

Chapter 5

Rhinitis and Sinusitis



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Normal Anatomy of the Nose and Sinuses

The nose is an orifice for breathing that filters, moisturizes, and regulates the temperature of air as it enters the nose, pharynx, and lung and provides for olfaction. It is divided into two compartments by a nasal septum. Short, somewhat stiff, sensitive hairs, located at the nasal entrance, allow for enhanced tactile stimuli which can result in nasal itching and sneezing. The superior, middle, and inferior turbinates extend from the lateral walls of each side of the nose and occupy much of the free space within the nasal cavity. They overlie the superior, middle, and inferior nasal meatus, respectively, and can become edematous with various forms of rhinitis and rhinosinusitis and subsequently obstruct air-flow [1, 2]. The middle meatus is important because it contains three convoluted and narrow ostiomeatal pathways which drain the anterior ethmoid, frontal, and maxillary sinuses.

Several kinds of epithelial cells line the nasal cavity and sinuses. Stratified squamous epithelium is located at the distal vestibule of the nose and is continuous with the facial skin. The nasal cavity, sinuses, and respiratory tract are lined by respiratory epithelium which contains various cell types including ciliated columnar and goblet

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cells. Goblet cells, located within the epithelium, produce mucus which is mobilized and cleared by ciliated columnar epithelial cells. Specialized olfactory ciliated epithelium is located in the superior aspect of the nose. The epithelial lining of the nasal cavity is in constant contact with the external environment and is regularly exposed to changes in the ambient temperature and humidity, allergens, infectious agents, pollutants, and other airborne substances.

The amount of blood reaching the nose and nasal pharynx is controlled by the constriction and dilation of small arteries and arterioles, depending on physiologic and environmental influences. Subepithelial capillaries are fenestrated, making them capable of responding rapidly to the administration of intranasal medications. The olfactory nerve and branches of the trigeminal nerve, the ophthalmic and maxillary branches, innervate the nasal cavity. Sympathetic and parasympathetic nerve fibers cause vasoconstriction and vasodilatation, respectively, when appropriately stimulated [2].

The paranasal sinus cavities contain air and communicate with the nasal cavity via ostia, which are approximately 2–6 ml in diameter. Goblet cells lining the sinuses produce nitric oxide, which has both vasodilatory and antimicrobial properties. The exact function of the sinuses remains unknown [2], but each pair of sinuses depends on their respective ostiomeatal complex for ventilation and mucus drainage. Obstruction of these complexes can result in an increase or decrease in sinus pressure and place the affected subject at risk to develop acute or chronic rhinosinusitis [3]. Pneumatization of the sinuses begins at birth and is not complete until adolescence. The degree of pneumatization varies [3]. The sphenoid and frontal sinuses are the last to develop, and up to 10% of normal individuals do not have frontal sinuses.

The anterior and posterior ethmoid sinuses are situated medially to the orbits, bilaterally, and drain into the middle and superior meatus, respectively. The maxillary sinuses lie lateral to the nose on each side of the face between the maxilla and the orbits and drain into the middle meatus. The paired frontal sinuses arise within the frontal bone and drain into the middle meatus. The sphenoid sinuses lie posterior to the ethmoid cells and drain into the sphenoidal recesses on either side of the posterior nasal septum [3], superior to the superior nasal concha (Fig. 5.1).

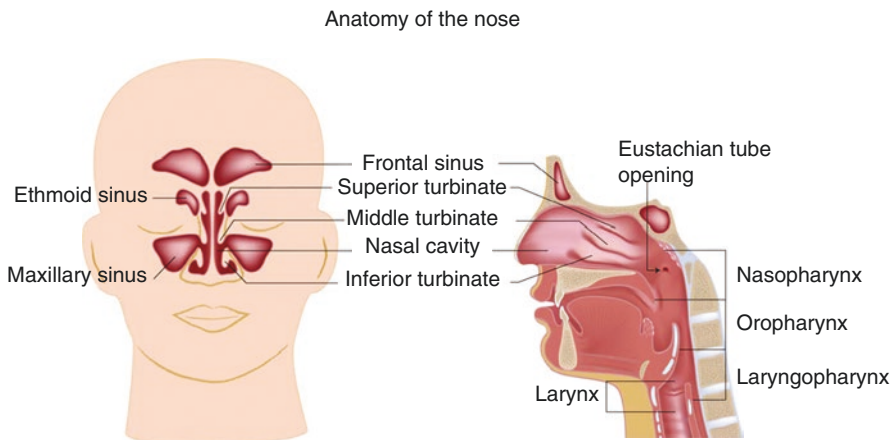


Fig. 5.1 Anatomy of nasal cavity and sinuses. (With permission from Dreamstime LLC)

Effects of Nasal and Sinus Disease on Asthma and General Health

Subjects with chronic diseases of the nose and sinuses, such as rhinitis, are at risk for other diseases. For example, with allergic rhinitis, subjects are three times more at risk to develop asthma [4, 5]. It is also a comorbid condition of this disease and “as goes the nose (i.e., in allergic rhinitis), so goes asthma.” Treatment of symptomatic allergic rhinitis improves asthma outcomes.

Allergic rhinitis, especially when not appropriately managed, can result in an increased incidence of otitis media, infectious rhinosinusitis, and other upper airway diseases [6, 7]. Infectious rhinosinusitis is also a comorbid condition of asthma. Allergic rhinitis and infectious rhinosinusitis often coexist [3]. Therefore, it is essential that they be diagnosed and managed correctly.

Pathophysiology of Atopic Diseases

The primary function of the upper airway epithelium is to warm, cool, and humidify the air and to defend the host against noxious agents, including pollutants, allergens, and infectious agents. Allergic rhinitis is caused by an allergic immune response in which specific IgE antibody combines with an allergen to which a subject is allergic and causes a hypersensitivity reaction. This reaction is also referred to as a type I hypersensitivity reaction [8]. Atopic subjects have a family history of atopic eczema, allergic rhinoconjunctivitis, and allergic asthma and therefore are genetically predisposed to develop these diseases.

IgE, the principle mediator of the immediate hypersensitivity reaction, attaches to mast cells present in blood vessels of connective tissues and mucosal membranes. Nonatopic subjects also produce IgE and have mast cells; however, because of their genetic predisposition (family history) and allergen exposure, atopic subjects become sensitized to specific allergens. When exposed to an allergen to which they are allergic, they develop an immediate hypersensitivity reaction, causing acute and chronic allergic rhinosinusitis and allergic asthma. Viral infections and environmental pollutants are thought to play a role in the sensitization process.

An example of an allergic reaction is a cat-allergic subject who develops allergic rhinitis when exposed to cat allergens. When aerosolized cat saliva and pelt proteins, sources of cat allergens, are inhaled, these allergens are absorbed onto mucosal surfaces, in this case, in the nose. Two IgE molecules located on a mast cell are bridged by the cat allergen, triggering the mast cell to release stored and newly generated vasoactive amines, such as histamine and proteases. They also generate and secrete products of arachidonic acid, such as prostaglandins and leukotrienes, and cytokines, such as tumor necrosis factor (TNF). These mediators cause an inflammatory response, vascular dilation, increased vascular permeability, and the recruitment of eosinophils, neutrophils, and Th2 cells (Fig. 5.2a, b). They also cause smooth muscle contraction in the bronchi, responsible for the bronchial constriction

