease in the developed and developing world. Infectious morbidity is significant in the malnourished, whether nutrient insufficiencies or overnutrition. Infections significantly compromise utilization of oral nutrition and the immune lymphoid tissue in the gastrointestinal tract disturbing the microbiome. Malnutrition predisposes a person to infection, and restoring the injured nutritional status improves immune integrity. Improving nutritional status reduces risk of infection, and when one does contract infection, there may be a reduction in the severity of systems.

Nutritional assessment currently makes use of many new technological modalities. The Integrative and Functional Medical Nutrition Therapy assessment model identification of "root cause(s)" of a condition starts by hearing the patient's story (see ▶ Chap. 39). When was the last time they felt well? Family history? Signs and symptoms? Diet history? Medications? Supplements? Toxin exposure? Other issues? The model explores the question of how a person's metabolism evolved to the current disease condition.

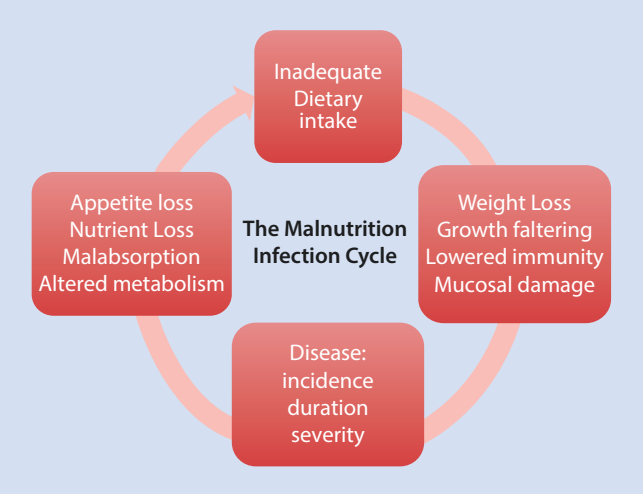

Fig. 20.6 The "vicious cycle" of malnutrition and infection. Spiral of malnutrition and infection [28]. (Adapted from Katona and Katona-Apte [28]. With permission from Oxford University Press)

Table 20.1 Immunonutrition assessment investigation tools

Test	Type	Practitioner options
Imaging	Diagnosis-related	Radiology
Functional testing	Digestive Hormonal Organic acids Structural	Functional medicine Endocrinology MD, DO, ND, LAc, RD, CNS, RN, NP, PA DC, DO, PT-classical
Mind-body	Psychology	MD, psychologist, family counselor therapist
Initial assessment and monitoring	Follow-up	Initial practitioner
	BIA	All; equipment required
	MSQ	All
	Monitoring abnormal test results	All
	Nutrition physical exam	All; more expanded with integrative and functional nutrition-trained practitioners
	Oxygen saturation monitor	All
	Thermometer	All; nutrition-trained practitioners will use temperature to consider thyroid functional status maintaining body temperature; rule out infection;

20.11.1 Laboratory

With laboratory data to examine, a diagnostic profile begins to emerge to clarify the priorities of core physiological

Table 20.2 Key immuno-nutrient insufficiencies/deficiencies associated with or causal for subclinical or acute infections; key immune-nutrients foundational for healthy immune endogenous defense

