Respiratory

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51.1 Impact of Nutrition and Lifestyle on Respiratory Health and Disease

51.1.1 Overview

Lung disease is far more prevalent worldwide than commonly thought. In fact, death from chronic lung disease is increasing, and as of 2017, chronic obstructive pulmonary disease (COPD) has become the third leading cause of death in the United States in the past decade, disproportionately affecting the elderly [1]. Another lung disease, asthma, affects 1 in 13, or about 25 million Americans, according to the Centers for Disease Control and Prevention and the National Center for Health Statistics [2]. This is 7.6% of adults, more women than men, and 8.4% of children. Asthma is the leading chronic disease in children [3]. This disease has been increasing since the early 1980s in all age, sex, and racial groups. In Europe, lung disease represents 15% of all deaths – the fourth leading cause. According to the World Health Organization (WHO), in 2008, 9.5 million people died from acute or chronic lung disease, representing one sixth of the global total deaths [4].

Worldwide, four respiratory disease categories appear in the top ten leading causes of death in 2010 [5]. Specifically, COPD was the third leading cause of death, followed by lower respiratory infections as the fourth, lung cancer as the fifth, and tuberculosis as the tenth [4]. The major risk factor is smoking, leading to 50% of all lung disease-related deaths in Europe, where smoking is more prevalent (28% prevalence) than in the United States (15% prevalence) by nearly twofold [6, 7]. Lung cancer, particularly non-small-cell lung cancer (NSCLC) subtype, is the leading cause of cancer-related death worldwide [8]. Added together, lung disease rivals the position for the top cause of death.

Throughout the life cycle, diet and lifestyle are important modifiable risk factors in the development, progression, and management of obstructive lung diseases, such as asthma and COPD [9], as well as restrictive lung diseases such as pulmonary fibrosis and sarcoidosis. Inflammation, in particular, seems to be the leading contributor toward the progression of lung diseases. As with many diseases, maintaining a healthy lifestyle, including sufficient sleep, low stress, regular exercise, a whole foods diet rich in phytonutrients from plants (fruits and vegetables), and potential anti-inflammatory supplements, is beneficial in supporting the body during these difficult diseases.

> Inflammation, in particular, seems to be the leading contributor toward the progression of lung diseases.

High inflammatory foods should be avoided, such as fried foods and foods disproportionately high in carbohydrates, sugar, alcohol, and excessive protein. A healthier suggestion would be a diet with more than half of all food consumed as vegetables, about one third as protein, and the remainder (one sixth) as other foods, such as fruits, dairy, grains, or starches. Some dietary supplements may also be recommended for their anti-inflammatory benefits, which will be discussed later in the chapter.

As human life expectancy increases, we can expect to see more chronic disease. The World Health Organization estimates that by 2030, chronic lung disease will account for 20% (one fifth) of all deaths [10], up from one sixth in 2008. Despite these growing numbers, relatively little human nutrition research exists for respiratory health, compared to other, less prevalent, diseases. Investigators in the areas of aging and lung biology suggest some hope, using genetics and animal models, as well as epidemiological research, to further the general medical approach to lung disease.

51.2 Anatomy and Physiology

51.2.1 General Anatomy

The pulmonary system is composed of the upper and lower respiratory tracts. Air flows in through the nose or mouth, past the frontal and maxillary sinuses, down the pharynx (throat), past the larynx (voice box), and then down the trachea. This makes up the upper respiratory tract. Once past the trachea, the air divides into the left and right bronchi, which supply the left and right lungs, each divided into five sections called lobes. The bronchi then divide into smaller bronchioles, at the end of which are air sacs called the alveoli. This makes up the lower respiratory tract [11] (◘ Fig. 51.1).

The diaphragm is the central muscle that is used for breathing. The intercostal muscles, located between the ribs, and the abdominal muscles are helpful for breathing out when the breath becomes labored, such as during exercise. The neck muscles and the muscles in the collarbone area help with breathing when the other muscles are compromised or impaired. In some neurological diseases, such as amyotrophic lateral sclerosis (ALS) [see ▶ Chap. 51, Newton], nerve damage from the brain to breathing muscles can result in impaired movement of these muscles and thus impaired breathing.

In certain cases, such as in lung cancer when a lobectomy, removal of part of the lung, is required, there is an expected decrease in short- and long-term pulmonary function and oxygenation. However, respiratory muscle strength may be preserved [13]. In a pneumonectomy, removal of the entire lung, dramatic changes in thoracic anatomy take place, such as elevation of the hemidiaphragm, hyperinflation of the remaining lung, and influx of fluid into the post-pneumonectomy space [14, 15].

51.2.2 Cellular Physiology: Membrane Structure Determines Function – Very Important Barrier

There are phagocytic macrophages on the cellular surface of the alveoli, Type I epithelial cells and Type II epithelial cells. Phagocytic macrophages destroy inhaled bacteria and serve

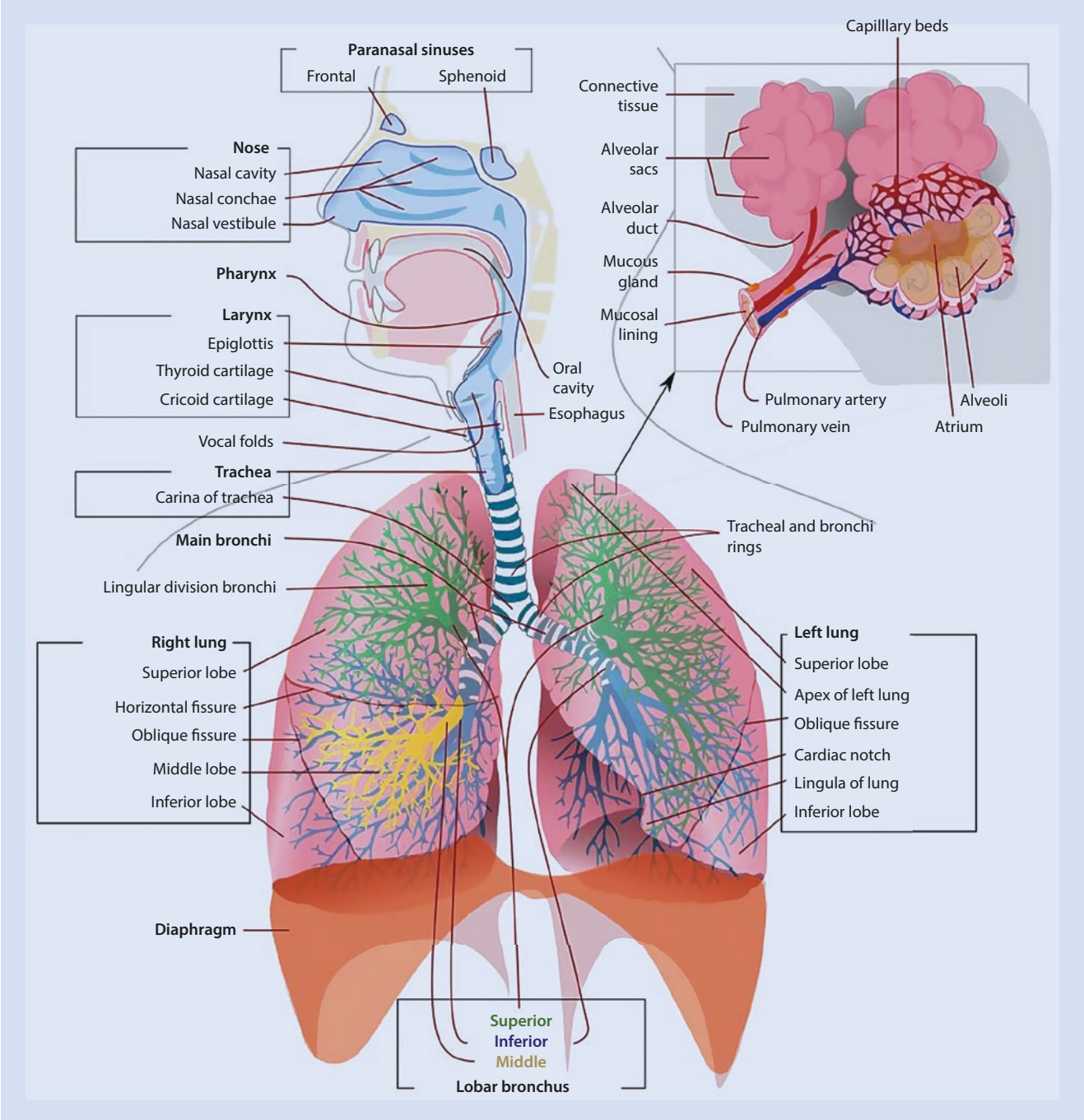


Fig. 51.1 Anatomy of the human respiratory system [12]. (Reprinted with permission from: ► https://en.wikipedia.org/wiki/Respiratory_system#/media/File:Respiratory_system_complete_en.svg)

an important role in suppressing or activating the immune response to antigens and pathogens, similar to dendritic cells discussed below. Macrophage function has been shown to be inhibited by cigarette smoke [16]. Alveolar macrophages also secrete enzymes, arachidonic acid metabolites, growth factors, immune response components, cytokines, and lymphocytes [17].

Type I cells are responsible for maintaining the structure of the alveolar wall, whereas Type II cells and Clara cells are responsible for the production of pulmonary surfactant (composed of 85–90% lipid and 10–15% protein as lecithin and myelin), which is essential for lung function. The surfactant reduces surface tension, facilitating easier stretching and collapsing of alveoli during respiration [18]. Diseases associated with inadequate surfactant production are acute/adult respiratory distress syndrome (ARDS) and infant respiratory distress syndrome (IRDS) [19]. IRDS is seen in premature babies born prior to 32 weeks of gestation due to immature development of pulmonary surfactant, which only begins to develop around the 20th week of gestation [18].

Dipalmitoylphosphatidylcholine, phosphatidylglycerol, and cholesterol compose the lipid portion of the surfactant, where apoproteins and proteins found in blood plasma compose the protein portion [18, 20]. The importance of cholesterol is minimized in today's medical community. Those with higher levels of cholesterol tend to have more in their fatty cell membranes which resist pathogenesis at a cellular level. Low cholesterol predicts a greater risk of dying from gastrointestinal, neoplastic, or respiratory diseases. It occupies 30–40% of our cell membranes, enhances the mechanical strength of the membrane, and reduces permeability [21]. It suppresses main-phase transition of the lipid bilayer [22].

Collagen, a fibrous protein, along with elastin and proteoglycans, is a fundamental component of the connective tissue that composes the lungs, and collagen is present in the blood vessels, bronchi, and alveolar interstitium [23]. Connective tissue in the lung is key for the passive diffusion of oxygen and carbon dioxide that characterizes alveolar-capillary gas [18]. Collagen homeostasis is vital to maintaining respiratory function, where collagen production and degradation are balanced. Dysregulated collagen homeostasis that favors collagen production over degradation can lead to pulmonary fibrosis and compromised lung function [24]. Some key nutrients to consider for collagen synthesis and cross-linking to maintain connective tissue integrity are vitamin C, vitamin B6, iron, copper, zinc [25], riboflavin, thiamin, and pantothenic acid [11].

The airways of the respiratory system (with the exception of parts of the nose and mouth) have cilia, special hairs coated with mucus that trap pathogens and other particles that enter with the air that is inhaled. Cilia are responsible for triggering this mucus upward toward the pharynx where these particles or bacteria can be coughed out or swallowed. Mucus present in the lungs can also trap inhaled particles such as viruses, bacteria, and smoke particulates [11, 12].

Along the lining of the respiratory tract, there are several types of cells that are involved in immune response, such as secretory cells (i.e., goblet cells and Clara cells) and mast cells. Ciliated epithelium and mucus secreted by glands present on airways, goblet cells, and the secretory products of Clara cells serve an important mechanism for lung protection. However, excessive goblet cells or hypertrophy of mucous glands may result in increased viscosity of mucus seen in pathologies like bronchitis [16]. Ciliary function is also impaired by cigarette smoke [16].

Dendritic cells are also found in the airway lining from the trachea to the alveoli. Immature dendritic cells phagocytize bacteria or other antigens, where they then mature and travel to lymphoid tissues to communicate with the immune system. This delivery of antigens can promote tolerance of the antigen by releasing anti-inflammatory cytokines. Conversely, this delivery can also trigger the opposite response if the antigen is recognized as a pathogen, where T lymphocytes are activated and inflammatory cytokines are released [16].

One potential cause of infections in the upper respiratory tract or bronchial tubes, such as bronchitis, or deep in the lungs, such as pneumonia, is when cilia become damaged and do not trap inhaled germs and particles as effectively. In diseases such as cystic fibrosis, thick mucus secretions can accumulate in the airways and lungs, making it hard to clear and thus increasing risk for infection. In asthma, specific inhaled particles can trigger a reaction causing the airways to narrow, restricting breathing [12].

Surface enzymes and factors can also be found in the lining of the airways that compose the majority of the innate immune system of the respiratory tract. These include:

- Lysozymes: found in leukocytes with bactericidal properties
- Lactoferrin: a bacteriostatic agent (inhibits bacterial reproduction) synthesized by lymphocytes and glandular mucosal cells
- Alpha-1 antitrypsin: an antiprotease to protect lung tissue from excessive enzymatic activity
- Interferon: an antiviral substance that may be produced by lymphocytes and macrophages
- Complement: participates as a cofactor in antigen-antibody reactions [16]

51.2.3 Gas Exchange

Gas exchange takes place in the alveoli so oxygen can enter the body to support metabolic function and the carbon dioxide product from these functions can be removed. This is accomplished through millions of capillaries in the alveoli. These capillaries in the alveoli then connect to arteries and veins that move blood throughout the body. The pulmonary artery supplies carbon dioxide-rich blood to these capillaries within the alveoli to remove carbon dioxide, and the oxygen-rich blood then gets delivered to the heart through the pulmonary vein. The lungs also serve the vital function of maintaining acid-base balance through changes in minute ventilation. These changes affect the pH of the blood by either retaining or excreting carbon dioxide [11].

Poor physiologic management of CO_2 and bicarbonate can lead to the conditions of respiratory acidosis and respiratory alkalosis. Respiratory acidosis is characterized by higher blood concentrations of CO_2 and H^+, caused by hypoventilation or decreased rate of breathing. Hypoventilation can have acute or chronic etiologies, resulting from COPD, interstitial lung diseases, respiratory muscle fatigue (i.e., extended asthma attack), or mechanical abnormalities (i.e., deformities).

Respiratory alkalosis is characterized by lower blood concentrations of CO_2 and H^+ due to hyperventilation, or increased rate of breathing. Possible causes of hyperventilation can also be chronic or acute, such as pneumonia and fever, increased stress and anxiety, liver disease, stroke or meningitis, pregnancy, overuse of aspirin and/or caffeine, excessive mechanical ventilation, or increases in altitude [18].

A pulse oximeter tool can be used to measure the percentage of oxygenated hemoglobin in an individual's blood to determine their overall respiratory status. Typically, oxygen

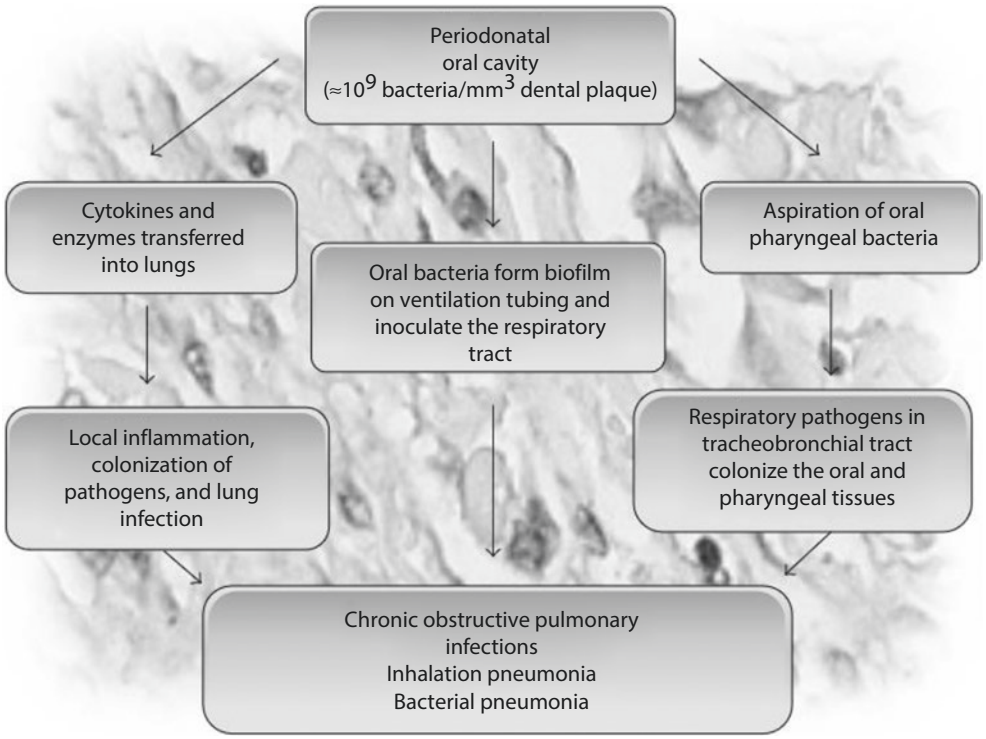


Fig. 51.2 Possible role of periodontal infection in respiratory disease. (Reprinted from Nagpal et al. [27]. With permission from Creative Commons)

saturations of 92% or less are indicative of central hypoxia [26]. Pulse oximetry is especially useful for assessing individuals with asthma and COPD [26].

51.2.4 Oral Health Connection

Oral health must also be considered as a contributing factor to respiratory health [27]. For example, in patients affected with periodontal disease, 1 mm of dental plaque could contain around 10^9 of bacteria. One potential mechanism of this connection is aspiration of bacteria from the oropharynx into the upper or lower respiratory tracts, leading to their adherence to the alveolar and bronchial lining, potentially colonizing respiratory ducts and causing respiratory infections. In addition, cytokines and enzymes associated with inflammation of periodontal tissues can be transferred into the lungs, potentially triggering or exacerbating lung infections [27] (Fig. 51.2).

A systematic review done in 2013 examined oral health in the elderly and its association with risk of aspiration pneumonia. This review suggested that maintaining oral health, such as brushing after each meal, cleaning dentures once per day, and professional oral healthcare, potentially reduced the amount of potential respiratory pathogens that resulted in lower incidence of aspiration pneumonia [28]. Several other systematic reviews have found that adequate oral hygiene plays an important role in preventing pneumonia, particularly in clinical settings where there is increased risk for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), as well as in older populations [29]. In addition, associations have been made between COPD and the risk of periodontitis, although systematic reviews have established that these associations are preliminary and further studies are needed [29].

Another important consideration in respiratory health is orofacial development and structure. Anatomical obstructions at the level of the nose and pharynx, such as those caused by allergic rhinitis and hypertrophy of the tonsils, pose an increased risk for obstructive sleep apnea syndrome and respiratory infections due to lack of airflow through the upper respiratory system [30].

51.2.5 Microbiome

It has been established that the lung has a microbiome of its own that may have a large impact on health and disease [31]. The fungal microbiome, or mycobiome, may also have a significant impact on respiratory health, although more research is needed to determine definitive associations [31]. Dysbiosis may occur in the lungs with a bacterial infection. A few specific bacterial strains have been studied, and one, in particular, *Pseudomonas aeruginosa*, seems to grow in inflammatory conditions. It then seems to encode inflammatory components causing further inflammation. Anti-inflammatory nutrients could help stop the cycle, and vitamin D use has some research supporting this. Recurrent bacterial respiratory infections may damage lungs and lead to worse outcomes in future lung disease [32].

An increased interest in research of the relationship of the airway and gut microbiome is indicating potentially positive results regarding the use of probiotics in pediatric populations that may aid in asthma prevention and intervention

[33, 34]. The gut-lung axis has also been established, where the microbiomes of the lung and gut have been immunologically linked and are thought to have an impact on respiratory disease [35, 36].