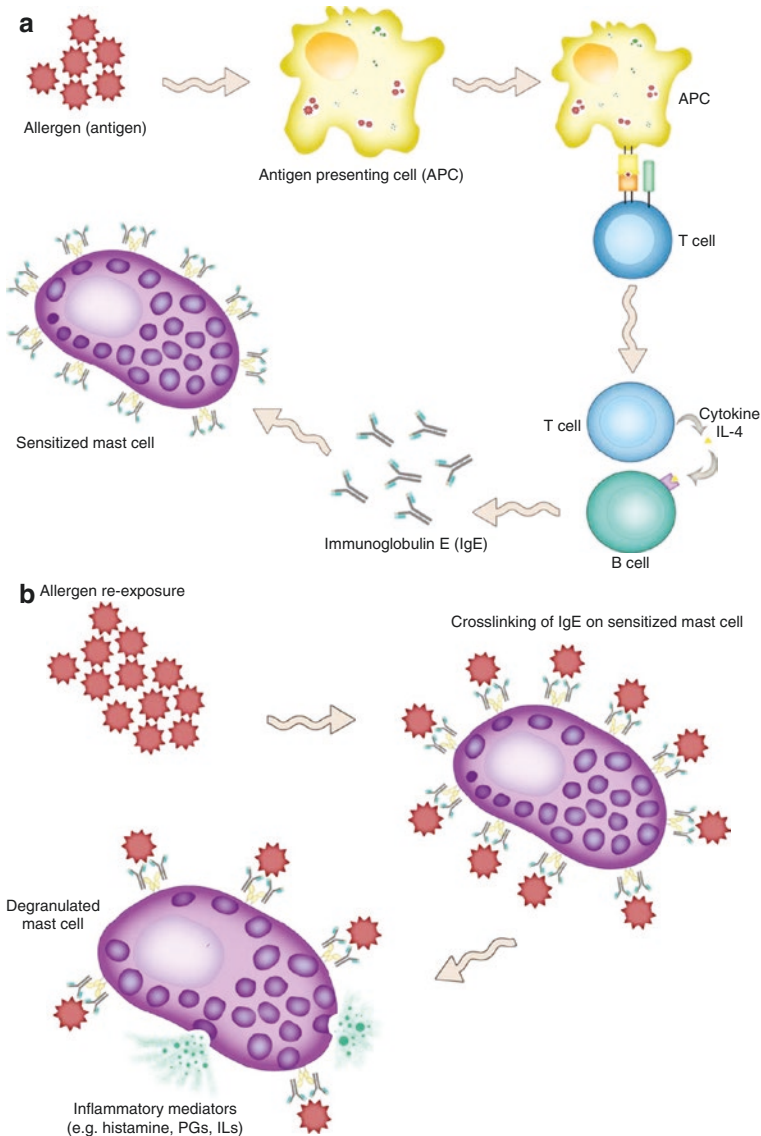


Fig. 5.2 (a) An allergen (antigen) is introduced via inhalation and is processed by the antigen-presenting cell (APC). The allergen is degraded into small amino acid chains and subsequently displayed on the major histocompatibility complex II (MHC II) for specific T-cell receptor (TCR) recognition. Once the specific TCR recognizes the processed allergen on MHC II, a series of events occur leading to T-cell activation. Activated T cells interact with specific B cells and become activated. Activated B cells, with the help of interleukin 4 (IL-4), undergo immunoglobulin class switching. Class-switched B cells become plasma cells and begin producing immunoglobulin E (IgE) specific to the allergen. Secreted IgE coat mast cells. (b) Upon re-exposure to an identical allergen, IgE attaches to mast cells via high-affinity IgE receptors (FcεRI) and recognizes the allergen, which cross-links IgE molecules. This cross-linking leads to mast cell degranulation and the secretion of stored and newly formed inflammatory mediators, e.g., histamine, heparin, prostaglandins (PGs), and various cytokines. These mediators are responsible for the early- and late-phase signs and symptoms of IgE-mediated allergic diseases

in allergic asthma. This inflammatory cascade triggers the symptoms of allergic rhinitis which includes sneezing, nasal itching, rhinorrhea, and nasal congestion; with asthma, this inflammation causes cough, wheezing, and shortness of breath. The inflammatory process can ultimately damage the epithelial tissues of the nose, sinuses, and lung.

Rhinitis or Rhinosinusitis During Pregnancy

The symptoms of rhinitis and rhinosinusitis can change during pregnancy. Some subjects improve, some worsen, and others remain the same [9]. One out of five pregnant women may be affected by allergic rhinitis, allergic asthma, or atopic eczema or a combination thereof [10]. In addition, the incidence of other types of rhinitis, for example, nonallergic rhinitis, may increase due to the physiologic and hormonal changes associated with pregnancy. Pregnancy-associated hormones effect nasal blood flow and mucosal glands causing edema and hyperemia of the nasal mucosa [10]. This can result in “rhinitis of pregnancy,” epistaxis, and worsening of underlying types of rhinitis and rhinosinusitis, which may be present before pregnancy or which occur during pregnancy. These topics are discussed below.

Rhinitis

Rhinitis is characterized by the presence of one or more of the following nasal symptoms: congestion, anterior or posterior rhinorrhea, sneezing, and pruritus [7]. It is often confused with rhinosinusitis, a term usually synonymous with sinusitis (Table 5.1). Poorly controlled rhinitis is a significant cause of impaired quality of life because of its associated facial discomfort, fatigability, cognitive impairment, and sleep disturbance [7, 11–13]. Appropriate management of rhinitis is also essential to optimally control asthma and sleep apnea. Various common types of rhinitis (Table 5.2) are caused by inflammation of the epithelial lining of the nasal cavity, such as occurs with allergic or infectious rhinitis [7]. Other forms of rhinitis include rhinitis of pregnancy, atrophic rhinitis, rhinitis medicamentosa, and rhinitis associated with systemic diseases, such as granulomatosis with polyangiitis (historically known as Wegener’s granulomatosis) or eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). These diseases can also present while a subject is pregnant and should be considered, especially with severe symptoms, in the differential diagnosis.

Table 5.1 Summary and comparison of rhinitis and sinusitis subtypes

	Allergic rhinitis	Nonallergic rhinitis (e.g., vasomotor, hormonal)	Infectious rhinitis (common cold)	Rhinosinusitis (sinusitis)
Duration	Varies	Varies	3–10 days; up to 2 weeks in smokers	Acute <4 weeks Subacute: 4–12 weeks Chronic: >3 months
Frequency	Allergen exposure	Perennial/varies	Acute	
Fever	–	Absent	+ Low grade	+
Nasal discharge	Watery	Prominent watery	Clear (viral) Purulent (bacterial)	+
Pruritus	+	Absent	–	–
Sneezing	+	Absent	+/-	+/-
Nasal congestion	Prominent in late phase	Prominent	+	+
Facial pain/pressure	–	+/-	+/-	+
Pain in upper teeth	–	+/-	+/-	+
Headache	–	+/-	+/-	+
Cough	+/-	–	+	+
Malaise	–	–	+/-	+
Notes	Seasonal	See subtypes	Pharyngitis	

Legend: + is present; +/- is present or not present; – is not present

Table 5.2 Type and causes of rhinitis

Common types and etiologies of rhinitis
Allergic rhinitis
Seasonal
Perennial
Nonallergic rhinitis
Pregnancy rhinitis
Vasomotor rhinitis
Gustatory rhinitis
Nonallergic rhinitis with eosinophilia syndrome (NARES)
Atrophic rhinitis
Mixed
CPAP-associated rhinitis (continuous positive airway pressure)
Rhinitis medicamentosa
Nasal decongestant sprays
Intranasal cocaine
Systemic medication-induced rhinitis
Oral contraceptives

Table 5.2 (continued)

Common types and etiologies of rhinitis
Erectile dysfunction drugs
Alpha-blockers
Some hypertensives
Aspirin and other NSAIDS
Some antidepressants
Some benzodiazepines
Systemic diseases
Hypothyroidism
Granulomatosis with polyangiitis (Wegener's granulomatosis)
Midline granuloma
Sarcoidosis
Cystic fibrosis
Immotile cilia syndrome (Kartagener)

Adapted from Peden [14]

Allergic Rhinitis

Etiology

Allergic rhinitis affects up to 60 million people in the United States, approximately 20% of all children and adults [15–18], including up to one-third of women of childbearing age [10, 19]. It becomes worse in approximately one-third of affected pregnant subjects [20]. It is characterized by symptoms which begin within minutes of allergen exposure often followed by a late-phase response 4–8 hours later. Early-phase symptoms include nasal congestion, sneezing, rhinorrhea, and pruritus. Eighty percent of subjects can also have allergic conjunctivitis which causes itching, redness, and tearing of the eyes. Congestion of the nose dominates the late-phase reaction [7]. Continuous allergen exposure results in chronic symptoms. When both the nose and eyes are affected, it is referred to as allergic rhinoconjunctivitis.

