

Differential Diagnosis in Allergy

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KEYWORDS

- Allergy differential diagnosis • Otologic diseases
- Otitis media with effusion • Eustachian tube dysfunction
- Ménière's disease • Nonallergic rhinitis
- Laryngopharyngeal reflux • Eosinophilic esophagitis

Key Points: DIFFERENTIAL DIAGNOSIS IN ALLERGY

- A thorough history and physical examination of the head and neck is paramount to an appropriate diagnosis of allergic and nonallergic diseases
- Otologic disease can be mediated by allergic and nonallergic mechanisms
- Structural anatomic problems—tonsillar and adenoid hypertrophy, septal deviation, nasal masses, laryngeal, and pharyngeal masses—should be readily diagnosed and managed to give the patient the best outcome
- Laryngopharyngeal reflux and eosinophilic esophagitis commonly mimic each other, with the latter often mediated by food hypersensitivities.

OVERVIEW: DIFFERENTIAL DIAGNOSIS OF ALLERGY

An otolaryngic allergist addresses a vast myriad of complaints. Many conditions need to be ruled out before the diagnosis of allergy can be made. This article discusses the differential diagnoses that need to be considered during the allergic evaluation. Using a local-regional discussion, the initial step in creating a differential diagnosis is a thorough history and physical examination of the head and neck. The physical examination should include a complete ear, nose, and throat evaluation with a microscopic ear examination and/or endoscopic nasal endoscopy, if indicated. The larynx and supraglottic area can be visualized with a mirror, a straight rod (using a 30°–70° scope), or a flexible fiberoptic scope, if the anatomy or gag reflex precludes the aforementioned techniques. Cincik and Ferguson¹ noted patients preferred examinations

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with a 30° rigid scope. This technique afforded superior visualization of the nose and larynx. Videostroboscopy of the larynx is reserved for specific voice complaints or vocal dysfunction. Swallowing and laryngopharyngeal reflux complaints may require transnasal esophagoscopy. **Table 1** lists a few of the common conditions that may be confused with allergy, which are outlined in the following sections.

OTOLOGIC CONDITIONS

There are many otologic conditions that may have a similar presentation to allergy. Otitis media (OM) refers to an inflammatory condition of the middle ear and does not refer to etiology or pathogenesis. OM has been subdivided into various subcategories: otitis media with effusion (OME), acute otitis media (AOM), recurrent acute otitis media (RAOM), and chronic otitis media with effusion (COM) Middle ear effusion is defined by the type of fluid noted behind the tympanic membrane. The fluid may be thick and viscous (mucoid), thin and watery (serous), or purulent (filled with pus). The duration of the disease is also used to classify the process: acute (0–3 weeks), subacute (3–12 weeks), and chronic (longer than 12 weeks).

Otitis Media with Effusion

OME is defined as a middle ear space with fluid in the absence of an acute ear infection. OM and OME represent greater than 2.2 million episodes diagnosed per year in the United States.^{1–3} OME is most prevalent in early childhood. Screening surveys have reported a point prevalence of middle ear effusion from infancy to age 5 years to range between 15% and 40%. The peak incidence is in the winter months.^{3–8} Allergy has been believed to play a major role in OME and is detailed in the article by Hurst elsewhere in this issue.⁹ On otoscopy, fluid is present without evidence of infection (**Fig. 1**). Many investigators have established a link between IgE-related diseases and OME.^{9–12}

Acute Otitis Media

AOM is a viral or bacterial infection associated with fever, ear pain, irritability, and may be associated with a concurrent upper respiratory tract infection. AOM is the most common childhood infection for which antibiotics are prescribed in the United States.^{13–15} The diagnosis is most closely associated with otoscopic findings of tympanic membrane bulging or redness. Coker and colleagues^{16,17} determined that otoscopic findings were critical in detecting the disease relative to subjective findings or complaints. The diagnosis of RAOM is made when recurrent ear infections are noted. The exact underlying mechanism is poorly understood and multifactorial. Risk factors associated with developing RAOM include male gender, sibling history of recurrent OM, early occurrence of infection, day-care attendance, parental

Table 1 Common conditions confused with allergy		
Otologic Conditions	Nasal Conditions	Laryngeal Conditions
Otitis media	Septal deviation	Laryngeal masses or tumors
Eustachian tube dysfunction	Nasal tumors	Laryngopharyngeal reflux
Otitis externa	Nasal irritants	Dysphagia
Ménière's disease	Chronic sinusitis	Eosinophilic esophagitis
	Medication rhinitis	Globus (foreign body sensation)
	Nonallergic rhinitis	—

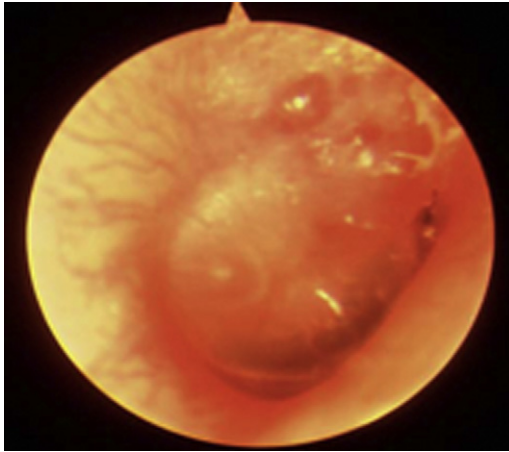


Fig. 1. Serous otitis media. Air fluid levels and “air bubbles” are present.

smoking, absence of breastfeeding, and second-hand smoke.⁷ A meta-analysis by Uhari and colleagues¹⁸ found that sibling history, day-care attendance, parental smoking, breastfeeding less than 3 months, and pacifier use are significant risk factors for AOM. COM has also be linked to underlying allergy (see Hurst and Venge⁹).

