Chapter 4

Corticosteroids and Their Use in Respiratory Disorders

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Additional information is available at the end of the chapter

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Abstract

Corticosteroids are adrenal hormones that play important physiologic roles including modulation of glucose metabolism, protein catabolism, alteration of calcium metabolism, regulation of bone turnover, suppression of immune system, and down-regulation of the inflammatory cascade. Because of their diverse effects, corticosteroids have been used therapeutically for treating a wide variety of auto-immune, rheumatologic, inflammatory, neoplastic and infectious diseases. In the field of pulmonology, corticosteroids have been used for the treatment of reactive airway diseases (such as asthma and allergic bronchopulmonary aspergillosis), chronic obstructive pulmonary disease, sarcoidosis, collagen vascular diseases (such as vasculitic disorders), eosinophilic pneumonitis, idiopathic interstitial pneumonias and infectious disorders (such as laryngotracheobronchitis). Different formulations of corticosteroids are commercially available including tablets, intravenous injections, intramuscular formulations and inhaled preparations. Long-term use of corticosteroids is often limited by their adverse effects, which include abnormal fat deposition, weight gain, diabetes mellitus, cataracts, glaucoma, osteoporosis, osteonecrosis, elevated risk of fractures, increased susceptibility to infections, proximal myopathy, depression, psychosis, adrenal atrophy with risk of Addisonian crisis, abdominal striae, acne vulgaris, delayed wound healing, easy bruising, electrolyte abnormalities and increased risk of peptic ulcer disease. As our understanding of corticosteroids advances, we may be able to identify individuals at higher risk of experiencing adverse effects.

Keywords: corticosteroids, glucocorticoids, respiratory diseases, airway disorders, asthma, chronic obstructive pulmonary disease, pneumonia, sarcoidosis

1. Introduction to corticosteroids

Corticosteroids are steroid hormones produced by the adrenal gland. Adrenal glands constitute the endocrine system of the body and are a pair of pyramidal shaped glands located

just above the kidneys on either side of the body. Because of their location, they are also known as suprarenal glands and are perfused by suprarenal arteries, which arise on either side from renal arteries [1]. These endocrine glands are important as they secrete a number of hormones into the blood, which play a vital role in maintaining homeostasis. With respect to the structure of the adrenal glands, they consist of an outer cortex and inner medulla. The adrenal medulla secretes catecholamines (epinephrine and norepinephrine), which are stress hormones and are mediators of the sympathetic autonomic nervous system [2]. The adrenal cortex itself comprises of three layers viz. zona glomerulosa, zona fasciculata and zona reticularis. These three layers are responsible for secreting mineralocorticoids, glucocorticoids, and adrenal androgens (sex hormones) respectively [3]. As the name suggests, mineralocorticoids are responsible for maintenance of fluid and mineral (electrolyte) balance; the chief mineralocorticoid is aldosterone. Glucocorticoids are involved in regulating glucose metabolism (glycolysis and gluconeogenesis) and storage (glycogenesis and glycogenolysis); the prototype glucocorticoid is cortisol. The primary adrenal androgen is dehydroepiandrosterone and possesses virilizing properties. Cortisol and other related hormones (such as 11-deoxycortisol and corticosterone) are collectively referred to as corticosteroids [4].

2. Physiologic effects

Corticosteroids play important physiologic roles in the human body and are referred to as "stress hormones" as they prepare the body during periods of physiologic stress. One of the most important actions of corticosteroids is their ability to up-regulate glucose synthesis [5]. Glycogen is the principal storage form of glucose in humans and is stored in various organs of the body, especially the liver. Glycogen is a multibranched polysaccharide and its structure consists of a core protein (glycogenin), which gives off multiple branches composed of glucose monomers [6]. Glycogen is produced by a biochemical pathway known as glycogenesis, which occurs chiefly in the liver. Glycogen is broken down during periods of fasting to provide a supply of glucose monomers. Glucose monomers can be utilized by all cells of the body through the processes of glycolysis. Pyruvate produced during glycolysis can then produce acetyl-CoA which can enter the Krebs cycle. Oxidation of glucose (in conjunction with the electron transport chain) produces adenosine 1,4,5-triphosphate (ATP), which is the energy currency of the cell. Stress hormones (such as catecholamines) generally up-regulate gluconeogenesis and glycogenolysis to induce hyperglycemia, which helps in fulfilling energy demands of various cells of the body [7]. Corticosteroids also induce fasting hyperglycemia by up-regulating gluconeogenesis; this is achieved by increasing expression of several key enzymes involved in gluconeogenesis including phosphoenol pyruvate-carboxykinase, fructose-1,6-bisphosphatase and glucose-6-phosphatase [8]. Cortisol and other corticosteroids are unique in that they up-regulate gluconeogenesis while inhibiting glycogenolysis. This seemingly contradictory effect of corticosteroids is important in intrauterine life when release of cortisol from the fetal adrenal gland helps in building glycogen stores in the fetal liver to prepare for delivery.

Protein metabolism is also affected by corticosteroids. Increased catabolism of proteins to amino acids provides a supply of alanine, which can be converted to glucose by the process of gluconeogenesis. Cahill cycle (glucose-alanine cycle) refers to a series of chemical reactions in which

amino groups and carbon skeletons from muscles are transported to the liver in the form of alanine, which are subsequently converted to glucose [9]. An essential enzyme for Cahill cycle is alanine aminotransferase (ALT), which is present in both muscles and liver. Alanine aminotransferase (also known as serum glutamate-pyruvate transaminase [SGPT]) is responsible for transferring an amino group from alanine to α-ketoglutarate, which results in the production of pyruvate and glutamate [10]. Pyridoxal phosphate is a co-factor for this reaction and is formed from pyridoxine (vitamin B_6). As corticosteroids up-regulate protein catabolism, they induce a state of negative nitrogen balance in the body, which is important during periods of starvation.

Corticosteroids have important effects on bone turnover and affect bone mass. Bone is a type of connective tissue composed of osteocytes, osteoblasts and osteoclasts [11]. Osteoclasts are derivatives of the reticuloendothelial system and are responsible for bone resorption. Osteoblasts are mesenchymal origin cells and are responsible for giving rise to osteocytes—the mature cells that make up bones. Osteoclasts and their progenitors express a receptor on their surface for nuclear factor-κB (NFκB) commonly referred to as RANK. Ligand for RANK (known as RANKL) is expressed on the surface of osteoblasts and RANK–RANKL interaction is necessary for the differentiation and formation of osteoclasts [12]. Osteoprotegerin (OPG) is a cytokine receptor that is secreted by stromal cells and osteoblasts, which acts as a decoy receptor for RANKL. Secretion of OPG is one of the mechanisms by which the body prevents excessive resorption of bones. Due to this reason, OPG is sometimes also referred to as "osteoclastogenesis inhibitory factor." Corticosteroids can affect bone turnover by inhibiting the secretion of OPG and increasing RANK–RANKL interaction, which leads to enhanced formation of osteoclasts. By tipping the balance in favor of osteoclasts, corticosteroids favor bone resorption and loss of mineral bone mass [13]. Calcium homeostasis in the body is tightly regulated by a number of hormones including parathyroid hormone (PTH), calcitonin and other hormones. Under physiologic conditions, serum calcium level is not drastically affected by corticosteroids. However, in pathologic states including Cushing's syndrome and Addison's disease, hypocalcemia and hypercalcemia (respectively) may be occasionally seen.

Vascular tone is also affected by corticosteroids, which has important implications during states of physiologic stress. Under resting conditions, cortisol and other corticosteroids are not necessary for maintaining vascular tone. However, during periods of stress, corticosteroids have a "permissive effect" for catecholamines and help in maintaining the vascular tone [14]. In patients with severe deficiency of glucocorticoids (such as Addison's disease), catecholamines are ineffective in increasing the blood pressure; this may manifest clinically as overt or orthostatic hypotension. This is especially important for patients with severe sepsis (or septic shock), myxedema coma, pituitary apoplexy and other diseases. Presence of stress hormones (including thyroid hormones and corticosteroids) is necessary for the optimal action of catecholamines, which helps in the maintenance of vascular tone and blood pressure [15]. This in turn maintains adequate perfusion of vital organs and allows the body to cope with physiologic stress.

Fluid status of the body is principally controlled by steroid hormones. Mineralocorticoids (such as aldosterone) are primarily responsible for maintaining the fluid and salt balance in the body. Renin is a hormone secreted by the juxtaglomerular apparatus of nephrons, which is responsible for cleaving angiotensinogen to angiotensin I. Angiotensinogen is produced in the liver and is a precursor to angiotensin I, which is produced in the circulation by action of renin. Angiotensin

I is then converted to angiotensin II in the pulmonary microvasculature through the action of dipeptidyl peptidase (commonly referred to as angiotensin converting enzyme [ACE]) [16]. Angiotensin II has at least four important effects in the body: (a) stimulation of aldosterone synthesis and secretion; (b) increasing thirst; (c) vasoconstriction; and (d) enhancing activity of sodium (Na^+)-hydrogen (H^+) exchanger in the proximal convoluted tubule of nephrons. The overall impact of angiotensin II is to retain salt and water with expansion of the effective circulating volume [17]. Aldosterone leads to further expansion of the extracellular fluid by increasing reabsorption of sodium (Na^+) and chloride (Cl^-) in the distal convoluted tubule of nephrons. At the same time, aldosterone increases tubular secretion of potassium (K^+) and loss of hydrogen (H^+) ions in the urine, which can potentially induce hypokalemia and metabolic alkalosis respectively. The overall effect of the renin–angiotensin–aldosterone system (RAAS) is to retain salt and water, thereby expanding the effective circulating volume and blood pressure. Although corticosteroids possess mainly glucocorticoid effects, they do have weak mineralocorticoid effects at physiologic concentrations. In disease states, and when used therapeutically, corticosteroids can have substantial mineralocorticoid activity with clinically significant effects on the body [18].

A number of other effects are also possessed by corticosteroids, which are not evident in physiologic states; however, in disease states, these actions can result in protean manifestations. Corticosteroids are necessary for optimal functioning of the body and excess or deficiency of these hormones can manifest as Cushing's syndrome or Addison's disease respectively. Cushing syndrome is most commonly iatrogenic and results from exogenous use of steroids, although it can also result from cortisol or adrenocorticotrophic hormone (ACTH)-secreting tumors (such as pituitary adenoma, adrenal adenoma or carcinoma, small cell carcinoma of lung, etc.) [19]. Common features of this disease include obesity, buffalo lump (lipodystrophy), moon facies, purple abdominal striae, easy bruising, depression, psychosis, cataracts, glaucoma, hypertension, hypokalemia and hypocalcemia. On the other hand, Addison's disease can be caused by auto-immune destruction of the adrenal gland (in developed countries) or infiltration of the adrenal gland by infections such as tuberculosis (in developing countries). Hypocortisolism manifests as weakness, fatigue, weight loss, hyperpigmentation of skin (due to increased release of ACTH from the pituitary gland), hyponatremia, hyperkalemia, orthostatic or resting hypotension, hypercalcemia, basophilia and/or eosinophilia [20]. Treatment of these diseases is directed at restoring the balance of steroid hormones back to normal. In the case of Cushing syndrome, the underlying cause is addressed (e.g. removal of primary tumor); rarely, bilateral adrenalectomy with exogenous replacement of steroids may be required. In Addison's disease, replacement of steroid hormones is generally needed for life. These two diseases exemplify the importance of corticosteroids and the deleterious consequences of their excess or deficiency on the human body.

3. Mechanism of action

From a therapeutic standpoint, corticosteroids have been exploited most for their anti-inflammatory and immunosuppressive effects [21]. While these properties of corticosteroids are not evident during physiologic states, they are clinically important in the treatment of numerous diseases including auto-immune diseases, neoplastic diseases, inflammatory disorders, rheumatologic conditions and infectious diseases (in conjunction with other drugs).