Diagnosis

A detailed history focusing on seasonal and perennial environmental exacerbations and exposures which triggers symptoms (pollen, cat and dog emanations, dust mites, fungi) and responses to medications, such as antihistamines and intranasal corticosteroids, is essential. A complete physical examination with emphasis on the head, eyes, ears, nose and oral pharynx, skin, and chest should follow. The nasal mucosa membranes are usually edematous, pale with clear mucus, all consistent

with the suspected diagnosis. The affected conjunctiva is often injected with accompanying chemosis (edema of the bulbar conjunctiva). Appropriate prick-puncture and intradermal skin tests or *in vitro*-specific IgE tests can help confirm historical suspected causative allergens associated with the disease [7], with *in vitro* tests preferred during pregnancy.

Treatment

Management of the pregnant versus nonpregnant subject does not significantly differ. Non-pharmacologic strategies, such as allergen and irritant avoidance, are important [21]. Data on the safety of rhinitis medications during pregnancy are reviewed in detail in Chap. 2. Nonsedating second-generation antihistamines, such as cetirizine and loratadine, are considered safe and are first drugs of choice. Montelukast is also considered safe to use during pregnancy, but it is not very effective. For more persistent symptoms, an intranasal corticosteroid can be utilized [19, 21], such as mometasone, beclomethasone, fluticasone, and others. Although the safety of nasal decongestants, such as phenylephrine and oxymetazoline, has not been studied directly, they appear to be safe with short-term use (less than 3 days), particularly after the first trimester. However, oral decongestants have been associated with birth defects, when used in the first trimester [19] (Table 5.3).

Allergen immunotherapy is another treatment modality by which allergen-sensitized subjects receive allergen vaccines to which they manifest allergy either by subcutaneous allergen immunotherapy (SCIT) or sublingual allergen immunotherapy (SLIT). SCIT is more often prescribed when multiple allergens are involved in the pathogenesis of the disease, *i.e.*, allergy to tree, grass, and weed pollen, dust mites, cat, dog, and other allergens. SLIT is primarily employed when the number allergens to which an individual is limited, *e.g.*, only grass pollen, ragweed pollen, and/or dust mites. When given over time, such therapy induces clinical tolerance to the allergens to which an individual is allergic. Such therapy does not usually begin during pregnancy. Allergen immunotherapy, depending on the risk/benefit, can be continued or discontinued during pregnancy [22]. For SCIT, the dose of allergen vaccine and the interval between injections are usually halved to decrease the potential of inducing a systemic allergic reaction which can affect the welfare of the fetus and mother [23]. SLIT is similar to SCIT except that the allergen vaccine or tablet for SLIT is delivered under the tongue and absorbed locally, not by the subcutaneous route. Information about SLIT safety during pregnancy is insufficient, but animal studies show no risk to the fetus. In general, allergen immunotherapy can be continued if tolerated before but should not be initiated during pregnancy [24].

Table 5.3 Summary of medications used in rhinitis management

Medication	Mechanism of action	Dosage	Pregnancy implications	Side effects
Intranasal cromolyn (NasalCrom®)	Acts locally to reduce calcium influx which decreases histamine degranulation from mast cells	Instill one spray (5.2 mg) in each nostril three to four times daily; may be increased up to six times daily	Based on available studies, cromolyn may be used for the treatment of allergic rhinitis in pregnant women	Burning sensation of the nose, nasal mucosa irritation, sneezing, stinging sensation of the nose, headache, unpleasant taste, cough, hoarseness, postnasal drip
Chlorpheniramine	Competes with histamine for H1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract	Immediate release: 4 mg every 4–6 h (not exceed 24 mg/24 h) Extended release: 12 mg every 12 h (not exceed 24 mg/24 h)	Based on available studies, cromolyn may be used for the treatment of allergic rhinitis in pregnant women	Drowsiness (slight to moderate), thickening of bronchial secretions, dizziness, excitability, fatigue, headache, nervousness, abdominal pain, diarrhea, increased appetite, nausea, xerostomia, urinary retention
Cetirizine (Zyrtec®)	Competes with histamine for H1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract	5–10 mg once daily, depending upon symptom severity	Maternal use of cetirizine has not been associated with an increased risk of major malformations. Cetirizine may be used for the treatment of allergic rhinitis during pregnancy	Drowsiness, headache, insomnia, fatigue, malaise, dizziness, abdominal pain, xerostomia, diarrhea, nausea, vomiting, pharyngitis, epistaxis, bronchospasm
Loratadine (Claritin®)	Long-acting tricyclic antihistamine with selective peripheral histamine H1-receptor antagonistic properties	10 mg daily once daily or 5 mg twice daily	Maternal use of loratadine has not been associated with an increased risk of major malformations. Loratadine may be used for the treatment of allergic rhinitis during pregnancy	Headache, drowsiness, fatigue, malaise, xerostomia, stomatitis

(continued)

Table 5.3 (continued)

Medication	Mechanism of action	Dosage	Pregnancy implications	Side effects
Montelukast (Singulair®)	Selective leukotriene receptor antagonist that inhibits the cysteinyl leukotriene receptor	10 mg once daily (in the evening)	Based on available data, an increased risk of teratogenic effects has not been observed with montelukast use in pregnancy	Headache, dizziness, fatigue, dyspepsia, gastroenteritis, toothache, pyuria increased serum AST and ALT, weakness, nasal congestion, epistaxis
Budesonide (Rhinocort®)	Controls the rate of protein synthesis; depresses release and activity of endogenous chemical mediators of inflammation (kinins, histamine, liposomal enzymes, prostaglandins) and the migration of polymorphonuclear leukocytes, fibroblasts; reverses capillary permeability and	One spray (32 mcg) in each nostril once daily (64 mcg/day)	Studies of pregnant women using intranasal budesonide have not demonstrated an increased risk of abnormalities. Intranasal corticosteroids are recommended for the treatment of rhinitis during pregnancy; the lowest effective dose should be used	Epistaxis, pharyngitis, bronchospasm, cough, nasal mucosa irritation
Mometasone (Nasonex®)	lysosomal stabilization at the cellular level to prevent or control inflammation	Two sprays (100 mcg) in each nostril once daily (200 mcg)	Intranasal corticosteroids, including mometasone, beclomethasone, and fluticasone,	Headache, viral infection, pharyngitis, cough, epistaxis
Beclomethasone (Qnasl®)		Two inhalations (160 mcg) in each nostril once daily (320 mcg daily)	may be acceptable for the treatment of rhinitis during pregnancy when used at recommended doses. Pregnant women adequately controlled on mometasone, beclomethasone, and fluticasone	Nasopharyngitis, dizziness, headache, altered sense of smell, anosmia, adrenal suppression (at high doses or in susceptible individuals), hypercorticism(at high doses or in susceptible individuals)
Fluticasone (Flonase®)		Two sprays (50 mcg/spray) per nostril once daily (200 mcg/day)	may continue therapy; if initiating treatment during pregnancy, use of an agent with more data in pregnant women may be preferred	Headache, dizziness, generalized ache, nausea and vomiting, abdominal pain, diarrhea, Pharyngitis, epistaxis, acute asthma, cough, pharyngolaryngeal pain

Table 5.3 (continued)

Medication	Mechanism of action	Dosage	Pregnancy implications	Side effects
Phenylephrine (Neo-Synephrine®)	Potent, direct-acting alpha-adrenergic agonist with virtually no beta-adrenergic activity; produces local	Instill 2–3 sprays in each nostril no more than every 4 h for ≤3 days	Decongestants are not the preferred agents for the treatment of rhinitis during pregnancy. Short-term use (<3 days) of intranasal phenylephrine or oxymetazoline may be beneficial to some patients, although its safety during pregnancy has not been studied. Should be avoided in the first trimester of pregnancy	Burning, nasal discharge, sneezing, stinging
Oxymetazoline (Afrin®)	vasoconstriction resulting in nasal decongestion	2–3 sprays into each nostril twice daily for ≤3 days (2 doses/24 h)		Dry nose, nasal congestion (rebound; chronic use), nasal mucosa irritation (temporary), sneezing
Pseudoephedrine (Sudafed®)	Directly stimulates alpha-adrenergic receptors of respiratory mucosa causing vasoconstriction; directly stimulates beta-adrenergic receptors causing bronchial relaxation, increased heart rate and contractility	Immediate release, 60 mg every 4 to 6 h; extended release, 120 mg every 12 h or 240 mg every 24 h	Oral pseudoephedrine should be avoided during the first trimester. There is risk of gastroschisis, small intestinal atresia, and hemifacial microsomia due to pseudoephedrine's vasoconstrictive effects	Cardiac arrhythmia, chest tightness, hypertension, palpitations, tachycardia, ataxia, dizziness, drowsiness, excitability, fatigue
Ipratropium (Atrovent®)	Local application to nasal mucosa inhibits serous and seromucous gland secretions	Two sprays (21 mcg/spray) in each nostril two or three times daily (total dose, 168–252 mcg/day)	Adverse events have not been observed in animal reproduction studies	Headache, dysgeusia, xerostomia, diarrhea, nausea, upper respiratory tract infection, epistaxis, pharyngitis, dry nose, nasal mucosa irritation, nasal congestion