EUSTACHIAN TUBE DYSFUNCTION

The eustachian tube connects the middle ear with the pharynx. It is a key component of the middle ear cleft, which consists of the middle ear, the mastoid, and the eustachian tube. The tube extends from the anterior inferior portion of the middle ear to the nasopharynx. In adults the tube is 15 mm below the tympanic ostium at an angle 45°

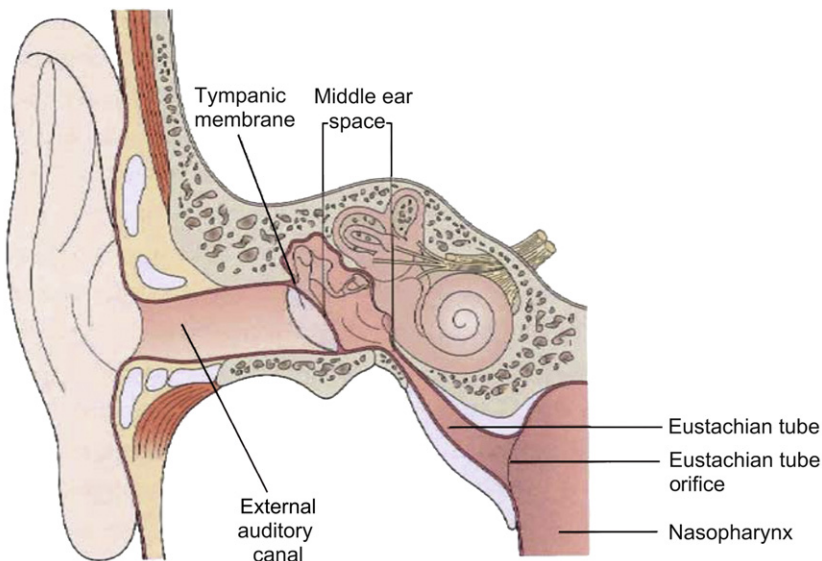


Fig. 2. Diagram of the middle ear cleft. (From Krouse J. Managing the allergic patient. Elsevier Health Sciences; 2008. p. 183; with permission.)

from the horizontal plane (**Fig. 2**).^{19,20} In children the tube is significantly shorter, and is at an angle 10° from the horizontal plane.¹⁹ This anatomic difference makes the middle ear cleft more vulnerable to inoculation with bacteria from nasopharyngeal secretions. The act of swallowing causes the tensor veli palatinae muscle to open and close the tube in order to ventilate the middle ear with atmospheric pressure.^{19,21} The eustachian tube appropriately allows secretions to drain from the middle ear into the nasopharynx, and also offers protection from the nasopharyngeal secretions.^{22–24}

Mechanisms of Eustachian Tube Dysfunction

Three main theories exist to explain why OM or OME develop. Some researchers believe that local inflammation at the nasal side causes retrograde edematous spread up the tube to cause obstruction. Others believe in a mucociliary dysfunction mechanism that results in physical stasis of secretions, resulting in mechanical blockage of the tube.^{22,25} The last theory proposed describes the direct inflammatory changes within the tube itself that result in edema, vascular engorgement, and hypersecretion of the lining of the tube. A closure of the middle ear space to the atmosphere occurs.²⁶ Once the middle ear space is closed off, the air diffuses into the bloodstream (nitrogen first, then oxygen). The loss of air causes a negative pressure relative to the surrounding tissues. This negative pressure causes retraction of the tympanic membrane. The negative pressure developed results in a transudate to develop in the middle ear space.^{26,27} Patients may complain of fullness or a pressure sensation in the ear. The tympanogram may be a B or C type, depicting fluid or a negative pressure, respectively (**Fig. 3**). The clinician must determine a cause for the tubal dysfunction and must carefully evaluate the ear and the nasopharynx for abnormalities.