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Inflammation is the response of the body to any noxious stimulus with an aim to eliminate the noxious stimulus and start the process of tissue repair. Inflammatory response of the body involves leukocytes, chemical mediators and vascular changes. Acute inflammation begins with a series of vascular changes that increases blood flow to the inflamed tissue. Chemical mediators of inflammation, such as histamine and serotonin, cause arteriolar vasodilation and venous vasoconstriction. This in turn promotes the exudation of fluid from the intravascular compartment to the interstitial space [22]. Leukocytes are then recruited to the area of inflammation through the expression of selectins on endothelium and integrins on leukocytes. Selectins are responsible for weak binding of leukocytes to the endothelium, which results in "rolling" of leukocytes along the endothelium. On the other hand, integrins are responsible for high-affinity binding of leukocytes ("adhesion") to the endothelium with pavementing of the endothelium with leukocytes. Through the interaction of various cell surface molecules, such as platelet–endothelial cell adhesion molecule-1 (PECAM-1), leukocytes migrate through the microvasculature into the interstitium [23]. Neutrophils, monocytes and macrophages can phagocytose microbes and other offending agents by binding to their pathogen-associated molecular patterns (PAMPs) using pattern recognition receptors (PRRs). Following phagocytosis, microbes are trapped inside vacuoles called "phagosomes," which are then fused with lysosomes to form phagolysosomes. Microbes and dead cells are thus degraded through the action of hydrolytic enzymes present inside lysosomes. Neutrophils and macrophages can also generate free radicals through the action of enzymes, which can damage different micro-organisms and offending agents [24].

A number of chemical mediators play a crucial role in the process of inflammation. These include biogenic amines, prostaglandins, leukotrienes, lipoxins, cytokines, chemokines, complement proteins, bradykinin, nitric oxide and other molecules [25]. Histamine and serotonin are biogenic amines and mediate vascular changes implicated in acute inflammation; histamine also causes bronchoconstriction. Prostaglandins are eicosanoids and have a variety of actions in the body. PGE_2 is the mediator of pain, $PGF_{2\alpha}$ causes increased vascular permeability, PGI_2 (prostacyclin) causes vasodilation and thromboxane A_2 causes platelet aggregation and vasoconstriction. Leukotrienes are derivatives of arachidonic acid and mediate bronchoconstriction. Lipoxins are lipid-derived autacoids that have a modulatory effect on the overall process of inflammation [26]. Bradykinin is a product of the kinin cascade and is derived by the action of kallikrein on high-molecular weight kininogen. This molecule irritates bronchiolar smooth muscle and mediates cough and vasodilation. Nitric oxide is released from endothelium and causes vasodilation. Complement cascade plays an important role in inflammation and is a part of the humoral immune system. Some complement proteins act as opsonins and anaphylatoxins. C5a, a complement protein, also causes chemotaxis of leukocytes to the area of inflammation. Cytokines are a group of small protein molecules that play various roles in the body including chemotaxis of leukocytes (chemokines), communication between leukocytes (interleukins), mounting fever (pyrogens) and so on [27]. All these chemical mediators play a crucial role in mounting an inflammatory response and pharmacologic interruption of their actions can blunt or modulate the inflammatory response.

Phospholipase A_2 is an enzyme that is responsible for the synthesis of arachidonic acid from phospholipids present in cell membranes of various cells. Arachidonic acid is an important lipophilic compound that serves as the precursor for the synthesis of prostaglandins, thromboxane A_2, leukotrienes and lipoxins (**Figure 1**). Cyclooxygenase is an enzyme that is responsible

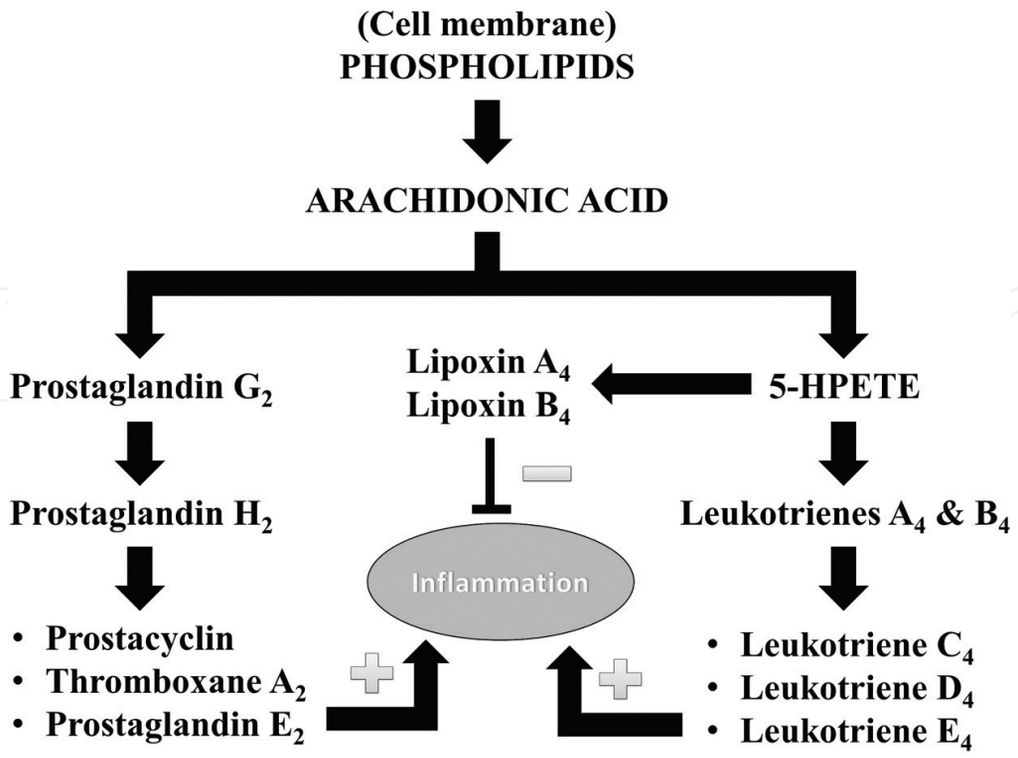

Figure 1. Arachidonic acid metabolism with cyclooxygenase and lipoxygenase pathways. *HPETE* = hydroperoxyeicosatetraenoic acid.

for the formation of prostaglandins from arachidonic acid. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen exert their anti-inflammatory effects by inhibiting cyclooxygenase and preventing formation of prostaglandins and thromboxane [28]. Arachidonic acid can also be acted upon by 12-lipoxygenase that results in the formation of lipoxins A_4 and B_4, both of which modulate inflammation by inhibiting neutrophil adhesion and chemotaxis. Another enzyme, 5-lipoxygenase, is involved in the synthesis of leukotrienes from arachidonic acid. Leukotrienes C_4, D_4 and E_4 induce bronchospasm, vasoconstriction and increased vascular permeability. Synthesis of arachidonic acid is inhibited by corticosteroids and this effect of corticosteroids is exploited therapeutically for treating inflammatory disorders [29].

The anti-inflammatory effects of corticosteroids are chiefly achieved by altering the synthesis of chemical mediators of inflammation. When commercially available corticosteroids are administered therapeutically, these molecules are readily absorbed and penetrate into various cells of the body due to their highly lipophilic nature. Glucocorticoids enter the cytosol of cells and bind to the glucocorticoid receptor. The glucocorticoid–receptor complex can repress the expression of pro-inflammatory genes by preventing translocation of certain transcription factors (especially NFκB) from the cytosol into the nucleus [30]. Moreover, the glucocorticoid–receptor complex can translocate into the nucleus and up-regulate transcription of anti-inflammatory genes by binding to "zing fingers" of glucocorticoid-response elements (GRE). Glucocorticoids inhibit translocation of NFκB by inducing the expression of IκB*α* inhibitory protein, which sequesters NFκB in the cytosol and prevents transcription of pro-inflammatory genes [31]. This is in turn inhibits the expression of pro-inflammatory genes and results in a blunted inflammatory response.

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One of the most important effects of glucocorticoids is the modulation of gene expression of enzymes involved in the metabolism of arachidonic acid. Most notably, glucocorticoids reduce the expression of the enzyme phospholipase A_2, which is responsible for the formation of arachidonic acid [32]. By inhibiting the formation of arachidonic acid, synthesis of prostaglandins, lipoxins, leukotrienes and thromboxane is inhibited. Since arachidonic acid metabolites mediate several key steps in the process of inflammation, their inhibition results in a blunted inflammatory response. Consequently, margination, chemotaxis and phagocytosis by phagocytes are inhibited by corticosteroids, which manifests as an overall anti-inflammatory effect. Additionally, through inhibition of the NFκB pathway, inflammatory cells begin to produce anti-inflammatory cytokines, which down-regulate the overall immune and inflammatory response. This has important therapeutic implications for the treatment of many diseases in which chronic inflammation lies at the core of their pathogenesis [33].

4. Formulations

Different formulations of corticosteroids are commercially available and have been used in a variety of diseases. Tablets, intravenous formulations and intramuscular preparations are available for systemic use. Systemic formulations are generally more efficacious as compared to other formulations (such as inhaled or topical steroids). However, this greater efficacy comes at the cost of increased adverse effects, which may be substantial in some cases [34]. Oral formulations are available for various corticosteroids with the most popular ones being prednisolone, methylprednisolone, hydrocortisone, and dexamethasone. Given the lipophilic nature of steroids, adequate absorption of steroids is achieved in most patients as they readily cross cell membranes of enterocytes [35]. Oral formulations are convenient for patients who require chronic use of steroids, such as lung transplant recipients. Tablets are the most commonly used oral formulation of corticosteroids. Prednisone syrup and dexamethasone oral solution or elixirs are also available, which may be useful for pediatric patients and those with feeding tubes. Conversion from one systemic steroid to another requires knowledge of equipotent dosages, which are provided in **Table 1**. Frequency of dosage is determined by the half-life and duration of action for individual corticosteroids; for instance, hydrocortisone lasts for 8–12 hours whereas dexamethasone may last for 36–72 hours [36].

Parenteral systemic formulations of steroids are also available and have a number of important uses. Intramuscular preparations of steroids, such as methylprednisolone or triamcinolone acetonide, are often used to provide a delayed release of steroids over a prolonged period of time with a relatively steady plasma concentration. Intravenous methylprednisolone and hydrocortisone are often used in patients with life-threatening or organ-threatening inflammatory conditions. Very high doses of steroids can be given intravenously (termed 'pulse therapy'), which have been postulated to have physicochemical effects on plasmalemma of various cells, which may modulate the function of transmembrane proteins [37]. Steroid therapy has also been employed via many other parenteral routes of administration. Intralesional triamcinolone acetonide injections have been used for the treatment of several dermatologic disorders, such as keloids, alopecia areata, granuloma annulare, lichen planus and psoriasis.

Steroids	Dexamethasone	Methylprednisolone	Prednisone	Hydrocortisone	Fludrocortisone
Glucocorticoid effect*	0.75 mg	4 mg	5 mg	20 mg	-
Mineralocorticoid effect*	-	-	50 mg	20 mg	100 mcg
Duration of action	36–72 hours (long)	12–36 hours (intermediate)	12–36 hours (intermediate)	8–12 hours (short)	12–36 hours (intermediate)

*Fludrocortisone has no glucocorticoid effect, while dexamethasone and methylprednisolone have negligible mineralocorticoid effects

Table 1. Comparison of equivalent doses of various steroids.

Gout and other inflammatory joint disorders have been treated with intra-articular injections of steroids. In the field of oncology, intrathecal administration of hydrocortisone along with chemotherapeutic drugs has been used for the treatment of leukemia [38].

Inhaled preparations of corticosteroids come in the form of nebulizer solutions, metered-dose inhalers or dry powder inhalers. Inhaled formulations are useful for the treatment of various airway disorders as these preparations exert their maximal effects locally with minimal systemic absorption. Consequently, the risk of systemic adverse effects is reduced, although oral thrush, dysphonia and systemic adverse effects can still occur with long-term use [39]. Most notably, children may have deceleration of growth velocity with the long-term use of corticosteroids [40]. In adults, long-term use of inhaled corticosteroids (ICS) may lead to accelerated loss of bone mass and possible ophthalmic side-effects (such as increased intraocular pressure and/or cataracts) [41]. The most commonly used inhaled steroids include beclomethasone, fluticasone, budesonide and mometasone. Nebulized delivery of respiratory solutions provides the best delivery of medications to the lower airways when compared with metered-dose inhalers or dry powder inhalers. Proper inhaler technique with or without the use of spacer devices may provide equivalent effects with powder/inhaled forms of steroids as compared to nebulizer administrations [42].