Nutrient	Infection: deficiency connection	Reference	Symptoms	Testing to consider
Immune modulators				
Vitamin D	Immune modulator	[29–31]	Mood disorders; bone loss; joint pain; compromised immunity	Vitamin D25OH
Vitamin A retinol	Mucosal immunity	[22, 24]	Mucosal bacterial/ viral infections	Vitamin A, retinol; β-carotene
Phytonutrients polyphenols		[32, 33]		
Rate-limiting cofactors				
Folate	NK cell activity Cytotoxic cellular immunity Modulate T cell responses	[34]	Fatigue Infection Mood disorder	Folate, serum FIGLU
Zinc	Regulates intracellular signaling pathways in innate and adaptive immune cells	[34–36]	Skin conditions Poor smell Poor taste Frequent illness Nail spots	Zinc, serum Zinc, RBC
Magnesium	>300 enzymes cofactor Urine excretion under stress		One of the most deficient minerals in the USA Muscle tension Cramps	Magnesium, serum RBC magnesium
Iodine	Thyroid metabolism requirement	[37, 38] *UIC values* <20 μg/L (severe iodine deficiency) 20–49 μg/L (moderate iodine deficiency) 50–99 μg/L (mild iodine deficiency), 100–199 μg/L (adequate iodine intake) 200–299 μg/L (more than adequate iodine intake) >300 μg/L (excessive iodine intake)	Cysts Fibrocystic breasts Hypothyroid In utero developmental	Urinary iodine concentration (UIC) Iodine, random blood
Amino acids Arginine Lysine Glutamine	Nitric oxide (NO) Gut barrier support	Low grade evidence [39] Herpes Simplex [40]	Perturbed protein metabolism Poor healing Express herpes simplex skin rash Poor gut barrier repair	Plasma or urine amino acid profile
Antioxidants				
Vitamin C	Regulates cellular humoral immune function; increase macrophage Antihistamine requirements increase during infection Antiviral	[27]	Connective tissue impairment Skin conditions Poor wound healing	*Blood* Vitamin C CPT 82180

Table 20.2 (continued)

Nutrient	Infection: deficiency connection	Reference	Symptoms	Testing to consider
Vitamin E full-spectrum	4 tocopherols + 4 tocotrienols protective from oxidative stress/lipid peroxides	[29, 41]	Oxidative stress Premature wrinkles Cysts Leg cramps	Vitamin E (tocopherol) CPT 84446
Selenium	Thyroid peroxidase metabolism with vitamin E Selenoproteins special effects on cellular immunity Resistance to viral infections	[36, 41]	Hypothyroid Low glutathione blood levels Impaired detoxification	*Blood* Selenium, RBC Selenium CPT 84255
Gut secretions				
Short-chain fatty acids (SCFA)	Intestinal cells Anti-inflammatory Microbiome-gut- brain axis via immune system/vagal nerve Mucosal immunity	[42–47]	Inflammation Perturbed uric acid cycle Colon disease	Fecal collection
Bile acids	Fat emulsification duodenum Carrier of toxins/elimination	[48, 49]	Perturbed fat digestion Suppressed detoxification enterohepatic circulation	*Blood* Bile acids, total CPT 82239 or fecal collection
Anti-nutrients				
Endocrine disruptors	Circadian rhythm disruption that can modulate immune function	[50, 51]	Hormonal imbalance Insomnia Cancer	Blood or urine
Damaged food components/Western diet and food preparation Trans fat Oxidized fat Toxic metals Toxic chemicals "new-to-nature molecules" (cookware, pest control, pollutants, processed, etc.)	The damaged high-heat foods Chemicals Toxic metals ingested in foods and from food utensils during food preparation	[52]	Toxicity Symptoms vary	Blood or urine
Environmental toxins Mold/mycotoxins Natural gas carcinogenic Chemical vapors Pesticides	Neuropsychiatric immune disruption Vulnerable to infections increased risk for kidney failure, fertility problems, cancer, birth defects	[53–56]	Toxicities Chronic kidney failure Infertility Cancer Developmental Frequent infections	Specialty labs

imbalances for nutrition and lifestyle therapy. When focusing on assessing the existence of infectious activity, and the priority within the etiology of a disease condition, consideration of the three most likely physiological areas of immune imbalances are *defense and repair*, *assimilation, and structural integrity* (Fig. 20.7).