Contact Dermatitis or Dermatophytid of the Ear

Contact dermatitis (A Gel and Combs type 4 hypersensitivity reaction, T-cell mediated) can occur as a result of using certain shampoos, perfumes, creams, or lotions. The metal in an ear ring (chromium or nickel) may cause a localized reaction (scaling, edema, erythema of the ear lobe). Ear drops or ear molds (made from plastic) from hearing aids may cause similar reactions in the canal or concha of the ear. In addition to contact hypersensitivities, the external ear is a common site of a dermatophytid or

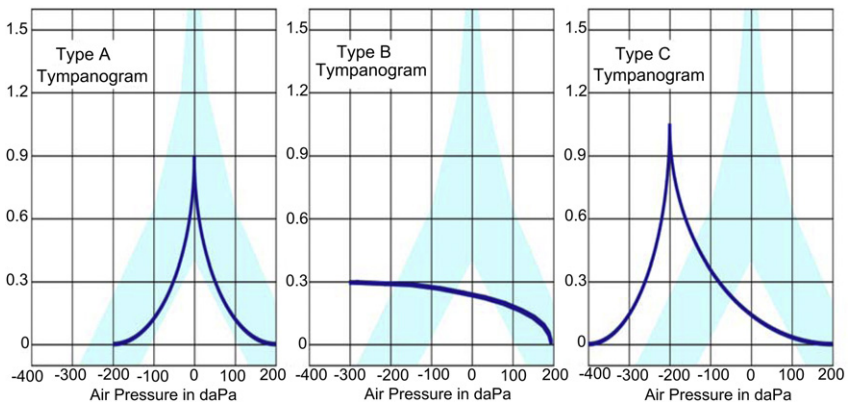


Fig. 3. Representative tympanograms: Type A, “normal pressure” in a normal patient; Type B, commonly referred to as “flat” in a patient with serous otitis media; Type C, “negative pressure” seen in patients with eustachian tube dysfunction. (Courtesy of Dr Brad Stach, Detroit, MI.)

ID reaction, characterized by preauricular or postauricular fissures and skin eruptions around the ear. This condition is a result of hematogenous spread of fungi or their allergic products (antigens) from the primary site of the fungal infection, usually the feet, to an alternative site on the body. Classic sites of the primary fungal infection are toe or fingernails, the skin, or vagina. *Tricophyton*, *Oidiomycetes* (Candida), and *Epidermophyton* are collectively referred to as TOE fungi, and are the most common fungi responsible for this reaction.^{28–30} On identification of a possible ID reaction, the otolaryngic allergist should investigate fungal infections in other areas of the body so to not overlook these abnormalities.

Ménière's Disease and its Mimics

There has been growing evidence that Ménière's disease is partly related to allergic disease; this is comprehensively reviewed in the article elsewhere in this issue on Ménière's disease. Ménière's disease is characterized by aural fullness, fluctuating hearing loss, tinnitus, and vertigo. Patients with Ménière's disease may be disproportionately afflicted by benign positional vertigo (BPV). Aural fullness can be simulated by eustachian tube dysfunction and Ménière's disease. Tinnitus is frequently associated with sensorineural hearing loss; however, when this hearing loss is in the low frequencies, the likelihood that Ménière's disease is the cause is greater than for the more common high-frequency hearing loss associated with presbycusis and loud noise exposure.

NASAL CONDITIONS

The differential diagnosis for nonallergic nasal congestion is large. Nasal congestion may occur as a result of the normal ebb and flow of the autonomic nervous system (the nasal cycle), or may occur with changes in the environment or inflammation locally at the mucosal level due to antigens. Nasal congestion may be the result of mucosal edema from an infection or hormonal changes. Physiologic nasal congestion appears to have the greatest effect on the turbinates. Usually this is not a problem unless a significant septal deviation or turbinate hypertrophy exists. Anterior rhinoscopy will miss significant pathology, especially when there is a septal deviation or when the turbinates obstruct and limit the examination. The most anterior source of nasal obstruction, often missed on examination with a nasal speculum or nasal endoscopy, is obstruction at the nasal valve. The nasal valve is located at the caudal end of the upper lateral cartilage, bound by the septum and the anterior border of the inferior turbinate. This valve provides 50% of the total airway resistance.³¹ Turbinate hypertrophy and nasal valve collapse are common findings, both of which give the sensation of obstruction to the patient.³² It is important to determine whether the turbinate will respond to topical decongestion. Unresponsive turbinates suggest autonomic dysregulation and may need to be addressed surgically. Blue, boggy turbinates (**Fig. 4**) suggest nasal allergy or nonallergic rhinitis with eosinophilia, and require further workup.

Choanal atresia/stenosis is a cause of nasal obstruction, but is usually diagnosed at birth if bilateral; however, unilateral atresia may escape diagnosis for many years. Cleft palate may present with excessive secretions in the nose resulting from the palatal defect. Clefts are also associated with significant feeding issues in early infancy.