(continued)

Table 5.3 (continued)

Medication	Mechanism of action	Dosage	Pregnancy implications	Side effects
Azelastine (Astelin®)	Competes with histamine for H1-receptor sites on effector cells and inhibits the release of histamine and other mediators involved in the allergic response	One or two sprays (0.1% solution) in each nostril twice daily or two sprays	Data related to the use of azelastine in pregnancy is limited; if treatment for rhinitis in a pregnant woman is needed, other agents are preferred	Bitter taste, headache, drowsiness, rhinitis, dysesthesia, dizziness, fatigue, epistaxis, burning sensation of the nose, pharyngitis, nasal discomfort, sneezing, nasal mucosa ulcer, pharyngolaryngeal pain

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Hormonal Rhinitis

Etiology

Pregnancy rhinitis (also called rhinitis of pregnancy) and menstrual cycle rhinitis are both examples of hormonally induced rhinitis. Pregnancy rhinitis is associated with nasal congestion usually beginning after the 2nd month of pregnancy [25] and occurs in approximately 30% of randomly selected women [26]. Its principle cause is an increase in prolactin, vasoactive intestinal peptide, placental growth hormone, progesterone, and estrogen which affect the nasal vasculature, resulting in vascular engorgement and increased mucosal gland activity [19]. Pregnancy rhinitis usually abates 2 weeks postpartum.

Diagnosis

The diagnosis is made clinically by an adequate history and physical examination. Other forms of rhinitis should be excluded.

Treatment

The treatment of hormonal rhinitis is similar to other nonallergic rhinitis syndromes and includes the avoidance of aggravating irritants. Some women can tolerate the symptoms of pregnancy rhinitis without medical management [2]; however, rhinitis in pregnancy is associated with increased snoring, possibly placing the mother at risk for sleep apnea and exacerbating hypertension associated with pregnancy.

This also may be a factor in the development of preeclampsia [27]. Treatment may include exercise, head of bed elevation, nasal alar dilatation, and nasal saline rinses. When these measures fail, intranasal corticosteroids, such as budesonide, can be administered, although intranasal fluticasone was not effective for pregnancy rhinitis in one study [28]. Decongestants such as oxymetazoline and pseudoephedrine may be used with caution with an appropriate risk-benefit discussion [7, 19, 29, 30]; however, they should not be administered until after the first trimester [2] as they may be associated with teratogenicity.

Infectious Rhinitis

Etiology

Infectious rhinitis, associated with an upper respiratory tract infection (URI) or common cold, is an acute inflammatory disease of the upper airway. URIs are primarily caused by an acute viral infection [31–35]. Common viruses include rhinovirus (30–50%), coronavirus (10–15%), influenza virus (5–15%), respiratory syncytial virus (5%), parainfluenza virus (5%), adenovirus (<5%), and enterovirus (<5%) [36] (Fig. 5.3). The incubation period is usually 24–72 h with symptoms persisting for 3–10 days [36, 37]. Symptoms include nasal congestion, clear to mucopurulent nasal discharge, a sensation of discomfort and pressure in the face, headache, olfactory disturbances, cough, and postnasal drip. A secondary bacterial infection sometimes occurs necessitating additional therapy. A bacterial etiology should be considered when the symptoms persist beyond 7–10 days or when symptoms worsen after transient improvement [7].

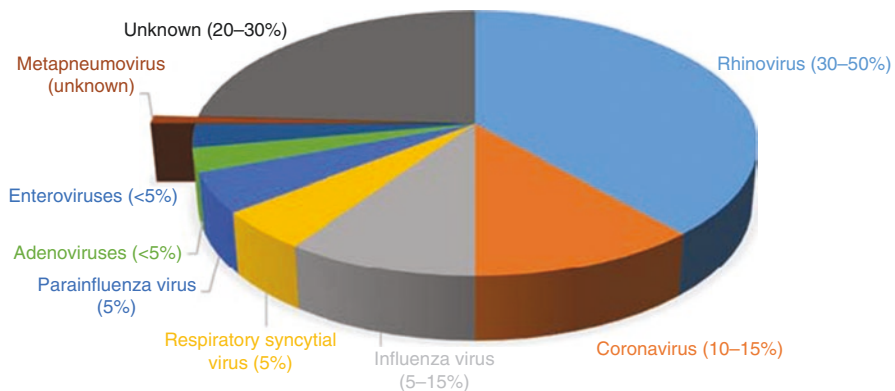


Fig. 5.3 Viral etiology of the common cold. (Adapted from Kirkpatrick [37])

Diagnosis

Infectious rhinitis is diagnosed clinically and is based on the history and physical examination [6, 7]. A culture of nasal secretions is usually not indicated because it does not accurately reflect the organisms in the sinuses causing the infection.

Treatment

Treatment of a viral URI during pregnancy is identical to that of the nonpregnant subject. Subjects are usually observed for 7–10 days with anticipated spontaneous resolution. Antibiotics are usually not necessary unless a primary or secondary bacterial infection is suspected [7, 32]. Decongestants should be used cautiously, particularly in the first trimester [19].

Antibiotics to be considered for a primary or secondary bacterial sinus infection include penicillin derivatives, including those that contain sulbactam/clavulanate and cephalosporins, erythromycin, and azithromycin [19]. Clindamycin can also be used when other antibiotics fail. Clarithromycin, fluoroquinolones, aminoglycosides, sulfonamides, tetracyclines, and vancomycin should not be considered first line, especially during the first trimester, due to potentially greater side effects. Appropriate antibiotic use is necessary until the subject's symptoms have resolved.

Nonallergic Rhinitis

Etiology

Nonallergic rhinitis, also referred to as vasomotor or idiopathic rhinitis, is thought to be vagally mediated. It is occasionally associated with gustatory rhinitis, i.e., rhinorrhea exacerbated by eating [7]. Subjects with nonallergic rhinitis appear to have heightened sensitivity to nociceptive stimuli such as aerosolized irritants, spicy foods, environmental temperature changes, alcohol ingestion, cold dry air, and even exercise [7, 38–41]. Symptoms are variable and consist mainly of nasal obstruction and rhinorrhea, both anteriorly and into the posterior pharynx (postnasal drip). Sneezing and pruritus are less common.

Diagnosis

Nonallergic rhinitis is diagnosed primarily after other types of rhinitis have been excluded. It is based on the characteristic history and physical findings, mainly nasal mucosal edema, and by the triggers which exacerbate the disease.

Treatment

Many women experience this type of rhinitis during pregnancy and it can be confused with pregnancy rhinitis. Symptomatic therapy includes elevating the head of the bed, avoiding irritants, and using intranasal saline. When such measures fail and symptoms persist, pharmacologic intervention can be considered. Intranasal ipratropium bromide is primarily used to treat excessive nasal secretion or rhinorrhea, which can occur both anteriorly and posteriorly, and is especially effective for gustatory rhinitis. Intranasal corticosteroids are the drugs of choice for eosinophilic nonallergic rhinitis (see below) and can be tried in other subjects with nonallergic rhinitis. Oral and topical antihistamines, such as azelastine, can also be considered, although their safety during pregnancy has not been studied. The topical antihistamine azelastine also is efficacious [7, 15, 42, 43], but has not been studied in human pregnancy. These are sometimes used along with the cautious use of nasal decongestants, which preferably should be avoided especially during the first trimester. Oxymetazoline drops or spray, with no more than one or two sprays in each nostril twice daily, ideally for no more than 3 days in a row, may be helpful in subjects with substantial nasal obstruction. Intranasal corticosteroids have been reported to protect against rhinitis medicamentosa [44, 45]; therefore, patients should be maintained on intranasal corticosteroids if oxymetazoline or its equivalent is used long term.