Topical formulations of steroids are available for use and have been utilized therapeutically for a wide variety of dermatologic conditions. Like inhaled forms, topical use of steroids provides local effects on the skin with some systemic absorption. Consequently, local effects of steroids are maximized, while systemic side-effects are minimized. However, use of a large amount of topical steroids, especially if continued over a long period of time, can result in significant systemic side-effects (as is the case with inhaled steroids) [43]. A number of vehicles are available for the topical delivery of steroids including ointments, creams, lotions, gels, foams and wet dressings. Topical steroids have been classified on the basis of their potency into 7 categories viz. least potent, low potency, lower-mid potency, medium potency, high potency, very high potency, and super-high potency. Using the correct vehicle and potency of topical steroids is of utmost importance as inadvertent use of a weak steroid preparation may lead to treatment failure, while use of a very potent topical preparation can lead to thinning and atrophy of the skin [44]. It is important to bear in mind that the potency of topical steroids is determined not only by the dermatologic diagnosis, but also by the area and extent of the skin that is affected. For instance, genital skin or intertriginous areas are exquisitely sensitive

to topical steroids, which make them suitable candidates for lower potency topical steroids. On the other hand, skin of palms and soles have thick stratum corneum (the uppermost layer of epidermis), which necessitates the use of more potent topical steroids.

5. Therapeutic use in respiratory disorders

Steroids have been approved for the use of various respiratory diseases for both pediatric and adult populations. Both systemic and inhaled formulations of steroids have been utilized for the treatment of various respiratory disorders. In most disorders, steroids exert a therapeutic effect through their anti-inflammatory or immunosuppressive effects [21]. In many diseases, steroids can be given in the form of short intermittent courses; examples include hypersensitivity pneumonitis, eosinophilic pneumonitis, allergic bronchopulmonary aspergillosis (ABPA), etc. In some diseases, such as bronchial asthma or chronic obstructive pulmonary disease (COPD), inhaled steroids are continued on a long-term basis as a maintenance therapy. Systemic steroid therapy may also be required on a long-term basis in patients with systemic disorders or diseases refractory to other therapies, for instance sarcoidosis or collagen vascular diseases. In many diseases requiring long-term immunosuppression, steroid-sparing agents (such as azathioprine, mycophenolate, cyclosporine, tacrolimus, etc.) can be introduced to taper off steroids and mitigate their long-term side-effects [45].

In the following lines, we discuss the use of corticosteroids in the management of various respiratory disorders. A general overview of each of these diseases is provided and along with a holistic view of how steroid therapy works in conjunction with other components of management.

5.1. Asthma

Bronchial asthma is a chronic inflammatory disorder of bronchi and bronchioles that results in intermittent and reversible bronchospasm [46]. Clinical features of the disorder include recurrent episodes of chest tightness, wheezing and shortness of breath. Most patients have a diurnal variation in their symptoms with worsening shortness of breath and cough towards the end of the day. Over time, patients tend to develop bronchial smooth muscle hypertrophy, goblet cell hyperplasia with hypersecretion of mucus, recruitment of eosinophils and a state of chronic inflammation within the airways. Genetic predisposition to type I hypersensitivity has been demonstrated in most patients with asthma, although environmental factors also play a central role in triggering attacks of asthma [47]. Asthma has been classified into multiple subtypes depending on the type of triggers that precipitate attacks of asthma viz. atopic asthma, non-atopic asthma, drug-induced asthma, occupational asthma, and exercise-induced asthma. Atopic asthma is characterized by a personal or family history of atopy, allergic rhinitis, eczema and hypersensitivity to allergens, such as pollens or dust mites [48]. In non-atopic asthma, patients do not have hypersensitivity responses to allergens; instead, attacks of asthma are precipitated by factors such as viral infections, cold temperature, inhaled gases (e.g. sulfur dioxide), etc. Drug-induced asthma is precipitated by drugs such as NSAIDs or aspirin, which tip the balance towards increased synthesis of leukotrienes with consequent bronchospasm. Likewise, occupational asthma is reportedly precipitated

by exposure to chemicals (e.g. anhydrides, isocyanates, acids) in various industries, such as paints, varnishes, adhesives and resins. Exercise-induced asthma is precipitated by exercise and diagnostic testing at rest may be normal in such cases [49]. Irrespective of the type of asthma, the core pathogenesis underlying all these types of asthma is similar.

The pathogenesis of asthma entails an inflammatory response affecting the bronchi and bronchioles, which is chiefly driven by a type 2 helper T (T_H2) lymphocytes. When an environmental allergen is inhaled, antigen-presenting cells (APCs) engulf the allergen and present it to T lymphocytes. As a consequence of this, a T_H2 cell-mediated inflammatory response is mounted. T_H2 cells produce an array of cytokines including interleukin (IL)-2, IL-4, IL-5 and IL-13. IL-2 acts upon other T lymphocytes to differentiate them into T_H2 cells and promote an amplified response [50]. IL-4 activates B lymphocytes and promotes immunoglobulin class switching to immunoglobulin E (IgE) production. IL-5 acts on bone marrow to increase differentiation and proliferation of eosinophils. Eotaxin is another cytokine produced by airway epithelial cells and serves to recruit eosinophils. IL-13 is believed to stimulate mucus production from mucus glands and goblet cells. Through these cytokines, T_H2 promote a humoral immune response that results in production of high circulating levels of allergen-specific IgE. IgE binds to mast cells and cross-linking of mast cell-bound IgE results in degranulation of mast cells with release of histamine, tryptase and heparin sulfate. Histamine is a potent bronchoconstrictor and is the chief mediator of bronchoconstrictor in atopic asthma. Repeated exposure to the same allergen results in stronger activation of T_H2 lymphocytes. A state of chronic inflammation persists within the bronchioles and results in *airway remodeling*, which is a histopathological hallmark of chronic asthma [51].

Numerous pharmacologic and non-pharmacologic modalities are used in the management of patients with asthma. Non-pharmacologic approaches include avoidance of allergens by removing carpets from houses, avoiding exposure to animal dander, using personal protective equipment while at work (in cases of occupational asthma), maintaining a clean environment (reducing exposure to dust mites), and so on. Pharmacologic treatment options include short-acting β_2-adrenoceptor agonists (SABA), short-acting muscarinic antagonists (SAMA), long-acting β_2-adrenoceptor agonists (LABA), ICS, phosphodiesterase (PDE) inhibitors (such as theophylline), anti-leukotrienes (such as montelukast), systemic corticosteroids, and immunotherapy (such as omalizumab and mepolizumab) [52]. SABA causes bronchodilation by stimulating β_2-adrenergic receptors on the smooth muscle layer of bronchioles. As β_2-adrenoceptors are G-protein coupled receptors (GPCRs), their stimulation (G_s) results in activation of adenylyl cyclase and increased levels of cyclic adenosine monophosphate (cAMP) inside smooth muscle cells. This in turn activates protein kinase A and results in phosphorylation of myosin light chain kinase, which essentially deactivates this enzyme. Consequently, dephosphorylation of myosin light chain occurs via the unregulated action of myosin light chain phosphatase, which causes smooth muscle relaxation and bronchodilation. PDE inhibitors (such as theophylline and aminophylline) act in a similar manner by inhibiting degradation of cAMP (caused by PDE), which results in increased level of cAMP in smooth muscle cells [53]. This results in bronchodilation in the same manner as SABA, except that the β_2-adrenoceptor and adenylyl cyclase are not involved in this pathway. SAMA causes bronchodilation by blocking muscarinic receptors and preventing vagal stimulation. Moreover, SAMA also blocks muscarinic

M_3 receptors present on smooth muscle cells of bronchioles and prevent bronchoconstriction in response to a variety of stimuli. Anti-leukotrienes effectively block bronchoconstriction in response to leukotrienes C_4, D_4 and E_4 by either blocking their target receptors (montelukast) or reducing their synthesis (zileuton). Omalizumab is a humanized monoclonal antibody directed against free circulating IgE and reduces levels of IgE, thereby reducing sensitivity to allergens [54]. Mepolizumab is an antibody that binds IL-5 and blocks the signaling pathways activated by IL-5 [55]. While mepolizumab reduces activation and recruitment of eosinophils, its exact mechanism of action in the treatment of asthma remains unclear.

Corticosteroids act through multiple pathways in controlling asthma and are useful in the treatment of acute exacerbations of asthma as well as long-term maintenance therapy [56]. Systemic and ICS act in a similar manner and their chief effect is reduction of airway inflammation by blocking the NFκB pathway. Corticosteroids reduce the expression of the enzyme phospholipase A_2, which results in decreased synthesis of arachidonic acid and its metabolites [21]. Reduced levels of leukotrienes promote bronchodilation and relieve airway obstruction. Anti-inflammatory activity of corticosteroid over a long period of time can retard airway remodeling, thereby reducing smooth muscle cell hypertrophy, thickening of the basement membrane, and goblet cell hyperplasia [56]. Corticosteroids also have immunosuppressive properties, which enable them to reduce levels of IgE and inhibit proliferation of T_H2 and B lymphocytes [31]. By reducing transcription of IL-4 and IL-5, corticosteroids also inhibit eosinophil recruitment and activation. Furthermore, by blocking the synthesis of IL-13, mucus secretion is reduced, which can further relieve airway obstruction.

Corticosteroids form a cornerstone of the management of asthma. Management of acute exacerbation of asthma requires accurate assessment of the severity of the exacerbation and appropriate triage [57]. Airway, breathing and circulation need to be secured as in any other emergency condition. Inhaled oxygen and SABA therapy are the first and foremost in the management of acute exacerbations. Intravenous terbutaline (β_2-agonist) may also be used. Systemic corticosteroids should also be administered to all patients with a moderate to severe acute exacerbation of asthma, although their onset of action is after several hours. If patients do not respond to acute SABA therapy, intravenous magnesium sulfate and/or aminophylline infusion may also be considered. Patients with signs of fatigue (such as mental status changes or normalization of arterial carbon dioxide levels) may require endotracheal intubation and mechanical ventilation. In patients with long-standing asthma, a stepwise approach to therapy has been proposed [58]. Again, accurate assessment of asthma control is essential to tailor therapy to individual patients. The first step of therapy consists of non-pharmacologic measures and rescue medication (inhaled SABA) as needed. The second step is to add a low-dose ICS (controlled medication) along with a rescue medication (inhaled SABA) as needed. The third step is to either add LABA along with ICS or to increase the dose of ICS to medium dose. The fourth step is to use LABA along with medium-dose ICS therapy, or to add another agent (such as an anti-leukotriene or a PDE inhibitor). The fifth step is to use high-dose ICS therapy along with LABA with or without other agents mentioned in step 4. The sixth step is the use of systemic corticosteroids and/or immunotherapy along with other therapies as mentioned in steps 1–4. Generally, refer to an asthma specialist should be considered for patients who persistently require step 4 or higher therapies [59].

5.2. Chronic obstructive pulmonary disease

COPD refers to a group of obstructive lung diseases which are characterized by progressive and irreversible limitation to airflow in the setting of a chronic inflammatory state of the airways and/or lung parenchyma. Generally, emphysema and chronic bronchitis are two entities included under the heading of COPD, although these entities are not mutually exclusive and may co-exist in a patient. Emphysema is characterized by destruction of the wall and interstitium of the lung parenchyma leading to irreversible dilatation and enlargement of acini, thereby leading to air trapping within the lungs [60]. Depending on the etiology of emphysema, it can affect either whole of the respiratory acinus (pan-acinar emphysema) or portions of it (centriacinar, distal acinar or irregular emphysema). Clinically, patients with emphysema have been referred to as 'pink puffers' as they tend to have a lean built, breath with pursed lips, are often tachypneic, and appear pink due to hypercapnia (carbon dioxide retention). In contrast, chronic bronchitis is characterized by the presence of a productive cough for ≥3 consecutive months over a period of at least 2 years [61]. Interestingly, chronic bronchitis has a 'clinical' definition as opposed to emphysema, which is defined on the basis of morphologic and histopathological features. Patients with chronic bronchitis often have pathology affecting the larger airways (i.e. bronchi) as opposed to the air-space (parenchymal) disease seen in patients with emphysema. 'Blue bloaters' is a term used to refer to patients with chronic bronchitis as they often have resting cyanosis due to hypoxemia and polycythemia, and fluid retention due to right-sided heart failure ('cor pulmonale'). All patients with COPD do have a number of features in common. All patients have a demonstrable obstructive defect on pulmonary function testing, which differentiates them from those with restrictive lung diseases. Moreover, patients with COPD generally have a progressive, irreversible obstructive process, which differentiates them from the intermittent, reversible obstruction seen in patients with asthma [62]. From a physiologic standpoint, all patients with COPD have a higher than normal lung compliance, which increases the tendency for alveoli to collapse, and makes expiration difficult. Air trapping results in elevated residual volume and increased total lung capacity, but a reduced forced vital capacity. Consequently, patients have an elevated functional residual capacity at rest. Moreover, as the disease process progresses, patients with emphysema develop a defect in diffusion of gases and impaired gas exchange. All these processes increase the work of breathing and impair oxygenation and ventilation [63].