51.2.6 Autophagy

The autophagy mechanism within our microenvironment provides a constant "cleanup" system to recycle cell debris from microscopic biowaste generated by dynamic cellular biochemistry [37]. Enzymes such as neutrophil elastase function like garbage disposals recycling waste molecules. Alpha-1 antitrypsin is a thermostat-like control factor that signals the proteolytic enzymes to stop and protect healthy tissue from being affected. Antiproteases in the lung, such as alpha-1 antitrypsin, are required to prevent the overactivity of neutrophil elastase to prevent the degradation of healthy lung tissue. Those with the genetic mutations of A1AT deficiency are at disadvantage, and subsequent lung tissue damage can occur promoting lung diseases like COPD, asthma, bronchitis, and emphysema.

Key components of lung structure are elastin and collagen, which provide support for the bronchioles and clusters of alveoli (acini). The key enzyme present in these cells is neutrophil elastase, which is responsible for the destruction of respiratory bacteria. Protease and antiprotease imbalance in the lung resulting in emphysema can be caused by alpha-1 antitrypsin deficiency and nicotine in cigarette smoke or polluted inhalant exposure [18]. IFMNT approaches to the A1AT-deficient patient assess for nutrient insufficiencies for some of the important connective tissue, collagen, and elastin system key nutrients: vitamin C, vitamin D, biotin, balanced fatty acids, and gut microbiome. When insufficiencies or deficiencies are identified, appropriate food and dietary supplementation interventions can be recommended. It should be noted that if an individual is identified with A1AT deficiency genotype, the status of liver health should also be assessed, as A1AT pathophysiology can express in liver cirrhosis.

More recent studies of respiratory disease [38] have revealed the relationship with bacterial or viral infections exacerbating the individual's genotype eliciting expression of the associated diseases. One of the most recognized inherited conditions of altered autophagy mechanisms is alpha-1 antitrypsin deficiency, with 80–100 genetic variants affecting severity of lung expression.

Low levels of circulating A1AT allow potentially harmful enzymes like neutrophil elastase to remain in the lungs unchecked. Low levels of A1AT, and the consequent proliferation of neutrophil elastase, leave lung tissue vulnerable to destruction, resulting in a decline in lung function.

51.2.7 Category of Respiratory Diseases

There are several categories of lung disease and many diseases within those categories (Table 51.1).

51.3 Micronutrients Important for Lung Function: Food-Based and Supplemental

Some micronutrients and phytonutrients have important antioxidant and methyl-donating properties important for the lungs and therefore have great role in a nutritional approach to lung health.

51.3.1 Iron

Iron's interaction with the lungs is essential. It carries oxygen from the lungs to the peripheral parts of the body, as well as carbon dioxide back to the lungs to be exhaled. However, too little or too much iron can pose a problem for the lungs. Before iron administration, it is important to rule out hemochromatosis, or iron overload, for an individual.

Iron-deficiency anemia often presents in many chronic diseases including those of the lung, such as COPD, lung cancer, and IPF [57]. Increased mortality, decreased quality of life, increased hospital admissions, and cost of treatment have been reported for those with chronic disease and low iron [58]. Anemia of chronic disease (ACD) is usually at the root of this. ACD is often the result of inflammation. Inflammatory proteins, including IL-6, stimulate the production of hepcidin in the liver, which inhibits absorption and increases storage of iron resulting in a functional iron deficiency. Typical iron markers, such as transferrin saturation, total iron binding capacity (TIBC), and ferritin, are also affected by inflammation and are less useful markers in chronic disease. Soluble transferrin receptor (sTFR) seems to be a lesser known marker that is less affected by inflammation [59].

Because of the difficulty with iron absorption, intravenous iron is often used to replete deficiencies. As iron is a pro-oxidant, researchers studied any negative repercussions. There does not seem to be any increased oxidative stress with intravenous iron, but glutathione, the body's endogenous super antioxidant, does seem to decrease, likely in response to the pro-oxidative activity of iron. In a recent study, administration with vitamin E was seen to eliminate these negative effects [57].

Excessive iron can also be problematic for lung health for those with the genetic mutation for hemochromatosis (HFE). Disorders of iron overload are increasingly being recognized as risk factors for most of the chronic diseases like cardiovascular, Alzheimer's, and cancer [60]. High iron can catalyze the formation of highly reactive hydroxyl radicals, oxidative stress, and programmed cell death. In the instance of lung cancer and other cancers affecting the lungs, tumors sequester iron for their own growth, usually leaving the patient with iron-deficiency anemia. In fact, 90% of cancer patients undergoing chemotherapy are iron deficient. Inflammation also plays a role in iron homeostasis. The pro-inflammatory cytokines cascade down to affect the proteins that regulate

Table 51.1 Table of lung diseases

Category	Disease	Definition	Source
Obstructive lung disease	Asthma	Chronic inflammatory lung disease, triggered by either an IGE allergic reaction or nonallergic factors and results in reversible airway obstruction and inflammation of the airway	[11]
	Chronic obstructive pulmonary disease (COPD)	Disease that restricts airflow through either inflammation of the lining of the bronchial tubes or destruction of alveoli Increased risk of emphysema if genetic variant of alpha-1 antitrypsin deficiency and smoking or exposed to high levels of air pollution	[11]
	Bronchiectasis	A disorder of the airways that leads to airway dilation and destruction, chronic sputum production, and a tendency toward recurrent infection	[39]
	Bronchiolitis	Airway injury that can be caused by infections, irritants, toxic fumes, drug exposures, pneumonitis (typically viral), organ transplants, connective tissue disorders, vasculitis, or other insults	[40]
	Dyspnea	Shortness of breath or difficulty breathing	[11]
	Emphysema	Thinning and destruction of the alveoli, resulting in decreased oxygen transfer into the bloodstream and shortness of breath. Increased risk of emphysema if genetic variant of alpha-1 antitrypsin deficiency and smoking or exposed to high levels of air pollution	[11]
	Alpha-1 antitrypsin deficiency	A deficiency of A1AT, a protein produced in the liver that protects the lungs from excessive neutrophil elastase, an autophagic enzyme. A1AT may also accumulate in liver and cause liver disease	[55]
	Obstructive sleep apnea syndrome (OSAS)	A sleep disorder characterized by repetitive upper airway obstructions despite respiratory effort causing sleep fragmentation caused by repetitive arousals	[56]
Restrictive pathophysiology-parenchymal disease	Idiopathic pulmonary fibrosis (IPF)	Disease in which tissue deep in the lungs becomes thick and stiff, or scarred, over time. The formation of scar tissue is called fibrosis	[41]
	Asbestosis	Fibrotic lung disease resulting from extensive inhalation of asbestos fibers	[42]
	Desquamative interstitial pneumonitis (DIP)	Form of idiopathic interstitial pneumonia that is more common in cigarette smokers but may be seen in nonsmokers, in patients with underlying connective tissue diseases or those exposed to inorganic dust/particles	[43]
	Sarcoidosis	Immune-mediated systemic disorder that is characterized by granuloma formation of the lung parenchyma and the skin	[44]
Restrictive pathophysiology-neuromuscular weakness	Amyotrophic lateral sclerosis (ALS)	Progressive neurological disease that affects the motor neurons of the nervous system	[11]
	Guillain-Barre syndrome	Progressive immune system attack on the peripheral nerves, usually following an infectious illness such as a respiratory infection. May eventually cause respiratory distress syndrome	[11]
Restrictive pathophysiology-chest wall/pleural disease	Kyphoscoliosis	Kyphoscoliosis: a deformity of the thoracic cage that results in restriction of the lungs and impairs pulmonary function	[45]
	Ankylosing spondylitis	Autoimmune inflammatory disorder characterized by inflammation of the axial skeleton and peripheral joints	[46]
	Chronic pleural effusions	Chronic accumulation of fluid between the two outer membranes surrounding the lungs	[11]
Pulmonary vascular disease	Pulmonary embolism	Blood clot that typically originates from thrombi in the deep venous system of the legs and travels to the lungs	[47]
	Pulmonary arterial hypertension (PAH)	Progressive disorder of primary pulmonary arterial vasculopathy characterized by a mean pulmonary arterial pressure >25 mm Hg at rest (>30 mmHg during exercise)	[48]

Table 51.1 (continued)

Category	Disease	Definition	Source
Malignancy	Adenocarcinoma	About 40% of lung cancers are adenocarcinomas. These cancers start in early versions of the cells that would normally secrete substances such as mucus	[49]
	Squamous cell (epidermoid) carcinoma	About 25–30% of all lung cancers. These start in early versions of squamous cells, which are flat cells that line the inside of the airways in the lungs. Often linked to a history of smoking and tend to be found in the central part of the lungs, near the bronchus	[50]
	Large cell (undifferentiated) carcinoma	About 10–15% of lung cancers. It can appear in any part of the lung and tends to grow and spread quickly. A subtype of large cell carcinoma, known as large cell neuroendocrine carcinoma, is a fast-growing cancer that is very similar to small-cell lung cancer	[51]
	Small-cell lung cancer (SCLC)	About 10–15% of lung cancers are SCLC. Typically start in the cells lining the bronchi and parts of the lung such as the bronchioles or alveoli	[52]
Infectious diseases	Pneumonia	Inflammation of the lungs, usually caused by bacteria, viruses, or fungi	[11]
	Bronchitis	Inflammation and eventual scarring of the lining of the bronchial tubes accompanied by restricted airflow, excessive mucus production, and persistent cough	[11]
	Tracheitis	Bacterial infection that can develop in the trachea	[53]
	Infant respiratory distress syndrome	Also known as hyaline membrane disease (HMD) or respiratory distress syndrome, this condition affects the alveolar ducts and terminal bronchioles in which the hyaline membrane is a fibrinous material composed of blood and cellular debris, caused by the absence of proper surfactant production due to an immature or poorly developed lung	[54]
	Upper respiratory infection (URI)	Acute infections involving the nose, sinuses, pharynx, larynx, trachea, and bronchi, referred to as the common cold	[11]
	Bronchopulmonary dysplasia (BPD)	Chronic lung disorder which may affect infants who have been exposed to high levels of oxygen therapy and ventilator support	[11]
Other	Cystic fibrosis	Disease characterized by abnormally thick mucus secretions from the epithelial surfaces of many organ systems, including the respiratory tract, the gastrointestinal tract, the liver, the genitourinary system, and the sweat glands	[11]
	Acute lung injury	Clinical and radiographic changes in lung function associated with critical illness (acute respiratory distress syndrome is most severe form)	[11]

iron homeostasis [61]. Iron can also impair cytokine secretion, which can leave those with an iron overload much more susceptible to infection, increasing the morbidity and mortality of infectious diseases, including those of the lung [59].

Oxidative stress may contribute to injury of lung tissue, causing further fibrosing in those lung diseases with that characteristic. Allele variants in the genes associated with iron homeostasis (C282Y, S65C, and H63D HFE) are significantly more common in those with idiopathic pulmonary fibrosis (IPF) than those without IPF (40.4% IPF patients vs 22.4% non-IPF) and are associated with higher iron-dependent oxygen radical generation [62].

Iron is implicated in lung pathology. Monitoring iron status and using supplements or diet to aid the body in increasing or decreasing the iron load are imperative for the nutritionist working with lung disease patients. Choosing a good non-constipating form of iron is important, such as iron glycinate.

51.3.2 The B Vitamins

The B vitamins are also important to monitor for lung health. Vitamin B6 and its bioactive form, P-5-P, are typically known to protect DNA from mutation or damage [63]. However, there is mixed evidence on its role for lung cancer. Some research has shown that it is helpful for lung cancer patients as it is important for apoptosis when using chemotherapy, because it sensitizes cancer cells to apoptosis [63]. However, research in 2017 showed that adult male smokers taking greater than 20 mg vitamin B6/day for long periods tended to have a greater risk for lung cancer. Many variables, including genetic variants, form of B6, and the status of other co-nutrients may be at play [64]. Other studies showed that men in the top quintile of vitamin B6 serum concentration had about one half the risk of lung cancer, and specifically, vitamin B6 and folate were inversely associated with risk of lung cancer [65].

Because of disagreement in research, particularly with smokers or former smokers, using food first for B vitamins may be a prudent way forward. Good sources of vitamin B6 are fish, chickpeas, chicken, potatoes, turkey, bananas, ground beef, and winter squash.

Pyridoxal kinase (PDXK) is the enzyme that converts pyridoxine and other vitamin B6 precursors to its bioactive form of P-5-P. Dysfunction of this enzyme is a good prognostic for lung cancer and other lung diseases. *MTHFR 1298AA* genotype is associated with a higher risk of lung cancer in women but not in men. The *MTHFR 677TT* genotype was associated with a significantly decreased risk of lung cancer in women but not in men. In contrast, the *MTHFR C677T* and *A1298C* polymorphisms interacted with smoking status in men but not in women [66]. Methylation gene testing is imperative to understand the patient's status.

Some studies suggest that a higher intake of riboflavin (vitamin B2) may protect against lung cancer in smokers [67]. Folate deficiency was also associated with asthma and attacks of shortness of breath [8].

51.3.3 Acid/Alkaline

Correcting acidosis may preserve muscle mass in diseases where wasting is an issue, such as COPD or IPF. For those receiving chemotherapy, a higher pH (more alkaline status) is helpful for muscle mass protection. High alkaline diets contain more fruits and vegetables, and those supply more magnesium, which is needed to activate vitamin D. As discussed below, vitamin D is extremely helpful for lung health.

Sleep quality involves maintaining adequate 7–8 hours with good sleep hygiene (see ▶ Chap. 34). Good REM cycling, feeling refreshed upon awakening, and other characteristics of good sleep play significant roles in maintaining healthy acid-base balance.

Dietary intake of the minerals magnesium, potassium, sodium, chloride, and calcium promotes the balance of acid-base microenvironment. After exposure and tissue retention of toxic minerals and metals, these substances can contribute to perturbations in the acid-base metabolic milieu.

Some conditions reduce oxygen intake and should be addressed. One of the most common oxygen-impairing conditions is sleep apnea, altered sleep with random halting of breathing during sleep that is often accompanied by snoring. Other limiting conditions are respiratory diseases like COPD, A1AT deficiency, asthma, cystic fibrosis, etc.

51.3.4 Vitamin A

Vitamin A is an important antioxidant and a general umbrella term for several fat-soluble retinoids, including retinol, retinal, and retinyl esters. There are also other substances that are provitamin A carotenoids or precursors to vitamin A. Two forms are found in foods, the preformed forms of retinol or retinyl esters, which are found in dairy, fish, caviar, and meats (especially liver), and the provitamin A carotenoids, including the most important and common provitamin A carotenoid, beta-carotene, as well as others including alpha-carotenes and cryptoxanthin, which are found in plant-based foods. Our bodies must convert these two forms within our cells to retinal and retinoic acid, the active forms of vitamin A in the body. New studies of the gene, β-carotene 15,15′-monooxygenase (BCMO1), which is responsible for the enzymatic conversion of β-carotene to vitamin A, are revealing that individuals with heterozygous or homozygous BCMO1 SNPs have 30–60% less efficient conversion than those with normal gene function (see ▶ Chap. 17) [68]. Other carotenoids found in food, such as lycopene, lutein, and zeaxanthin, are not converted to vitamin A but have other antioxidant benefits in the body. Most vitamin A is stored in the liver as retinyl esters, and deficiency is not visible until these stores are nearly depleted.

Vitamin A's role as an antioxidant helps the lungs in several ways, including maintaining alveolar epithelium cells and preventing development of respiratory tract infections. Most of the developed world's population does not have a risk of deficiency due to sufficient vitamin A intake. However, most people with cystic fibrosis have pancreatic insufficiency, which reduces the ability to absorb fat and therefore the fat-soluble vitamins A, D, E, and K. According to a study in 2002, between 15% and 40% of people with cystic fibrosis had a vitamin D deficiency, also a fat-soluble vitamin. With the addition of pancreatic replacement treatments, better nutrition, and vitamin A supplementation, deficiency has become rare. However, improved vitamin A status has not been thoroughly studied as of 2018, and therefore it is largely unknown if an improved vitamin A status has any effect on cystic fibrosis [69].

Vitamin A deficiency has been shown to be associated with emphysema in rats. Smoke exposure significantly decreases vitamin A concentration in lung tissue, significantly more in those with COPD [70].

Retinoic acid seems to play a beneficial role in the treatment of IPF. A review showed that in all studies, retinoic acid decreased fibrosing, the formation of collagen, and reduced the expression of alpha-smooth muscle actin (alpha-SMA), all hallmarks of IPF [71].

It is important to not take large doses of vitamin A if one is in a malnourished state as it can cause toxicity and should be monitored with blood testing of vitamin A retinol. Nourish the body with all foods and all nutrients slowly.

The non-provitamin A carotenoids have also shown some benefit. Lycopene, found in high amounts in guavas, watermelon, tomatoes, papaya, grapefruit, sweet red peppers, asparagus, purple cabbage, mangos, and carrots, slowed forced expiratory volume (FEV) decline in former smokers [70].

51.3.5 Vitamin D

Vitamin D's importance with lung health cannot be understated. Vitamin D deficiency, or even insufficiency, is linked to

accelerated decline in lung function, increased inflammation, and reduced immunity in chronic lung diseases. Vitamin D has a role in the regulation of inflammation, immunity, cellular proliferation, senescence, differentiation, and apoptosis. Sufficient vitamin D levels are correlated with better asthma control, better immune response related to respiratory infections, and reduced severity of exacerbations with COPD and asthma when exposed to inflammation-causing pathogenic activity [72].

Vitamin D is obtained through sunlight on the skin (without sunscreen) and very few dietary sources. Therefore, supplementation is generally recommended. Higher vitamin D levels are shown to be protective in many lung disease states. Sufficient levels improve treatment response with medications and reduce asthma severity [68]. With infectious diseases of the lung, higher vitamin D concentrations are shown to have a protective action [6]. Vitamin D has a protective effect on lungs of smokers, and higher levels of vitamin D inhibit the pro-fibrotic phenotype of lung fibroblasts and epithelial cells. Current data suggest an inverse association between serum vitamin D and lung cancer risk, and vitamin D deficiency at 16–20 weeks' gestation is associated with impaired lung function and asthma at 6 years of age [73].

Lower levels of vitamin D are associated with an increased risk for respiratory infections, cystic fibrosis, chronic obstructive pulmonary disease, and interstitial lung disease [74].

51.3.6 Vitamin C

Vitamin C is an important antioxidant that helps decrease oxidative damage in the body, including in lung tissue. It is also essential for lipid metabolism. It is present in the airway surface liquid and creates an interface between the epithelial cells and the external environment. Vitamin C is a cofactor in collagen synthesis, which can aid in repair of bronchial and alveolar tissue when damaged. It also provides beneficial control of lipid peroxidation of cellular membranes, including those surrounding as well as those within intracellular organelles. Vitamin C has some of the best lung protective capabilities, according to current research.

Vitamin C may also diminish oxidative attack on nonlipid nuclear material and is an antioxidant component of plasma and extracellular fluids surrounding the lungs. It is an antioxidant that not only fights oxidative stress but also reduces oxidized vitamin E and glutathione, allowing them to become active as antioxidants again. Vitamin C is anti-inflammatory and is helpful in all inflammatory states of the lung, even allergies.

There are many ways in which vitamin C, along with its antioxidant partners, glutathione, vitamin E, vitamin A, and plant-based phytonutrients, affects lung health. It is well established that increased levels of vitamin C in the diet improve health outcomes for smokers and their offspring, as smoking depletes vitamin C [75, 76]. Vitamin C is also helpful in fighting infectious diseases such as respiratory infections and pneumonia, COPD regardless of smoking status, asthma, and lung cancer [77]. Specifically, in certain lung cancers, vitamin C, along with other nutrients such as lysine, proline, epigallocatechin gallate, and zinc, can inhibit the proliferation of certain carcinoma lines and induce apoptosis, as well as inhibit lung cancer metastasis [78]. Even in lung transplants, vitamin C is helpful against oxidative stress by reducing glutathione and lowering lipid peroxidation, along with vitamins A and E [79, 80].