Nonallergic Rhinitis with Eosinophilia Syndrome (NARES)

Etiology

Nonallergic rhinitis with eosinophilia syndrome (NARES) is a nonallergic inflammatory form of rhinitis. Subjects have perennial symptoms including sneezing, watery rhinorrhea, nasal pruritus, congestion, and intermittent decreased olfactory sensation [46, 47]. Its prevalence and etiology are unknown. The characteristic association is the eosinophilia found on nasal smear of greater than 5% [7, 48–51] and a lack of demonstrable allergy as determined by skin or in vitro allergen testing [7].

Diagnosis

The diagnosis of NARES is supported by the history and physical exam examination, greater than 5% eosinophilia on nasal smear and the lack of positive in vivo or in vitro allergy tests.

Treatment

Conservative treatment should include the aforementioned nonallergic rhinitis strategies. These include avoiding aggravating irritants, such as smoke and other pollutants. Some cases may respond to exercise, head of bed elevation, and nasal alar dilatation [7]. The pharmacologic treatment of NARES includes topical intranasal corticosteroids such as budesonide [7, 52, 53]. Intranasal ipratropium is effective to reduce symptoms of rhinorrhea [7, 15].

Occupational Rhinitis

Etiology

Occupational rhinitis, either allergic or nonallergic, is caused by allergens or irritants, respectively, that are encountered in the workplace. Examples of substances that can induce allergic rhinitis include animal and food emanations. Detergents, such as those containing chlorine or ammonia, can be associated with nonallergic occupational rhinitis. Occupational asthma may accompany rhinitis.

Diagnosis

The diagnosis of occupational rhinitis, like other forms of rhinitis, is based on the history and physical exam. IgE sensitization can be demonstrated by in vivo or in vitro tests, with in vitro tests again preferred during pregnancy. Nasal allergen challenge can be useful to determine the suspected cause of symptoms [7, 54, 55] but would usually be deferred to postpartum. Eosinophils, basophils, eosinophilic cationic protein, and tryptase are biological markers that are increased on nasal lavage following an allergen challenge in IgE-dependent sensitization.

Treatment

The ideal treatment of occupational rhinitis is to avoid the aggravating substances causing the symptoms. Site visits may be beneficial, which can be both diagnostic and allow for planning of site-specific changes. In addition, the Occupational Safety and Health Administration (OSHA) requires employers to keep on-site reports of potential substances which should be reviewed. When conservative measures fail and symptoms persist, intranasal corticosteroids can be considered. Decongestants such as oxymetazoline and pseudoephedrine may be used after the first trimester with appropriate risk-benefit ratio [7, 19, 29, 30]. See discussion above about the concomitant use of intranasal corticosteroids with long-term oxymetazoline.

Drug-Induced Rhinitis and Rhinitis Medicamentosa

Etiology

Drug-induced rhinitis is caused by a variety of different medications, some of which include ACE inhibitors [56], alpha-receptor antagonists [57], phosphodiesterase inhibitors [58], beta-blockers, and calcium channel blockers. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) can exacerbate rhinitis associated with aspirin-exacerbated respiratory disease [7, 59, 60], a phenotype of asthma associated with nasal polyps, asthma, and severe intolerance to NSAIDs.

Rhinitis medicamentosa develops from the prolonged use of topical alpha-adrenergic agents such as oxymetazoline and phenylephrine. Symptoms are caused by hypertrophy of the nasal mucosa, loss of nasociliary structures, and goblet cell hyperplasia with subsequent rebound nasal obstruction from the repeated use of these medications. It can develop in as little as 3 days, but often at much longer intervals of use. Nasal septal perforation can result as a complication. The use of intranasal cocaine can similarly cause rhinitis medicamentosa. Subjects may develop tachyphylaxis and the need for more frequent dosing to achieve adequate decongestion.

Diagnosis

The diagnosis of topical drug-induced rhinitis is obtained by detailed history and physical examination. The nasal mucosa can appear inflamed with mucosal membrane ulcerations, bleeding with minimal mucus, which is especially true with the use of topical/intranasal adrenergic agents and illicit drug use. The rhinitis associated with most oral medications is primarily nasal mucosal edema and nasal congestion.

Treatment

The ideal treatment of oral drug-induced rhinitis is to stop the medication(s) causing the problem [7]. If the medication primarily causing nasal congestion cannot be discontinued, symptomatic therapies of various forms can be tried. Management also includes elevating the head of bed, nasal dilatation, and the use of intranasal corticosteroids.

Rhinitis medicamentosa is treated by stopping the offending agent and the use of intranasal corticosteroids. It is important to inform subjects with rhinitis medicamentosa that the symptoms may worsen temporarily once the offending agent is discontinued. A short burst of oral corticosteroids can be helpful but should be used with caution, due to potential risk of low birth weight, premature birth, preeclampsia, and possibly birth defects with first trimester use.

Atrophic Rhinitis

Etiology

Atrophic rhinitis or “empty nose syndrome” is caused by nasal mucosal atrophy, resulting in nasal erosion and crusting, blood and blood clots, and dryness and sometimes a foul odor. The etiology of primary idiopathic atrophic rhinitis is unknown. However, this disease is also associated with recurrent and chronic infection, chronic granulomatous disease (such as tuberculosis), repeated surgery, or radiation therapy. Secretions may be purulent [7, 61]. Superinfection, if suspected, is commonly due to *Pseudomonas aeruginosa* and *Staphylococcus aureus* [61].

Diagnosis

The history and physical examination are essential to make the diagnosis. The nasal mucosal membranes are usually dry, ulcerated, and covered by crusty exudates. Nasal cavities may appear to be larger than usual because of underlying bone resorption. Nasal septal perforation can result in a “saddle nose” deformity [62].

Secondary atrophic rhinitis can be suspected if any two or more of the following criteria are present: subject-reported recurrent epistaxis or episodic anosmia, clinician-documented nasal purulence, crusting, the presence of a chronic inflammatory disease such as sarcoidosis, granulomatosis with polyangiitis (Churg-Strauss syndrome), or two or more sinonasal surgeries [61, 63]. The diagnosis is clinical, but a computerized tomography (CT) scan may be helpful to evaluate the subject for an underlying systemic disease. Nasal biopsy can help confirm a diagnosis.

Treatment

Primary should be distinguished from secondary atrophic rhinitis, wherein the underlying disease should be treated. Treatment of primary atrophic rhinitis consists of nasal saline washes to remove crusty exudates and debris from the nose, topical mupirocin, and if secondary infection is present, appropriate antibiotics [7]. Mupirocin has not been studied in pregnancy.

Rhinosinusitis

Acute or chronic rhinosinusitis is characterized by purulent rhinorrhea, postnasal discharge, anosmia, nasal congestion, facial discomfort, headache, fever, and cough (Table 5.1). It is common in pregnancy [63–65]. The term rhinosinusitis indicates that the nose and the sinuses are affected. Typically, infectious rhinitis secondary to a viral upper respiratory tract infection (URI) precedes infectious rhinosinusitis associated with inflammation of the nasal cavity and the sinuses. It is classified

based on symptom duration [66]: acute rhinosinusitis is defined as symptoms lasting less than 4 weeks, subacute rhinosinusitis as symptoms lasting 4–12 weeks, recurrent acute rhinosinusitis as four or more episodes of rhinosinusitis per year, and chronic rhinosinusitis, as symptoms lasting for greater than 12 weeks. All forms of sinusitis are primarily medical and not surgical problems just as is any chronic inflammatory disease. The diagnosis is made clinically and by rhinoscopy. A CT scan should only be obtained when a complication or surgery is contemplated. An abnormal CT scan does not confirm the diagnosis, as mucosal thickening and air fluid levels can occur with a URI and can take several weeks to resolve. These findings can also occur with allergic rhinitis and rhinosinusitis. Mucosal thickening, cysts, and polyps present in the sinuses are mostly incidental findings.

Acute and Subacute Rhinosinusitis

Etiology

Acute rhinosinusitis (ARS) is classified based on its etiology, being either viral or bacterial, and thus termed acute viral rhinosinusitis (AVRS) or acute bacterial rhinosinusitis (ABRS), respectively. Symptoms of both overlap but include those listed above. AVRS can lead to ABRS, which is characterized by symptoms persisting for more than 10 days with objective confirmation of purulent discharge from the nares or posterior pharynx. Most cases of acute rhinosinusitis are of viral origin, with approximately 0.5–2.0% progressing to ABRS, typically caused by secondary infections with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus* [67, 68] (Fig. 5.4).