Nasal Masses

Nasal masses or enlarged adenoids cause nasal obstruction. Enlarged adenoids may need to be removed if they are obstructing the posterior nasopharynx. A differential diagnosis for tumors in the nasal cavity includes chordoma, chemodectoma,

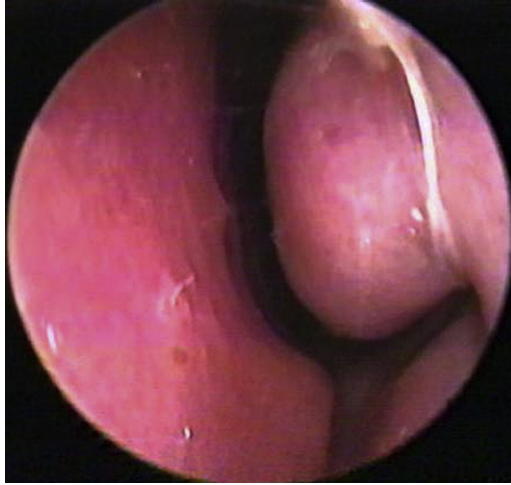


Fig. 4. Pale and boggy inferior turbinates in a patient with allergic rhinitis.

neurofibroma, angiofibroma, inverting papilloma, squamous cell carcinoma, sarcoma, encephalocele, or meningocele.

Nasal Irritants

There are several substances that may cause nasal irritation resulting in mucosal edema and erythema. Chemical exposures may result in type 1 (immediate) or type 4 (delayed) Gel and Coombs reactions. Repeated exposures are usually necessary to develop allergic reactions to various chemicals.^{33,34} There are more than 3800 different chemical compounds in cigarette smoke that cause increased sensitivity of the airways to allergens. Passive smoking in children has been shown to lead to higher rates of childhood infections, higher middle ear effusion rates, decreases in pulmonary function tests, increased childhood asthma rates, and sudden infant death syndrome.^{35,36}

“Sensory irritation” is acute and reversible eye, nose, and throat irritation that occurs after exposure to coarse particulate matter or water-soluble gases or vapors.³⁷ Nonallergic, noninfectious building-related illness or “sick building syndrome” is predominantly related to sensory irritation.³⁸ Indoor irritations include extremes of temperature or humidity, combustion products (poorly functioning combustion appliances, cigarette smoke, improper exhaust ventilation), volatile organic compounds (from furnishings) or reactive chemicals, such as cleaning products (ammonia, chlorine).³⁹ Environmental control with subsequent reduction of exposure to the noxious substance is recommended, if possible, to reduce nasal exposure.

Nonallergic Rhinitis

Nonallergic rhinitis (NAR) is defined as any nonimmune-related rhinitis, and consists of a cluster of syndromes that cause rhinitis. In 1998 Dykewicz and colleagues⁴⁰ noted, in a guideline of the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology, that 50% of the patients who presented for allergic rhinitis actually had some other form of rhinitis. NAR may be triggered by endogenous or exogenous stimuli. The nose responds similarly in inflammation and irritation: sneezing, congestion, rhinorrhea, and itching. This response leads to similar presentation for allergy and NAR. NAR is considered a “diagnosis of exclusion” by many allergists. After

allergy testing is negative, it is the clinician's responsibility to determine which diagnostic category best describes the patient's complaints.

Settipane and Lieberman⁴¹ divided nonallergic rhinitis into 12 categories (**Box 1**). The different types are described briefly here. A complete description by Wilson and colleagues is available elsewhere in this issue and is beyond the scope of this article.

Vasomotor Rhinitis (Idiopathic Rhinitis)

In the article by Settipane and Klein,⁴² vasomotor rhinitis (VMR) was the most common diagnosis in 61%, nonallergic rhinitis with eosinophilia syndrome (NARES) in 33%, sinusitis in 16%, BENARS (blood eosinophilia nonallergic rhinitis syndrome) in 4%, elevated IgE in 12%, and hypothyroid state in 2% of patients. VMR implies idiopathic, perennial, nonallergic rhinitis with a negative skin test, normal IgE levels, and with no inflammatory changes on nasal cytology. VMR symptoms are more obstructive/congested as compared with sneezing, rhinorrhea, and itching. Itching, sneezing, and eye irritation are more commonly seen in allergic rhinitis. At present, this disorder is thought to be related to excessive parasympathetic activity or reduced sympathetic activity of the nasal mucosa. There are other theories that have been proposed but lack definitive evidence.⁴³

NARES

This disorder was first described by Mullarkey and colleagues⁴⁴ in 1980. Patients with NARES typically have more intense nasal symptoms of watery rhinorrhea, pruritus, sneezing paroxysms, hyposmia, and have negative skin or in vitro tests for allergy. Nasal smears are characterized by diffuse eosinophilia. Fifteen percent to 33% of the adults with NAR are found to have this condition.^{42,44} NARES may be associated with Samter's triad (asthma [non-IgE mediated], aspirin sensitivity, and nasal polyposis) or may be a variant of this disease. BENARS is felt to be a subset of NARES, and is defined by elevated numbers of eosinophils in the peripheral blood.

Box 1

Types of nonallergic rhinitis

- Vasomotor rhinitis (unknown etiology)
- NARES (nonallergic rhinitis with eosinophilia syndrome)
- Basophilic/metachromatic nasal disease
- Conditions associated with sinusitis
- Nasal polyp rhinitis
- Metabolic conditions
- Vaculitides/autoimmune and granulomatous diseases
- Drug-induced rhinitis
- Structurally related rhinitis
- Atrophic rhinitis
- Physical/irritative rhinitis
- Occupational rhinitis

Data from Settipane RA, Lieberman P. Update on nonallergic rhinitis. Ann Allergy Asthma Immunol 2002;86:494–508.