The literature suggests these benefits can be achieved at 500–3000 mg/day. Check iron status before administering vitamin C supplementation as vitamin C doubles iron absorption from foods.

51.3.7 Vitamin E

Vitamin E's primary role is as an antioxidant, breaking free radical chain damage and preventing peroxidation of lipid molecules. This vitamin also is promising with regard to beneficial effects on lung function preservation. Oxidative stress and inflammation are key features in many lung diseases; therefore nutrients with antioxidant capacity can be useful. A few studies suggest that alpha-tocopherol found in sunflower and olive oils has a beneficial effect on FEV (forced expiratory volume), whereas gamma-tocopherol found in canola, soybean, and corn oils has a negative effect on FEV [81]. However, from these authors' perspective, this is likely due to the source and type of the oils, which can be inflammatory, rather than the form of vitamin E. For example, a recent study showed that gamma-tocopherol was protective in allergic asthma [82]. In addition, sufficient levels of vitamin E, in the alpha-tocopherol form, were found to reduce susceptibility of the elderly to acquiring pneumonia. Some of the positive effects of vitamin E are synergistic with vitamin C [83].

51.3.8 Phytonutrients

Phytonutrients have been found to have two effects with respect to lung disease: one is a symptom-improving pattern, and the other is a rate-reducing pattern [84]. Idiopathic pulmonary fibrosis (IPF) is largely characterized by reduced antioxidant and increased inflammatory action. Recent literature is showing the ability of certain flavonoids, in particular quercetin, to reduce inflammation and act as a strong antioxidant countering the pro-oxidant environment of IPF. Quercetin is recognized as the most potent ROS scavenger. Taken together with glutathione, the impact is even greater, and it seems to help improve the antioxidant and inflammatory status more for those with IPF than non-diseased controls [85].

Curcumin has been shown to slow or limit fibrosing in murine studies related to lung, liver, or kidney fibrosing [86–89]. It has also been shown to attenuate metastatic melanoma in the lungs when delivered in a nanoparticle [90]. The potential for curcumin is interesting and hopeful.

Fisetin and fenugreek have also been studied as useful phytonutrients that help combat inflammation in lungs

[91, 92]. Fisetin is found in apples, strawberries, persimmons, cucumbers, and onions, among many other fruits and vegetables. Fenugreek is a plant used frequently in South and Central Asian cooking, where both the seeds and leaves are used. There are now supplements available for both of these phytonutrients. This is a reminder to eat a primarily plant-based diet when combating inflammation and to broaden our palates to include healthy foods and ingredients from other cultures than our own.

Lastly, the powerful antioxidant cannabidiol (CBD), from the cannabis and closely related hemp plants, is a powerful shield against oxidative stress, prevalent in lung disease [93].

51.3.9 Minerals

The research is not robust regarding lung function and minerals, and most has been done with regard to cystic fibrosis where bone density is associated with general nutritional status, including minerals. There have also been many studies trying to determine a correlation between mineral status and COPD, where, again, the research shows that mineral status is not predictive but overall nutrient status may fall if not monitored. In contrast, one study in Japan showed an inverse association between dietary calcium and the risk for COPD [94]. In an NIH-AARP Diet and Health Study, magnesium, iron, selenium, zinc, and copper intakes, both dietary and supplemental, were studied with respect to lung cancer. Mineral *supplementation* did not affect lung cancer risk, yet *dietary* intake of calcium, along with vitamin D, and iron reduced the risk, and dietary intake of magnesium increased risk [95]. Boron has been shown to be protective against lung cancer, along with other nutrients, at levels of 3 mg/day [96].

There is some research showing that selenium is helpful, particularly for smokers, for improved FEV. Higher magnesium status is correlated to better FEV but is not yet seen as an association. This may be due to magnesium's role as the vitamin D activator. There have been a few studies showing increased copper levels are related to decreased FEV. Some recent research has also shown that dietary zinc and iron are associated with reduced lung cancer, but the same was not seen with calcium, copper, magnesium, or selenium [97]. Low mineral bone density is prevalent at a higher rate among cystic fibrosis patients, and therefore supplementation with vitamin D, vitamin K2, magnesium, calcium, and the trace minerals can be helpful [98].

51.3.10 Alpha Lipoic Acid

Alpha-lipoic acid (ALA) is a powerful antioxidant endogenously produced in the human body from foods such as yeast, organ meats, spinach, broccoli, and potatoes and is both water- and fat-soluble. ALA, along with N-acetyl cysteine (NAC), glycine, and vitamin C, is an important precursor to glutathione, which is a powerful endogenous antioxidant and the primary antioxidant in the lungs. ALA has been shown to be anti-inflammatory in lung tissue in those with acute lung injury, and the proposed action is via inhibition of the NF-kappaB signaling pathway [99].

ALA has also been shown to downregulate some cancer-promoting actions prevalent in lung cancer, likely by this same pathway [100]. It also may alleviate nicotine-induced lung oxidative stress [101].

51.3.11 NAC

N-acetyl cysteine (NAC), another precursor to glutathione, is a powerful antioxidant on its own as well. In relation to the lungs, NAC helps the clearance of mucus in the lungs by pulmonary cilia. This has been shown to be effective at 400–600 mg/day in divided doses [102]. There is significant research on NAC and lung health, showing improvement with nearly all lung issues, including nearly 40 studies showing improvement for bronchitis [103], infectious diseases by reducing the bacterial count [104], smokers, and people with asthma and COPD, through both its antioxidant effects and by reducing the viscosity of sputum and mucus. At an oral dose of 1800 mg/day, the mean glutathione concentration in lung tissue increased by 49% on one study [105]. There are additional studies showing improvement for those with COPD, asthma, cystic fibrosis, pulmonary fibrosis, and symptoms related to allergies or other infections. The dose that has been studied and has been shown to be most useful is 600 mg twice daily and more effective if nebulized [106, 107]. Both ALA and NAC supplementation should be accompanied by vitamin B6 and the complex of B vitamins to prevent an elevation in liver enzymes (Fig. 51.3).

51.3.12 Micronutrient Testing

There are several specialty labs that conduct micronutrient analysis and functional testing, such as Genova Diagnostics and SpectraCell. These tests can be useful for evaluating levels of individual nutrients as they function in the body, rather than just in serum, which is not an accurate indicator of tissue or functional status.

51.4 Macronutrients Important for Lung Function: Food-Based and Supplemental

51.4.1 Fats and Fatty Acids

Patients suffering from COPD, interstitial lung disease, and other diseases tend to have muscle and weight loss related to respiratory acidosis, and increasing weight and muscle mass helps with quality of life. Respiratory acidosis occurs with CO_2 buildup where the lungs are no longer able to effectively exchange O_2 and CO_2. Nutritional supplementation should attempt to reduce metabolic CO_2 production. Fat

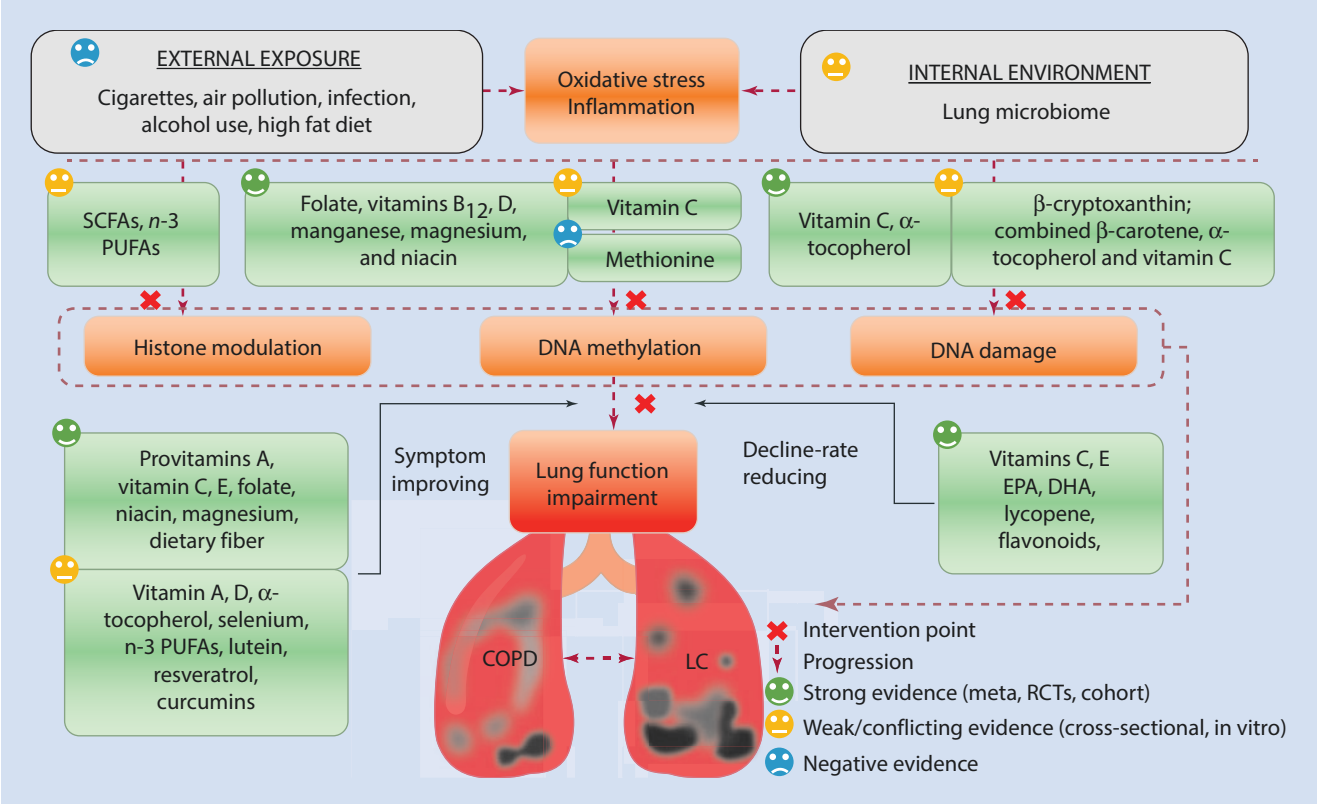


Fig. 51.3 Micronutrients and phytochemicals in the pathogenesis of chronic obstructive pulmonary disease (COPD) and lung cancer (LC). Summary of potential protective micronutrients and phytochemicals in the pathogenesis of chronic obstructive pulmonary disease (COPD) and lung cancer (LC). External and internal factors lead to oxidative stress and inflammation and thus initiate COPD and LC pathogenesis. Interventions against external exposure are not satisfying, while targeting the lung microbiome is promising. Recent studies have revealed strong evidence on protective nutrients in DNA methylation and damage, but studies on histone modulation are limited to animal or cell experiments. Epidemiological studies about micronutrients and phytochemicals in later key event lung function impairment are abundant and have identified different intervention patterns, including symptom improvement and a decline rate-reducing pattern. PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; SCFA, short-chain fatty acid; RCT, randomized controlled trials [108, 109]. (Reprinted from Zhai et al. [70]. with permission from Creative Commons License 4.0: ▶ https://creativecommons.org/licenses/by/4.0/)

metabolism produces less CO_2 than carbohydrate metabolism, so emphasizing a higher fat, lower carbohydrate diet can be helpful [110].

In general, a high intake of omega-6 fatty acids is associated with poorer forced expiratory volume (FEV) in patients with lung disease because of their pro-inflammatory nature. However, a complete fatty acid panel or a red blood cell membrane fatty acid test would reveal more details about the status of an individual's omega-6 pathway. Certain omega-6s and the work of their corresponding metabolizing enzymes such as elongase and delta-5 or delta-6-desaturase may allow healthful omega-6s (linoleic (LA), gamma-linolenic (GLA), lipoxins [111], prostaglandin 1 series metabolites) to flow down an anti-inflammatory pathway instead. Important cofactors for this pathway are vitamin B2, vitamin B3, vitamin B5, vitamin B6, biotin, vitamin C, zinc, and magnesium.

Lipid metabolism dysregulation is understood to be part of the pathogenesis of idiopathic pulmonary fibrosis. In IPF, free fatty acids play a role in the proliferation of fibroblasts. Certain fats, in particular palmitic acid, oleic acid, and linoleic acid, are elevated in the lungs of those with IPF, whereas stearic acid is low. Stearic acid is found in meat, poultry, fish, grain products, and milk and milk products. The palmitic, oleic, and linoleic acids enhance the TGF-ß1-induced expression of α-smooth muscle actin (SMA) and collagen type 1 in MRC-5 cells, which can lead to fibrosis. Stearic acid inhibits the levels of these fibrosing cells. Stearic acid also improves the thrombogenic and atherogenic risk factor profiles [112].

In one study on patients with COPD, omega-3 fatty acids were found to reduce inflammation in bacterial infections of the lungs without suppressing the ability to clear the bacteria. Those taking EPA, DHA, ALA, and GLA had improved exercise capacity and had lower risk of developing COPD [113].

Although results have been mixed over the years possibly due to doses used in studies, a recent 2018 prospective study showed that PUFAs (omega-3s) from fish help prevent lung cancer and can be part of treatment during lung cancer. In general, the strongest evidence for improved lung function and slowing decline is with the EPA and DHA forms of omega-3 fatty acids [114]. Because of toxicity issues in fish, increasing quality supplements vs fish intake may be more prudent.

51.4.2 Protein

Protein is essential for all lung conditions, and lack of it can result in poorer pulmonary function, decreased exercise capacity, and increased risk exacerbations. Since many lung diseases have oxidative stress as a characteristic, it can cause protein carbonylation which may negatively affect DNA expression and lipid membranes. Nutritional supplementation with added protein and healthy carbohydrates can increase body weight and muscle strength and improve quality of life. Those with COPD, interstitial lung diseases, and others that affect oxygen absorption and CO_2 exhalation have greater levels of hypoxia and sometimes respiratory acidosis, which exacerbates the loss of muscle through oxidative stress and inflammation.

Supplementation of free essential amino acids versus complete proteins has been shown to help prevent muscle wasting among COPD patients. Muscle-building exercise is often prescribed for those with COPD and interstitial lung diseases [115]. Supplemental L-carnitine at 2–6 g/day for 1–2 weeks increased the capacity of COPD patients to rehabilitate and build muscle and helped inspiratory muscle strength.

51.4.3 Carbohydrates

Carbohydrates should be monitored for sufficient but not excessive levels. More CO_2 is produced with the utilization of carbs versus fats for energy. Therefore, with gas exchange being an issue with most lung disorders, a slightly higher fat and lower carbohydrate diet may be indicated. It is worth mentioning fiber for a moment, as it is mostly delivered in carbohydrate-rich foods. There is evidence that consuming whole fruits and vegetables higher in dietary fiber is associated with reduced severity of asthma and COPD [116]. A diet that derives its carbohydrates from vegetables and fruits rather than from processed carbohydrates such as grains, breads, pasta, or added sugars will deliver fewer carbohydrate grams.

51.5 Endogenous Essential Respiratory Metabolites

51.5.1 Glutathione

Glutathione (GSH), a tripeptide composed of cysteine, glutamine, and glycine and produced from methionine, is in every cell in the body. It is the most powerful and abundant endogenous antioxidant in the airway epithelial lining and is responsible for detoxification of electrophilic compounds, the scavenging of free radicals, and modulation of cellular processes such as DNA synthesis and repair, differentiation, apoptosis, and immune function [117]. It is also a heavy metal chelator. It is more effective than some other antioxidants because it is intracellular and extracellular. In isolated type II alveolar epithelial cells, extracellular glutathione inhibits hyperoxia-induced injury, inhibits pro-inflammatory cytokine release, and promotes cell growth. It is obviously very important to maintaining lung function as this is the inflammatory process that begins lung cell or tissue damage, as mentioned above. The highest levels of glutathione concentrations in the body are in the lungs, liver, and brain. GSH depletion leads to activation of NF-kB (pro-inflammatory signaling) and increased pro-inflammatory gene transcription and cytokine release from histone deacetylase suppression in epithelial cells. Total and reduced GSH concentrations are much lower in people with ARDS, pulmonary fibrosis, and hypersensitivity pneumonitis than observed in healthy adults. Alterations in alveolar and lung GSH metabolism are widely recognized as a central feature of many inflammatory lung diseases such as idiopathic pulmonary fibrosis, acute respiratory distress syndrome, cystic fibrosis, and asthma [118].

We make glutathione in the body with cysteine and methionine, and it is difficult to take exogenously because digestion can destroy it. The precursors of cysteine (essential), glutamine, and glycine and cofactors (vitamin C, vitamin E, vitamins B1, B2, B6, and B12, folate (B9), minerals selenium, magnesium, and zinc, and alpha-lipoic acid, see below) are therefore recommended so that the body can produce it on its own. The two enzymes necessary to produce it, gamma-glutamylcysteine synthetase and glutathione synthetase, must also be functioning well. We also recycle glutathione if the precursors and cofactors are available. Cysteine is usually the most rate-limiting precursor, and many people supplement with N-acetylcysteine to provide the body with this nutrient. Although glutathione is produced in every cell of the body, the greatest production is in the liver, so focusing on liver health is important to maintain good glutathione production. Production declines with age and with lung disease, as well as other conditions.

There are very few foods containing glutathione; they are raw or very rare meat, especially liver, unpasteurized milk and other unpasteurized dairy products, and freshly picked fruits and vegetables, such as avocado and asparagus. However, as mentioned earlier, it may be destroyed during digestion. Glutathione contains sulfur molecules, which may be why foods high in sulfur help to boost its natural production in the body. These foods include:

- Cruciferous vegetables, such as broccoli, cauliflower, Brussels sprouts, and bok choy
- Allium vegetables, such as garlic and onions
- Eggs
- Nuts
- Legumes
- Lean protein, such as fish and chicken

Other foods and herbs that help to naturally boost glutathione levels include:

- Milk thistle (a liver-regenerating herb)
- Flaxseed
- Guso seaweed
- Whey

Glutathione is also negatively affected by insomnia. Getting enough rest on a regular basis can help increase levels.

Addressing a drop in glutathione for lung health involves maintaining good levels of the precursors and cofactors mentioned above. A good way to bring in the less abundant amino acid cysteine is to take N-acetylcysteine (NAC). Doses of 400–600 mg were more effective than placebo in reducing symptoms [117]. Supplemental selenium can also help with glutathione production. Glutathione supplementation has also become more effective. There are several forms, from capsules to topical liposomal, which have shown good absorption.

Inhaled GSH has good research for use in cystic fibrosis (CF), chronic otitis media with effusion (OME), HIV seropositive individuals, idiopathic pulmonary fibrosis (IPF), and chronic rhinitis. It is not recommended for asthma due to significant side effects, and additional evidence is needed to determine if use with emphysema is recommended although theoretically it should be useful. It is also not recommended to use inhaled GSH during cancer chemotherapy treatment as it may interfere with the medication's actions. The mechanism of action of inhaled glutathione is limited to the upper airways and lungs and does not seem to affect serum levels. Before considering inhaled GSH treatment, the patient should undergo urine sulfite sensitivity testing using a readily available special test strip called "EM-Quant 10013 Sulfite Test." If positive, inhaled GSH should not be used as bronchoconstriction may occur.