Cigarette smoking has been implicated as the main etiologic factor in the pathogenesis of COPD [64]. Exposure to inhaled pollutants and toxins leads to production of free radicals and oxidant stress that can damage the airway epithelial lining. On-going exposure to such inhaled pollutants leads to accumulation of inflammatory cells (such as neutrophils, macrophages and lymphocytes) with release of proteolytic enzymes and a cascade of pro-inflammatory cytokines. This process of active chronic inflammation leads to destruction of elastin contained in the pulmonary interstitium, which leads to dilatation of acini — the hallmark feature of emphysema. Cigarette smoke in particular has been shown to inhibit α_1-antitrypsin — an enzyme that inhibits neutrophilic elastase and prevents destruction of elastin. Inhibition of α_1-antitrypsin by cigarette smoking leads to unregulated activity of neutrophilic elastase and consequent destruction of acini. Similarly, in patients with congenital deficiency of α_1-antitrypsin, pan-acinar emphysema sets in early in life, in the absence of any history of cigarette smoking [65]. In patients with chronic bronchitis, cigarette smoking leads to hyperplasia

of mucus-secreting glands in the larger airways; this is an adaptive response of the body to the irritants contained in cigarette smoke. Accumulation of mucus plugs, co-existent emphysema and bronchiolitis results in airflow obstruction in patients with clinical features of chronic bronchitis [63]. In cases of both emphysema and chronic bronchitis, the core feature of pathogenesis is on-going exposure to inhaled toxins and a state of chronic inflammation within the smaller airways [60]. This explains why smoking cessation is the most important therapeutic intervention in patients with COPD and reduces overall mortality in such patients.

Corticosteroids have an important role in the overall management of patients with COPD. As is the case with asthma, corticosteroids provide a therapeutic effect in patients with COPD by inhibiting bronchoconstriction, promoting bronchodilation, suppressing the immune response, and having an overall anti-inflammatory effect [66]. In patients with acute exacerbation of COPD, SABA and SAMA are the first-line therapeutic agents. The use of non-invasive positive pressure ventilation (NIPPV) can reduce the need for endotracheal intubation and reduces overall mortality in such patients. Systemic corticosteroids and antibiotics also have an important role in the treatment of acute exacerbation of COPD, although the onset of their action is delayed. Nebulized corticosteroids (such as budesonide) may also be added along with other therapies. In patients with refractory respiratory failure or contraindications to NIPPV, endotracheal intubation and mechanical ventilation may become necessary. In the management of patients with stable COPD, ICS are a cornerstone of therapy. The optimal therapy for such patients is based on their degree of airflow limitation (quantified by the forced expiratory volume in first second of expiration [FEV_1]) and clinical symptoms (quantified by the COPD assessment test [CAT] and/or modified Medical Research Council [mMRC] scores) [67]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifies patients into one of four stages (I–IV) depending on their degree of airflow limitation ($FEV_1 \geq 80\%$, FEV_1 50–79%, FEV_1 30–49% and $FEV_1 < 30\%$ respectively). In patients with GOLD stage III–IV COPD, ICS should be used in conjunction with other therapies [68]. As in patients with asthma, SABA or SAMA are used as rescue medications as needed. LAMA alone or LABA combined with ICS may be combined with ICS depending on the degree of airflow limitation and clinical symptoms in individual patients. Roflumilast, a PDE inhibitor, may also be used in patients with COPD who have frequent exacerbations despite other treatment modalities [69]. In patients with advanced COPD, lung volume reduction surgery or lung transplant may be needed to improve quality of life [70]. In patients with advanced COPD who have a limited life expectancy and/or contraindications to lung transplant, hospice care may be the best strategy to improve patients' symptoms.

5.3. Pneumonia

Pneumonia is a term often used to indicate an infection affecting the pulmonary parenchyma. Pneumonitis is a term that specifically refers to any inflammatory process affecting the pulmonary parenchyma, whether infective in origin or otherwise. However, in different publications, the two terms are often used interchangeably. For the purpose of this chapter, we use the term 'pneumonia' to refer specifically to infections affecting the pulmonary parenchyma.

Pneumonia is an extremely common illness affecting approximately 450 million people a year and is also a leading cause of death among all parts of the world and across all age

groups [71]. In the United States, pneumonia alone accounts for almost one-sixth of all deaths. These figures seem plausible as the epithelial lining of the lungs are continuously exposed to the atmosphere which contains a high burden of pollutants and microbes. Impairment in host immunity, mucociliary apparatus and/or cough reflex can predispose people to the development of pneumonia. Acute bacterial pneumonias tend to have an acute onset of a lobar pneumonia with exudation of fibropurulent material in the alveoli and hepatization (consolidation) of lungs. Intracellular microbes cause an *atypical pneumonia* with a subacute presentation and mononuclear interstitial infiltrates. Chronic pneumonia is usually secondary to fastidious mycobacteria or fungal infections, which lead to granulomatous inflammation and possible cavitation of lung parenchyma. A variety of microbial pathogens can cause pneumonia and the predisposition to infection with a particular organism is determined by several factors, such as age, co-morbidities, vaccination status, use of immunosuppressive drugs, exposure to animals, presence of microbial reservoirs, hospitalization status, presence of endotracheal or tracheostomy tube, alcoholism, smoking, malnutrition, and so on and so forth [72]. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Legionella pneumophila*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis* and *Pneumocystis jiroveci* are some of the well-known causative organisms of pneumonia. While the aforementioned list is by no means exhaustive, a causative organism cannot be isolated in most cases of community acquired pneumonia (CAP) [73]. A number of explanations have been proposed to explain this phenomenon with the most likely explanation being that a significant proportion of patients have pneumonia secondary to viruses, which cannot be isolated by routine microbiological methods.

Corticosteroids are not routinely used in all cases of pneumonia. From a theoretical perspective, the use of corticosteroids in patients with pneumonia would seem counterintuitive. Pneumonia is an infection of the pulmonary parenchyma and use of antimicrobials seems to be the prime management. Corticosteroids have been avoided in most cases of pneumonia due to concerns that their immunosuppressive effects may actually worsen the underlying infection. However, corticosteroids do have a role to play in selected patients with pneumonia. The most well-established use of corticosteroids is in patients with severe *Pneumocystis jiroveci* pneumonia as defined by a resting arterial partial pressure of oxygen (PaO_2) of less than 70 mm Hg or an alveolar–arterial (A–a) gradient of PaO_2 of 35 mm Hg or more (both on room air) [74]. In such patients, corticosteroids have been shown to provide a clear benefit in terms of overall mortality and reduction in respiratory failure. Apart from this, there have been several studies that have assessed the use of steroids in patients with severe pneumonia in general. A randomized placebo-controlled trial by Torres et al. demonstrated that the use of a short course of methylprednisolone among patients with severe CAP reduced treatment failure [75]. A meta-analysis of 12 randomized clinical trials published in 2015 concluded that the use of systemic corticosteroids in adults hospitalized with CAP may reduce overall mortality by 3%, decrease hospital stay by 1 day and cut need for mechanical ventilation by 5% [76]. Clinical guidelines generally recommend that steroids be considered for all patients with CAP requiring hospitalization, especially those requiring admission to the intensive care unit, although the benefits and harms should be weighed on a case-by-case basis.

5.4. Allergic bronchopulmonary aspergillosis

ABPA is a pulmonary disorder characterized by a hypersensitivity reaction to the allergens of the fungus *Aspergillus fumigatus*, which occurs in patients with a history of bronchial asthma or cystic fibrosis (CF). [77] ABPA has been reported to occur in 1–3% of patients with asthma, while in patients with CF, its prevalence may be as high as 10% [78]. *A. fumigatus* is a spore-forming mold that occurs ubiquitously in nature. This fungus is medically important because it has been implicated in a number of diseases viz. ABPA, aspergilloma, invasive pulmonary aspergillosis, allergic fungal rhinosinusitis and bronchial asthma. In patients with long-standing asthma or CF, *A. fumigatus* spores can grow within the lumen of airways and lead to the formation of hyphae (molds). These fungal hyphae can trigger an IgE-mediated hypersensitivity which results in bronchial inflammation and airway destruction. Clinically, ABPA manifests as a worsening of asthma or CF with patients complaining of wheezing and cough. Laboratory investigations may reveal eosinophilia and elevated levels of total IgE. Skin prick tests to *Aspergillus* and precipitins to *A. fumigatus* are positive. Radiologic studies may reveal fleeting pulmonary opacities in the acute stage and signs of central bronchiectasis in longstanding cases. Mucus plugging within the larger airways may be visible on roentgenograms and computed tomograms may lead to a characteristic "finger-in-glove" appearance [77]. A diagnosis of ABPA should be suspected in patients with a history of previously controlled asthma or CF, who develop unexplained worsening of their disease. Diagnostic criteria have been published in the literature in order to enable clinicians to vouchsafe a diagnosis of ABPA with certainty [79].

Management of ABPA entails the achievement of two separate goals: (a) attenuating the hypersensitivity response to *A. fumigatus*; and (b) decreasing the overall burden of *A. fumigatus* allergens. Systemic corticosteroid therapy is useful to achieve the former goal, while antifungal therapy (typically itraconazole) is required for the latter [77]. Prednisone in a dose of 0.5–2.0 mg/kg/day (or an equivalent) is often employed as first-line therapy. This dosage is maintained for a period of 1–2 weeks, beyond which the dosage can be modified to an alternate day regimen. Depending on the patient's response, dose of steroids can be reduced slowly and gradually weaned off over a period of 2–3 months. In patients who relapse when the dose of corticosteroids is reduced, itraconazole therapy can be especially useful [80]. As discussed previously for asthma and COPD, steroids afford a therapeutic effect in ABPA owing to their anti-inflammatory, immunosuppressive and bronchodilator effects. Recent studies have explored the role of omalizumab in the management of ABPA [81]. Small-scale studies suggest that omalizumab may be useful as a steroid-sparing agent in patients with either asthma or CF who develop chronic ABPA [82].

5.5. Sarcoidosis

Sarcoidosis is a multisystem disorder of unknown etiology characterized by the formation of non-caseating epithelioid cell granuloma. This disorder occurs 10 times more frequently among African Americans as compared to Caucasians and the incidence is higher among young and middle-aged women. Interestingly, this disease affects non-smokers more often than people who smoke. Most commonly, the disease may be discovered incidentally when a chest radiograph reveals bilateral hilar lymphadenopathy. Patients may also present with

a variety of clinical features including uveitis, xerophthalmia, parotidomegaly, xerostomia, lupus pernio, skin nodules, erythema nodosum, hypercalcemia, cardiac conduction system abnormalities, hepatomegaly and pulmonary infiltration. Given the undetermined etiology of sarcoidosis, it is a histopathological diagnosis of exclusion [83]. Nevertheless, two clinical variants of sarcoidosis are well-recognized and may suggest a diagnosis of sarcoidosis in the absence of histopathological evidence. Heerfordt-Waldenström syndrome refers to a constellation of clinical findings viz. fever, uveitis, parotidomegaly and facial palsy. Uveoparotid fever is another term used to refer to this syndrome and, in the appropriate setting, may obviate the need for a biopsy [84]. Another variant of sarcoidosis, Löffgren's syndrome, has been classically described in the literature, although it may be somewhat less specific as compared to uveoparotid fever. Löffgren's syndrome refers to a triad of erythema nodosum, arthralgia (or arthritis) and bilateral hilar lymphadenopathy [85]. Generally, women who present with Löffgren's syndrome tend to have a better prognosis compared to others. The diagnosis of sarcoidosis requires histopathological evaluation and is one of exclusion since its etiology is unknown. The hallmark feature on biopsies is the presence of non-caseating granuloma in different organs and tissues of the body without an alternative explanation. Laboratory investigations may also reveal elevated levels of ACE, although this is a non-specific finding. The differential diagnosis includes all granulomatous diseases, such as tuberculosis, histoplasmosis, berylliosis, silicosis and cat-scratch disease [83].