Basophilic/Metachromatic Nasal Disease

Basophilic/metachromatic nasal disease, also known as nasal mastocytosis, is very similar to NARES, as both require histologic diagnoses.^{45,46} The hallmark of this disease is mast cell infiltration of the tissue (>2000 per mm^3) with eosinophilia. Patients typically complain of nasal blockage, congestion, and rhinorrhea in comparison with the sneezing and pruritus seen in NARES. Pale boggy and bluish turbinates may be seen on examination. In contrast to NARES, nasal basophilic/metachromatic disease is not associated with nasal polyps, aspirin sensitivity, or asthma. Its etiology is currently unknown.

Conditions Associated with Sinusitis and Nasal Polyps

Chronic rhinitis does have a propensity to be associated with sinusitis, and is very common in our patient population.⁴⁷ These conditions are covered in other articles in this issue.

METABOLIC CONDITIONS

There are numerous metabolic conditions that can be a cause of NAR. Pregnancy, hypothyroidism, oral contraceptives, and estrogen replacement have all been associated with rhinitis. Rhinitis of pregnancy is characterized by obstruction and nasal congestion. There are a few theories regarding the physiologic cause of rhinitis of pregnancy. One is that the circulating blood volume is elevated, which may lead to venous pooling and nasal congestion. The second theory is nasal congestion arising from progesterone-induced smooth muscle relaxation. The third theory is nasal congestion due to the direct effects of estrogen on the nasal mucosa. Direct stimulation of the mucosa by estrogen causes nasal mucosal gland hyperactivity,^{48–50} which results in excessive, thick secretions leaving the patient congested. It is imperative that these patients be treated conservatively.

Vasculitides/Autoimmune and Granulomatous Diseases

There are several systemic diseases that may cause rhinitis. Churg-Strauss vasculitis,⁵¹ systemic lupus erythematosus,⁵² relapsing polychondritis,⁵³ and Sjögren syndrome⁵⁴ are autoimmune-related diseases associated with nasal complaints. Granulomatous diseases, such as sarcoidosis⁵⁵ and Wegener granulomatosis,⁵⁶ have been noted to cause common nasal symptoms and should be considered in the differential of systemic diseases that may cause rhinitis.

Drug-Induced Rhinitis

There are several drugs that cause nasal side effects (**Box 2**). Aspirin and nonsteroidal anti-inflammatory medications are associated with upper airway reactions including nasal polyposis and asthma. Psychotropic agents (ie, thioridazine, amitriptyline, perphenazine) and antihypertensive medications (ie, α -blockers, β -blockers, angiotensin-converting enzyme [ACE] inhibitors, vasodilators) may cause nasal congestion or other nasal symptoms. Oral contraceptives and/or hormonal replacement are well-known causes of rhinitis.^{57,58} With the increased use of phosphodiesterase type 5 inhibitors in men with erectile dysfunction, rhinitic complaints should trigger a discussion on medication use. Cocaine and topical decongestants/vasoconstrictors (ie, oxymetazoline, xylometazoline, phenylephrine, ephedrine) have been associated with rhinitis medicamentosa, and cause rebound nasal congestion and rhinitis. Decongestant use should be addressed when these types of complaints are mentioned during a patient encounter.

Box 2**Drugs with nasal side effects**

Aspirin

Nonsteroidal anti-inflammatory medications

Psychotropic medications

Antihypertensive medications

- α -blockers and β -blockers
- ACE inhibitors
- Vasodilators

Exogenous hormones

Topical decongestants

Structurally Related Rhinitis

Anatomic defects account for 5% to 10% of the complaints in nonallergic rhinitis. The structural abnormalities that may cause rhinitis include nasal septal deviation, turbinate hypertrophy, adenoid hypertrophy, nasal valve collapse, or masses. These conditions are described in detail in previous sections of this article.

Atrophic Rhinitis

Atrophic rhinitis is typically encountered in too aggressive turbinate reduction, granulomatous diseases, trauma, radiation damage, and chronic cocaine use. In undeveloped countries, bacterial infestation secondary to *Klebsiella pneumoniae* subspecies *ozaenae* causes nasal cavity crusting, bleeding, fetor, and mucosal atrophy, also leading to atrophic rhinitis. The nasal mucosa changes from a functional ciliated columnar respiratory epithelium to a nonciliated squamous metaplasia type that is nonfunctional. Mucociliary clearance and neurologic regulation no longer occur. The patient complains of nasal congestion and obstruction due to the loss of the normal laminar flow of the nasal cavity. These patients' nasal cavities are usually widely patent on examination despite subjective obstruction.⁵⁹

Physical/Irritant Rhinitis

This category includes physical changes in the environment including temperature, barometric pressure, inhaled substances, and ingested foods. Cold temperature changes have been reported to result in profuse rhinorrhea.^{60,61} Facial pressure, headaches, and rhinorrhea are common nasal complaints in patients who are exposed to extreme changes in barometric pressures (ie, aviation workers and mountain climbers). Mast cell degranulation and stimulation of irritated nerve endings are felt to be the offending mechanism's pathophysiology.^{61,62} Gustatory rhinitis occurs when a patient ingests a certain food, usually hot or spicy: mucoid or watery rhinorrhea ensues.^{41,63,64} This reaction occurs acutely and lasts as long as the person is ingesting the inciting substance. Raphael and colleagues⁶⁵ have theorized that the afferent sensory nerves are stimulated. This stimulation activates the parasympathetic nerves that supply the nasal mucosal glands, which causes the rhinorrhea and associated sweating and epiphora that may accompany the symptom complex. However, skin testing with abstracts of the suspected foods is commonly negative.