20.11.2 Assessment Laboratory and Clinical Tools

- Comprehensive Digestive Stool Analysis (CDSA) various labs provide CPT
- Ova and Parasitology (2–3 samples) CPT Code(s) 87177, 87209

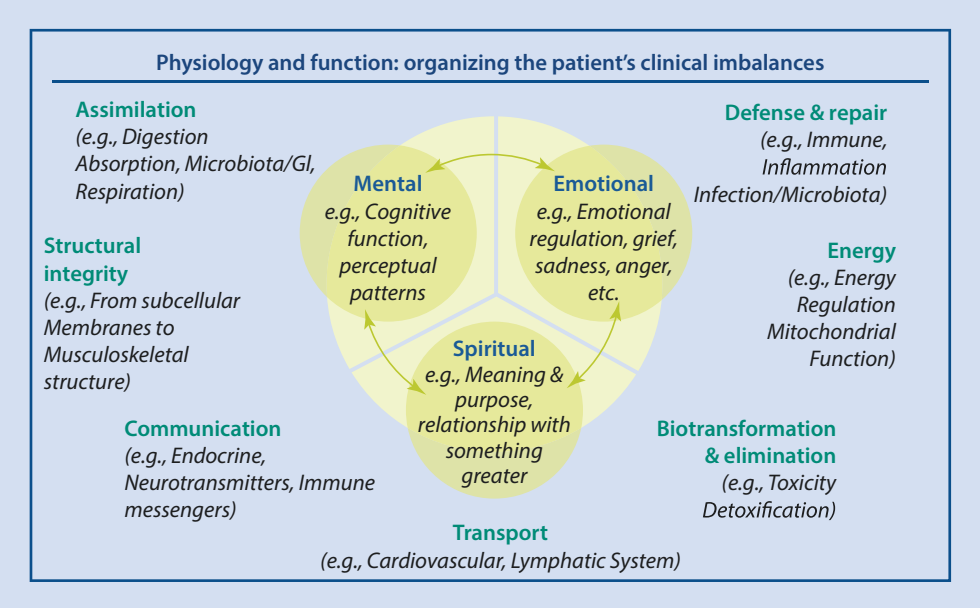

Fig. 20.7 IFM Matrix: physiology and function – organizing the patient's clinical imbalances [58]. (Used with permission from The Institute for Functional Medicine ©2015)

- Rule out other infections
- Calprotectin, fecal CPT 83993 [fecal calprotectin (FC]
- *Clostridium difficile* toxin/GDH with reflex to PCR (if diarrhea)
- Lactoferrin, fecal CPT 83631: leukocyte marker; intestinal inflammation
- Differentiate IBD from irritable bowel syndrome (IBS)
- Monitor patients with IBD for treatment response and relapse
- Diagnose inflammatory bowel disease (IBD)
- Occult blood, fecal

Defense and Repair Immune, Inflammation, and Infection/Microbiota Assessment Biomarkers

Blood

- Vitamin D 25-hydroxy
  Vitamin 25-OH serum levels have been associated with several comorbidities, such as infectious, autoimmune and neurological diseases, as well as neuromuscular disorders, which can lead to increased pain sensitivity [59–61]. Regarding the mechanisms of pain sensitization, vitamin D seems to stimulate anti-inflammatory processes in some cases and thus to relieve the painful sensation of many diseases [62–64].

- Vitamin A retinol [65]
  Vitamin A retinol is increasingly recognized in experimental and human studies to suppress inflammatory reactions and plays a significant role in normal mucosal immunity, regulation of T cell-dependent responses, antiviral activity [66], and cell trafficking.

  Adequate vitamin A status, whether from intake of preformed retinol or β-carotene, is important for preventing excessive or prolonged inflammatory reactions and infectious events [66].