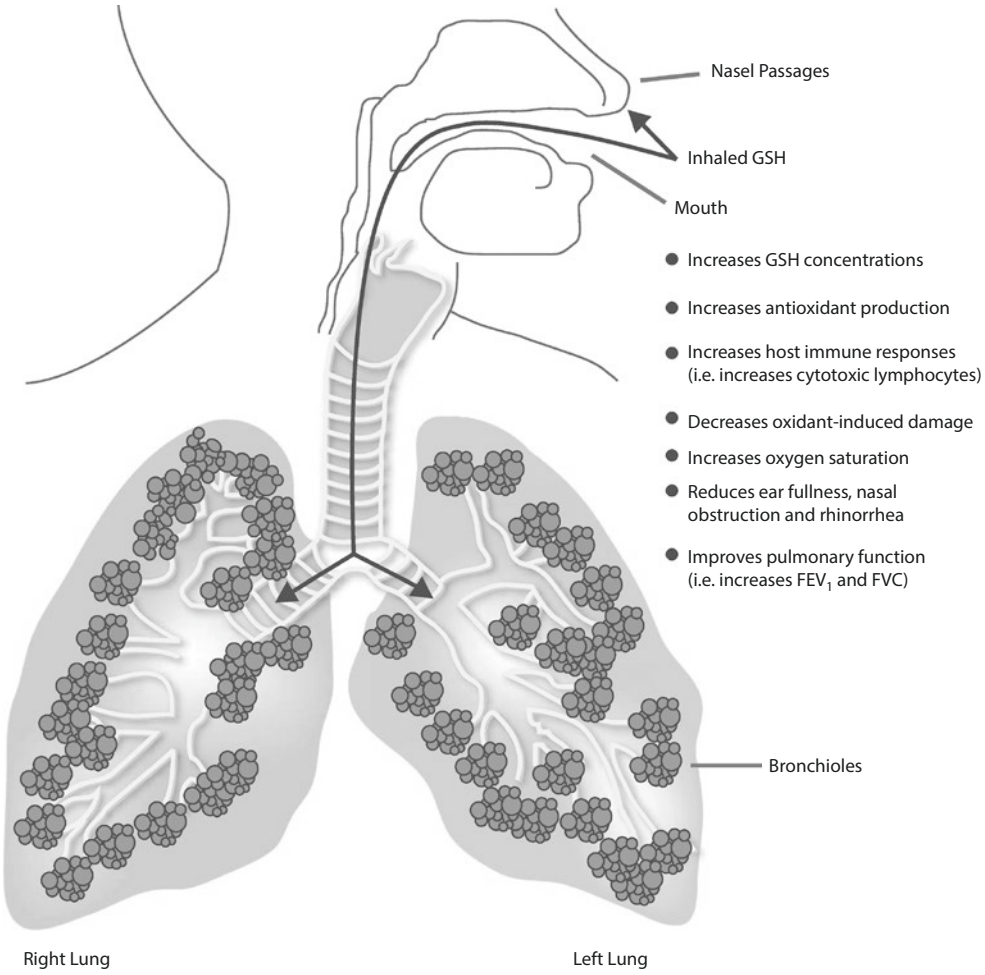
The recommended dose is 600–5000 mg per day, depending on response, and whether inhaled GSH is considered safe. Efficacy should be tested using a baseline pulmonary function test and a follow-up test after a prescribed time later [119] (◘ Fig. 51.4, ▶ Box 51.1). There are also serum tests for glutathione levels.

Box 51.1 Glutathione Cofactors

These cofactors are vitamin C; vitamin E; vitamins B1, B2, B6, and B12; folate (B9); minerals selenium, magnesium, and zinc; and alpha-lipoic acid.

What do the glutathione cofactors do that makes them so important?

- Direct cysteine toward glutathione production and increase cellular uptake of cysteine
- Help form the glutathione molecule out of the three precursor amino acids
- Help recycle glutathione from its oxidized GSSG form back to its reduced (active) GSH form
- Help maintain glutathione levels and keep the GSSG-GSH ratio balanced
- Recycle each other, improving overall antioxidant activity
- Stimulate the activity of the whole glutathione enzymatic system



◘ **Fig. 51.4** Inhaled GSH's mechanism of action. GSH, reduced glutathione; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity [119]. (Reprinted from Prousky [35]. With permission from Creative Commons License 3.0: ▶ https://creativecommons.org/licenses/by/3.0/)

Vitamin C – As an antioxidant, it assists glutathione in this function and has been shown scientifically to raise glutathione levels short term; it is recycled by glutathione from its oxidized state back to its active state, thus strengthening antioxidant defenses; vitamin C also recycles vitamin E and alpha-lipoic acid

Vitamin E – As an antioxidant it also assists glutathione in eliminating free radicals much like vitamin C; it is also required for the proper functioning of glutathione enzymes; it recycles vitamin C and alpha-lipoic acid

B vitamins – Vitamins B1 and B2 maintain glutathione and its enzymes in their active forms; vitamin B2 participates in the formation of a glutathione molecule; vitamin B6 influences glutathione synthesis indirectly as it is important for the proper functioning of amino acids including GSH precursors; vitamin B6 increases the amount of magnesium (a vital cofactor) that can enter cells; folate (B9) pushes cysteine toward glutathione production rather than homocysteine production; folate and vitamin B12 work together in amino acid metabolism and protein synthesis. You can read more vitamin B12 deficiency and its effect on immune health at ► http://www.immunehealthscience.com/vitamin-b12-deficiency.html

Selenium – Part of the enzyme glutathione peroxidase (GPx). Glutathione peroxidases, also known as selenoproteins, are a family of antioxidant enzymes that speed up the reaction between glutathione and free radicals

Magnesium – Required for the proper functioning of the enzyme gamma-glutamyl transpeptidase (GGT) involved in the synthesis of glutathione

Zinc – Zinc deficiency reduces glutathione levels, especially in red blood cells. However, zinc levels above normal have pro-oxidant properties and reduce glutathione too

Alpha-lipoic acid – An antioxidant produced by the body; it has been scientifically proven to enhance and maintain glutathione levels by stimulating enzymes involved in the synthesis of glutathione; it also helps increase the cellular uptake of cysteine, the crucial building block of glutathione; in addition, alpha-lipoic acid recycles vitamins C and E

Based on data from Ref. [124]

51.5.2 CoQ10

Co10 is a fat-soluble compound produced endogenously and also available through food and supplementation. It is required in the production of ATP, is a powerful antioxidant, and therefore is helpful against oxidative stress, an important issue in lung disease. CoQ10 achieves its strong effects through a set of different mechanisms. It influences genes through its epigenetic effect to reduce inflammation, helps with the immune system, and even reduces aging by reducing systemic oxidative stress and mitochondrial aging [120].

Lungs are the most susceptible organ to oxidant damage because they interact directly with oxygen. Therefore, it makes sense that antioxidants, and those that especially affect the lungs, are helpful in tissue and lung cell preservation [121].

CoQ10 levels are significantly lower in those with COPD and asthma with insignificant amounts of research on the levels of CoQ10 with other lung issues. It has been shown that supplementing patients with CoQ10 resulted in measurable benefits. In one study, patients with COPD using steroids to reduce inflammation were able to reduce their steroid dosage when using CoQ10 [122]. In another study, benefits were shown for COPD patients during exercise, measuring performance, tissue oxygenation, and heart rate at a low dosage of 90 mg/day [123]. The levels of CoQ10 in the blood have been shown to indicate the degree of systemic oxidative stress, which implies it could be used as a marker to assess COPD [121]. Several studies confirm the beneficial role of CoQ10 in decreasing oxidative stress, cardiovascular risk, and modulating inflammation during aging. Dosage levels of 1200 mg/day of CoQ10 have been shown to be therapeutic. However, in the reduced, more absorbable form, ubiquinol, 400 mg/day, was shown to be as effective.

51.6 Anti nutrients and Inhibitors of Lung Physiology

There is a wide range of toxins and anti-nutrients that can significantly impact the respiratory system. This can occur through acute or chronic exposure to these agents.

The Earth's air is the source of oxygen, and the lungs provide access to that oxygen to support life. The human need for oxygen is precarious because humans can only survive for about 6 minutes without the precious gas. From about 1760 to sometime between 1820 and 1840 in Europe and the United States, the ramp-up of new industrial revolution manufacturing processes opened a new era of increasing chemical and heavy metal atmospheric contamination. These pollutants can enter the body through breathing the polluted air. The more concentrated atmospheric pollutant densities cluster around areas of dense population. The dirty air provides a serious direct threat to those with respiratory diseases. An integrative and functional approach to assessing an individual with respiratory disease needs to include consideration of potential environmental contributors to the etiology of a condition. ◘ Table 51.2 lists environmental pollutants that are known to promote lung pathology.

A 2016 study published in the *Canadian Respiratory Journal* examined exhaled fractional nitric oxide (FeNO) – an indicator of inflammation in the lungs – in school children at three different schools located three different distances from a large steel mill [127]. Steel processing is known to be a source of ambient iron, nickel, lead, copper, vanadium, and zinc. The study found statistically significant differences in FeNO between the two closer schools compared to the farthest school from the mill, indicating potential increased lung inflammation caused by heavy metals and/or air pollutants [127].

51.6.1 Toxic Metals

Although acute metal toxicity is possible, chronic, low-grade exposure is more common and may contribute to respiratory complications and disease. An individual's ability to

Table 51.2 Environmental pollutants related to promoting respiratory disease

"Silent hazards" ingested or inhaled hazardous substances undetected until disease and death results and investigation is mounted to identify the cause [125]	
Natural sources – weather, geology, and pathogen exposure	
Dust	All respiratory stress
Volcanogenic air pollution	All respiratory stress
Mold/mycotoxins	Pneumoconiosis, COPD, all respiratory stress
Infection: viral, bacterial	Pneumococcal pneumonia Viral pneumonia
Anthropogenic – caused by human activity	
Smoking/tobacco	Lung cancer
Dental: mercury amalgam	Acute mercury inhalation poisoning
Dental: fluorosis/fluorine vapor	Pulmonary fluorosis [126]
Asbestos (construction materials/dust particles)	Lung cancer, mesothelioma
Nuclear radiation accidents/job exposure	Pulmonary inflammation, scarring, cancer
Coal mining	Pneumoconiosis, black lung disease
Coal combustion/mercury vapor	Acute mercury inhalation poisoning

eliminate these metals via detoxification in conjunction with gastrointestinal health and other factors can serve as important factors in whether or not these metals accumulate in the body.

51.6.1.1 Arsenic

Chronic arsenic exposure may be linked to respiratory complications [128]. Chronic arsenic ingestion via contaminated drinking water may be connected to respiratory symptoms such as chronic cough, shortness of breath, blood in sputum, and abnormal breath sounds [129]. Arsenic can also be ingested through foods such as rice and rice products, shellfish, and seaweeds, which have been shown to have high levels of inorganic arsenic (more toxic than organic arsenic found in fish) [120]. However, ingested inorganic arsenic is typically biotransformed and excreted in the urine [130]. That said, altered biotransformation has been observed depending on an individual's age, gender, nutritional status, and genetic polymorphisms responsible for the biotransformation of inorganic arsenic [130]. Chronic inhalation versus ingestion may result in irritation of the throat and respiratory tract [131]. Individuals most affected by arsenic exposure are children, nursing children, and infants of exposed pregnant mothers [132].

51.6.1.2 Cadmium

Acute inhalation of cadmium may lead to dyspnea and coughing [133]. Long-term exposure to cadmium has been reported to contribute to emphysema, dyspnea, and inflammation of the nose, pharynx, and larynx [123]. Individuals most affected by cadmium toxicity are those with occupations with cadmium exposure, such as those who work in certain types of factories, women, due to higher intestinal absorption because of low iron stores, and residents of Asia due to high intake of rice grown in contaminated soil [134].

The 2013 US National Health and Nutrition Examination Survey (NHANES) demonstrated an association between obstructive lung disease and serum lead and cadmium concentrations in the blood, where cadmium was shown to partially mediate the association between smoking and obstructive lung disease [135]. In the 2015 Korean NHANES, obstructive lung function was found to be associated with higher serum blood levels of cadmium and lead as well [136].

The specific mechanism of heavy metal burden and its effects on respiratory health must be further investigated. Although testing and treatment of heavy metal burden have its limitations, it is worth considering as heavy metal accumulation can wreak havoc on the body. An example of heavy metal testing that can be used in practice is urine provocation testing with a chelating agent, such as FDA-approved DMSA. Eliminating heavy metals from the body can be potentially harmful and requires careful monitoring and guidance by an experienced healthcare professional.

51.6.2 Air Pollutants

Air pollutants that are used as indicators of air quality are carbon monoxide, lead, nitrogen dioxide, ozone, particles, and sulfur dioxide [137]. Air pollution has been shown to have adverse effects on human health [138]. A 2017 systematic review and meta-analysis done in China showed an association between respiratory disease and ambient nitrogen dioxide, which is increased through fuel combustion, industrial production, and fuel exhaust [129]. Diesel exhaust particles in particular have been associated with an increase in cytokines such as IL-2, IL-6, and IgE in nasal mucosa [139]. Nitrogen dioxide in particular can potentially contribute to respiratory disease as it is a free radical that is highly reactive and poorly water-soluble and can be deposited in the lungs when inhaled [138]. In another study performed in England, air concentration of nitrogen dioxide was significantly associated with respiratory hospital admissions [140].

Other pollutants, such as fine particulate matter and ozone, have been shown to significantly affect respiratory function in COPD patients [141]. Increased ozone exposure has also been associated with increased airway inflammation and respiratory symptoms along with decreased respiratory function in children [142].

Optimization of nutrition and antioxidant status is essential to combating the potential health effects of air pollutants.

Several studies have shown that nutrients such as vitamin C, vitamin E, vitamin D, omega-3 PUFA, and B vitamins have demonstrated a protective effect against the damage done by particulate matter [143]. It would be reasonable to assume having adequate stores and ability to utilize these nutrients may protect against other insults to the respiratory system as discussed in this section through their anti-inflammatory properties.

51.6.3 Chemicals

Acute and chronic exposure to certain chemicals can also pose a risk to respiratory health. Obtaining a full occupational and social history when assessing individuals is important in order to identify any potential exposure to chemicals.

One of the most well-known and common toxic chemical exposures that affects respiratory health is cigarette smoke. Smoking cigarettes has been identified as a main cause of COPD [144]. Increased oxidative stress from inhaling cigarette smoke appears to activate the NF-KB inflammatory pathway, increasing the production of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and IL-8 and tumor necrosis factor-α (TNF-α) [144]. It also appears to reduce anti-inflammatory cytokines such as IL-10 [145].

Electronic cigarettes, or E-cigs, have been increasing in popularity in recent years and are marketed as a better alternative to tobacco cigarettes. However, recent evidence suggests that the vapor and associated chemicals produced by E-cigs may be harmful to the respiratory system, although further research is needed to determine the mechanism [146, 147].

Exposure to metalworking fluid aerosols has been associated with asthma, hypersensitivity pneumonitis, impaired lung function, allergic alveolitis, and sinusitis [148]. A 2015 review also identified an association between occupational exposure to pesticides and increased risk of asthma and chronic bronchitis [149].

There are many chemicals that are toxic when inhaled. For example, inhalation of chlorine is toxic to the lungs, where low doses can cause airway injury and high doses can cause both airway and alveolar injury [150]. These injuries can manifest as dyspnea, hypoxemia, pulmonary edema, and pneumonitis [150]. High doses of carbon dioxide, such as that released from dry ice, can also induce respiratory failure.

51.7 Stress

51.7.1 Stress Overview

Stress may also play a role in respiratory health and the body's ability to combat insults imposed on the respiratory system.

From a physiological standpoint, it is worth noting that acute stress via activation of the sympathetic nervous system increases ventilation through the production of glucocorticoids [139]. Repeated acute stress may also affect growth and repair mechanisms [139].

Chronic biological stress in the form of infections can also be inflammatory and negatively affect the immune system and may affect an individual's susceptibility to respiratory complications. See the *Chronic Infections and Respiratory Health section on page #* below for further information on this association.

However, appropriate amounts of physical stress, such as in the form of exercise, can be beneficial to respiratory health. Some research has indicated a benefit of aerobic exercise to respiratory muscle strength in cystic fibrosis patients [151].

51.7.2 Biological Stress

Chronic stress can be defined as recurrent acute stress or inability to moderate acute stress responses [139]. This can be in the form of physical or emotional stress. Chronic stress and negative emotions such as depression, anxiety, and anger may be linked to endocrine and immune processes [152].

Immunoglobulin E (IgE) and cytokine production, as well as respiratory inflammation, are markers that characterize the asthma response and have been shown to respond to stress in some capacity [139]. It has been hypothesized that increased stress may increase susceptibility to air pollution given its effects on the inflammatory response [139].

Another connection between emotions and respiratory health is acknowledged in East Asian medicine, noting the association between the lungs and feelings of sadness, grief, and anxiety [153] (◘ Table 51.3).

51.8 Disease States

51.8.1 Asthma

51.8.1.1 Background

Asthma is a chronic inflammatory lung disease, triggered by either an IgE allergic reaction or nonallergic factors, and results in reversible airway obstruction and inflammation of the airway [11]. It is characterized by recurrent episodes of wheezing, breathlessness, coughing, and chest tightness [11]. Severe asthma or asthma that is chronic or poorly controlled may lead to airway and lung remodeling that involves deposition of fibrotic tissue which leads to constriction of the bronchi [18].

Although the exact mechanisms have not yet been identified, compromised nutritional status, such as deficiencies in selenium, zinc, and vitamins A, C, D, and E, has been connected to asthma [155]. The pathophysiology of asthma, nutrition considerations, genotypic characteristics, and lifestyle influences will be discussed in this section.

There are numerous potential triggers to the development and/or exacerbation of asthma which can be summarized in ▶ Box 51.2.

The various causes of asthma have led to the classification of several different subtypes and endotypes of asthma in hopes of choosing more targeted treatments.

Table 51.3 Anti-nutrients of the lung and potential mechanisms

Anti-nutrient	Mechanism/hypothesized mechanisms
Toxic metals (e.g., arsenic, cadmium)	Inhaled cadmium (Cd) is deposited in the alveoli where it is then absorbed into the bloodstream Cd is transported to erythrocytes or bound to albumin, where it is then taken up by the liver to form a complex with metallothionein (MT) Cd interferes with the absorption of zinc and competes for the same enzyme binding sites Enzymatic activity of zinc-dependent enzymes reduces Preferential binding of Cd to MT can cause zinc deficiency Altered biotransformation and excretion of ingested arsenic via contaminated water are linked to respiratory complications Chronic inhalation of arsenic may result in irritation of respiratory tract
Air pollutants	Diesel exhaust particles in particular have been associated with increase in cytokines such as IL-2, IL-6, and IgE in nasal mucosa [139] Nitrogen dioxide is a free radical that is highly reactive and poorly water-soluble and can be deposited in the lungs when inhaled [102] Rising pollen and mold counts [154] Increasing ozone [154]
Chemicals	Increased oxidative stress from inhaling cigarette smoke may activate the NF-KB inflammatory pathway, increasing the production of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor-α(TNF-α) Cigarette smoke may reduce anti-inflammatory cytokines such as IL-10 [145]
Stress	Repeated acute stress may also affect growth and repair mechanisms [139] IgE and cytokine production, as well as respiratory inflammation, are markers that characterize the asthma response and have been shown to respond to stress in some capacity [139] Increased stress may increase susceptibility to air pollution given its effects on the inflammatory response [139]

Box 51.2 Suspected Triggers and/or Risk Factors for the Development or Exacerbation of Asthma (1) [18]; (2) [25]; (3) [156]

(1)
- Cigarette smoke
- Air pollution
- Grass, mold, plants
- Pet dander
- Cockroach droppings
- Cold temperatures
- Viral infections (i.e., respiratory syncytial virus (RSV))
- Stress
- Physical exertion
- Decreased exposure to dirt
- Frequent use of antibiotics in early childhood and adolescence
- Overuse of aspirin and acetaminophen in early childhood and adolescence

(2)
- Food allergy
- Monosodium glutamate (MSG)
- Sulfites
- Reactive hypoglycemia
- Sodium chloride
- Trans fatty acids
- Obesity

(3)
- Maternal obesity during pregnancy
- Low vitamin D

51.8.1.2 Pathophysiology

The pathophysiology of asthma is complex and not fully understood, due in part to its heterogeneous nature, which necessitates its organization into individual phenotypes and endotypes. This organization is important to be able to utilize targeted treatments by identifying the root causes of the symptoms. However, more research is needed to more clearly identify the specific pathological mechanisms of each phenotype and particular treatment responses [156].

Two of the most common asthma phenotypes are allergic and nonallergic asthma [147]; allergic is characterized by increased Th2 immunity (Th2 high) and nonallergic defined by varying mechanisms depending on the trigger (Th2 low) [157] (see also ▶ Chap. 19).