Air pollution can occur indoors or outdoors. Known substances to cause nasal irritation include dust, sulfur dioxide, formaldehyde, wood smoke, cigarette smoke, ozone, and volatile chemicals.⁶⁶ Patients complain of dryness, sneezing, congestion, and rhinorrhea. The exact mechanism is unknown but has been theorized in the section on nasal irritants in this article.^{33,34} Ozone and volatile chemicals have been shown to induce a neutrophilic influx in the mucosa.⁶⁷

Occupational Rhinitis

The incidence of occupational rhinitis is estimated to be 5% to 15%.⁶⁸ A complete medical and workplace history is important because these patients have multiple complaints, including sensory abnormalities with altered sensations of smell. Patients may also have nosebleeds, crusting, impaired mucociliary transport, and nasal hyperactivity. Immunologic hyperreactivity is discussed in previous sections. Allergens may include animal proteins, wheat, latex, pyrethrum in insecticides or other garden products, acid anhydrides in adhesives, and toluene in body spray paints.^{69,70} Annoyance reactions occur in patients with heightened olfactory awareness. These patients complain about perfumes, exhaust fumes, room deodorizer, cleaning agents, floral fragrances, and cosmetics. Irritant reactions occur when a specific respiratory irritant is inhaled beyond a threshold level. Air pollution and ozone are examples of irritants in large cities that are discussed regularly in the news. Tobacco smoke, toluene, paint fumes, nitrogen oxide, and formaldehyde are other examples of nasal irritant.⁷¹ Chronic exposure to formaldehyde, wood, leather, dust, nickel, or chlorophenol is associated with hypertrophic mucosa, metaplasia, and carcinoma in some cases.⁶⁸ A corrosive reaction results after exposure to high concentrations of soluble chemical gases causing inflammation to nose, mouth, ocular mucosa, and skin. Mucosal and skin burns as well as ulcerations may occur. Chemicals known to cause corrosive reactions include ammonium chloride, vinyl chloride, hydrochloric acid, organophosphates, and acrylamide. Irritants cause neurogenic inflammation, which is believed to be the predominant pathway model for chemical sensitivity.⁷² Irritant receptors on sensory nerves (ie, C fibers) induce neuropeptide release. Vasodilation and edema ensue, which results in a nonimmune-mediated inflammation.

ORAL CAVITY CONDITIONS

There are not many oropharyngeal mimics of allergy. Otolaryngic allergists should be comfortable diagnosing cobblestoning and/or redness on the mucosa of the posterior pharyngeal wall, when it exists, from chronic postnasal drainage and discharge. Tonsillitis, both exudative and nonexudative, should be straightforward. It is important that tonsillar and adenoid hypertrophy be recognized and removed when appropriate. In early childhood, "failure to thrive" and obstructive sleep apnea are common manifestations of children with clinically significant adenotonsillar hypertrophy. Prompt recognition and removal is most effective in these cases.⁷³

Otolaryngologists are often called to see patients with lip or tongue swelling caused by angioedema in the emergency room (**Fig. 5**). A significant percentage of the patients are found to have angioedema from ACE inhibitors.⁷⁴ This response is felt to be non-IgE mediated and is related to the kinin metabolic pathway. One-third of patients with angioedema are admitted to hospital, while one-tenth require intensive care⁷⁵ dependent on the etiology and severity. Patients may complain of cough while on ACE inhibitors. This response tends to occur in females more readily than in males, and seems to occur early in therapy.^{76,77} The cough is restricted to patients on ACE inhibitors and is not found in those on ACE blockers. Rarely, C-1 esterase inhibitor

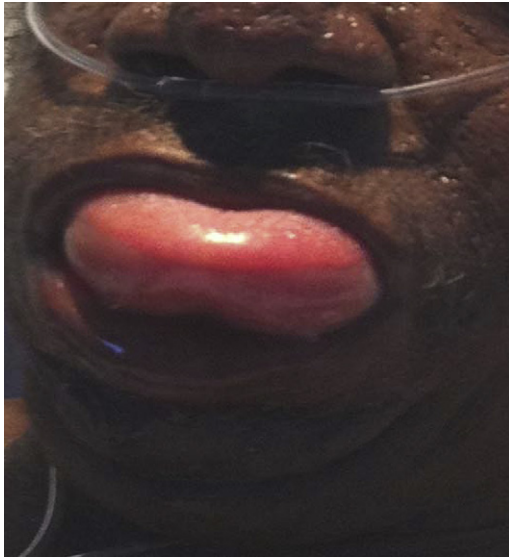


Fig. 5. Tongue and lip swelling in a patient with angiotensin-converting enzyme inhibitor-related angioedema.

levels need to be checked to rule out hereditary angioedema. Angioedema may also occur in severe anaphylaxis. Other signs and physical findings are usually present in these patients.