Management of sarcoidosis is dependent upon the severity and extent of the disease at the time of diagnosis. Pulmonary sarcoidosis has been traditionally described to have four stages [86]. Stage I refers to the presence of hilar lymphadenopathy and/or mediastinal lymphadenopathy in the absence of any lung infiltration. Stage II refers to the presence of pulmonary reticular opacities (predominantly in upper lung zones) along with hilar and/or mediastinal lymphadenopathy. Stage III refers to the presence of pulmonary fibrosis and/or reticular infiltrates with resolution of hilar and/or mediastinal lymphadenopathy. Stage IV refers to an advanced stage of "burnt out" disease in which diffuse pulmonary fibrosis with volume loss and bronchiectasis is evident in the absence of any lymphadenopathy. Fortunately, a substantial proportion of patients with pulmonary sarcoidosis do not require treatment as most of them have asymptomatic, non-progressive disease. Treatment is necessary for patients who have severe disease at the time of presentation, those who report bothersome symptoms, or those who demonstrate evidence of progressive disease upon follow-up [87]. Likewise, in patients with extra-pulmonary disease, treatment is generally indicated to prevent end-organ damage. First-line treatment is to begin prednisone at a dose of approximately 40 mg/day (0.6 mg/kg) and continue for about 4–6 weeks. If there is no clinical and/or radiographic improvement, this dose of prednisone (or an equivalent steroid) can be continued for another 4 weeks. Once the patient shows evidence of clinical improvement, reduction in dosage of steroids can be started. There is no evidence available to support a particular steroid tapering schedule. Most clinicians would gradually reduce the dose of prednisone to 10–15 mg/day (approximately 0.2 mg/kg); this maintenance dose of prednisone (or an equivalent steroid) would then be continued for a period of approximately 6 months with frequent monitoring of pulmonary function tests (PFTs) and radiologic studies. The usual duration of treatment with prednisone (or equivalent steroid) is almost 1 year. In cases where patients have disease refractory to steroids, patients experience relapses when steroids are tapered, or patients develop serious adverse effects related to steroids, steroid-sparing

immunosuppressive agents (methotrexate, azathioprine or biologic agents) can be tried [88]. For patients who are at risk of steroid-induced adverse effects and have stage I-II pulmonary disease (or evidence of slowly progressive disease), inhaled corticosteroid therapy may be a feasible alternative to systemic corticosteroids [89]. Budesonide 800–1600 mcg inhaled twice daily has been most studied in this context. Fluticasone propionate 500–1000 mcg inhaled twice daily is also a possible alternative option.

5.6. Collagen vascular diseases

Collagen vascular diseases comprise of a group of disorders characterized by auto-immunity to antigens contained within blood vessels and extracellular matrix of various organs. A large number of diseases affecting connective tissue of the body are included under this heading. A substantial proportion of rheumatologic diseases and auto-immune vasculitides are included in this category with the most notable ones being systemic sclerosis (SSc), polymyositis (PM), dermatomyositis (DM), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), Goodpasture syndrome (GPS) and relapsing polychondritis (RPC). Sometimes, vascular diseases are also included in this category irrespective of whether auto-immunity is implicated in pathogenesis or not.

Nearly all collagen vascular diseases can affect the lung in a variety of ways. This is not surprising since the lungs are rich in both connective tissue and blood vessels. Abundant pulmonary vasculature is necessary for gaseous exchange, while abundant collagen and elastin fibers in the interstitium are necessary to support the dynamic chest wall–lung breathing system [90]. In the following lines, we briefly discuss the spectrum of pulmonary pathologies seen in various collagen vascular diseases and the role of steroids in their management.

SSc is a disorder characterized by progressive fibrosis affecting multiple organs of the body including the skin, kidneys, lungs and other organs [91]. Within the pulmonary system, SSc can lead to the development of ground-glass opacities, which can slowly progress to fibrosis of the lung parenchyma. The most common pattern of pulmonary fibrosis seen in SSc is similar to that of usual interstitial pneumonitis (UIP) and may be histologically indistinguishable from rheumatoid lung or idiopathic pulmonary fibrosis (IPF). In some cases, SSc may involve the lung in a pattern similar to that of idiopathic non-specific interstitial pneumonitis (NSIP). Progressive pulmonary impairment in SSc is a sign of worse prognosis and mandates aggressive treatment [92]. The decision to start treatment with immunosuppressive agents is based on clear evidence of progressive pulmonary damage as demonstrated by radiologic worsening or decline in pulmonary function as measured by PFTs. Two pharmacologic agents have been studied for the treatment of SSc-related interstitial lung disease (ILD): mycophenolate and cyclophosphamide [93]. Mycophenolate is often prescribed as monotherapy and the usual duration of immunosuppressive therapy is approximately 2 years. Cyclophosphamide therapy can be given as intravenous injections or oral therapy and it is generally combined with corticosteroid therapy. Oral cyclophosphamide is given daily and necessitates a higher cumulative dosage of the drug; on the other hand, intravenous cyclophosphamide is given once monthly and allows a lower cumulative dosage with a lower incidence of adverse effects.

Cyclophosphamide therapy is continued for a few months and thereafter, it is transitioned to an alternative immunosuppressive agent (such as azathioprine or mycophenolate). Most clinicians prefer a daily oral dosage of low-dose prednisone (7.5–10 mg) along with cyclophosphamide as it is associated with a lower incidence of scleroderma renal crisis. However, some small studies have also reported the use of pulse-dose methylprednisolone along with cyclophosphamide [94]. Generally, pulse steroid therapy should be reserved for patients with SSc who have another organ-threatening manifestation necessitating their use.

PM and DM are auto-immune diseases that primarily affect muscles and skin, but in severe cases, involvement of other organ systems (including the respiratory system) can occur. The pathogenesis of PM entails a primary injury to skeletal muscles that is mediated by T lymphocytes, while in DM, immune complex deposition occurs in blood vessels and skin followed by complement activation that leads to injury and inflammation of the skin and muscles [95]. Pulmonary manifestations may be due to aspiration pneumonitis (a consequence of bulbar muscle weakness), respiratory failure (secondary to diaphragmatic involvement or chest wall muscle weakness) and/or acute alveolitis. ILD associated with PM or DM has been associated with the presence of antibodies against aminoacyl-transfer ribonucleic acid (tRNA)–synthetase and can occur as part of the antisynthetase syndrome [96]. The spectrum of ILD associated with PM/DM ranges from a chronic, slowly progressive UIP to an acute interstitial pneumonitis with diffuse alveolar damage (DAD); NSIP or bronchiolitis obliterans organizing pneumonitis (BOOP) can also occur [97]. Depending on the severity of the disease, glucocorticoid therapy alone or in association with other immunosuppressive agents may be required. Since most patients with PM/DM require systemic glucocorticoid therapy, such corticosteroid therapy may suffice for the pulmonary manifestations as well in many cases. In patients with severe disease at baseline or rapidly progressive ILD, pulse-dose methylprednisolone therapy followed by systemic glucocorticoid therapy (such as prednisone 1 mg/kg/day) along with cyclophosphamide (or other immunosuppressive agents) may be required. Intravenous immunoglobulin (IVIG) and/or rituximab have also been used in severe cases [98]. In most patients who receive glucocorticoid therapy, another immunosuppressive agent (usually azathioprine or mycophenolate) is also started at the same time and continued for a prolonged period of time (as glucocorticoids are tapered off).

SLE is a systemic auto-immune disease with protean manifestations that can affect nearly every organ-system of the body, but, occurs more frequently in women. Diagnosis is based on exclusion of alternative diagnoses and by applying the classification criteria proposed by the American College of Rheumatology (1997) or Systemic Lupus International Collaborating Clinics (2012) [99]. Pulmonary manifestations of SLE include pleuritis or pleural effusions, pulmonary hypertension, diffuse alveolar hemorrhage (DAH), acute interstitial pneumonitis, ILD and/or shrinking lung syndrome (SLS) [100]. ILD associated with SLE can take one of several histologic forms including NSIP, UIP, BOOP, lymphocytic interstitial pneumonitis (LIP), follicular bronchitis and/or nodular lymphoid hyperplasia. The general approach to the management of these pulmonary manifestations is similar to that for PM/DM associated ILD. Aggressive immunosuppressive therapy (i.e. pulse steroid therapy along with cyclophosphamide, rituximab or IVIG) is used for patients with acute interstitial pneumonitis or DAH. Plasmapheresis may also be employed for the management of patients with

DAH. NSAID therapy (if not contraindicated) is used for patients with pleuritis [101]. Long-term immunosuppressive therapy may be required for patients with ILD or SLS.

RA is an auto-immune disorder that results in chronic, symmetric, progressive, erosive poly-arthritis which can affect any synovial joint of the body. Extra-articular manifestations of this disease are common and occur in 20–40% of affected patients. Pulmonary manifestations may include arthritis of the cricoarytenoid joints, vasculitis affecting the recurrent laryngeal nerve, bronchiolitis obliterans, pleuritis with pleural effusions, pulmonary nodules, pulmonary hypertension and/or UIP [102]. Management of RA is with disease modifying anti-rheumatoid drugs and/or biologic agents [103]. NSAIDs may be used for management of pain. Short courses of systemic corticosteroids are used to manage acute exacerbations of RA. Systemic corticosteroid therapy is also useful for patients who develop rheumatoid vasculitis or bronchiolitis obliterans. ILD associated with RA is treated in a similar fashion as that due to SLE or PM/DM [104].

GPA, EGPA and MPA are small-vessel vasculitides associated with the presence of antineutrophil cytoplasmic antibodies (ANCA). GPA is a necrotizing, granulomatous vasculitis that frequently affects the nose, paranasal sinuses, upper airways, lungs and kidneys [105]. EGPA is a granulomatous vasculitis that is often associated with a history of asthma and eosinophilia, but can involve multiple organ-systems of the body [106]. MPA is another ANCA-related small-vessel vasculitis that is non-granulomatous and can affect multiple organ-systems of the body, although it usually spares the paranasal sinuses and upper airways [107]. GPS is an auto-immune disorder characterized by the formation of auto-antibodies against type IV collagen present in basement membrane. This disease principally affects the alveolar and glomerular basement membranes resulting in DAH and rapidly progressive glomerulonephritis respectively [108]. DAH and/or DAD can also occur in GPA, EGPA or MPA. Treatment of these disorders entails aggressive immunosuppression; pulse steroid therapy is combined with either rituximab or cyclophosphamide therapy. IVIG and/or plasmapheresis are also used in conjunction with immunosuppression. Patients who receive cyclophosphamide therapy are usually switched over to an alternative immunosuppressive agent, such as azathioprine or methotrexate. Patients who received rituximab initially may be maintained on the same agent or switched over to azathioprine or methotrexate [109].

RPC is a rare auto-immune disease that leads to inflammation and destruction of cartilaginous structures of the body. Auricular chondritis (sparing the earlobe), nasal chondritis (may lead to saddle-nose deformity), scleritis (or episcleritis), orbital pseudotumor, non-erosive arthritis, laryngeal inflammation, tracheal stricture, bronchial obstruction with post-obstructive pneumonia, and/or mitral or aortic regurgitation are some of the prominent clinical features of this disease [110]. Approximately one-third of cases occur in association with other rheumatologic diseases or malignancy. Patients with auricular or nasal chondritis and/or arthritis in the absence of other organ involvement can be treated with NSAIDs alone. Systemic corticosteroid therapy is used in patients with life or organ-threatening disease [111]. Dapsone or other immunosuppressive agents may be used in combination with, or in place of, corticosteroids; evidence does not support the use of any particular immunosuppressive agent over others. Surgical treatment or airway stenting may be required in patients who develop laryngeal or tracheal disease [112].

5.7. Eosinophilic pneumonitis

Eosinophilic pneumonitis may present either as an acute eosinophilic pneumonia or a more indolent chronic eosinophilic pneumonia. Patients with acute idiopathic eosinophilic pneumonia generally present with an acute febrile illness and progressive respiratory failure [113]. Most patients have a history of new onset or resumption of cigarette smoking, although heavy inhalational exposure to fine sand and dust may also precipitate this illness. Peripheral eosinophilia is generally absent at presentation, although it may develop later in the disease. Computed tomography usually shows bilateral patchy ground-glass opacities or reticular infiltrates. Bronchoalveolar lavage (BAL) may reveal a preponderance of eosinophils. Lung biopsies usually show marked eosinophilic infiltration of the interstitium and alveolar spaces with DAD and absence of hemorrhage or granuloma [114]. Treatment is with systemic corticosteroid therapy (usually prednisone 1 mg/kg) continued for a period of 2 weeks followed by a gradual taper over the next 4 weeks. Most patients respond dramatically to steroids within 24–72 hours and respiratory failure resolves rapidly [115].