Allergic asthma involves the ingestion of typically harmless environmental triggers (listed in Table 51.3) by antigen-presenting cells in the bronchi, which interact with immature helper T cells that, in turn, trigger an unwarranted allergic response [18]. This reaction occurs from repeated exposure to a trigger and is referred to as the type 1 hypersensitivity response [18]. This increased Th2 immunity upregulates eosinophilic inflammation, tissue damage, airway hyperresponsiveness, and bronchoconstriction [113]. Mast cell activation disorders, which is characterized by diseases and conditions related to mast cell mediators and the activation of mast cells, must also be considered when addressing allergic asthma [158].

In contrast, nonallergic asthma can be caused by other factors such as anxiety, exercise, stress, dry air, cold air, viruses, hyperventilation, smoke, or other irritants [11].

Table 51.4 A few of the proposed phenotypes and endotypes and their characteristics

Proposed phenotype or endotype	Clinical findings	Biomarkers	Epidemiology	Proposed mechanisms/genetics	Medications
Phenotypes					
Allergic asthma	Allergic rhinitis Allergen-associated symptoms	Positive skin prick tests (SPT) High IgE High FeNO	Childhood onset History of eczema	Th2 dominant Th2 pathway single-nucleotide polymorphisms	Less responsive to inhaled corticosteroids IgE antagonists (omalizumab) are typically more effective [159]
Nonallergic asthma [156]	Asthma not associated with allergic	May be neutrophilic, eosinophilic, or contain only a few inflammatory cells	Additional research needed	Additional research needed	Less responsive to inhaled corticosteroids
Severe late-onset hypereosinophilic asthma (see box below on eosinophilic asthma)	Severe exacerbations, late-onset disease	Blood and sputum eosinophils	20% of severe asthmatics	Nonatopic Genetics unknown	Oral corticosteroids, IL-5 antibody therapy potential treatment
Endotypes					
Allergic bronchopulmonary mycosis (ABPM)	Severe Mucus production	Blood eosinophils High IgE High FeNO	Adult onset Long duration Poor prognosis	Colonization of airways Human leukocyte(HLA) and rare cystic fibrosis (CF) variants	Oral corticosteroids(not inhaled) and oral antifungal agents can be effective [159]
Cross-country skiing-induced asthma (CCSA) [107]	Exposure to dry, cold air provoking wheezing Airway remodeling, thickening of basement membrane	Increased lymphocytes, macrophages, neutrophils Seldom eosinophils	Induced at very cold temperatures during strenuous exercise	Nonatopic Unknown	Usually not responsive to glucocorticoids [159]

Based on data from Ref. [157]

Individuals suffering from nonallergic asthma will tend to be less responsive to Th2-targeted treatments due to a differing immune response at play [157].

Some of the additional proposed phenotypes are eosinophilic, exacerbation-prone, exercise-induced, fixed obstruction/airflow limitation, poorly steroid-responsive, and adult-onset obesity-related [159]. Several of the proposed endotypes are summarized in Table 51.4.

The American Partnership for Eosinophilic Disorders defines eosinophilic asthma as a type of asthma characterized by especially high levels of eosinophils, more commonly developed later in adulthood, although may occur in some children [160]. Many with eosinophilic asthma do not have underlying allergies or history of allergic conditions such as eczema, food allergy, and hay fever, which are thought to be seen more in people with allergic asthma [160]. In contrast to allergic asthma, the cause of eosinophilic asthma is still unknown.

Histamine intolerance must also be considered in assessing the root cause of asthma. Ingesting histamine-rich foods and beverages such as bananas, grapes, strawberries, citrus fruits, tomatoes, nuts, chocolate, pineapples, fish, spinach, fermented foods, and beverages [161] has been shown to provoke a histamine response that may result in asthma exacerbations, among many other potential signs and symptoms [162].

Disruptions in redox, or oxidation/reduction, reactions in addition to hindered antioxidant defense have been

found to be a risk factor for asthma severity and development [163]. The levels of glutathione, one of the lung's most predominant antioxidants in both reduced and unreduced forms, are thought to be important for lung homeostasis and tied to asthma [163]. More research is needed to determine the exact differences in the pathophysiologies of the various subtypes of asthma in order to develop more targeted treatments.

51.8.1.3 Key Nutrient Cofactors for Respiration and How to Modulate Toward Optimum

Minerals such as zinc, selenium, copper, and manganese may serve as cofactors to major enzymes with antioxidant activity in the lung, such as superoxide dismutase, catalase, and glutathione peroxidase [164]. Asthma has been associated with decreased activity of these enzymes [165].

Low selenium intake has been associated with multiple chronic diseases including asthma [163]. Selenium serves as a cofactor to glutathione peroxidase, an enzyme with antioxidant activity in the lung that is responsible for maintaining GSH/GSSG redox balance [163].

Imbalance between oxidants and antioxidants seems to serve an important role in asthma. Levels of nonenzymatic antioxidants glutathione, ascorbic acid, alpha-tocopherol, lycopene, and beta-carotene, in addition to antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase, were significantly lower in asthmatic children compared to healthy controls [165]. The amino acids glycine and glutamine, which are important in glutathione synthesis, were also found to be significantly lower in children with asthma [165].

DHA has also been found to be abundant in airway mucosa, where it is decreased in individuals with asthma and cystic fibrosis [166].

Magnesium is known to elicit the relaxation of bronchial smooth muscle, decrease responsiveness to histamine, have an anti-inflammatory effect, and decrease the susceptibility of animals to developing anaphylactic reactions [25]. It is estimated that two-thirds of the population in the Western world is not consuming the recommended daily allowance of magnesium [167]. Magnesium can be used intravenously as an effective treatment of acute asthma attacks. One double-blind controlled trial that used 1.2 g of magnesium sulfate when patients did not respond to treatment with beta-agonists found decreased likelihood of hospitalization and improved lung function [168]. Magnesium sulfate as an adjunct therapy with bronchodilators and steroids has also been shown to have a benefit in children with moderate to severe asthma [168]. Although the exact mechanism is not yet known, magnesium is thought to increase glutathione concentrations in the lung [169].

More research is needed to determine additional associations between specific nutrients and asthma. However, optimization of the nutrients discussed in this section has the potential to reduce the severity and/or progression of asthma (◘ Fig. 51.5).

51.8.1.4 Key Genotypic Characteristics of Topic and Nutritional Influence

Asthma has a strong genetic component, with more than 100 genes associated with it in varying degrees across many populations [18]. More recent potential genetic associations include Filaggrin, which encodes for the epithelial barrier; ORMDL3, which encodes transmembrane protein; beta-2 adrenergic receptor gene, expressed throughout smooth muscle and epithelial cells of the lung; and interleukin-4 receptor gene, which has a variant associated with elevated IgE [171].

51.8.1.5 Key Dietary and Food Patterns to Promote Disease or Wellness in Asthma Nutrition Status

A 2011 systematic review and meta-analysis showed that deficiencies in selenium, zinc, vitamins A, C, D, and E, and low fruit and vegetable intake could be associated with the development of asthma [155]. Although this data is tenuous due to lack of randomized controlled trials, it does give some indication of the relationship between nutrition status and dietary patterns with respect to asthma development. More research needs to be done to isolate the impact of these nutrients and dietary patterns on asthma prevention and development.

Dietary Patterns

A 2015 review conducted by Berthon and Wood noted the protective effects of the Mediterranean diet for allergic respiratory diseases as evidenced by epidemiological studies. This diet emphasizes minimally processed plant foods in the form of fruit, vegetables, cereals, beans, breads, nuts, seeds, and olive oil and low to moderate intake of dairy, poultry, fish, and wine, as well as low intake of red meat [172]. This association was the strongest in children, where the Mediterranean diet had a protective effect on atopy, wheezing, and asthma symptoms [172]. However, there is less data available to support this pattern in adults.

The same review noted an association between the "Western" diet, which emphasizes refined grains, red and cured meats, French fries, sweets and desserts, and high-fat dairy products and increased risk of asthma in children [172]. A meta-analysis and systematic review done in 2014 showed a reduction of risk in childhood wheezing with high fruit and vegetable intake and also showed negative association between fruit and vegetable intake and asthma risk in adults and children [173].

Food Allergy

In contrast, food allergy has been especially linked with allergic asthma in children [161]. A study examining food allergy in asthmatic children identified higher serum levels of IgE in asthmatic children compared to healthy controls, where all asthmatic children in the study were also identified as having a positive skin prick test (SPT) to various food allergens [174].

A study done on 322 children under the age of 1 diagnosed with asthma, with or without allergic rhinitis, was

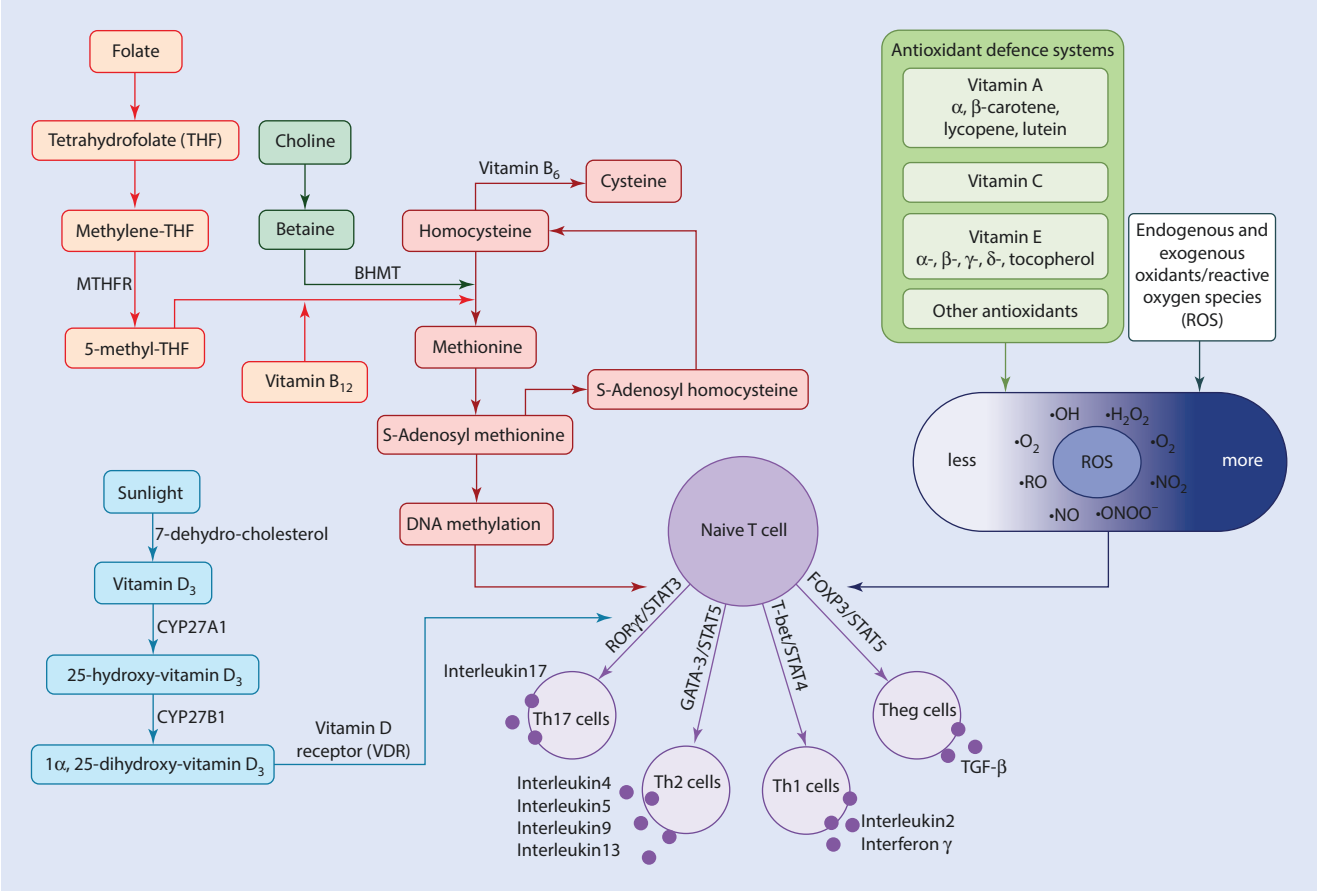


Fig. 51.5 Potential mechanisms of methyl donors and vitamins. Potential mechanisms of action of methyl donors and vitamins **a**, **c**, **e**, and **d** on Th1 and Th2 immune responses. BHMT, betaine-homocysteine methyl-transferase; RORγt, retinoic acid-related orphan receptor γt; GATA-3, GATA binding protein 3; T-bet, T-box transcription factor; FOXP3, forkhead box P3; STAT, signal transducer and activator of transcription . (Reprinted from Han et al. [170]. With permission from Elsevier)

placed on a meat-based formula of carrots, beef, broccoli, and apricots for 6 weeks. It was found that 61% had nearly complete resolution of symptoms [25]. This same study also found that the most common food triggers were milk, egg, chocolate, soy, legumes, and grains [25].

While food allergy as a cause of asthma is more common in children, hidden food allergy has been reported to be the root cause of asthma in around 40% of adults [25]. Improvement in respiratory symptoms was also seen in a small study of adults given an antigen-free elemental diet in a hospital setting [25].

Removal of food triggers has also been linked to improvement in exercise-induced asthma [25].

Identifying food allergies can be a complicated process because many of the testing methodologies such as skin prick tests (SPTs) and blood tests can yield false-positive results for up to 50–60% of cases, according to the Food Allergy Research & Education Organization [175]. A food elimination diet and/or oral food challenge can be a powerful tool in determining food allergy specific to asthma symptoms, where a dietitian or nutritionist in conjunction with physician and/or allergist can serve an important role through this process to support the individual.

51.8.1.6 Mechanisms and Relevance to Asthma as a Chronic Disease

Oxidative stress may play a key role in the development of asthma, which can also be true for the development of chronic diseases such as cardiovascular disease, diabetes, and cancer [117].

It has been shown that obesity may be a risk factor for people with and without allergy and may worsen pre-existing asthma [159]. Individuals with asthma are twice as likely to have gastroesophageal reflux disease (GERD) than people who do not have asthma, especially those resistant to treatment [159].

Celiac disease and asthma have also been linked. An Italian cohort study was done that showed a significant association between treated asthma and celiac disease, where antibiotic exposure in the first year of life was controlled for and not found to contribute to this association [176]. It has also been found that individuals with celiac disease following a gluten-free diet experienced improvement in asthma symptoms [25].

Key Toxin-Related Influences

It is well-known that toxic exposure to particulate matter, airborne pollutants, or cigarette smoke can trigger asthma symptoms [165]. More specifically, a dose-dependent

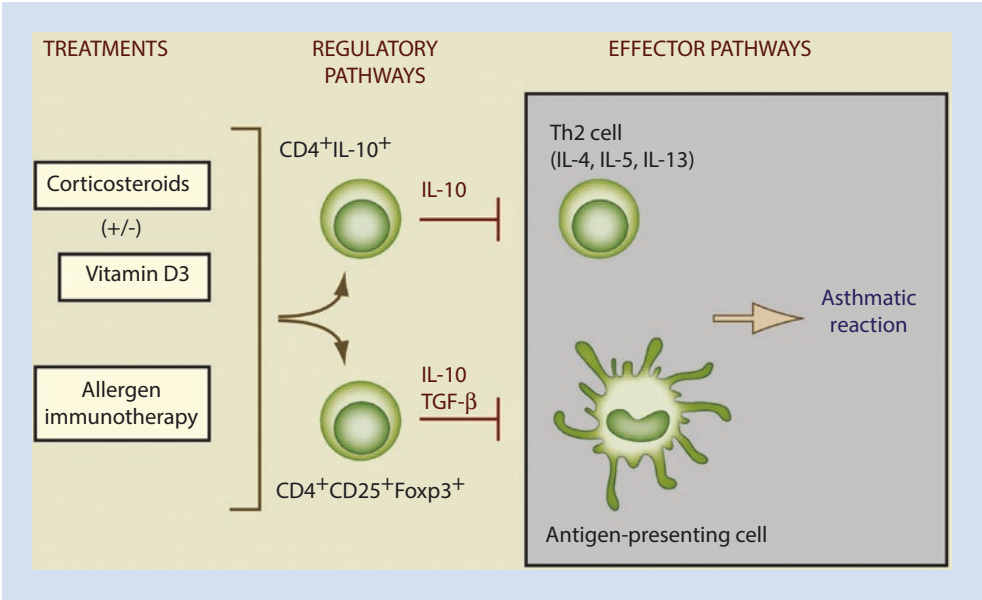


Fig. 51.6 Effect of asthma treatments on regulatory pathways. (Reprinted from Lloyd and Hawrylowicz [177]. With permission from Elsevier)

relationship between cigarette smoke exposure and rates of asthma has been shown [165]. Traffic density and asthma exacerbations have also been clearly demonstrated [165].

Certain medications may also serve as triggers to asthma. Aspirin-exacerbated respiratory disease (AERD) is considered another asthma subtype caused by nonsteroidal anti-inflammatory drugs (NSAIDS) and is characterized by asthma, chronic rhinosinusitis, and acute respiratory reactions [159]. In addition, overuse of antibiotics in childhood has been linked to asthma [18], indicating a connection between the microbiome and asthma development.

Allergic bronchopulmonary mycosis (ABPM) noted in Table 51.4 is caused by a hypersensitivity reaction to fungal colonization of the airways [159]. This is typically caused by the fungus *Aspergillus fumigatus*. Without treatment, this may lead to fixed airflow obstruction and bronchiectasis [159].

51.8.1.7 Key Lifestyle Influences

The progression of asthma is complex and multifaceted, from preconception through childhood and adulthood. Research suggests that early life events are largely predictive for regulatory mechanisms within the pulmonary immune system [177]. For example, prenatal exposure to a farming environment, one rich in microbial compounds, is thought to influence innate immune patterning in the mother which may affect the development of the neonatal immune system [177]. This influence in immune patterning can be seen through higher expression of Toll-like receptors 2 and 4 and CD14 on peripheral blood cells, which implies possible desensitization to allergens in children [178]. T regulatory cells, which serve an important role in immune regulation and are thought to play an important role in asthma by suppressing the Th2 inflammatory response to harmless air particles, have been shown to be impaired in the cord blood of neonates at hereditary risk for allergy [179].

In the 2017 study performed by Singh et al. looking at serum IgE and cutaneous sensitivity to food allergens in asthmatic children here was a negative correlation of total IgE and duration of breastfeeding, indicating a connection between breastfeeding and the immune response [174].

Additionally, reduced maternal intake of vitamins D and E and zinc during pregnancy has been associated with increased asthma symptoms in children [180, 181]. Vitamin D has been associated with the maintenance and/or development of the T regulatory cells stated earlier in mice; however more research is needed to determine a definitive association in humans [177].

A clinical trial performed on non-smoking asthmatic patients showed higher vitamin D levels were associated with greater lung function; furthermore, supplementation with vitamin D showed improved treatment response to glucocorticoids [182]. Vitamin D may also directly increase the anti-inflammatory cytokine, interleukin (IL)-10 and also enhance steroid-induced IL-10 production (see Fig. 51.6) [177]. More research is needed to determine the exact mechanism of vitamin D in asthma and respiratory disease.

51.8.1.8 Conventional Assessments

Beta-agonists, combined with corticosteroids, serve as the primary conventional therapy [183]. Typically, a short-acting beta-agonist will first be prescribed to manage symptoms as needed, where low-dose inhaled corticosteroids may also be prescribed [156]. If symptoms persist, it is recommended to evaluate problems such as adherence to use, inhaler technique, or persistent allergen exposure and comorbidities [156]. Once these are ruled out, the step-up treatment is a combination of an inhaled corticosteroid with a long-acting beta-agonist [156]. A summary of other conventional treatments and their mechanisms can be found in Table 51.5 below.