LARYNGEAL CONDITIONS

There are numerous laryngeal conditions that need to be ruled out before an allergic laryngeal diagnosis may be considered. Many conditions are diagnosed with a complete history and physical examination, including a laryngeal mirror examination or a flexible fiberoptic examination. Benign and malignant laryngeal lesions are considered in the differential diagnosis. Acute laryngitis needs to be differentiated from chronic laryngitis. Acute laryngitis may occur as a result of an acute infectious cause (bacterial or viral) or may occur in the setting of acute anaphylaxis or supraglottitis with vocal changes, but is almost always self-resolving within several months. Chronic laryngitis may be the result of vocal misuse, allergic changes, or laryngopharyngeal reflux (LPR). LPR is one of the most commonly encountered diagnoses associated with the symptom of postnasal drainage or vocal complaints. Often patients may exhibit both signs and symptoms of allergic laryngitis and LPR.

Laryngopharyngeal Reflux

Gastroesophageal reflux (GER) is the retrograde movement of stomach contents into the esophagus in the absence of belching or vomiting.^{78–80} Gastroesophageal reflux disease (GERD) occurs when GER is associated with other signs, symptoms, or complications. LPR is retrograde flow of reflux material into the esophagus and larynx.

It is estimated that 30% of Americans suffer from GERD, while 7% to 10% experience daily heartburn and 25% to 30% have weekly symptoms.^{78,81–83} Between 25 and 75 million Americans are affected by GERD.⁸³ Thirteen percent of all Americans use antacids 2 or more times a week.⁸³ The estimate of GERD in patients presenting to

the otolaryngology clinic is been estimated to be 4% to 10%.⁸⁴ Fifty percent of the patients who were evaluated for speech and voice disorders in the clinics of Koufman and colleagues⁸⁵ had LPR.

Laryngeal inflammation is responsible for the signs and symptoms of LPR. These symptoms include a globus sensation, throat clearing, vocal fatigue, voice breaks, sore throat, neck pain, excessive throat mucus, chronic or nighttime cough, dysphagia, odynophagia, postnasal drip, halitosis, ear pain, laryngospasm, asthma exacerbation, diminished singing range, heartburn or regurgitation, and hoarseness. In addition, LPR can occur in a subpopulation of patients who do not have classic GERD. These patients present with laryngeal findings without the classic heartburn and substernal pain seen in GERD patients.⁸⁶ Belafsky and colleagues⁸⁷ developed a Reflux Symptom Index (RSI), which includes a self-administered survey of 9 questions used to assess patients with LPR. The instrument has proved to be reproducible and valid.⁸⁸ Each question has a rating from 0 (no problem) to 5 (severe problem). A score of 10 or greater is associated with a high likelihood of a positive dual-channel pH probe.⁸⁹ In another study, these investigators demonstrated that improvements in the RSI were noted before changes in physical findings occurred.⁹⁰

Diagnosis is made using direct visualization of the vocal folds with a mirror examination, an endoscope, or a videostrobe. Physical findings seen in patients with reflux include laryngeal edema, loss of clear epithelial markings, hypervascularity of the posterior commissure and arytenoids, hyperkeratosis of the posterior commissure (pachydermia), increased mucous production, laryngeal ulceration, granuloma formation, subglottic stenosis, and pseudosulcus formation. This thickening of the under-surface of the vocal fold extends from the anterior portion of the vocal fold to the posterior commissure (**Figs. 6 and 7**). By contrast, true sulcus vocalis involves the free edge of the vocal fold and extends to the vocal process. The presence of pseudosulcus is sensitive and specific for reflux 70% and 77% of the time, respectively.⁸⁹ Other studies found the positive predictive value of pseudosulcus in detecting LPR to be 90%.⁹¹

A Reflux Finding Score has also been developed by Belafsky and colleagues.⁸⁸ This scale evaluates 8 findings associated with reflux. Seven of these findings involve edematous changes to the larynx and associated structures. Only one finding is associated with redness or erythema of these structures. Scores may range from 0 to 26. A score of 7 or higher is associated with a positive pH probe with a 95% certainty.

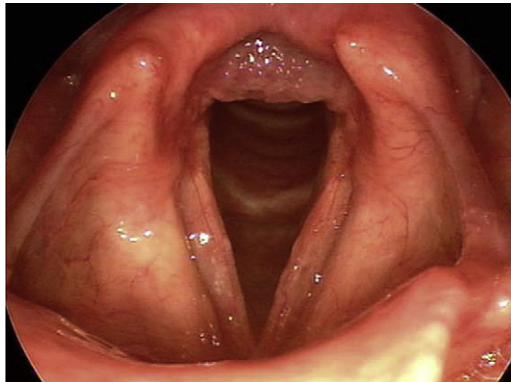


Fig. 6. Severe laryngeal pachydermia in a patient with laryngopharyngeal reflux. (Courtesy of Dr Glendon Gardner, Detroit, MI.)