Chronic eosinophilic pneumonia is an idiopathic disorder that presents with cough, fever, dyspnea and wheezing that progress over a period of several weeks to months. Radiologic findings of this disorder have been classically described as the "photographic negative of pulmonary edema" i.e. bilateral peripheral pleural-based opacities [116]. BAL reveals a predominance of eosinophils with the eosinophil count often exceeding 25% of leukocyte count. BAL and/or lung biopsy are also useful in excluding alternative causes, such as drug-induced or infectious causes. Treatment of chronic eosinophilic pneumonia is similar to that for acute eosinophilic pneumonia, although systemic corticosteroid therapy is generally tapered slowly over a period of 6 months (or more) [117].

5.8. Lymphocytic interstitial pneumonitis

LIP is characterized by benign polyclonal proliferation of lymphocytes with infiltration of pulmonary interstitium and alveolar spaces with lymphocytes and plasma cells. This disorder often occurs in association with rheumatologic diseases or human immunodeficiency virus (HIV) infection [118]. Patients may be asymptomatic or they may present with cough, dyspnea and/or constitutional symptoms. Radiologic studies may reveal ground-glass opacities, centrilobular nodules (or masses), septal thickening and/or lung cysts. Thoracoscopic or open lung biopsies are necessary in most cases to confirm the diagnosis and exclude alternative diseases [119]. Treatment of patients with asymptomatic disease may be watchful waiting with frequent monitoring. For patients with symptomatic disease, systemic corticosteroid therapy (usually prednisone 0.5 mg/kg/day) is used and gradually tapered over a period of 6–12 months. For patients who do not respond to steroids or relapse during taper, other immunosuppressive agents (azathioprine, cyclosporine, cyclophosphamide or rituximab) may be used [120]. For patients with HIV infection, highly active antiretroviral therapy is used as first-line treatment (instead of corticosteroid therapy). However, corticosteroid therapy will be needed for patients with HIV infection who continue to experience worsening LIP despite antiretroviral therapy [121]. Infrequently, LIP may undergo malignant transformation and evolve into a pulmonary lymphoma.

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5.9. Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (also known as extrinsic allergic alveolitis) refers to a group of diseases that develop secondary to numerous agricultural dusts, microorganisms, bioaerosols and/or reactive chemical species. Prompt diagnosis of hypersensitivity pneumonitis is important as the disease is reversible in its early stages. Correct diagnosis is usually based on a compatible exposure history, clinical assessment, radiographic findings and response to avoidance of the suspected etiologic agent [122]. Acute hypersensitivity pneumonitis often occurs following heavy exposure to an inciting agent and is usually confused with CAP. Patients present with fever, chest pain, cough and dyspnea about 6 hours following exposure. In most cases, symptoms improve within a few days after cessation of exposure to inciting agent, although radiographic resolution requires several weeks. Skin testing to allergens is not useful and serum precipitins may have a high false negative rate. Bronchoscopy with BAL shows lymphocytosis exceeding 20% (often >50%) and the BAL CD4+/CD8+ ratio is usually decreased to less than 1.0 [123]. Characteristic radiographic findings on computed tomography include mid-to-upper zone predominance of centrilobular ground-glass or nodular opacities with signs of air-trapping. Histopathological findings may reveal poorly formed granulomas and/or a patchy mononuclear infiltration near the alveolar walls [124]. Subacute hypersensitivity pneumonitis presents with productive cough, dyspnea, fatigue, anorexia, and weight loss. Most patients have mixed obstructive and restrictive abnormalities on PFTs with a reduction in diffusion capacity. Radiographic findings may include diffuse micronodules, ground-glass opacities, or mild fibrotic changes predominantly involving the middle to upper lung zones. Bronchoscopy with BAL may reveal lymphocytosis and negative cultures. Lung biopsy may reveal poorly formed, noncaseating granulomas in the pulmonary interstitium with fibrosis and bronchiolitis [125]. Removal of the inciting agent results in complete resolution of findings over a longer period of time (weeks to months) and most patients require systemic glucocorticoid therapy. In the chronic progressive form of hypersensitivity pneumonitis, patients present with cough, dyspnea, fatigue, and weight loss. Physical examination may reveal digital clubbing and hypoxemia. Radiographic studies will show widespread pulmonary fibrosis; BAL may reveal lymphocytosis. Lung biopsy is necessary to demonstrate granulomatous pneumonitis, diffuse interstitial pneumonitis, bronchiolitis obliterans and distal destruction of alveoli (honey-combing) with densely fibrotic zones [126]. At this stage, removal of exposure to the inciting agent will only lead to partial improvement. Corticosteroid therapy (usually 0.5–1 mg/kg/day of prednisone) should be prescribed to all symptomatic patients with hypersensitivity pneumonitis. Gradual tapering of steroid dosage can be started after 2 weeks and tapered over the ensuing 2–4 weeks in most patients [127]. In patients with chronic hypersensitivity pneumonitis and extensive pulmonary fibrosis, lung transplantation may be a viable treatment option.

5.10. Idiopathic interstitial pneumonitis

IIP refer to a group of idiopathic ILDs that are characterized by infiltration of the pulmonary interstitium with inflammatory cells and consequently result in progressive fibrosis. IIP is a broad umbrella category that includes a number of different disease entities with distinct histologic patterns, natural course and prognosis [128]. The American Thoracic Society (ATS) and

European Respiratory Society (ERS) classification [129] has recognized 6 major IIPs: (i) idiopathic pulmonary fibrosis (IPF); (ii) idiopathic NSIP; (iii) cryptogenic organizing pneumonitis (COP); (iv) respiratory bronchiolitis (RB) associated ILD; (v) acute interstitial pneumonitis (AIP); and (vi) desquamative interstitial pneumonitis (DIP). Two other ILDs are also included in the ATS/ERS classification as rare IIP viz. idiopathic LIP and idiopathic pleuroparenchymal fibroelastosis (PPFE). A category of unclassifiable IIP is also included in the ATS/ERS classification which is reserved for those IIPs which do not fit the criteria for any specific category of IIP.

IPF and idiopathic NSIP are both ILDs that run a chronic course with most patients experiencing symptoms for many months prior to diagnosis. IPF usually presents in the sixth to seventh decades of life. Typical radiologic findings include bibasilar subpleural fibrosis with traction bronchiectasis and honeycombing in the later stages. IPF is characterized histologically by a UIP pattern with a temporal and geographical heterogeneity, patchy involvement of the lung parenchyma, presence of architectural distortion and fibroblast foci and absence of features suggesting an alternative pattern [130]. Two novel tyrosine kinase inhibitors—pirfenidone and nintedanib—have been approved for the treatment of IPF [131]. Despite this, the overall prognosis for IPF remains poor. Systemic corticosteroid therapy is often employed for patients who develop acute infective exacerbation of IPF, although high quality evidence in support of this practice is lacking [132]. Idiopathic NSIP is a distinct clinical entity and tends to have a subacute presentation and a better prognosis as compared to IPF. Histologically, NSIP is characterized by temporal and geographical homogeneity with uniform involvement of the lung parenchyma, mononuclear cell infiltration of the interstitium and relative preservation of lung architecture [133]. The term "non-specific" is used because the histologic appearance of NSIP lacks the characteristic features of UIP, DIP, RB-ILD or AIP. Radiologic findings include bibasilar subpleural reticular shadowing with traction bronchiectasis, ground-glass opacities and absence of honeycombing. Alternative causes of NSIP, such as collagen vascular diseases, drugs and infections, need to be excluded. Treatment of NSIP is with systemic corticosteroid therapy, usually prednisone 1 mg/kg, gradually tapered over 6–12 months [134]. Pulse-dose methylprednisolone therapy has also been used in those with severe disease on presentation. In patients who relapse or remain refractory despite systemic corticosteroid therapy, a second immunosuppressive agent is added to prednisone.

Cigarette smokers tend to have a number of subclinical pulmonary interstitial abnormalities identifiable on histopathology [135]. These subclinical abnormalities do not meet the criteria for any particular ILD or IIP. Smoking-related ILD include RB-ILD, DIP and Langerhans cell histiocytosis. Langerhans cell histiocytosis is a separate disease entity and is generally not included under the heading of IIP. Both DIP and RB-ILD occur in smokers, usually with a smoking history of over 30 pack-years, most often in the third to fourth decades of life; men are more commonly affected [136]. In DIP, radiologic studies reveal bilateral ground-glass opacities without the peripheral reticular shadowing typical of UIP. In RB-ILD, radiologic findings may include scattered ground-glass opacities along with bronchial wall thickening. Lung biopsy in DIP shows uniform histopathological findings and lacks the patchy nature typical of IPF. Honeycombing is characteristically absent and a striking feature is the presence of numerous "smokers' macrophages" within the distal airspaces [137]. DIP is actually a misnomer as these macrophages were originally believed to be desquamated pneumocytes. A *smoker*

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macrophage is a macrophage that contains fine brown pigment flecked with tiny blackish particles; these cytoplasmic particles stain well with Prussian blue (iron content) and periodic acid Schiff (polysaccharides) stains. RB-ILD has a histopathological appearance somewhat similar to DIP in that numerous smoker macrophages are noted; however, these pigmented macrophages are abundant within the lumen of respiratory bronchioles [138]. Moreover, the histopathological findings seen in RB-ILD have a *bronchiolocentric* distribution, whereas DIP tends to affect the lung in a rather uniform and diffuse manner. The management of DIP and RB-ILD is similar; smoking cessation is the first line of management [139]. For patients who continue to experience symptoms and have worsening PFTs, systemic corticosteroid therapy is used. Rarely, other immunosuppressive agents may be used if patients do not improve, although evidence in this regard is scarce. Given the considerable overlap between RB-ILD and DIP, some researchers have suggested that the two categories may be merged together into a single group [140].

COP is the term applied to the idiopathic form of BOOP. This clinical disorder is characterized by an inflammatory pneumonitis and a proliferative bronchiolitis that results in excessive proliferation of granulation tissue within the smaller airways [141]. COP often presents with an acute or subacute clinical picture and mimics CAP with a lack of response to antibiotics. Patients are most often in their fifth or sixth decades of life and both sexes are affected equally. In many cases, a flu-like illness may precede the onset of COP. As is the case with other IIP, secondary causes of organizing pneumonia (such as drugs, collagen vascular diseases and infections) need to be excluded. PFTs reveal a restrictive defect with impairment of gaseous exchange (diffusion capacity). Radiologic studies show multiple patchy ground-glass opacities or peripheral consolidations [142]. Bronchoscopy with BAL is often performed to exclude other diagnoses such as infections, drug-induced pneumonitis, hypersensitivity pneumonitis, chronic eosinophilic pneumonitis and malignancy. In COP itself, BAL typically reveals a "mixed pattern" of increased cellularity (i.e. smaller proportion of macrophages and higher proportions of lymphocytes, neutrophils and eosinophils). Although transbronchial lung biopsy may be performed at the time of bronchoscopy, most patients suspected of having COP or other ILD require a thoracoscopic or open lung biopsy (i.e. via thoracotomy) to yield adequate specimens for histopathological evaluation [143]. Systemic corticosteroid therapy is the mainstay of treatment. Prednisone 1 mg/kg/day is usually started, unless the patient has severe symptoms or frank respiratory failure in which cases, IV methylprednisolone 500–1000 mg/day for 5 days may be used initially. Patients usually respond clinically to corticosteroids within a few days to a few weeks. Corticosteroid therapy is generally tapered over a period of 6–12 months. Other immunosuppressive agents may be used in patients who have COP refractory to steroids, or those who relapse frequently despite moderate doses of corticosteroids [144].

AIP (also known as Hamman-Rich syndrome) has a much more aggressive and acute disease course as compared to other ILD and it is similar to acute respiratory distress syndrome (ARDS) in terms of its worse prognosis. In fact, AIP differs from ARDS only in that it has no identifiable triggering event (i.e. it is idiopathic); otherwise, the histological pattern of AIP is identical to that for ARDS (DAD) [145]. Clinically, it presents with acute onset of rapidly worsening respiratory failure with diffuse airspace shadowing on plain radiographs. Computed tomography reveals bilateral diffuse ground glass opacities and/or consolidations with lobular sparing. The histologic hallmark of AIP is DAD as characterized by diffuse airspace

organization with or without the formation of hyaline membranes and alveolar septal thickening (due to diffuse organizing fibrosis) with a geographic and temporal homogeneity [146]. As for other IIP, cultures should be negative and granulomas, viral inclusions or eosinophils should be absent on histopathology. AIP requires aggressive treatment with high doses of glucocorticoids—typically methylprednisolone 1–2 g/day in divided doses for 3–5 days, followed by systemic glucocorticoid therapy for several weeks to months [147]. The mortality of AIP is almost 50%, and even in patients who survive the acute illness, recurrence of AIP or progression to a chronic ILD frequently occurs [148].