Unfortunately, conventional methods for the treatment of asthma may have harmful side effects. For example, the use of

Table 51.5 Conventional medications used in the treatment of asthma

Medication type	Medication name	Mechanism
Short-acting β2-agonists (inhaled)	Albuterol Levalbuterol Pirbuterol	Counteract the inhibitory effect on the beta-2 adrenergic receptor resulting in dilation of bronchial passages and relaxation of bronchial smooth muscle; lasts for 4–6 hours
Long-acting β2-agonists (inhaled)	Bambuterol Formoterol Salmeterol	Same as short acting, except effect lasts for about 12 hours
Corticosteroids (oral and inhaled)	Inhaled: Budesonide Flunisolide Fluticasone propionate Mometasone Oral: Dexamethasone Hydrocortisone Methylprednisolone Prednisolone	Bind to glucocorticoid receptor which leads to expression of anti-inflammatory proteins, some of which block expression of pro-inflammatory modulators
Anticholinergics/muscarinic antagonists	Ipratropium bromide	Blocks acetylcholine, which leads to dilation of bronchial airways and relaxation of bronchial smooth muscle
Leukotriene antagonists	Montelukast Zafirlukast	Block binding of leukotrienes to receptors on bronchial cells
Oral methylxanthines	Theophylline Oxtriphylline	Methyl xanthine found in tea Used less commonly due to side effects Relaxes airways due to inhibition of phosphodiesterases; acts as a functional antagonist in airway smooth muscle [171]

Based on data from Ref. [18]

systemic glucocorticoids may lead to immunosuppression, cataracts, and osteoporosis, where long-acting beta-agonists have the potential of increasing asthma exacerbation risk and death [25]. Beta-agonist desensitization is thought to be one of the reasons for increasing asthma exacerbation risk and death [184].

51.8.1.9 Integrative and Functional Medical Nutrition Therapy (IFMNT) Assessment of Asthma

Related to several subtypes of asthma and their differing pathophysiologies, it is important to first determine the subtype before deciding on treatment. For example, in an individual with allergic asthma, this could be a potentially simple fix once the allergen that exacerbates symptoms is identified. A more conventional approach may involve starting the individual on an inhaled corticosteroid or an IgE antagonist (i.e., omalizumab) [159], rather than identifying the root cause of the patient's symptoms. While medications may be warranted until the trigger is identified, finding the underlying causes may not be common practice in many conventional settings.

In contrast, the IFMNT assessment takes a much deeper dive into identifying triggers and any nutrient insufficiencies, inflammation or immune dysregulation, biochemical individuality, lifestyle, energy dysfunction, toxic load, sleep, and stress issues are taken into account. With this information, the practitioner can make more targeted dietary, lifestyle, and supplement recommendations to obtain sustained resolution of symptoms by treating the root cause (Table 51.6, Fig. 51.7, ▶ Box 51.3).

51.8.1.10 IFMNT Case Study: Asthma

Client Overview

A 26-year-old female presented with a complaint of reactive airway disease, which was diagnosed as asthma and had been prescribed inhalers. She reported that she felt like she had difficulty breathing most of her life, especially when exercising. However, her condition was not severe enough to seek help until she was 25 years of age. She reported a lot of stress during this time related to applying for a postgraduate training position. She also reported 1 year prior to diagnosis developing new allergic symptoms.

Her past medical history was significant for conditions related to airways, including chronic sinus infections, strep throat, bronchitis, and recurrent pneumonia.

She could not remember the last time she felt well but assumed it was sometime as a young child. Her nutrition and health goals were to breathe better and to not have to rely on inhalers. The following data was collected on her initial visit.

Table 51.6 Summary of an integrative and functional medical nutrition therapy assessment

Nutrient insufficiencies	**Intake-digestion-utilization (IDU):** Adequacy of nutrient-dense foods to begin to assess nutritional status Organic or nonorganic to assess toxic load and nutrient intake Food preparation and processing to assess nutrient content and identify potential contaminants (e.g., plastic endocrine disruptors) Assess food sensitivities or intolerances to identify potential triggers Microbiome status: assess comprehensive digestive stool analysis for microbiology and fermented food intake; history of antibiotics or microbiota agonists (medications, toxins, stress, etc.) Toxin intake via plastics or inhalation and skin absorption which may affect immune response Assess flavonoids intake as they are antioxidant and anti-inflammatory compounds with mast cell inhibitory action; adequacy may reduce airway reactivity Consider celiac disease and gluten intake as potential inflammatory antigens **Mineral** Assess and restore zinc, selenium, magnesium, manganese, iron, and iodine status to normal reference. Caution to not supplement or intake of food sources higher than reference **Antioxidants** Assess and restore antioxidant balance; vitamins A, C, D, and E and glutathione Assess quercetin intake (leafy vegetables, broccoli, red onions, peppers, apples, grapes, black and green tea, red wine) as it may act as mast-cell stabilizing agent inhibiting release of histamine, TNF-alpha release, formation of prostaglandin D2, reducing interleukin production Consider supplementation of quercetin if quercetin intake is low [185] **Protein status** Assess and restore to support connective tissue and immune status Ensure adequate glutamine and glycine intake **Oils/lipid/fatty acids** Assess fatty acid balance as DHA important in lung tissue integrity Assess adequate serum cholesterol and fat intake to support lipid bilayer important for cellular function in lung (epithelial cells, surfactant production, etc.) **Methylation** Assess methylation status and detoxification capacity of toxins related to asthma exacerbation; important assessment biomarkers suggested: MCV/MCH, homocysteine, methylmalonic acid, RBC Folate, genomic methylation SNPs
Inflammation/immune dysregulation	Assess asthma biomarkers to help identify root cause (see Fig. 51.7, and Quote Box: What is Periostin?) Eosinophils Exhaled nitric oxide (FeNO) Periostin IgE: Total IgE, IgE specific foods, and chemicals Diamine oxidase (DAO) Assess Th2 immunity: Th1 and Th2 Cytokine Blood Test Panel [187]
Biochemical individuality	Signs and symptoms Assess when the individual experiences wheezing, breathlessness to identify the cause, and when did the initial symptom occur? Phenotype Consider the various asthma phenotypes Associated genes: Filaggrin: codes for epithelial barrier ORMDL3: encodes transmembrane protein Beta-2 adrenergic receptor gene: expressed through smooth muscle and epithelial cells of lung IL-4 receptor gene: variant associated with elevated IgE IL-10 gene promoter SNPs A1AT (alpha-1 antitrypsin) gene Environmental history Prenatal exposure to allergens with influence on immune patterning Developmental BPA exposure [188]
Lifestyle	Activity Assess whether asthma is exercise-induced Community Evaluate hobbies, occupation, household environment, and potential exposures to allergens or asthmatic triggers as listed in Fig. 51.3
Energy dysfunction	Assess overweight or obesity, including inflammatory visceral adiposity

(continued)

Table 51.6 (continued)

Toxic load	Evaluate exposure to fungus to identify allergic bronchopulmonary mycosis Assess individual's medication history, considering short- and long-term use of conventional treatments Evaluate exposure to particulate matter, airborne pollutants, cigarette smoke, or toxic metals such as cadmium and arsenic
Sleep and stress	Assess sleep adequacy (7–9 hours with 5-hour REM sleep) and quality (good sleep hygiene with little light/sound/EMF disturbance) to support detoxification of toxins that may worsen respiratory status and aid in repair of damaged lung tissue

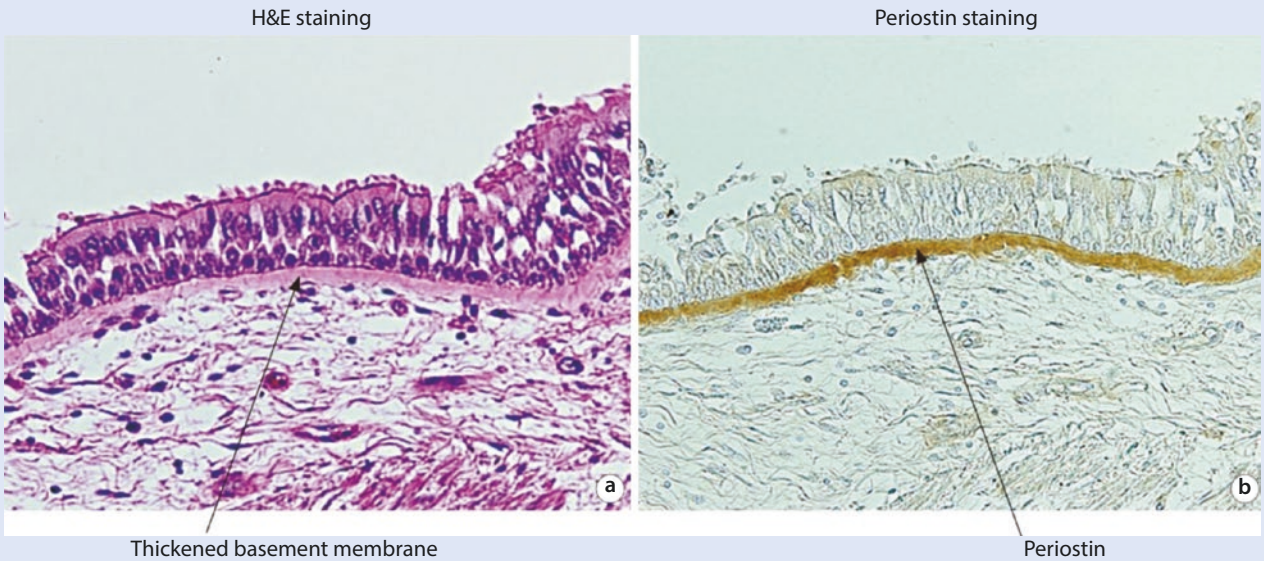


Fig. 51.7 Functions of periostin in inflammation. Functions of periostin in inflammation. Expression of periostin in asthmatic patients. The histochemical localization of periostin in asthmatic patients is depicted. The left and right panels show bronchial tissues from an asthmatic patient in H&E staining **a** and immunostaining **b** of periostin. Periostin in the right panel is stained brown and is localized in the thickened basement membrane in asthmatic patients. (Reprinted from Izuhara et al. [186]. With permission from The Korean Academy of Asthma, Allergy and Clinical Immunology)

Box 51.3 What Is the Inflammatory Influence of Periostin on Tissues and Organs?

Periostin plays a role in the pathogenesis of allergic diseases, including asthma, as it is associated as a downstream molecule of the cytokine, IL-13. Periostin is used as a biomarker for type 2 immunity and can be used to determine the potential effectiveness of medications used to treat asthma, such as anti-IgE antibodies and anti-IL-13 antibodies. Asthmatic patients with high serum periostin tend to be aspirin intolerant, eosinophilic, late asthma onset, and have a high nitric oxide fraction. High periostin can also indicate a reduced response to inhaled corticosteroids [186, 224].

Symptoms/Complaints at First Visit

Extreme exhaustion, depression, ADD, anxiety (accompanied by panic attacks), constipation, pain in legs, neuropathy in feet (numbness and tingling), rapid heartbeat, and a very severe rash on feet known as chilblains.

Past Medical History

- UTIs – recurrent as a child.
- Poor immune function (frequent infections).
- Antibiotic use (very frequent from childhood into adulthood).
- Sinus infections, strep throat, and bronchitis – she had recurrent sinus infections and strep throat about once a year every year and often this would lead to bronchitis, she could not remember if she had these issues before middle school.
- Depression, anxiety, ADD.
- Acne.
- Peptic ulcers.
- Yeast infections – multiple throughout college.
- Eczema.
- Two recent episodes of pneumonia the last episode resulted in her asthma diagnosis.
- Asthma.

- Several medical consults (cardio, rheumatologist, etc.). Most recent, rheumatologist, with suspicion of lupus. Diagnosis was not lupus; no recommendations for further care made.
- Past Surgical History
- Wisdom teeth removed
- Deviated septum surgery

Pharmaceutical Use

- Albuterol inhaler for acute asthma attacks taken prn
- Inhaled corticosteroid inhaler for long-term use; taken once daily
- Yaz birth control for acne and to prevent pregnancy; taken once daily

Timeline

Birth

- Vaginal birth, breastfed for 6 months

Childhood

- Hx of cyst on face, for which she had to undergo several treatments to remove (unsure of what the treatment was or what type of cyst)
- Parents divorced at 2 years old
- Frequent UTIs

Adolescence

- 8th grade: severe case of strep throat, undiagnosed for several weeks, led to being immobile for almost 2 weeks
- 8th–12th grade: was often sick (strep, sinus infections, bronchitis); described it as being constantly sick from fall through winter every year; also developed eating disorder during this time; had severe menstrual cramps (induced vomiting) accompanied by acne, which led to being put on birth control at age 17 as a precursor to Accutane (never prescribed); chronic constipation starting during this time

University

- Freshman – sophomore year: eating disorder was most severe during this time.
- First semester of freshman year: developed digestion issues, after eating certain foods (especially Mexican or salsas), stomach would become distended, experienced pain, and often would result in vomiting. Pain so severe during finals week she was admitted to ER with no diagnosis. CT scan revealed possible peptic ulcers.
- Junior–senior year: depression, anxiety, and inability to focus were most severe during this time which resulted in missing a lot of class and struggling as a student; suffered multiple panic attacks; gained a lot of weight (from 120 to 180 lb); end of senior year became engaged to be married – moved to Dallas, TX.

Young Adulthood

- Lived in Dallas for 6 months, continued to experience depression and anxiety and weight gain, and moved back to home state
- Initially started running (~2 miles a day) and experiencing inability to breathe, diagnosed with pneumonia, prescribed inhaler to help with running; other symptoms: eczema around the eyes and neck (after running outside), pain in calves, numbness and poor circulation in feet (pulse not detected by several health professionals), and development of chilblain rash (very painful, itching, lasts about 3–4 weeks from development to resolution); increased running – ran a half-marathon. Visited PCP and several specialists for help with chilblain rash with no resolution or diagnosis; lost a lot of weight (from 170 to 140 lb).
- Ongoing increased depression, anxiety, and inability to focus; PCP Rx Cymbalta (depression and anxiety); Cymbalta discontinued after ~2 months (did not tolerate side effects), continued psychological therapy for several months; chilblain rash continued. Stopped running long distances. Gained weight back (from 140 to 170 lb); subsequently saw blog for integrative RD and followed suggestion to eliminate gluten and focusing on whole foods diet.
- Chilblains and eczema began to resolve while following integrative RD recommendations of gluten-free diet with some improvements. However, difficulty breathing got worse, and diagnosis of asthma was made with fast-acting inhaler used for exercise; as time progressed, breathing continued to worsen, led to daily inhaler use. Weight at this time is still at around 170 lb.

Social

- Stress: very high (graduate student and completing internship)
- Sleep: variable, sometimes <6 hours and sometimes >9 hours
- Physical activity: some yoga and HIIT running
- Exposures: pet dander and Teflon cookware

Nutrition (In General)

- History of chronic dieting and disordered eating
- No known food allergies but suspected gluten sensitivity
- Consult with IFMNT nutritionist, diet whole foods, completely gluten-free diet. Minimal dairy whole fat (mostly from Greek yogurt, butter, and cheese)

Fats and Oils Questionnaire: Initial Survey

- Omega 9-MUFAs: High
- Omega-6: High (mainly from commercial meats and eggs)
- Omega-3: Low
- Saturated: High (mainly from dairy sources)
- Damaged: High (trans, hydrogenated, deep fried, charred meats)

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Nutritional and Lifestyle Data Collected

Clinical

Anthropometrics

- Height: 5′7″
- Weight: 170 lbs
- BMI: 26.6
- Waist circumference: 34″
- Waist/height ratio: 0.51
- Blood pressure: 122/74
- Body composition: not completed at initial intake

Nutrition Physical Exam

- Acne present along the jawline and on the neck
- Appeared overweight and bloated
- Appeared tired and had trouble recalling certain details
- Tongue, nails, etc. not checked at initial intake visit

Genotypic Risks

- IL-13 c112T (+/−)
- HLA-DQA2 (+/+), HLA-DQA1 (+/−)
- VDR (+/+)
- Several (+/+) for phase II related genes
- MTHFR C677T (+/−) and several other (+/+) (+/−) for genes related to methylation and methionine/homocysteine pathways

Biochemical

Blood Lab Results

- MCV 101 (H) (79.3–98.6)/MCH: 32.0 (H) [27.0–31.0]
- Na: 137 (lower end of normal) [133–143]
- K: 3.8 (lower end of normal) [3.5–5.0]
- Bicarbonate: 23 (L) [24–32]
- Glucose: 85 (higher end of normal) [60–97]
- Creatinine: 0.54 (L) [0.70–1.40]
- ALT: 29 (L) [30–65]
- HDL: 74 WNL

Structural

- Hx eczema – breakdown of the skin
- Gut barrier likely compromised evidenced by Hx of ulcers, poor immune function, yeast infections, cyst, constipation, etc.
- Nail structure very good
- Hair: reported frequent shedding, but hair structure appeared healthy

Signs/Symptoms/Medical Symptom Questionnaires (MSQ)

- MSQ total score of 87 [REFERENCE > 50 significant imbalances]
- High MSQ categories: lungs, skin, and weight

Nutrition Assessment: NIBLETS

Intake

- High dairy diet (consumed dairy products at most meals and snacks), consumed three smaller meals with three snacks in between
- Meals and snacks balanced with protein, fat, and carbs, with carbs coming from fruits and vegetables and fat mainly from full fat cheese, Greek yogurt, and butter
- Mostly nonorganic produce and commercially raised meats

Digestion, Assimilation, and Elimination

- Hx of peptic ulcers and chronic constipation (BM ~1–2 times a month)
- BMs currently at about 2 × per week on encounter

Utilization, Cellular, and Molecular (*MAPDOM*)

- Hx of likely gluten sensitivity.
- Presented symptoms of possible dairy sensitivity (bloating, acne, asthma).
- Evidence for compromised intestinal barrier.
- Minerals: infrequent BMs could indicate low fiber or low mineral status (Mg); when BMs do occur, they are hard and dry (low Mg); severe menstrual cramps (low Mg); labs showed low K and Na, on Yaz birth control (low zinc and low B vitamins).
- Antioxidants: consumed adequate fruits and vegetables each day.
- Protein: has some evidence of poor/slowed wound healing as evidenced by sore on leg that has not completely healed after a year; cuts that take months to heal.
- D and fat-soluble A, E, and K vitamins – Hx of poor immune function (low D), VDR +/+ (low D and possibly A).
- Oils/fatty acids: high omega-6/omega-3 ratio, higher intake of damaged fats, very low intake of omega-3.
- Methylation: symptoms of depression, anxiety, ADD combined with MTHFR C677T snp and on Yaz (low B6 and folate).

Inflammation

- Eicosanoid fatty acids status – suspect issues with PGE1 series pathway to control inflammation due to following signs and symptoms: allergies, autoimmune condition (asthma), peptic ulcers, eczema, and severe menstrual cramps
- Immune function – suspect gut dysbiosis due to following S&S: poor immune function, yeast infections, Hx frequent antibiotic use, cyst, and constipation

Body Composition

- Genetic makeup that indicated prone to gluten and dairy sensitivity, low vitamin D status, and impairment in methylation

Lifestyle

- Low exercise, high stress, and food sensitivities

Energy

- Fatigue

Toxin Load

- Known genetic SNPs in phase 2 detoxification.

- Dairy could be considered a toxin contributing to overall toxic load on body.

Sleep and Stress

- Either sleeps too much or not enough
- Reported high stress due to completing dietetic internship and master's degree at the same time, also Hx of long-term stress with parents' divorce at young age and stress related to relationships

Nutrition Diagnosis

- Suspect dairy sensitivity related to impaired GI structure and genetic susceptibility evidenced by autoimmune condition (asthma), Hx of strep, and HLA-DQ2 & 1 SNPS
- Altered GI function related to gut microbe dysbiosis evidenced by poor immune function, constipation, Hx of yeast infections, cyst, and frequent antibiotic use

Plan

1. Trial of dairy-free diet for 3 months. Then add back sources of dairy (separately) to see if symptoms return. Log any symptoms experienced during the reintroduction of dairy in a food journal.
2. Supplements:
   - Vit D + K2 (5000 IU + 90 mcg) daily
   - Natural Calm Mg (daily, morning and night)
   - Fish oil (2000 mg daily)
   - Broad spectrum probiotic + fermented foods
   - BioActive B complex (includes 50 mg P5P B6 and 800 mcg 5 THF)
   - 260 mg GLA evening primrose oil and zinc
3. Aim to eat three larger meals a day, allowing space in between of ~ 5 hours; increase omega-3 intake by adding in small fatty fish, such as sardines or anchovies, once per week and taking fish oil; decrease omega-6 intake, switch from conventionally raised meats to organic, pasture-raised; and replace fat in diet from dairy with coconut sources, more nuts, and avocados.