- high sensitivity CRP (hs-CRP)
  High-sensitivity C-reactive protein (hs-CRP) is an acute-phase-reactant marker of systemic inflammation most often promoted by bacterial infection, central adiposity, neoplastic activity, or traumatic injury. The ideal level of hs-CRP is ≤0.6. hs-CRP elevation implies potential bacterial infection. The most common infections with elevated hs-CRP are periodontitis or necrosis of the jawbone. If an elevated CRP >1.0 and clinical oral exam and report of bleeding upon flossing or brushing, appropriate referral to a biological dentist for evaluation is warranted. If no dental/oral infection is identified, further investigation as to the root cause of the elevated hs-CRP is warranted. It is important to rule out a recent traumatic injury that may be related, and hs-CRP should be retested in a month or two to observe if injury affected the hs-CRP.
- CBC with differential
- Complete metabolic panel (CMP)
- Lipid panel
- Sed rate
- TSH
- **Bacterial/viral evaluation**
  - CMV IgG Ab CPT 86644–0.5 ml red top serum
  - CMV IgM Ab CPT 86645–0.5 ml red top serum
  - Epstein-Barr virus (EBV) antibody panel ((IgM, VCA IgG, EBNA IgG) – CPT 86664, 86,665–1 ml red top serum
  - EBV early antigen D antibody (IgG) – CPT 86663–1 ml red top serum
  - *Chlamydophila pneumoniae* antibodies (IgG, IgA, IgM) – CPT 86631 86,632 1 ml red top serum
  - Mycoplasma IgG/IgM – CPT 8673–86,738 – 1 ml red top serum

- Herpesvirus 6 antibodies (IgG, IgM) – CPT 86790, 86,790 (×2)– 0.5 ml red top serum
- ASO CPT 86060–1 ml SST
- ANA W/RFX – CPT 86038–1 ml red top serum

- **Immune function**
  - Natural killer cells, functional – CPT 88184, 88,185–10 ml (WB) green tube
- **Toxin load**
  - Heavy metals panel, blood – CPT 82175, 83,655, 83,825 – (WB) royal blue EDTA
    Includes: arsenic, lead, mercury
  - Cadmium, blood – CPT 82300 – (WB) royal blue EDTA trace element (REF)
- **Fecal**
  - Microbiology, fecal
  - Ova and parasitology
- **Urine**
  - Urinalysis (urine)
  - Organic acids (urine)
  - Complete hormone panel
- **Saliva or blood Genomic testing**
  - (saliva)

Structural integrity Membrane structure affects the function of transport and communication at the cell membrane site and receptors; review if history of head/neck/dentition/back injury may affect brainstem and vagal nerve immune-related function; structure, dysfunction occurs. Dietary intake of these lipid groups is reflected in their endogenous structure and function [67].

- Cell membrane fluidity (BIA phase angle, fatty acid status)
- Structural: spinal alignment
- Dental: periodontitis – infection of the tissues that surround the teeth
- Cervical C1–C7 – brainstem and vagal assessment – check vagal tone [68]
- Thoracic T1–T5 – stenosis or injury, increased pain resulting in exaggerated immune inflammatory response
- Lumbar L1–L5 – stenosis or injury increased pain resulting in exaggerated immune inflammatory response

20.11.3 Key Nutrients Influencing the Risk of Infectious Disease (Fig. 20.8)

20.11.3.1 Vitamin D, A, E [69]

These fat-soluble vitamins have many metabolic roles, but for the focus on the immune system in this chapter, the role of immune modulation is discussed. The fat-soluble vitamins function synergistically; even the vitamin D and A receptors share the RXR nuclear receptor influencing each other. It is worth noting in nature that vitamins D2/3 and A are found in their food-rich sources together (e.g., liver, caviar/roe, egg yolk, etc.).

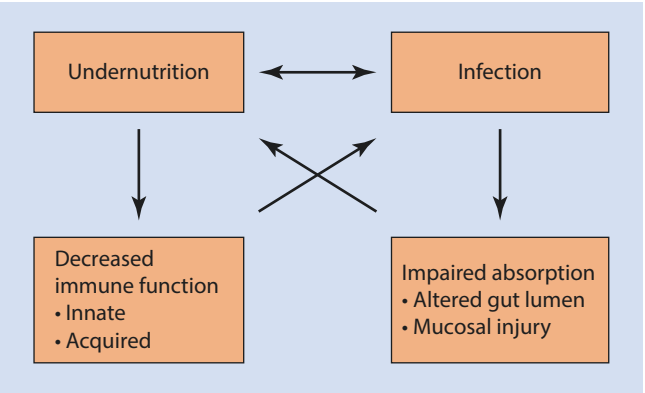

Fig. 20.8 Interactions between malnutrition and infection [28]. (Adapted from Katona and Katona-Apte [28]. With permission from Oxford University Press)