5.11. Laryngotracheitis (croup)

Laryngotracheitis (also known as croup) is a viral infection caused by parainfluenza viruses (most commonly, type 1) and often affects children in the first 3 years of life with a slight predisposition for boys. Clinical symptoms include low-grade fever, dyspnea, inspiratory stridor and a characteristic *barking* cough. In older children, hoarseness may also be noticeable. In some cases, inflammation may extend to the lower airways and result in laryngotracheobronchitis or even superimposed bacterial laryngotracheobronchopneumonitis [149]. While croup is typically caused by parainfluenza viruses, other viruses may also cause croup in certain cases; these include respiratory syncytial virus, influenza virus, rhinoviruses and human metapneumoviruses [150]. Plain chest radiographs may show narrowing of the subglottic area, frequently referred to as the *steeple* sign—owing to its resemblance to the steeple of a church). It should be noted here that croup is different from bacterial tracheitis, acute epiglottitis and viral bronchiolitis. Bacterial tracheitis is a bacterial infection of the trachea that results in a thick purulent exudate in the trachea, frequently with involvement of the lower airways (tracheobronchopneumonitis) [151]. Acute epiglottitis is an infection that was frequently caused by *Haemophilus influenzae* prior to the widespread use of the "Hib" vaccine. Most cases in vaccinated children and adults are caused by streptococcal or staphylococcal infections. Epiglottitis generally has a more rapid onset and aggressive course than croup and children tend to have high-grade fever and a toxic appearance [152]. Airway obstruction may be precipitated by physical examination or manipulative procedures, such as laryngoscopy. Viral bronchiolitis is an infection that usually occurs in infants and children below the age of 2 years. Most infections are caused by respiratory syncytial virus and present with fever, cough, dyspnea and wheezing [153]. Bronchiolitis is treated with supportive care only and corticosteroids have no role in management.

Treatment of croup involves supportive care with humidified oxygen therapy and anti-pyretics, adequate hydration, corticosteroids and nebulized epinephrine [154]. A strong body of evidence suggests that the use of *either* nebulized budesonide or single-dose dexamethasone provides benefits in terms of reducing length of hospital stay and decreasing visits to the emergency department [155]. The Westley croup score can be used to grade the severity of croup [156]. Patients with mild croup may be managed at home with a single dose of oral dexamethasone 0.6 mg/kg. Patients with moderate croup may be admitted to the hospital and administered an intramuscular or intravenous dose of dexamethasone along with repeated nebulizations of epinephrine [157]. In patients with severe croup and impending respiratory failure, admission to the intensive care unit may be necessary with a plan for endotracheal intubation in the presence of anesthesiologist and/or otorhinolaryngologist.

5.12. Exacerbation of cystic fibrosis

CF is an autosomal recessive disorder that results from genetic mutations in the cystic fibrosis transmembrane conductance regular (*CFTR*) chloride channel. CF is the most common lethal genetic disorder in the European population with an incidence of about 1 in 2500 live births [158]. The most common genetic mutation responsible for CF worldwide is the ΔF508 mutation which results in deletion of a phenylalanine residue at the 508′ position of the *CFTR* channel. This mutation has a prevalence of about 70% in patients with CF. Interestingly, of the 2000 mutations described in *CFTR*, only 4 of the remaining mutations have a prevalence of greater than 1% [159]. In some parts of the world, mutations other than the ΔF508 mutation are relatively common; for instance, the G551D mutation is common in the Middle East region [160–164]. Despite the development of novel targeted therapies for CF patients [165], the median survival for CF patients remains at 37 years—although it has been consistently improving over the past few decades [166]. In patients with CF, defective functioning of the CFTR gene results in protean manifestations, such as sinonasal polyposis, bronchiectasis, chronic pancreatitis with pancreatic insufficiency, CF-related diabetes mellitus, gut pathologies (meconium ileus, meconium ileus equivalent and intestinal atresia), osteoporosis, malnutrition, infertility and delayed puberty [159]. However, the most disabling of these manifestations is lung disease; defective mucociliary clearance leads to recurrent and persistent infections with virulent organisms, resulting in progressive and cumulative lung damage and development of bronchiectasis and end-stage lung disease [166].

Patients with CF frequently present with recurrent and disabling infective exacerbations of their lung disease. The microbiologic agents implicated in pneumonia and lower respiratory tract infections among patients with CF are distinct from that of the general population [167–170]. The management of pulmonary disease in patients with CF is best carried out in dedicated CF centers with a multidisciplinary team that is experienced in the care of such patients [171]. In patients presenting with acute infective exacerbations of CF, good evidence is available to substantiate the role of antibiotics, pulmonary toilet, bronchodilators, ventilatory support and mucolytics [172]. The use of corticosteroids in the management of patients with CF is controversial. Systematic reviews of randomized controlled trials suggest that the use of inhaled or systemic corticosteroid on a chronic basis in patients with CF without evidence of asthma or ABPA causes more harm than meaningful benefits [173, 174]. However, in patients with CF who present with an acute infective exacerbation, some data suggest that short-term corticosteroid therapy may be beneficial. In a randomized controlled trial, Tepper and colleagues demonstrated that use of a short course of intravenous hydrocortisone in patients with acute infective exacerbation of CF provided a greater and sustained improvement in pulmonary function [175]. However, guidelines from the CF Foundation conclude that larger studies would be needed to further evaluate the efficacy of corticosteroids in acute exacerbations of CF vis-à-vis their safety [176].

5.13. Acute respiratory distress syndrome

ARDS is the development of acute hypoxic respiratory failure in response to an identifiable inciting event, which is characterized pathologically by a diffuse inflammatory process involving the lung that leads to increased vascular permeability, generalized alveolar edema, loss of aerated tissue and markedly decreased lung compliance [177]. ARDS can occur in response to

a wide range of etiologies including sepsis, acute pancreatitis, trauma, drowning, burns, aspiration, transfusion-related acute lung injury, and so on; however, all these clinical entities are grouped together under the heading of ARDS as their clinical management is similar [178]. Clinically, ARDS presents with worsening hypoxemia and respiratory failure that develops within 24–72 hours of an inciting event. Patients typically have severe tachypnea and hypoxemia with accessory muscle use and respiratory distress on examination; chest auscultation may reveal bilateral diffuse crackles. Plain radiographs reveal bilateral airspace shadowing, which may be patchy in the initial stages, and coalesce later to a more homogeneous pattern in later stages. Arterial blood gas analysis will typically show respiratory alkalosis with hypoxemia and an elevated A–a gradient. The degree of hypoxemia can be quantified by the ratio of PaO_2 to the fraction of inspired oxygen (FiO_2) [179]. Computed tomography reveals widespread airspace opacities that may coalesce and are more prominent in the dependent parts of the lung. Histopathologically, the hallmark feature of ARDS is DAD (similar to AIP) with or without the presence of focal alveolar hemorrhage and hyaline membranes [180]. As per the Berlin definition, ARDS can be diagnosed if a patient has impairment in oxygenation (as measured by a PaO_2/FiO_2 ratio of ≤300 mm Hg) with bilateral airspace opacities on chest radiographs (not fully explained by lung collapse, pulmonary nodules or pleural effusions) that started within a week of a known clinical insult and are not secondary to cardiac failure or fluid overload as assessed by an objective assessment method (such as echocardiography) [181]. The PaO_2/FiO_2 ratio can be used to quantify the oxygenation impairment and stratify the severity of ARDS into severe ($PaO_2/FiO_2 \leq 100$ mm Hg), moderate (PaO_2/FiO_2 101–200 mm Hg) or mild (PaO_2/FiO_2 201–300 mm Hg) [182].

Management of ARDS is centered on mechanically ventilating patients with lung protective strategies. Low tidal volume ventilation is the mainstay of management while tolerating permissive hypercapnia and using high PEEP to maximize alveolar recruitment and prevent atelectasis [183]. In patients with very severe ARDS, prone positioning techniques and extracorporeal membrane oxygenation may be necessary to support life [184]. The use of corticosteroids in patients with ARDS is controversial and remains contentious to date. There is good evidence to suggest that corticosteroids should not be used >14 days after onset of ARDS as there is no demonstrable benefit and clear evidence of harm [185]. Moreover, in patients who develop ARDS due to a *steroid-responsive* etiology, corticosteroids should be used early in the course of the disease [186]. In patients with severe ARDS secondary to a disease process that is not treated with corticosteroids, initiation of systemic corticosteroids early (<14 days) in the course of the disease may offer some benefit. Several meta-analyses have been published to evaluate the impact of steroids on mortality in ARDS and their results have been conflicting. Three meta-analyses suggest that there is no benefit of steroids in terms of overall mortality, but, they help to improve gas oxygenation, reduce duration of mechanical ventilation and decrease overall stay in the ICU [187–189]. Two other meta-analyses reported that use of systemic corticosteroids provided a reduction in overall mortality and reduced the duration of mechanical ventilation [190, 191]. In the light of such conflicting evidence, use of systemic corticosteroids in patients with severe ARDS remains at the discretion of the treating clinician. Critical care physicians should assess each case individually and decide whether to administer corticosteroids or not based on their perceived benefits and possible adverse effects.

5.14. Lung transplantation and transplant-related complications

Lung transplant is used as a treatment modality for a wide variety of disorders that lead to end-stage lung disease with the most common ones being COPD, IPF, CF, α_1-antitrypsin deficiency and idiopathic pulmonary arterial hypertension [192]. Both single-lung and double-lung transplantation procedures are increasingly being performed; however, the availability of donor lungs is the main limiting factor to the number of procedures that can be performed. The basic selection criteria for lung transplantation include: (a) the presence of severe lung disease for which medical therapy is unavailable or ineffective and mortality without transplantation is estimated to be >50% within 2 years; (b) satisfactory psychosocial support system; (c) likelihood to withstand lung transplant surgery is >80%; and (d) absence of other comorbidities that would limit life expectancy in the first 5 years post-transplantation [193]. Absolute contraindications to lung transplant include psychosocial problems or non-adherence to medical therapy, cigarette smoking, alcohol dependency, substance abuse, uncontrolled or untreatable infection, malignancy in the last 2 years, uncorrectable bleeding diathesis, significant coronary artery disease that is not amenable to revascularization, significant dysfunction of other vital organs, severe obesity (body mass index ≥35 kg/m^2), active infection with *Mycobacterium tuberculosis*, or significant deformity of the chest wall or spine that would be expected to cause a severe restrictive defect post-transplant [194]. Apart from these absolute contraindications, there are a number of other diseases or conditions that are considered relative contraindications to lung transplant. Interestingly, use of systemic corticosteroids perioperatively was prohibited in the past due to concerns of poor healing of the newly formed anastomosis [195]. However, most evidence has shown that use of prednisone in doses of up to 0.3 mg/kg pre-transplantation does not increase the risk of complications [196].

Corticosteroids are an important part of immunosuppressive therapy for patients undergoing lung transplantation. At the time of the surgical procedure, an initial dose of 500–1000 mg of methylprednisolone is administered intravenously as soon as the donor allograft's vasculature and bronchus are anastomosed to the recipient's respective structures, and allograft reperfusion is established. Corticosteroid therapy is then continued at a dose of 0.5–1 mg/kg/day of prednisone (or equivalent) and gradually tapered down to a goal of 5–10 mg/day of prednisone (or equivalent) over a period of 6 months [197]. Depending on the transplant center's protocols and characteristics of the recipient (age, primary lung disease, panel reactive antibodies, etc.), induction therapy may or may not be administered post-transplantation. For induction therapy, the most commonly used agents are basiliximab, alemtuzumab or anti-thymocyte globulin [198]. Pre-medication with acetaminophen, diphenhydramine and corticosteroids (methylprednisolone 125 mg IV once) is required prior to infusion of alemtuzumab or anti-thymocyte globulin. Maintenance immunosuppression is then employed with a combination regimen consisting of a glucocorticoid (usually prednisone), a calcineurin inhibitor (usually tacrolimus or cyclosporine) and an anti-metabolite (usually mycophenolate or azathioprine) [199]. Occasionally, an mTOR (mechanistic target of rapamycin) inhibitor, such as sirolimus or everolimus, may also be used be as part of the maintenance immunosuppressive regimen; however, mTOR inhibitors should not be used in the first 3 months post-lung transplant as they may lead to fatal bronchial dehiscence [200].