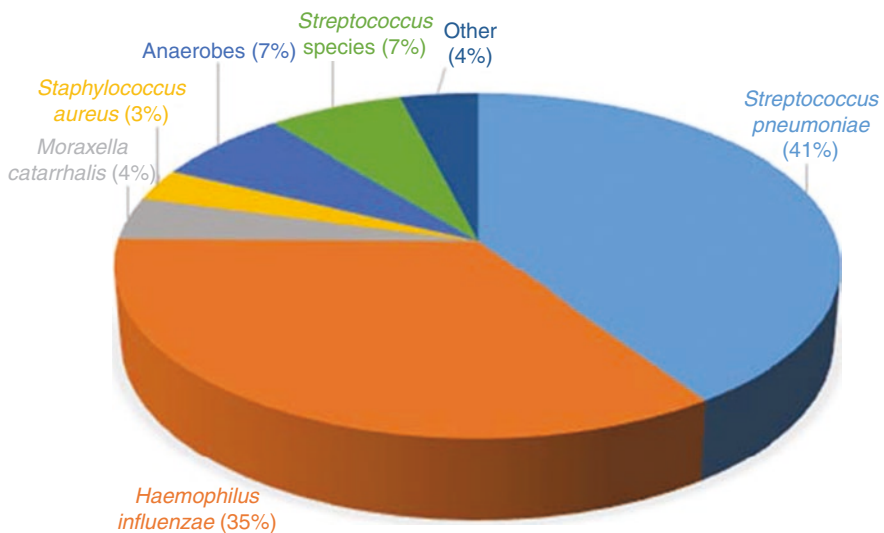


Fig. 5.4 Pathogens which cause acute bacterial rhinosinusitis. (Adapted from Chow et al. [67])

Diagnosis

The diagnosis of ARS is based on the history and physical with clinical symptoms lasting for several weeks or less. Of considerable concern is the individual who develops a secondary bacterial infection manifested by a fever associated with purulent nasal discharge and facial discomfort or pain, again, usually following a viral respiratory tract infection. Rhinoscopy may be necessary to confirm the diagnosis. Indication for referral are subjects who are not responding to antibiotics or who have persistent fever, periorbital edema and erythema, cranial nerve palsies, abnormal extraocular muscle function, proptosis, vision changes, severe progressive headaches, altered mental status, or signs of meningeal inflammation [3, 69]. Presentation of acute rhinosinusitis and subacute rhinosinusitis are similar and are solely differentiated by the duration of illness.

Treatment

Treatment of AVRS is conservative. An intranasal corticosteroid, such as budesonide, is a treatment of choice. Double-blind controlled studies indicate efficacy for acute viral rhinosinusitis. Intranasal decongestants, such as oxymetazoline, may also be used for nasal mucosa edema, preferably after the first trimester, but should only be used temporarily and then discontinued unless used in conjunction with intranasal corticosteroids. Other medications such as antihistamines and oral decongestants may also be helpful.

The treatment of ABRS is similar; however, antibiotics are necessary. Intranasal corticosteroids plus amoxicillin, amoxicillin-clavulanic acid, or a second- or third-generation cephalosporin are first-line drugs. In penicillin-allergic subjects, a macrolide, such as azithromycin, is recommended. When necessary, trimethoprim-sulfamethoxazole (TMP-SMX), particularly in penicillin-allergic subjects, may also be utilized, but its use has been associated with folate deficiency in the mother and neural tube defects in the newborn. Duration of therapy is variable but should be continued until the subject is well and clear of discolored nasal discharge for up to 5 days. Sinus puncture and saline irrigation may be helpful to both diagnose and treat the disease as it has few side effects and may help reduce discomfort or pain [2].

Risk of Disease Versus Treatment

The main complication of untreated AVRS is the progression to ABRS. Some complications of ABRS include orbital cellulitis, preseptal (periorbital) cellulitis, intracranial or epidural abscess, osteomyelitis of the surrounding bones, and meningitis [3, 68]. AVRS usually resolves on its own with or without supportive treatment such as antihistamines, decongestants, and intranasal corticosteroids.

Recurrent Acute Rhinosinusitis

Etiology

Recurrent acute rhinosinusitis (RARS) is diagnosed when four or more episodes of ABRS occur over a year with resolution of symptom between infections. Symptoms of RARS are similar to ABRS.

Diagnosis

The diagnosis is made clinically. Nasal endoscopy and occasionally imaging studies should be considered to rule out any underlying abnormalities in the soft tissue or bony structure which could predispose to RARS, such as bony abnormalities of the ostiomeatal complex and sinus cavities. These are uncommon.

Treatment

Treatment of RARS is identical to ABRS. In addition, an underlying etiology must be ruled out. Various forms of rhinitis, particularly allergic rhinitis, may predispose to all types of rhinosinusitis. One study indicates that the chronic use of antibiotics or intranasal corticosteroids is not beneficial in reducing the number of episodes per year [66]. Subjects with recurrent acute rhinosinusitis should be evaluated for a primary or secondary immunodeficiency and other predisposing illnesses such as cystic fibrosis, ciliary dysfunction, and anatomical abnormalities [3]. A referral to a competent allergist/immunologist is helpful for this purpose.

Chronic Rhinosinusitis

Etiology

Chronic rhinosinusitis (CRS) is an inflammatory condition involving the paranasal sinuses lasting for more than 3 months. It may begin with an acute viral respiratory tract infection that fails to resolve. Symptoms and signs vary in prevalence and severity, including nasal congestion; anterior and posterior mucopurulent discharge; facial discomfort, pressure, or fullness; headaches; and olfactory disturbance. Fatigue, malaise, cough, and sleep disturbances can also be present. Subtypes of CRS include CRS with nasal polyposis (CRS with NP), CRS without nasal polyposis (CRS without NP), and allergic fungal rhinosinusitis (AFRS). Mucosal remodeling can occur as it occurs in severe asthma, potentially resulting in irreversible chronic upper airway disease [3, 66].

Diagnosis

The presence of two or more symptoms and signs for greater than 3 months is suggestive of CRS. These include (1) mucopurulent discharge, (2) nasal obstruction or congestion, (3) facial pain, (4) pressure or fullness in the face, and (5) decreased sense of smell. It also ideally requires documentation of inflammation by means of one or more of the following: (1) purulent discharge or edema in the middle meatus or anterior ethmoid region (rhinoscopy), (2) nasal polyps (rhinoscopy), or (3) radiographic imaging consistent with the clinical diagnosis of chronic sinusitis [3, 66, 70]. Subjects with chronic sinusitis, particularly when associated with chronic infection, should be evaluated for a primary or secondary immunodeficiency and other predisposing illnesses such as cystic fibrosis, ciliary dysfunction, and anatomical abnormalities [3]. A referral to a competent allergist/immunologist is helpful for this purpose.

- *CRS with Nasal Polyposis* (CRS with NP)
CRS with NP accounts for 20–33% of CRS and is characterized by the presence of nasal polyps usually emanating from the middle meatus, gradual worsening nasal congestion, a feeling of fullness and pressure in the face, anterior and posterior pharyngeal purulent drainage, and anosmia. Fever and facial discomfort are usually absent. Translucent, yellow-gray or white, and often glistening polyps are usually visible with anterior rhinoscopy. Edematous nasal turbinates are often mistaken for polyps, the former of which are pink, sensitive to touch, and appear similar to surrounding mucosa [3, 66, 70].
- *CRS without Nasal Polyposis* (CRS Without NP)
CRS without NP is the most common form of CRS accounting for approximately 60–65% of cases. Differentiating CRS without NP and RARS may be difficult. The former has persistent and the latter intermittent symptoms and signs. Symptoms and signs include facial fullness, discomfort or pain, anterior/posterior purulent change, and fatigue. An elevated temperature is rare. The pathophysiology of this disease is not completely understood [3, 66, 70].
- *Allergic Fungal Rhinosinusitis*
Allergic fungal rhinosinusitis (AFRS) accounts for 5–10% of all CRS and is usually caused by the colonization of the mucosal membranes of the upper airway and sinuses with a noninvasive fungus, the most common of which is *Aspergillus fumigatus*, and a subsequent allergic response. Subjects with AFRS often have asthma, NP, and allergic rhinitis, and it occurs in immunocompetent subjects. The signs and symptoms are similar to that of CRS with NP. Subjects with AFRS, however, usually have a pathognomonic “peanut butter” appearing mucus drainage from the nares or posteriorly into their oral pharynx [3, 66, 70].