Lipids Phospholipids, oils, and fat foods – RBC fatty acid, lipid panel tests. The phospholipids, sterols, and eicosanoid fatty acids and their metabolites give structural and functional influences on cell signaling and prostaglandin "hormone-like" regulation to transport of components in and out of the cell compartments to nourish and regulate immune response of inflammation, hormonal modulation, and other undiscovered functions. When there is poor structure, poor function follows (see ▶ Chap. 10).

Methyl nutrients Vitamins B6, folate, B12, riboflavin, betaine, biotin, choline, SAMe, and amino acids methionine, cysteine, serine, and glycine [70, 71].

Methyl nutrients support the process of methylation with many roles within human metabolism, with DNA methylation being the underlying mechanism, and currently appear to be the primary messengers of epigenetic expression (see ▶ Chap. 18) identified in the etiology of developing cardiovascular, cancer, and neurological disease conditions. Methyl nutrients include vitamins (folate, riboflavin, vitamin B12, vitamin B6, choline) and amino acids (methionine, cysteine, serine, glycine).

Methylation involves biochemical pathways where the B vitamins and other cofactors like amino acids are rate-limiting cofactors.

20.12 Homocysteine Catabolism (Fig. 20.9)

20.12.1 Folate Metabolism

Folate is critical to many metabolic pathways like nucleic acid precursors, several amino acids, and erythropoiesis, the process in which new erythrocytes are produced. Elevated mean

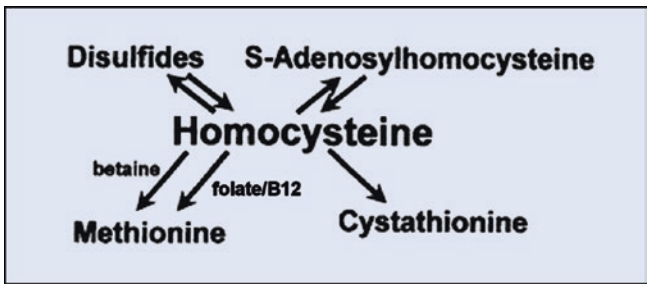

Fig. 20.9 Homocysteine major metabolic pathways in humans [72]. (Reprinted from Dudman et al. [72]. With permission from Oxford University Press)

corpuscular volume (MCV)on a complete blood count can suggest folate deficiency. Folate deficiency can be part of the etiology of enlarged RBC, or megaloblastic anemia, from ineffective erythropoiesis. Vitamin B6 and B12 are cofactors also involved in erythropoiesis [73].

20.12.2 Methionine Metabolism

Methionine metabolism occurs predominantly in the liver tissue with two components: a transsulfuration pathway, involving homocysteine reduction to glutathione, and a transmethylation cycle with folate and methyl nutrients producing *S*-adenosylmethionine (SAMe). Thus, methionine metabolism is dependent on dietary intake of vitamins B12, B6, and folate. SAMe is key in regulating epigenetic expressions of multiple pathways and, when deficient, leads to ramifications of nutritional and immune injury [74] (see ▶ Chap. 17).

20.12.2.1 Phytonutrients

Inflammation: powerful pigment-rich polyphenols found in a variety of fruits, vegetables, grains, nuts, teas, herbal spices, and legumes have anti-inflammatory properties. Plant chemicals include antioxidants and antibacterial and antiviral mechanisms. Even though phytonutrients are not considered essential nutrients, the evidence is mounting of their critical role health maintenance and anti-aging.

Biomarkers of phytonutrient status: poor dietary intake of high polyphenol foods. Significant biomarkers for inflammation can be related to poor vegetable and fruit intake and lack of or imbalance in dietary intake of healthy fats and oils (see ▶ Chap. 57).