Transplant rejections represent a significant problem in the world of transplantology. Corticosteroid therapy forms an integral component of the management of both acute and chronic graft rejections. In general terms, a graft rejection is the immune response of the recipient to the donor's graft, which results in dysfunction and failure of the transplanted organ. From a pathological perspective, graft rejection can be cell-mediated or humoral graft rejection depending on whether cytotoxic T lymphocytes or antibodies are implicated in immunopathogenesis respectively. In chronologic terms, rejection is classified into hyperacute, acute or chronic rejection based on temporality [201].

Hyperacute rejection occurs within 24 hours of transplantation (usually in the first few minutes to hours) and results in severe hypoxemia and other signs of graft failure. Such a graft rejection occurs due to preformed circulating antibodies in the recipient that are directed against antigens of the donor. Treatment involves therapeutic plasma exchange (to remove preformed antibodies), IVIG (to bind circulating antibodies & prevent them from interacting with transplanted tissues) and rituximab (to deplete B lymphocytes and prevent further formation of antibodies) [202]. All patients who develop hyper-acute rejection are already on high-dose steroids as part of their usual post-transplant care. Additional therapies, such as bortezomib (proteasome inhibitor) or eculizumab (monoclonal antibody to C5 complement protein), are also employed in most cases. While the outcome of hyperacute rejection is dismal in most cases, HLA typing and "virtual cross-match" of donor and recipient have made it a rare occurrence [203].

Acute lung allograft rejection usually occurs within the first 6–12 months of transplantation and it is cell-mediated in most cases. In acute cellular lung graft rejection, treatment is with pulse-dose methylprednisolone along with intensification of the maintenance immunosuppressive regimen [204]. Patients with persistent graft rejection may be treated with repeated courses of pulse-dose methylprednisolone along with other therapies, such as anti-thymocyte globulin, alemtuzumab and/or mTOR inhibitors (sirolimus or everolimus). Cases of acute humoral lung graft rejection developing weeks to months after transplantation are less common. Such cases are managed with a combination of therapeutic modalities including pulse-dose methylprednisolone, therapeutic plasma exchange, IVIG, rituximab and/or intensification of maintenance immunosuppression [205]. Empiric antibiotics are often initiated in patients with acute lung graft rejection until results of microbiologic and histopathological studies are available.

Chronic lung transplant rejection remains a major source of late morbidity and mortality for lung transplant recipients [206]. Chronic lung allograft rejection may manifest as either bronchiolitis obliterans or a restrictive allograft syndrome. Bronchiolitis obliterans is the predominant subtype of chronic lung graft rejection and has a worse prognosis [207]. It is usually detected as an obstructive defect on PFTs. Histopathologically, fibrosis in the lower airways (bronchioles) with formation of dense scar tissue is typical [208]. In some patients, an unexplained obstructive defect on PFTs is noted in the absence of definitive histopathological evidence of bronchiolitis obliterans; such patients are termed to have bronchiolitis obliterans syndrome. In restrictive allograft syndrome, patients have a demonstrable restrictive defect on PFTs and evidence of fibrotic changes involving the upper lung lobes [209]. In most cases, chronic lung allograft rejection is irreversible and most patients eventually require retransplantation [210]. However, several therapeutic options may be tried in such patients (depending on the

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transplant center's preferences) including intensification of the immunosuppressive regimen, addition of azithromycin, use of montelukast, use of mTOR inhibitors, trial of anti-thymocyte globulin, total lymphoid irradiation or extracorporeal photophoresis [211].

6. Adverse effects

The adverse effects of corticosteroid therapy are significant and, in most circumstances, these effects are a compelling reason to limit the dose and/or duration of their use [18]. In many of the chronic diseases discussed in this chapter, toxicities of steroid therapy are a major source of morbidity. Additionally, most patients with such chronic diseases are often on immunosuppressive therapy or other toxic medications that may lead to cumulative toxicity. While systemic glucocorticoid therapy is associated with the most number of adverse effects, inhaled glucocorticoid therapy can also have some adverse effects, although they tend to be generally less severe [40–42]. Moreover, some of the adverse effects of corticosteroids do not manifest until complications develop. For instance, loss of bone mineral density may go on unchecked until a patient develops vertebral collapse [212]. Luckily, most of the adverse effects of steroids are potentially reversible with time once corticosteroids are discontinued.

Side effects of systemic corticosteroids pertain to almost all systems of the body. Long-term corticosteroid therapy can cause skin thinning, dermal atrophy and purpura, especially on the dorsum of hand and forearm [213]. Dermal atrophy is a consequence of reduced collagen synthesis due to inhibition of protein synthesis. Purpura is a combined consequence of dermal atrophy and increased fragility of vessels, which predisposes to bleed in response to minor stress. In a case–control study, Karagas and co-workers reported that the risk of non-melanoma skin cancer was increased among patients who used corticosteroids [214]. Cushingoid striae occur due to overstretching of the skin with rupture of vessels within the skin. Steroid-induced acne is also a well-known dermatologic adverse effect of steroids [215]. Ophthalmic adverse effects of corticosteroids include cataracts, increased intraocular pressure and development of glaucoma [216]. Cataracts most commonly occur in a posterior subcapsular location and are often bilateral [41]. Central serous chorioretinopathy is another rare ophthalmic side effect of corticosteroids [217]. Redistribution of body fat with truncal obesity, buffalo hump and moon facies (Cushingoid features) develop when corticosteroids are used over a long period of time in high doses [218]. Prolonged periods of hyperglycemia predispose patients to the development of diabetes mellitus and central adiposity, which in turn leads to increasing insulin resistance. Insulin resistance and hyperinsulinemia lead to increased synthesis of very low-density lipoproteins and increase triglyceride levels and adipose tissue in the body [219]. Moreover, since many pharmacologically used corticosteroids have weak mineralocorticoid properties, they can lead to fluid retention, hypertension, hypokalemia and mild metabolic alkalosis. All these effects can culminate in accelerated atherosclerosis and increased incidence of cerebrovascular events and coronary artery disease [220]. Moreover, fluid retention and hypertension can worsen cardiac failure. Fluid retention can also be problematic in patients with pre-existing renal disease. In the gastrointestinal system,

corticosteroids can lead to a number of adverse effects including gastritis and gastrointestinal bleeding [221]. Corticosteroids may also impair healing of peptic ulcers and mask signs of gastrointestinal perforation; however, in patients taking glucocorticoids alone, routine use of proton pump inhibitors is not recommended [222]. Proton pump inhibitors should be given to patients who are taking corticosteroids along with either aspirin or other NSAIDs [223]. Fatty liver is another adverse consequence of prolonged corticosteroid use. In the musculoskeletal system, glucocorticoids lead to accelerated bone loss due to decreased osteogenesis and increased osteolysis [224]. Corticosteroid use can lead to osteoporotic fractures; interestingly, vertebral fractures have been reported in patients treated with glucocorticoids, even with a normal bone mineral density [225]. Avascular necrosis, especially of the head of femur, is a serious adverse effect of glucocorticoid therapy [226]. In children, prolonged use of corticosteroids can lead to slowed growth or even, permanent growth impairment [227]. Corticosteroids can also lead to myopathy, which manifests as proximal muscle weakness, although muscle enzymes (serum creatine kinase) are within normal limits [228]. With respect to the reproductive system, corticosteroid use may lead to menstrual irregularities and decreased fertility in both sexes [229]. Moreover, use of high doses of corticosteroids during the first trimester of pregnancy may elevate the risk of cleft palate slightly [230]. The risk of fetal intrauterine growth restriction is also elevated in women who take corticosteroids throughout pregnancy [231]. Corticosteroids have also been shown to have a number of adverse effects on the central nervous system, especially when used in high doses [232]. Neuropsychiatric effects may include feeling of euphoria, anxiety, depression, mania, delirium or even psychosis. In a study by Shin et al. [233], patients with RA who were treated with oral glucocorticoids had a higher risk of having cognitive impairment. In another study by Keenan and colleagues [234], use of corticosteroids was associated with an adverse outcome on explicit memory at a period of 1 year. Last, but not the least, the immune system is also adversely affected by glucocorticoid therapy and immunosuppression leads to an increased risk of infections, decreased response to vaccines, poor wound healing and lymphopenia [235, 236]. Neutrophilia seen with corticosteroid therapy is a mere consequence of demargination of the neutrophil pool.

Close monitoring of such patients for the development of adverse effects is essential [237]. Routine monitoring should include blood pressure charting, weight charting, regular physical examination, lipid profile and fasting plasma glucose. Determination of bone mineral density and monitoring of intraocular pressure should be considered for patients who are receiving high doses of corticosteroids for a prolonged duration [238]. Specifically, patients with pre-existing co-morbid conditions, such as diabetes mellitus, hypertension, dyslipidemia, heart failure, peptic ulcer disease and osteoporosis, are at a much higher risk of developing adverse effects and must be monitored vigilantly [239].

In summary, corticosteroid therapy is a double-edged sword in patients with chronic diseases who are dependent on steroids. Adverse effects pertaining to nearly every system of the body can occur with the use of corticosteroids, which mandates that patients be treated with the lowest possible dose of corticosteroids for the minimum duration possible. Inhaled corticosteroid therapy can provide a therapeutic effect in many airway disorders, while reducing the risk of many steroid-induced adverse effects at the same time. Thus inhaled therapy for airway disorders should be preferred over systemic corticosteroid therapy, whenever possible.

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Conflict of interest

The authors have no conflict of interests to disclose. The authors have no conflict of interests to disclose.

Abbreviations

A–a	alveolar–arterial
ABPA	allergic bronchopulmonary aspergillosis
ACE	angiotensin converting enzyme
ACTH	adrenocorticotrophic hormone
AIP	acute interstitial pneumonitis
ALT	alanine aminotransferase
ANCA	antineutrophil cytoplasmic antibody
APC	antigen presenting cell
ARDS	acute respiratory distress syndrome
ATP	adenosine 1,4,5-triphosphate
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
BOOP	bronchiolitis obliterans organizing pneumonitis
cAMP	cyclic adenosine monophosphate
CAP	community acquired pneumonia
CAT	COPD assessment test
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
COP	cryptogenic organizing pneumonitis
COPD	chronic obstructive pulmonary disease
DAD	diffuse alveolar damage
DAH	diffuse alveolar hemorrhage
DIP	desquamative interstitial pneumonitis
DM	dermatomyositis
EGPA	eosinophilic granulomatosis with polyangiitis

ERS	European Respiratory Society
FEV_1	forced expiratory volume in first second of expiration
FiO_2	fraction of inspired oxygen
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GPA	granulomatosis with polyangiitis
GPCR	G-protein coupled receptor
GPS	Goodpasture syndrome
GRE	glucocorticoid-response elements
HIV	human immunodeficiency virus
ICS	inhaled corticosteroids
IgE	immunoglobulin E
IL	interleukin
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IVIG	intravenous immunoglobulin
LABA	long-acting β_2-adrenoceptor agonist
LAMA	long-acting muscarinic antagonists
LIP	lymphocytic interstitial pneumonitis
mMRC	modified Medical Research Council scale
MPA	microscopic polyangiitis
mTOR	mechanistic target of rapamycin
NFκB	nuclear factor-κB
NIPPV	non-invasive positive pressure ventilation
NSAID	non-steroidal anti-inflammatory drug
NSIP	non-specific interstitial pneumonitis
OPG	osteoprotegerin
PAMPs	pathogen-associated molecular patterns
PDE	phosphodiesterase
PECAM-1	platelet–endothelial cell adhesion molecule-1
PFT	pulmonary function test
PM	polymyositis

PPFE	pleuroparenchymal fibroelastosis
PRR	pattern recognition receptor
PTH	parathyroid hormone
RA	rheumatoid arthritis
RAAS	renin–angiotensin–aldosterone system
RANK	receptor activator for nuclear factor-κB
RANKL	receptor activator for nuclear factor-κB ligand
RB	respiratory bronchiolitis
RPC	relapsing polychondritis
SABA	short-acting β_2-adrenoceptor agonist
SAMA	short-acting muscarinic antagonists
SGPT	serum glutamate-pyruvate transaminase
SLE	systemic lupus erythematosus
SLS	shrinking lung syndrome
SSc	systemic sclerosis
T_H1	type 1 helper T
T_H2	type 2 helper T
tRNA	transfer ribonucleic acid
UIP	usual interstitial pneumonitis

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