Treatment

Appropriate treatment of CRS reduces the signs and symptoms of the disease and improves the quality of life. It primarily involves controlling mucosal inflammation and edema, improving sinus tract ventilation and drainage, treating the

microorganisms involved, and trying to reduce the frequency of exacerbations. This is accomplished by ruling out an underlying immunodeficiency disease, by treating the underlying allergic disease when present, and by administering appropriate immunizations [70].

Medical management of CRS typically involves topical corticosteroids which reduce inflammation, antibiotics to treat the offending microorganisms, and nasal irrigation to promote sinus drainage [66]. Systemic corticosteroids are sometimes indicated to decrease inflammation but usually only for a short period of time. Evidence-based medicine is lacking for most forms of treatment. Intranasal corticosteroids, such as budesonide, versus systemic corticosteroids are preferred especially during pregnancy. If indicated [65, 66, 70], an antibiotic regimen such as amoxicillin-clavulanate acid is usually the first drug of choice. Others include a macrolide, such as erythromycin, or clindamycin or metronidazole, although the latter medication is contraindicated in the first trimester. Other antibiotics to consider include cefuroxime, cefdinir, cefpodoxime, azithromycin, or TMP-SMX (in penicillin-allergic only) [2, 71]. Antifungals have not been proven to be helpful but are sometimes utilized; however, they have not been shown to be safe to use during pregnancy.

Conclusion

Allergic diseases and other forms of rhinitis and rhinosinusitis affect approximately one-third of women in the childbearing age [9, 19]. When poorly controlled, they affect the quality of life and could potentially harm the mother and fetus [13]; therefore, they require a proper diagnosis and effective treatment.

Sleep-disturbed breathing is one of the most common symptoms reported with untreated rhinitis and rhinosinusitis in both pregnant and nonpregnant subjects [70, 72]. Other sequelae include generalized malaise, cognitive and psychiatric problems, impaired exercise tolerance, decreased self-esteem, depression, and decreased work productivity [72]. Specifically, among pregnant subjects suffering from these diseases, the quality of life in the third versus the second trimester appears worse.

References

1. Baraniuk JN, Kim D. Nasonasal reflexes, the nasal cycle, and sneeze. *Curr Allergy Asthma Rep.* 2007;7(2):105–11.
2. Adkinson NE, Bochner BS, Burks AW, Busse WW, Holgate ST, Lemanske RF, et al. *Middleton's allergy: principles and practice* 2014. Available from: <https://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C20101657276>.
3. Peters AT, Spector S, Hsu J, Hamilos DL, Baroody FM, Chandra RK, et al. Diagnosis and management of rhinosinusitis: a practice parameter update. *Ann Allergy Asthma Immunol.* 2014;113(4):347–85.

4. Leynaert B, Neukirch C, Kony S, Guenegou A, Bousquet J, Aubier M, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol.* 2004;113(1):86–93.
5. Spector SL. Overview of comorbid associations of allergic rhinitis. *J Allergy Clin Immunol.* 1997;99(2):S773–80.
6. Sexton DJ, McClain M. The common cold in adults: diagnosis and clinical features. In: UpToDate, Hirsch MS, Aronson MD, Libman H, editors. UpToDate. Waltham: UpToDate Inc.. <http://www.uptodate.com>. Accessed on 26 June 2017.
7. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol.* 2008;122(2 Suppl):S1–84.
8. Abbas AK, Lichtman AH, Pillai S. Basic immunology functions and disorders of the immune system. St. Louis: Elsevier; 2016. Available from: <https://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C20140041366>.
9. Pali-Scholl I, Namazy J, Jensen-Jarolim E. Allergic diseases and asthma in pregnancy, a secondary publication. *World Allergy Organ J.* 2017;10(1):10.
10. Pali-Scholl I, Motala C, Jensen-Jarolim E. Asthma and allergic diseases in pregnancy a review. *World Allergy Organ J.* 2009;2(3):26–36.
11. Powell H, Murphy VE, Hensley MJ, Giles W, Clifton VL, Gibson PG. Rhinitis in pregnant women with asthma is associated with poorer asthma control and quality of life. *J Asthma.* 2015;52(10):1023–30.
12. Law A, McCoy M, Lynen R, Curkendall SM, Gatwood J, Juneau PL, et al. The additional cost burden of preexisting medical conditions during pregnancy and childbirth. *J Womens Health (Larchmt).* 2015;24(11):924–32.
13. Gilbey P, McGruthers L, Morency AM, Shrim A. Rhinosinusitis-related quality of life during pregnancy. *Am J Rhinol Allergy.* 2012;26(4):283–6.
14. Peden D. An overview of rhinitis. In: Corren J, Feldweg AM, editors. UpToDate. Waltham: UpToDate Inc. <https://www.uptodate.com/contents/an-overview-of-rhinitis>. Accessed 23 Nov 2018.
15. Druce HM, Spector SL, Fireman P, Kaiser H, Meltzer EO, Boggs P, et al. Double-blind study of intranasal ipratropium bromide in nonallergic perennial rhinitis. *Ann Allergy.* 1992;69(1):53–60.
16. Settipane RA. Rhinitis: a dose of epidemiological reality. *Allergy Asthma Proc.* 2003;24(3):147–54.
17. Varjonen E, Kalimo K, Lammintausta K, Terho P. Prevalence of atopic disorders among adolescents in Turku, Finland. *Allergy.* 1992;47(3):243–8.
18. Smith JM. A five-year prospective survey of rural children with asthma and hay fever. *J Allergy.* 1971;47(1):23–30.
19. Goldstein G, Govindaraj S. Rhinologic issues in pregnancy. *Allergy Rhinol (Providence).* 2012;3(1):e13–5.
20. Schatz M, Zeiger RS. Diagnosis and management of rhinitis during pregnancy. *Allergy Proc.* 1988;9(5):545–54.
21. Ridolo E, Caminati M, Martignago I, Melli V, Salvottini C, Rossi O, et al. Allergic rhinitis: pharmacotherapy in pregnancy and old age. *Expert Rev Clin Pharmacol.* 2016;9(8):1081–9.
22. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol.* 2011;127(1 Suppl):S1–55.
23. Metzger WJ, Turner E, Patterson R. The safety of immunotherapy during pregnancy. *J Allergy Clin Immunol.* 1978;61(4):268–72.
24. Greenhawt M, Oppenheimer J, Nelson M, Nelson H, Lockey R, Lieberman P, et al. Sublingual immunotherapy: a focused allergen immunotherapy practice parameter update. *Ann Allergy Asthma Immunol.* 2017;118(3):276–82 e2.
25. Ellegard E, Karlsson G. Nasal congestion during pregnancy. *Clin Otolaryngol Allied Sci.* 1999;24(4):307–11.