Resource: The Rainbow Diet. Color Can Heal Your Life [75]

20.12.2.2 Minerals: [76]

Zinc critical role in the function of immune cells

Potassium principal intracellular cytosol electrolyte

Iodine thyroid hormone structure, brain development

Selenium thyroid peroxidase metabolism with vitamin E, selenoproteins special effects on cellular immunity resistance to viral infections. Central to glutathione peroxidase structure

Iron weaken cell-mediated immunity; decreases in neutrophil action

Magnesium co-factor in >300 enzymes affecting all systems

20.13 Key Lifestyle Factors Influencing the Risk of Infectious Disease

20.13.1 Sleep (see ▶ Chap. 45)

Sleep and circadian rhythm have a great influence on the integrity of the immune system. Much evidence has accrued over the past decades associating poor sleep quantity and quality with weakening of the immune system, increasing vulnerability to infection.

20.13.2 Stress (see ▶ Chap. 47)

Chronic stress impacts every biological and psychological system. The chemical microenvironment under long-term stress pushes the immune system response into chronic inflammation. The vicious cycle continues until the threshold of resilience and adaptation is exceeded, leading to vulnerability to many chronic diseases including infection.

20.14 Movement (see ▶ Chap. 36)

20.14.1 Examples of Chronic Disease Connections with Infectious Disease

20.14.1.1 Heart Disease/Cardiovascular Association with Infectious Processes

- *Infectious risk*: *Chlamydia pneumonia*, group A *Streptococcus* [77].
- *Dental*: periodontitis, necrosis of the jaw.
- *Rheumatic heart disease*: [78].
- *Bacterial endocarditis* (cardiac inflammation and scarring triggered by an autoimmune reaction to infection with group A *Streptococci*).
- *Pancarditis* (involving inflammation of the myocardium, endocardium, and epicardium); follows pharyngitis infection without antibiotic treatment.
- *Rheumatic chronic disease*: mitral valve stenosis almost always originates from rheumatic conditions and expresses and perfusion insufficiency. Rheumatic conditions are highly associated with underlying infection [79]. A previous infective endocarditis should be ruled out if there are symptoms of unexplained fever, malaise, or weight loss [80].

20.14.1.2 Oncology

Etiology of cancer can be related to infectious disease.

Viral EBV, CMV. Herpes simplex, herpes zoster, HIV, HPV

Bacterial *H. pylori*, *Mycoplasma pneumoniae*

Fungal Candida, mycotoxins

Mycoplasma *M. pneumonia, M. genitalium, M. hominis, ureaplasma urealyticum, U. parvum*

Parasites trichinosis [81], blastocystis hominis, tropical parasites

20.14.1.3 Neurological

Alzheimer's disease Viruses of life-long carriage are typically asymptomatic, strongly associated immunologic, and virologic characteristics with Alzheimer disease neuropathology increasing amyloid plaque and neurofibrillary tangles (NFTs): herpes simplex virus-1 (HSV-1), long-term cytomegalovirus (CMV) [82].

Developmental plasticity Due to fetal and early childhood metabolic plasticity influences by the environment, negative toxic exposures and infectious processes in utero or in childhood can influence the risk of later chronic adverse conditions, especially noncommunicable disease (NCD). This fact has driven the public health drive for vaccination programs during the first year of birth [83]. The importance of maternal health nutrition status and free from infectious disease lays the foundation for fetal growth. Developmental epigenetics studies provide insight into the importance of epigenetic marks occurring in utero and recognition of new biomarkers to provide interventions for prevention and treatment [83].

20.14.1.4 Respiratory (see ▸ Chap. 52)

Acute respiratory infection can derive from viral, bacterial, or mold/mycotoxin exposure. The risk for an individual can be related to exposure environment and genotype (e.g., cystic fibrosis, alpha-1-antitrypsin, Wegener's granulomatosis). More extensive discussion on respiratory conditions and infection is presented in ▸ Chap. 52.