Follow-Up

- Patient presented ~6 months after the initial visit (September 2015). Her breathing had improved immensely. She was able to stop taking her Albuterol inhaler before exercise, recently stopped daily inhaler.
- After dairy-free diet for 3 months, reintroduced dairy (cheese, butter, yogurt). Asthmatic symptoms returned about 2–3 days after the addition of each. Noticed the more dairy consumed, the worse her symptoms became.
- At time of appointment, diet whole foods, gluten-free, and dairy-free. Weight loss 10 lb within the first month of going dairy-free, continued to lose some weight. When reintroduced dairy symptoms of bloating and increase in weight, which resolved returning to dairy-free diet.
- BMs are regular now at ~ *2 × daily*.

Anthropometrics

- Height: 5′7″
- Weight: 155 lb
- BMI: 24.2
- Waist circumference: 32 inches
- Waist/height ratio: 0.477

Medical Symptom Questionnaire (MSQ)

- Highest categories: lungs and eyes (had recent accidental exposure to a little bit of dairy)

Fats and Oils

- Omega-9: HIGH, healthy
- Omega-6: Lowered and increased GLA
- Omega-3: Normal, healthy
- Saturated: Normal, balanced healthy sources
- Damaged: Reduced 45%

Outcome

This patient case followed some common patterns in the development of chronic disease and the comorbidities that are common, especially autoimmune conditions like asthma. The first is the genetic susceptibility of the individual; several SNPs are prone to dairy sensitivity. Second, significant evidence for gut dysbiosis, promoted compromised gut barrier, can contribute to the development of dairy sensitivity. Third is the exposure to dairy protein antigen. Diet history evidenced trigger for asthmatic condition.

Additionally, inflammation, immune dysfunction, and methylation issues present. Signs and symptoms significant for decrease in PGE1 series anti-inflammatory pathways. Low dietary omega-3s potential contributor to asthma. Immune dysfunction evidenced by extensive history of infection-antibiotic use. Genomic SNP MTHFR C667T gene, which indicated a greater need for folate. The use of Yaz birth control and symptoms of depression, anxiety, and ADD known further to deplete B6 and folate.

The diet and supplements recommended targeted control of inflammation, restore gut ecology, promote proper methylation, and replete nutrient insufficiencies. Results from 6-month follow-up showed successful outcome in helping improve breathing and wean her off of inhalers.

This case is an example of the IFMNT approach able to address the complexity of the whole patient story and bring the metabolic priorities into a manageable intervention program for the individual.

51.8.2 Chronic Infection and Respiratory Health

51.8.2.1 Upper Respiratory Tract Infection

One study found that the composition of the nasopharyngeal microbiota in children was linked to the frequency of upper respiratory tract infections and acute sinusitis [189]. A study that intranasally inoculated mice with *Lactobacillus*

fermentum reduced the amount of *S. pneumoniae* in the respiratory tract and increased the number of macrophages in the lung and lymphocytes in the trachea [189]. These findings may indicate a benefit of manipulating the upper respiratory tract microbiota with orally or nasally administered probiotics in the prevention and/or treatment of upper respiratory tract infections.

51.8.2.2 Fungal, Viral, and Bacterial Infections

Allergic bronchopulmonary mycosis (ABPM) is caused by a hypersensitivity reaction to fungal colonization of the airways. This is typically caused by the fungus *Aspergillus fumigatus*. Without treatment this may lead to fixed airflow obstruction and bronchiectasis [159].

Guillain-Barre syndrome (GBS) is a rare neurological disorder in which the body's immune system attacks the peripheral nervous system, known as the network of nerves located outside of the brain and spinal cord [190]. It is often preceded by a bacterial or viral infection. There are several potential mechanisms in which these infections trigger GBS. If an individual contracts a *Campylobacter jejuni* bacterial infection, antibodies made to fight this infection can attack axons in motor nerves, which can potentially cause paralysis and respiratory failure [190]. *Campylobacter* can be ingested via contaminated food or other exposures [190].

Pérez-Guzmán 2005 states that hypocholesterolemia is common among tuberculosis patients and suggests that cholesterol should be used as a complementary measure in antitubercular treatment [8].

51.8.3 Alpha-1 Antitrypsin Deficiency (A1AT Deficiency)

Alpha-1 antitrypsin (A1AT) deficiency is an underrecognized disease in the United States, with around documented 100,000 people suffering from it, according to the Alpha-1 Foundation. This deficiency is inherited through autosomal codominant transmission, meaning affected individuals have inherited an abnormal AAT gene from each parent [191]. Individuals with this deficient allele present with AAT levels at less than 35% to low-end normal levels [191].

However, it is also possible for individuals with a variant of this allele to be asymptomatic given different environmental conditions or lifestyle factors, such as refraining from smoking to reduce lung disease development risk [191] (▶ Box 51.4).

51.8.3.1 Lungs

A1AT deficiency most often manifests in the lungs as chronic obstructive pulmonary disease (COPD) (i.e., emphysema or bronchiectasis or "genetic COPD"). A1AT deficiency is often undiagnosed because people with genetic COPD experience the same symptoms as people with COPD, such as [191]:

- Shortness of breath
- Wheezing
- Recurring chest colds
- Low exercise tolerance
- Year-round allergies

Box 51.4 Genomic Variants of Alpha-1 Antitrypsin Deficiency

Normal genotype M M

- Most common abnormal genes are called S and Z
- Abnormal variant combinations:
  - ZZ (highest risk)
  - SZ (lower risk increasing if smoker, inhalant pollutants)
  - MZ (lower risk of carrying an A1AT gene variant; considered "carriers")
- Alpha-1 is the most commonly known genetic risk factor for emphysema
- Up to 3% of all people diagnosed with COPD may have undetected Alpha-1
- Alpha-1 can also lead to liver disease. The most serious liver diseases are cirrhosis and liver cancer
- The World Health Organization (WHO), American Thoracic Society (ATS), and the European Respiratory Society (ERS) recommend that everyone with COPD be tested for Alpha-1

Alpha-1 is a progressive disease that benefits from early detection. It can cause serious lung diseases, such as COPD and emphysema when undiagnosed. In some cases, Alpha-1 can also cause liver disease [225]

Symptoms related to the lung [225]:

- Shortness of breath
- Wheezing
- Chronic bronchitis, which is cough and sputum (phlegm) production that lasts for a long time
- Recurring chest colds
- Less exercise tolerance
- Year-round allergies
- Bronchiectasis

The only way you will know for sure if you have genetic COPD due to alpha-1 is to get tested.

51.8.3.2 Liver

A1AT deficiency can manifest in the liver as cirrhosis.

Symptoms Related to the Liver

- Unexplained liver disease or elevated liver enzymes
- Eyes and skin turning yellow (jaundice)
- Swelling of the abdomen (ascites) or legs
- Vomiting blood (from enlarged veins in the esophagus or stomach)

51.8.3.3 Skin

A1AT expresses sometimes in the skin as panniculitis [191]. Panniculitis typically appears as raised red spots on the skin, which may break down and give off an oily discharge. While panniculitis spots (called nodules) may appear anywhere on the body, the most common places are the thighs, buttocks, and areas subject to injury or pressure.

51.8.3.4 A1AT Biochemical Mechanisms

The alpha-1 antitrypsin (A1AT) protein protects the body, especially fragile lung tissues, from the damaging effects of a powerful enzyme called neutrophil elastase that is released from white blood cells. In A1AT deficiency, a genetic mutation reduces levels of the protective protein in the bloodstream. A1AT deficiency can lead to chronic obstructive pulmonary disease (COPD), specifically emphysema, and liver disease. Smoking, which can inhibit what little A1AT protein an affected person does have, increases the risk of lung disease.

Alpha-1 antitrypsin deficiency is completely determined by mutations in a single gene. The severity of symptoms is mostly a function of which mutations a person has and how many copies. However, smoking can greatly increase the risk of lung disease due to AAT mutations.

23andMe reports data only for the PI∗M, PI∗S, and PI∗Z versions of the gene that encodes AAT. Keep in mind that it is possible to have another mutation that causes this condition that is not included in this report [192]. A1AT deficiency is a genetic disorder that reduces circulating levels of a protein that protects the lungs by trapping A1AT in the liver, where the protein is produced, and prevents A1AT from entering circulation. A1AT deficiency can lead to chronic obstructive pulmonary disease (COPD), specifically emphysema, and liver disease.

When a disease-causing mutation is fairly common, as the PI∗S and PI∗Z mutations are in Europeans, it suggests that the mutation actually conferred an evolutionary advantage at one time. Some researchers have suggested that several thousand years ago when the PI∗Z and PI∗S mutations first arose, these versions of the gene for A1AT gave people a survival advantage by creating an environment in their lungs that helped fight off infections. The scientists theorize that the antimicrobial benefits of the AAT mutations outweighed the cost of an increased risk of COPD and liver disease in the era before antibiotics were available [193].

51.8.3.5 Liver Cirrhosis

In contrast to lung disease, manifestation of liver disease related to A1AT can be referred to as a "toxic gain of function," due to accumulation of mutant A1AT protein rather than protease deficiency within the liver [144].

51.8.4 Pulmonary Fibrosis

51.8.4.1 Overview

When taken together, fibrotic lung diseases are the leading cause of mortality worldwide. Under the umbrella of interstitial lung disease (ILD), pulmonary fibrosis (PF) is the most common. Any ILD that involves scarring of the lungs falls in the pulmonary fibrosis category. Pulmonary fibrosis is the scarring of lungs, which destroys tissue over time, making it impossible to transfer oxygen from inhaled air into the bloodstream. There are more than 200 different diseases under the pulmonary fibrosis umbrella. Because PF is often misdiagnosed or goes undiagnosed, there is not an accurate count of those with these diseases. However, it is estimated that as many as 1 in 200 adults over 60, or 200,000 people in the United States, are affected [184]. There are more than 50,000 deaths from IPF every year in the United States. More people die each year from idiopathic pulmonary fibrosis than from breast cancer [194].

There are other forms of interstitial lung disease including the newly identified pleuroparenchymal fibroelastosis, cryptogenic organizing pneumonia (COP), desquamative interstitial pneumonitis, nonspecific interstitial pneumonitis, hypersensitivity pneumonitis, acute interstitial pneumonitis, interstitial pneumonia, sarcoidosis, and asbestosis [195].

Symptoms include cough and dyspnea, restrictive pulmonary function tests with impaired gas exchange, and progressive lung scarring. The disease progresses with an initiation of inflammation. Fibrosing starts with the action of transforming growth factor-β (TGF-β)-dependent differentiation of fibroblasts to myofibroblasts, which then express α-SMA (smooth muscle actin) [196].

After the TGF-β-dependent differentiation of fibroblasts to myofibroblasts, which express α-SMA, there is sustained, excessive deposition of collagen by the myofibroblasts in the lung interstitium leading to the progressive lung damage in patients with PF [185]. Research published in 2011 supported the idea that dysfunctional type II AECs (alveolar epithelial cells) facilitate lung fibrosis through increased susceptibility to injury, leading to excessive and dysregulated remodeling [197]. The disease seems to progress in steps, and inflammation is not typically present continuously, except during certain periodic episodes of deterioration (◘ Fig. 51.8).

There are five main categories of PF causes: drug-induced, radiation-induced, environmental, autoimmune, and occupational. Of these five, four have identifiable causes. Some of the autoimmune diseases that can lead to PF are rheumatoid arthritis, scleroderma, Sjogren's syndrome, polymyositis, dermatomyositis, and antisynthetase syndrome.

Idiopathic pulmonary fibrosis (ILP) is defined as PF with an unknown cause, including a genetic cause for some families [see ◘ Fig. 51.9]. The symptoms of ILP are a dry, hacking cough, shortness of breath, fatigue, chest discomfort, loss of appetite, and unexplained weight loss, all caused by the fibrosing of the lungs.

Diagnosis can be difficult, and PF is often misdiagnosed as COPD or other more common lung diseases. In addition, in the recent past, path to a true diagnosis was invasive. Since damage to the lungs, even through a diagnostic biopsy, can trigger further lung damage or a period of fibrosis, many physicians or patients are cautious with a biopsy approach to diagnosis. Since the current treatments are limited, one must evaluate whether defining the exact form of PF is necessary for treatment and follow-up. Difficulty breathing, crackling sounds while breathing, and low oxygen levels are the first indicators. Clubbed fingernails may also be a symptom.

High-resolution CT scans are performed, which can show scarring. The pulmonologist will ask many questions

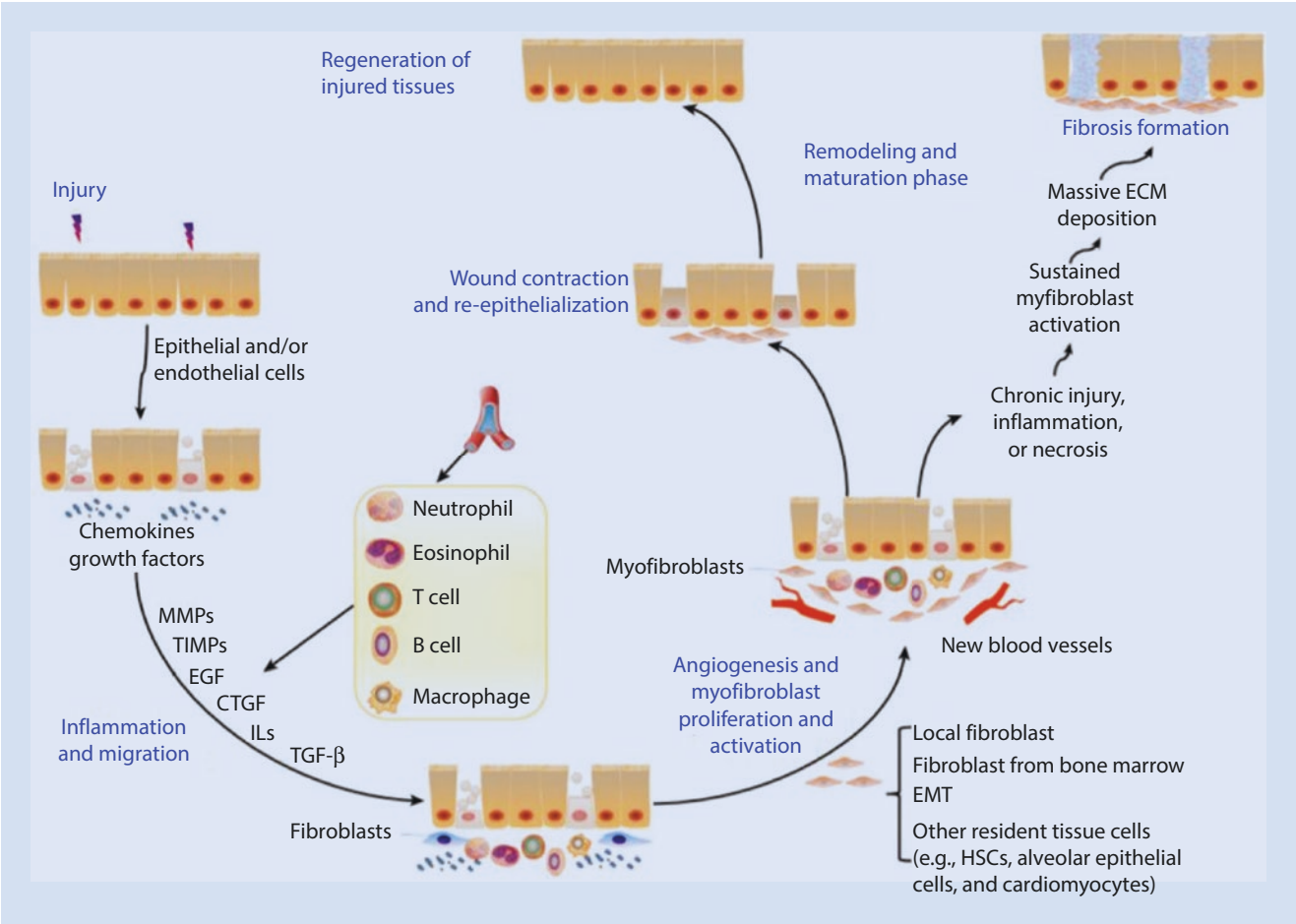


Fig. 51.8 The cellular and molecular mechanisms of fibrosis in multiple organs. The cellular and molecular mechanisms of fibrosis in multiple organs. Once an injury occurs in an organ, epithelial and/or endothelial cells are impaired, which results in the release of chemokines and growth factors, including IL-13 and TGF-b1. Macrophages and monocytes are recruited and activated, both of which further release cytokines and chemokines and further induce fibroblast activation. Activated fibroblasts transform into a-SMA-expressing myofibroblasts and migrate into the wound along the fibrin lattice. ECM is excessively accumulated, and some parenchymal cells (hepatic stellate cells in the liver, tubular epithelial cells in the kidney, alveolar epithelial cells in the lung, or cardiomyocytes in the heart) are further differentiated into myofibroblasts or fibroblasts by the stimulation of cytokines and chemokines, especially for TGF-b1. After the inflammatory phase, two events occur. One is the regeneration of injured tissues followed by wound contraction and reepithelialization. In contrast, once chronic injury, inflammation, and necrosis occur, myofibroblasts are perpetually activated, and excessive ECM is deposited, finally resulting in fibrosis formation. CTGF, connective tissue growth factor; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial-mesenchymal transition; HSC, hepatic stellate cell; IL, interleukin; MMP, matrix metalloproteinase; TGF, transforming growth factor; TIMP, tissue inhibitors of metalloproteinase. (Reprinted from Chen et al. [198]. With permission from Elsevier)

and order more blood tests to try to distinguish between the 200 forms of PF. The future is pointing to molecular endotyping as a more accurate way to diagnose. Molecular endotyping includes genetic, metabolic, transcriptional, and environmental factors to help determine the pathophysiology [199].

Genetic research has been progressing for a couple decades with illuminating results. There are more than a dozen genetic variants that have been associated with this family of diseases. Researchers now believe at least 20% of idiopathic pulmonary fibrosis (IPF) patients with multiple family members suffering from IPF have some common familial genetic variants, which may allow researchers to eventually drop the term idiopathic and further define various forms or categories, with differing progression or outcome. The name given to this version of interstitial pneumonias is familial interstitial pneumonia (FIP) [200] [see Fig. 51.10].

Currently two categories of genetic focus have been defined: those genes related to telomere biology (shorter telomeres) and those related to surfactant protein processing. The genes related to shorter telomeres are *TERT*, *TERC*, *hTR*, *DKC1*, and *RTEL1*. More mutations have been found in the *TERT* gene, which encodes the protein component of telomerase, than any other gene. Further research may allow targeted therapies to affect the genetic expression associated with the development of IPF [201, 202]. A common variant within the promoter of the *MUC5B* gene is the most replicated single-nucleotide polymorphism related to familial and sporadic forms of IPF as well as early radiographic findings of IPF [203] (Figs. 51.9 and 51.10).