26. Schatz M, Zeiger R, Falkoff R, Chambers C, Macy E, Mellon MH. Asthma and allergic diseases during pregnancy. In: Middleton's allergy: principles and practice. [Internet]. 8th ed; 2014. p. 951–68. Available from: <https://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C20101657276>.
27. Ellegard EK. Pregnancy rhinitis. *Immunol Allergy Clin N Am*. 2006;26(1):119–35, vii.
28. Ellegard EF, Hellgren M, Karlsson NG. Fluticasone propionate aqueous nasal spray in pregnancy rhinitis. *Clin Otolaryngol*. 2001;26:394–400.
29. Gilbert C, Mazzotta P, Loebstein R, Koren G. Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. *Drug Saf*. 2005;28(8):707–19.
30. Werler MM, Sheehan JE, Mitchell AA. Maternal medication use and risks of gastroschisis and small intestinal atresia. *Am J Epidemiol*. 2002;155(1):26–31.
31. Fendrick AM, Saint S, Brook I, Jacobs MR, Pelton S, Sethi S. Diagnosis and treatment of upper respiratory tract infections in the primary care setting. *Clin Ther*. 2001;23(10):1683–706.
32. Gwaltney JM Jr. Acute community-acquired sinusitis. *Clin Infect Dis*. 1996;23(6):1209–23; quiz 24–5.
33. Wald ER, Guerra N, Byers C. Upper respiratory tract infections in young children: duration of and frequency of complications. *Pediatrics*. 1991;87(2):129–33.
34. Gwaltney JM. Acute sinusitis and rhinosinusitis in adults. In: UpToDate, Rose BD, editors. UpToDate. Waltham: UpToDate Inc. <http://www.uptodate.com>. Accessed on 22 Jul 2017.
35. Wald ER. Clinical features, evaluation, and diagnosis of acute bacterial sinusitis in children. In: UpToDate, Rose B, editors. UpToDate. Waltham: UpToDate Inc. <http://www.uptodate.com>. Accessed on 20 Jul 2017.
36. Heikkinen T, Jarvinen A. The common cold. *Lancet*. 2003;361(9351):51–9.
37. Kirkpatrick GL. The common cold. *Prim Care*. 1996;23(4):657–75.
38. Cruz AA, Naclerio RM, Proud D, Togias A. Epithelial shedding is associated with nasal reactions to cold, dry air. *J Allergy Clin Immunol*. 2006;117(6):1351–8.
39. Shusterman D, Balmes J, Murphy MA, Tai CF, Baraniuk J. Chlorine inhalation produces nasal airflow limitation in allergic rhinitic subjects without evidence of neuropeptide release. *Neuropeptides*. 2004;38(6):351–8.
40. Silvers WS. The skier's nose: a model of cold-induced rhinorrhea. *Ann Allergy*. 1991;67(1):32–6.
41. Silvers WS, Poole JA. Exercise-induced rhinitis: a common disorder that adversely affects allergic and nonallergic athletes. *Ann Allergy Asthma Immunol*. 2006;96(2):334–40.
42. Banov CH, Lieberman P, Vasomotor Rhinitis Study G. Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. *Ann Allergy Asthma Immunol*. 2001;86(1):28–35.
43. Nelson BL, Jacobs RL. Response of nonallergic rhinitis with eosinophilia (NARES) syndrome to 4% cromoly sodium nasal solution. *J Allergy Clin Immunol*. 1982;70(2):125–8.
44. Rael EL, Ramey J, Lockey RF. Oxymetazoline hydrochloride combined with mometasone nasal spray for persistent nasal congestion (pilot study). *World Allergy Organ J*. 2011;4(3):65–7.
45. Baroody FM, Brown D, Gavanescu L, DeTineo M, Naclerio RM. Oxymetazoline adds to the effectiveness of fluticasone furoate in the treatment of perennial allergic rhinitis. *J Allergy Clin Immunol*. 2011;127(4):927–34.
46. Jacobs RL, Freedman PM, Boswell RN. Nonallergic rhinitis with eosinophilia (NARES syndrome). Clinical and immunologic presentation. *J Allergy Clin Immunol*. 1981;67(4):253–62.
47. Mullarkey MF. Eosinophilic nonallergic rhinitis. *J Allergy Clin Immunol*. 1988;82(5 Pt 2):941–9.
48. Ellis AK, Keith PK. Nonallergic rhinitis with eosinophilia syndrome. *Curr Allergy Asthma Rep*. 2006;6(3):215–20.
49. Schiavino D, Nucera E, Milani A, Della Corte AM, D'Ambrosio C, Pagliari G, et al. Nasal lavage cytometry in the diagnosis of nonallergic rhinitis with eosinophilia syndrome (NARES). *Allergy Asthma Proc*. 1997;18(6):363–6.

50. Settipane GA, Klein DE. Non allergic rhinitis: demography of eosinophils in nasal smear, blood total eosinophil counts and IgE levels. *N Engl Reg Allergy Proc.* 1985;6(4):363–6.
51. Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. *Thorax.* 1991;46(12):895–901.
52. Banov CH, Woehler TR, LaForce CF, Pearlman DS, Blumenthal MN, Morgan WF, et al. Once daily intranasal fluticasone propionate is effective for perennial allergic rhinitis. *Ann Allergy.* 1994;73(3):240–6.
53. Wight RG, Jones AS, Beckingham E, Andersson B, Ek L. A double blind comparison of intranasal budesonide 400 micrograms and 800 micrograms in perennial rhinitis. *Clin Otolaryngol Allied Sci.* 1992;17(4):354–8.
54. Gorski P, Krakowiak A, Ruta U. Nasal and bronchial responses to flour-inhalation in subjects with occupationally induced allergy affecting the airway. *Int Arch Occup Environ Health.* 2000;73(7):488–97.
55. Nielsen J, Welinder H, Ottosson H, Bensryd I, Venge P, Skerfving S. Nasal challenge shows pathogenetic relevance of specific IgE serum antibodies for nasal symptoms caused by hexahydrophthalic anhydride. *Clin Exp Allergy.* 1994;24(5):440–9.
56. Materson BJ. Adverse effects of angiotensin-converting enzyme inhibitors in antihypertensive therapy with focus on quinapril. *Am J Cardiol.* 1992;69(10):46C–53C.
57. Plosker GL, Goa KL. Terazosin. A pharmacoeconomic evaluation of its use in benign prostatic hyperplasia. *PharmacoEconomics.* 1997;11(2):184–97.
58. Vitezic D, Pelcic JM. Erectile dysfunction: oral pharmacotherapy options. *Int J Clin Pharmacol Ther.* 2002;40(9):393–403.
59. Bavbek S, Dursun AB, Dursun E, Eryilmaz A, Misirligil Z. Safety of meloxicam in aspirin-hypersensitive patients with asthma and/or nasal polyps. A challenge-proven study. *Int Arch Allergy Immunol.* 2007;142(1):64–9.
60. Ediger D, Sin BA, Heper A, Anadolu Y, Misirligil Z. Airway inflammation in nasal polyposis: immunopathological aspects of relation to asthma. *Clin Exp Allergy.* 2005;35(3):319–26.
61. deShazo RD, Stringer S. Atrophic rhinosinusitis. In: UpToDate. Corren J, Feldweg AM, editors. UpToDate. Waltham: UpToDate Inc. <http://www.uptodate.com>. Accessed on 26 June 2017.
62. Kameswaran M. Fibre-optic endoscopy in atrophic rhinitis. *J Laryngol Otol.* 1991;105(12):1014–7.
63. Ly TH, deShazo RD, Olivier J, Stringer SP, Daley W, Stodard CM. Diagnostic criteria for atrophic rhinosinusitis. *Am J Med.* 2009;122(8):747–53.
64. Sorri M, Hartikainen-Sorri AL, Karja J. Rhinitis during pregnancy. *Rhinology.* 1980;18(2):83–6.
65. Brook I. Microbiology and antibiotic management of chronic rhinosinusitis. In: UpToDate, Calderwood SB, Corren J, Bloom A, editors. UpToDate. Waltham: UpToDate. <http://www.uptodate.com>. Accessed on 07 June 2017.
66. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, Ashok Kumar K, Kramper M, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg.* 2015;152(2 Suppl):S1–S39.
67. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis.* 2012;54(8):e72–e112.
68. Rosenfeld RM. Clinical Practice. Acute sinusitis in adults. *N Engl J Med.* 2016;375(10):962–70.
69. Patel ZM, Hwang P. Uncomplicated acute sinusitis and rhinosinusitis in adults: treatment. In: UpToDate, Deschler DG, Calderwood SB, Bond S, editors. UpToDate. Waltham: UpToDate Inc. <http://www.uptodate.com>. Accessed on 06 Jul 2017.
70. Hamilos DL. Chronic rhinosinusitis: clinical manifestations, pathophysiology, and diagnosis. In: UpToDate, Corren J, Deschler DG, Feldweg AM, editors. UpToDate. Waltham: UpToDate Inc. <http://www.uptodate.com>. Accessed on 07 Jul 2017.
71. Laibl V, Sheffield J. The management of respiratory infections during pregnancy. *Immunol Allergy Clin N Am.* 2006;26(1):155–72, viii.
72. deShazo RD, Kemp S. Allergic rhinitis: clinical manifestations, epidemiology, and diagnosis. In: UpToDate, Corren J, Feldweg AM, editors. UpToDate. Waltham: UpToDate Inc. <http://www.uptodate.com>. Accessed on 13 Jul 2017.