20.14.1.5 Autoimmune (see ▸ Chap. 49)

Autoimmune conditions are inflammatory. Ongoing research has identified genetic relationships with susceptibility to developing autoimmune conditions, but coexisting infections can contribute to the etiology of an individual's disease. The human leukocyte antigen (HLA) group of genes is highly associated with risk of developing autoimmunity. HLA DQ2 and HLA DQ8 reside within the HLA gene group, and are known risks for developing celiac disease [84].

Comprehensive Human Leukocyte Antigen Panel
HLA DR1/3/4/5, DQ Intermediate Resolution CPT 81375
LabCorp Specialty Labs

20.14.2 Vaccination

During the twentieth century, the discovery and use of antibiotics began the breakdown of natural microbiota throughout the gastrointestinal tract and other microbiome-containing orifices. It is recognized at the time of this publication that the current epidemic of "superbugs" has resulted from overuse and misuse of antibiotics and antimicrobials. After the discovery of antibiotics, more pharmaceuticals were discovered to be providing strong manipulation of body systems and perturbing nutrient functions, such as steroid medications weakening connective tissue resulting in the increased need for vitamin C, biotin, and zinc. In addition, after World War II, there was the introduction of many "new-to-nature" molecules to agricultural practices and as additives to the food supply [85]. All of these new introductions into the human environment have altered the immune system, contributing to weakening defense systems. The twenty-first century is introducing even more organic and inorganic molecules that need more extensive investigation about their safety.

Two examples of concern:

1. *Fecal microbiota for transplantation* (FMT) implanting foreign bacteria from a donor into the gastrointestinal tract of a patient. The US Food and Drug Administration (FDA) has not officially approved FMT procedures but supports the area of scientific discovery. In 2019, implants performed for two immune-compromised patients from a single donor contained drug-resistant organisms. One of the patients died. Clinical trials were suspended and the FDA has warned all fecal matter for FMT should be tested for drug-resistant bacteria [86, 87]. This event illustrates the potential risk of FMT as a source of life-threatening infections.
2. *Vaccinations* have strong pro and con public opinion, but all sides agree in vaccine safety monitored by the US FDA and the *Centers for Disease Control and Prevention* (CDC). The principle of vaccination is based on the body's healthy adaptive immune response when exposed to a pathogen to develop protective antibodies to the pathogen. The most prominent concerns about vaccine safety are the additives to the vaccine preparations for preservation and effectiveness, the age at which vaccine is administered, and the number of vaccines given simultaneously. The most commonly used preservative adjuvants are aluminum, mercury-containing thimerosal [88], and formaldehyde. These compounds have known adverse effects. In 2011, the *International Agency for Research on Cancer* (IARC) named formaldehyde "a known human carcinogen" [89]. The US FDA has a reporting site for *Vaccine Adverse Event Reporting System* (VAERS) and *Wide-ranging Online Data for Epidemiologic Research* (WONDER) to provide public health information [90].

Thimerosal contains mercury, of which the *World Health Organization* (WHO) says that exposure, even in small amounts, "may cause serious health problems and is a threat to the development of the child in utero and early in life." "Mercury is considered by WHO as one of the top ten chemicals or groups of chemicals of major public health concern" [91]. Aluminum is a known neurotoxin and can play a significant role in neurological diseases. Reported elevated levels of aluminum found in Alzheimer's patient brains increases public concern. There is no evidence of harm for aluminum content in single vaccines, but concern for the accumulation of total aluminum in multiple-dose vaccine vials is not known.

The use of vaccines has become a highly debated political issue with states overhauling fundamental changes in their vaccine laws toward mandatory vaccination. Integrative and functional medical practitioners tend to embrace "first do no harm" and at least recommend parents base their decisions with full knowledge of the pros and cons of vaccinations for their individual child. There is no clear evidence of why some children and adults have mild to life-threatening side effects after receiving a vaccine.

If there is a suspected reaction to a vaccine, the *National Vaccine Injury Compensation Program* (NVICP) exists to provide financial compensation to individuals who have documented injury [92].