Locus	Gene	SNP	IPF risk	IPF survival
2q14	*IL1RN*	rs408392	Yes	
		rs419598	Yes	
		rs2637988	Yes	
3q26	*hTR*	rs6793295	Yes	
4q13	*IL8*	rs4073	Yes	
		rs2227307	Yes	
4q22	*FAM13A*	rs2609255	Yes	
4q35	*TLR3*	rs3775291		Harmful
5p15	*TERT*	rs2736100	Yes	
6p21	*CDKN1A*	rs2395655	Yes	Harmful
6p21	*HLA-DRB1*		Yes	
6p24	*DSP*	rs2076295	Yes	
7q22	Intergenic	rs47274443	Yes	
10q24	*OBFC1*	rs11191865	Yes	
11p15	*MUC5B*	rs35705950	Yes	Protective
	MUC2	rs7934606	Yes	
	TOLLIP	rs111521887	Yes	
	TOLLIP	rs5743894	Yes	
	TOLLIP	rs2743890	Yes	Protective
13q34	*ATP11A*	rs1278769	Yes	
14q21	*MDGA2*	rs7144383	Yes	
15q14-15	Intergenic	rs2034650	Yes	
17q13	*TP53*	rs12951053	No	Harmful
	TP53	rs12602273	No	Harmful
17q21	*MAPT*	rs19819997	Yes	
17q21	*SPPL2C*	rs17690703	Yes	
19q13	*DPP9*	rs12610495	Yes	
19q13	*TGFB1*	rs1800470	No	Harmful

Fig. 51.9 Summary of common genetic variants linked to (IPF). (Reproduced with permission of the © ERS 2019: European Respiratory Journal 33(1):99–106. ► https://doi.org/10.1183/09031936.00091607. Published 31 December 2008)

Gene	Reported % of FIP
TERT	8-15%
RTEL1	5%
hTR	<1%
DKC1	<1%
TINF2	<1%
SFTPC	2-25%
SFTPA2	<1%
ABCA3	<1%
Unknown	75-85%

Fig. 51.10 Rare genetic variants linked to familial interstitial pneumonia (FIP). (Reproduced with permission of the © ERS 2019: *European Respiratory Journal*. 33(1):99–106. ► https://doi.org/10.1183/09031936.00091607. Published 31 December 2008)

51.8.4.2 Conventional Treatment

Conventional treatment is typically palliative. The American Thoracic Society recognizes that supplemental oxygen and transplantation are the only suggested treatments for IPF. Supplemental oxygen is prescribed, and the need for oxygen increases over the progression of the disease. Keeping the oxygen saturation level over 90% (normal is in the upper 90s) is ideal and is how healthcare providers determine the level of supplemental oxygen to be used. Cardiovascular exercise, in this case called pulmonary rehabilitation, is recommended to maintain as much use of the lungs as possible.

Infrequently, nutrition and counseling are recommended and are placed into the category of symptom management. Nutrition can have a significant role in the management of this disease, but little implementation exists in some of the proposed protocols.

There are currently two medications available in the United States with minor impact on the disease progression: nintedanib (commonly called Ofev) and pirfenidone (Esbriet). Histopathological quantification showed similar amounts of dense collagen fibrosis, fibroblast foci, and alveolar macrophages in untreated or pirfenidone- or nintedanib-treated IPF patients [204]. Both have significant side effects, including fatigue and GI issues, and patients may have to evaluate their quality of life versus length of life. Other anti-inflammatories or immune-suppressing medications used are corticosteroids, mycophenolate mofetil/mycophenolic acid (CellCept®), or azathioprine (Imuran®). Immune-suppressing drugs may be harmful for those with short telomeres, and researchers are exploring this potentially contradictory recommendation [205].

Lung transplantation is a final effort. About 1,000 lung transplants in the United States go to those with PF, which

is half of all transplants. With the prevalence of this disease closer to 200,000, this is a small fraction of those with the disease. Some of those with the transplant go on to live productive lives, while others develop PF again, in the transplanted lungs. Overall, there is a shorter life expectancy in those with PF, because of telomere shortening. Bone marrow or immune response abnormalities have been found in some IPF cases before and after lung transplantation, which increases the associated morbidity.

51.8.4.3 Integrative and Functional Nutrition Medical Therapy

As stated above, inflammation occurs at the beginning and throughout the progression of all fibrosing diseases, including those of the lungs. Therefore, reducing inflammation is one wise strategy to slow fibrosing. There are several nutrients that can help slow or reverse the inflammation involved in the fibrosing process. The following two-part diagram shows where in the fibrosing pathogenesis each phytonutrient acts [198] (◘ Fig. 51.11).

A few of those compounds are discussed in more detail here.

Curcumin, the active constituent in the common spice turmeric, has been shown to reduce fibrotic activity in several studies. In mice, curcumin inhibited collagen secretion of IPF fibroblasts. It affects the signaling of TGF-β, in a dose-specific manner, resulting in reduced expression of α-SMA, which is responsible for inappropriate fibrosing. This was shown in vitro and in vivo in mice, with intraperitoneal, but not oral, administration. At the time of the study, oral ingestion of curcumin was not adequately absorbed into plasma, and there was greater than ten times plasma concentration of curcumin following an intraperitoneal injection [88]. However, some new oral products on the market are showing greater absorption.

The results of this study suggest more research into curcumin, including improved delivery into patients. For example, some delivery options may include nebulized curcumin directly into the lungs, binding it to highly absorbable agents for oral use or liposome-encapsulated curcumin suitable for intravenous use (already shown to be effective in an animal model).

According to manufacturers of curcumin products, some are more readily absorbed than others. One study on fibrosing suggested that a dose of around 2200 mg curcumin split into three doses taken with meals including pepper (bioperine) achieved doses that were sufficient to exert the desired therapeutic effect.

Research into using quercetin also has some promising results in slowing the progression of IPF. Quercetin reversed lung fibrosing in mice and reversed the disease progression normally caused by typical pulmonary senescence markers [206].

It is worth mentioning that N-acetylcysteine (NAC), a long-used therapeutic agent for breaking down mucus in the lungs, has not been found to be effective in those with IPF. In fact, due to its acidic nature, it has even been shown to be harmful when used in the inhaled form [207].

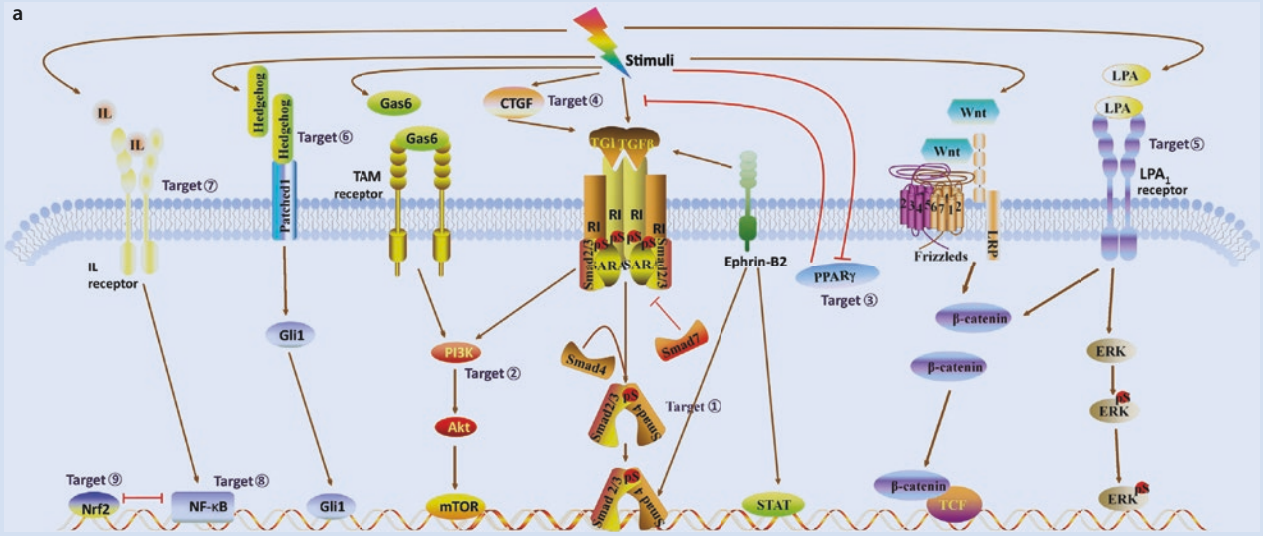
Several of the drugs being developed have a natural product as a model or foundation. Until a drug or gene therapy is developed that stops or reverses this disease, it may make sense for the patient to focus on anti-inflammation and reducing myofibroblast activation, the extracellular matrix (ECM) accumulation, and the epithelial-mesenchymal transition (EMT) process. The phytochemicals listed in ◘ Fig. 51.11 would be good ones to investigate.

51.8.4.4 Genetics and Telomeres

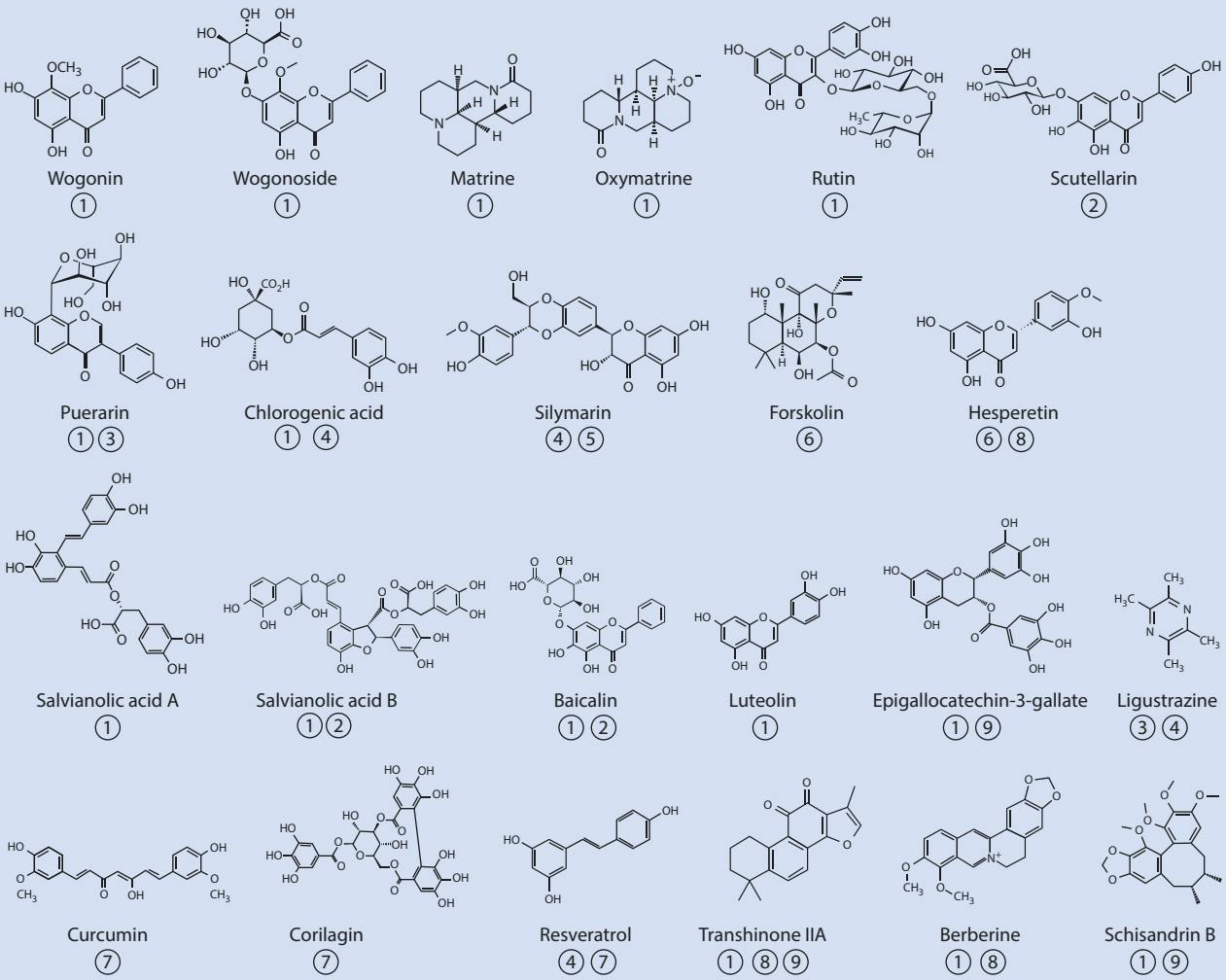
With the recent identification of genes associated with ILD, a call for gene-related therapies both related to telomere lengthening and connective tissue disease has been initiated, and this type of therapy, as with any disease, could be personalized [208]. One recent study looked at various biomarker values as a more precise way of diagnosing. The biomarker molecules were classified according to their involvement into alveolar epithelial cell injury, fibroproliferation, and matrix remodeling as well as immune regulation. Furthermore, genetic variants of TOLLIP, MUC-5B, and other genes associated with a differential response to treatment and with the development and/or the prognosis of IPF were identified. Research into personalized medicine for treatment is starting [209].

Although controversial, because of the lack of research on interpretation of the results, telomere length testing is available directly to consumers and through healthcare

◘ **Fig. 51.11** Antifibrosis therapy. The molecular mechanisms and therapeutic targets of natural products against fibrosis. **a** TGF-b exerts a profibrotic effect through Smad-dependent [Target (1)] and Smad-independent pathways [Target (2)]. In the Smad-dependent pathway, TGF-b1 directly phosphorylates and activates the downstream mediator Smad2 and Smad3 through TGF-b receptor I, and then Smad2 and Smad3 bind Smad4, which forms a complex that moves into the nucleus and initiates gene transcription. Smad7, transcribed by Smad3, is a negative regulator of TGF-b/Smad signaling, and the imbalance between Smad3 and Smad7 contributes to fibrosis. PI3K, ERK, and p38 MAPK are downstream mediators of the Smad-independent TGF-b pathway. PPARg [Target (3)] could inhibit TGF-b to reduce fibrosis, while CTGF [Target (4)], a matricellular protein, contributes to wound healing and virtually all fibrotic pathology. Additionally, Gas6 contributes to fibrosis through the TAM receptor, which further activates the PI3K/Akt pathway. Similarly, LPA triggers fibrosis through the LPA1 receptor [Target (5)] that stimulates b-catenin to induce fibrogenesis. The activation of the hedgehog pathway [Target (6)] induces the transcriptional activity of Gli to express target genes, which have an important role in interstitial fibrosis, undergoing myofibroblast transformation and proliferation. IL pathway [Target (7)] stimulates NF-kB [Target (8)] to activate TGF-b to induce fibrogenesis, while Nrf2 [Target (9)] antagonizes NF-kB activity to protect against fibrosis. **b** The chemical structures of isolated compounds and their therapeutic targets are presented. CTGF, connective tissue growth factor; IL, interleukin; LRP, low-density lipoprotein receptor-related protein; RI, transforming growth factor-b receptor I; RII, transforming growth factor-b receptor II; SARA, Smad anchor for receptor activation; STAT, signal transducer and activator of transcription; TCF, T-cell factor; TGF, transforming growth factor. (Reprinted from Chen et al. [198]. With permission from Elsevier)


a
Stimuli
IL
IL
Target⑦
IL receptor
Hedgehog
Hedgehog
Patched1
Target⑥
Gas6
Gas6
TAM receptor
CTGF
Target④
TGFβ
RI
RII
Smad2/3
Smad4
Smad7
Ephrin-B2
PPARγ
Target③
Wnt
Wnt
Frizzleds
LRP
β-catenin
β-catenin
TCF
LPA
LPA
Target⑤
LPA1 receptor
ERK
ERK
Gli1
Gli1
PI3K
Target②
Akt
mTOR
Target①
STAT
Target⑨
Nrf2
Target⑧
NF-κB

b


Wogonin ①
Wogonoside ①
Matrine ①
Oxymatrine ①
Rutin ①
Scutellarin ②
Puerarin ①③
Chlorogenic acid ①④
Silymarin ④⑤
Forskolin ⑥
Hesperetin ⑥⑧
Salvianolic acid A ①
Salvianolic acid B ①②
Baicalin ①②
Luteolin ①
Epigallocatechin-3-gallate ①⑨
Ligustrazine ③④
Curcumin ⑦
Corilagin ⑦
Resveratrol ④⑦
Transhinone IIA ①⑧⑨
Berberine ①⑧
Schisandrin B ①⑨

practitioners. There are a few different methods: quantitative polymerase chain reaction, or qPCR, which has a 20% variability rate, and flow cytometry and fluorescent in situ hybridization, or Flow-FISH, which has a 5% variability rate. Most research labs use Flow-FISH for research.

Telomere length is a hot topic in research, the antiaging industry, and with popular health blogs. Shorter-than-average telomeres have also been linked to heart disease and heart failure [163, 210, 211], cancer [212], diabetes [213], and osteoporosis [214]. Research has shown ways to slow telomere shortening. Some include reducing stress, meditation, practicing loving kindness (a technique encouraging compassion) [215], reducing exposure to air pollution and toxins [216], cardiovascular exercise [217], and a healthy fat and high vegetable diet [218, 219]. One study showed that 45 minutes of cardiovascular exercise three times per week resulted in longer telomeres representing 10 years of biological age, similar to those of marathon runners, compared to those who didn't exercise much or at all [220]. Intermittent fasting, which reduces oxidative stress and keeps weight in check, has exploded in the scientific literature as a way to increase longevity and slow telomere shortening [221, 222].

Nicotinamide adenine dinucleotide (NAD+) supplements may also help maintain telomere length by activating sirtuins, the antiaging enzymes; PARPs, which are involved in DNA repair; and CD38, which plays a role in insulin production. Another supplement, cycloastragenol, derived from the herb astragalus, has also been shown to activate telomerase in mice. An ingredient called TA-65 has been derived and is used in supplements [223].

Overall, a healthy lifestyle and diet seem to delay the shortening of telomeres. With relation to PF, the gene mutations involved in telomere shortening may or may not be influenced by the above interventions. More research is needed for this.

Pulmonary fibrosis is a devastating disease with no management or a known cure. The integrative and functional medicine nutritionist can help her/his patient by managing weight, encouraging a healthy diet full of anti-inflammatory foods and encouraging a healthy lifestyle with exercise and stress reduction. There is some promising research into natural supplement use to target the different areas of progression within the disease process and some ongoing drug and gene therapy development to follow.

51.9 Conclusion

The prevalence of lung disease in the United States and worldwide is growing and will continue to grow rapidly with the deterioration of Earth's atmosphere, which is caused by pollutants such as industrial and construction toxins and volcanic and wildfire particulates. Poor maternal, childhood, and adult nutrition from micronutrient-poor diets resulting in nutrient insufficiencies, not necessarily nutrient *deficiencies*, is also contributing to increased lung disease diagnoses or poorer results during treatment [226, 227]. Lifestyle choices and habits also play a role in the development of many of the lung diseases in today's world, such as smoking or vaping, which uses chemicals that are poorly studied to date. Other lung diseases have their roots in genetics.

Some key processes drive many lung diseases, with the inflammatory process being the most important, according to current literature. Nutrition can be of great help with inflammation, using a diet rich in whole foods providing micronutrients and phytonutrients. Understanding genetics is also key to unraveling the causes and potential future treatments for many lung diseases. Those patients with both genetic and environmental determinants, such as in those who smoke and have genes associated with COPD, are at the greatest risk [228].

Despite the prevalence of lung disease, there is a general lack of nutrition knowledge among practitioners, including familiarity with the research about the use of nutrition for prevention, slowing disease progression, or as a treatment of lung disease. Historically, nutrition has been used in a supportive role, primarily monitoring macronutrients to prevent weight loss, muscle atrophy, and acid/alkaline balance. Although this is extremely important, more attention needs to be directed toward emphasizing micronutrients and phytonutrients. Research is strong regarding the benefits of vitamins, minerals, and pre- and probiotics, and indeed, some integrative and functional practitioners are using vitamin and mineral nutritional therapy in oral, intramuscular, and intravenous applications, when allowed, in practice. A newer area of research is around nutraceuticals, including targeted vitamins, minerals, and plant-derived constituents concentrated to therapeutic doses. Some exciting research around the use of curcumin and quercetin, for example, has been shown to dampen inflammation to the point of disrupting the disease process (see above). The expanding knowledge of the microbiome is identifying the importance of the lung and airway microbiome in respiratory health.

More research, and indeed more education for nutritionists around the existing research, is needed to fully understand the best opportunities for the use of nutrition in the treatment or prevention of lung disease.

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