General considerations for parents that may increase vaccine safety for a child:

- Is my child sick the day of a scheduled vaccine? If yes, best to reschedule.
- Has my child had a reaction to any previous vaccination?
- Do our family or I have a history of vaccine reactions, neurological disorders, or immune system conditions like Sjogren's, lupus, celiac, eczema, etc.? If yes, document your child's personal and family history [90].
- What are the vaccination laws in the state in which I live?

If agreeing to vaccination, recommend limiting vaccinations to one vaccine administration at a time instead of multiple vaccines. Single-use vials of vaccines, if available, can be considered to reduce exposure to preservatives like thimerasol (mercury-containing) and formaldehyde.

Genomic counselors can be sought to discuss currently identified *single-nucleotide polymorphisms* (SNPs) that may be associated with increased risk of vaccine reaction.

Ensure your child is in good nutrition status, eating a balanced whole-food, low-pesticide, fruit- and vegetable-rich, low-sugar diet with adequate intake of vitamins D, A, and C, essential fatty acids, and bioactive forms of B vitamins from food or supplements if needed.

The US FDA has a reporting site for *Vaccine Adverse Event Reporting System* (VAERS) and *Wide-ranging Online Data for Epidemiologic Research* (WONDER) to provide public health information [90].

Several reports have shown that vitamin A deficiency results in a poor response to immunization, with generally low antibody responses to immunization with T cell-dependent antigens [93, 94].

20.15 Conclusion

This chapter reviews the importance of considering infection as a potential contributor to the etiology of any of the chronic diseases.

Infection can contribute to each type of chronic disease. Growing evidence is emerging that infections are most damaging to tissues and metabolism when they have continued as a prolonged burden on the immune system. Pathogens are generally attracted to specific tissue types and the disease that may develop for a unique individual may vary. Chronic diseases are characterized as long-latency, lifestyle, and diet-related diseases. An acute infection may either be resolved by a healthy immune system or survive and continue as a subclinical infection that is often not recognized but continues to wear on the immune system. Examples of commonly recognized subclinical infections that lead to increasing risk of a serious chronic disease: HPV risk of cervical or head/neck cancers, hepatitis C risk of liver cancer, Epstein-Barr virus risk of non-Hodgkin's lymphoma and some autoimmune conditions, and *C. pneumoniae* implicated in chronic illnesses, such as atherosclerosis, asthma, arthritis, multiple sclerosis, and many others. This chapter has described the association between a person's nutritional status and their vulnerability to infection. Individual nutritional status is a determinant of how well their body can respond to and resolve an infection, returning it to a state of wellness. The risk to get or not resolve an infection is greater from a compromised immune system when nutrient tissue levels are not optimized for an individual or able to provide adequate nutrient metabolic cofactors. Healthy nutritional status decreases risk of chronic diseases and vulnerability for long-latency prolonged infection [1, 3].

The healthy human body is equipped with defense features from conception throughout life to interact with the environment to protect from infection. Much of the defense starts with the skin barrier and microbiome at all body orifices to protect from pathogens entering and infecting. Another key is keeping the stomach acid-neutralizing pathogens or toxic organics from traveling further down the gastrointestinal tract where they could cause havoc and alter the powerful GI microbiome. These defenses guard pathogens and toxins from entering the blood and/or lymph circulation. Along with the internal milieu of the body, ethnic cultures have developed mores to support immune defense by traditions of toileting, diet, sleeping, sanitation (especially for food preparation and handwashing), and other complementary routines that minimize infection.

A growing recognition of the evidence of the pathophysiology of chronic disease reveals its contrast to acute disease by the long-term development often asymptomatic and not recognized. Subclinical infections can "smolder" unrecognized for many years, even beginning in utero and childhood, a stress on the immune system that often goes undiagnosed or there is unawareness of their significance. This chapter provides knowledge of assessment principles and specific immune-support nutrients and herbal components that can intervene if infections are identified. The increased clarity of scientific evidence supports "you and your genes are what you eat, digest, eliminate, sleep, move, avoid significant toxic exposure and live in a healthy relationship community" to live a long life that is vital and resilient and functional [95].

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