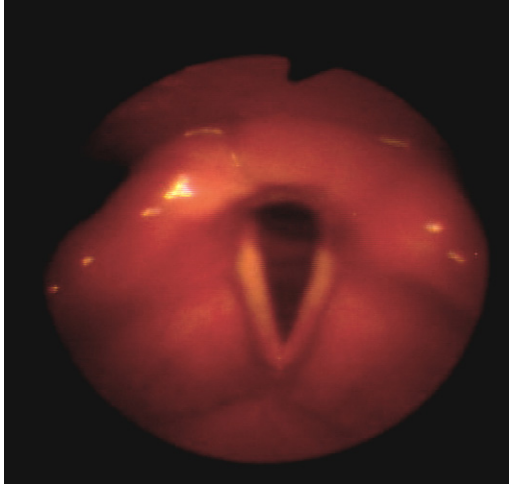


Fig. 7. Posterior glottic edema and erythema in a patient with laryngopharyngeal reflux.

Overall, this suggests that among all the aforementioned reflux findings, the clinical hallmark of extraesophageal reflux (EER) is edema as a result of reflux-induced trauma to the larynx.^{89,92–94} EER is synonymous with the term LPR for the purposes of this article.

Diagnostic Testing for LPR

Diagnostic tests used to assess for reflux include an esophagogram, sensory testing with endoscopy, pH testing, monometry, impedance testing, and direct biopsy using transnasal endoscopy. A barium esophagogram may be useful to assess the esophagus for any type of structural or functional abnormality. An esophagogram is usually ordered together with a dynamic swallowing study to evaluate the whole swallowing mechanism at one time. The dynamic swallow is often performed with a speech and language pathologist. Findings that may be seen with this test include strictures, rings, webs, hiatal hernia, erosive esophagitis, candida esophagitis, cricopharyngeal bars, extrinsic compression, motility disturbances, aspiration, residuals in the pharynx, diverticula, and underlying neoplastic processes. Unfortunately, the sensitivity of the esophagogram in detecting EER is low (20%–60%) and its specificity is 64% to 90%, with an accuracy of 69%.⁹⁵

Laryngeal Sensory Testing

Laryngeal sensory testing has been shown to be helpful in identifying EER.^{94,96} The posterior laryngeal edema that results from reflux may be quantified with sensory testing. A pressure-generated pulse of air is delivered to the vocal fold, and the laryngeal adductory reflex is initiated to contract the vocal fold. As the edema progresses on the vocal fold, the puff of air required to elicit a response becomes much greater (5 mm or more). This test was found to be as sensitive and specific for reflux as the pH probe (50% and 83%, respectively). As patients improved with treatment, the pulse of air required to elicit a response decreased as the “neuropathy due to edema” improved.⁹⁶ Unfortunately, this method functions most as a research tool, as many otolaryngologists do not use a sensory testing device.

pH Probe Testing

The dual pH probe is considered the gold-standard test to assess for reflux. There is considerable controversy regarding the technique and what is considered a “normative” value. In addition, patient tolerance for the procedure is often poor. Merati and colleagues⁹⁷ performed a meta-analysis on 16 studies in the literature and found that laryngeal probe acid exposure time was reliable in differentiating patients with LPR from normal subjects. Some of the patients in this study who were considered to have LPR actually would have normal pH probes by gastroenterology criteria. These patients may have been suffering from other conditions such as nonacid reflux, sinusitis, allergies, and postnasal drip.⁸⁶ Dual pH probes are the accepted devices to identify EER. Postma⁹⁸ demonstrated that 59% of the patients he studied would have been inappropriately diagnosed as having a negative pH probe based on only one esophageal probe. The pharyngeal sensor was needed to make the diagnosis.^{98,99} Fourteen percent of Koufman’s patients⁸⁵ had a positive upper probe result despite a normal esophageal pH acid exposure time. Although the pH probe is the gold standard, the test is invasive, has a sensitivity of only 75% to 80%, and the false-negative rate may approach 50%.¹⁰⁰ Poor calibration and small variation of probe placement may affect the results.⁹⁸ Close monitoring of patient activities during the test is essential. Patient positioning, diet, reflux symptoms, and smoking habits should be carefully monitored.

While there is general agreement for normative values from the distal esophageal probe in determining whether reflux is present, controversy exists regarding the normative values of the proximal pH probe. Most researchers have agreed that a pH drop to 4 or less is considered pathognomonic for EER.^{98,101} Others have documented that a small percentage of their normal subjects had proximal pH probe drops to 4 or less.^{102–104} Still others such as Hanson and colleagues,¹⁰⁰ Contencin and Narcy,¹⁰⁵ and Koufman¹⁰⁶ believe these criteria to be too rigorous and note that pepsin, the main cause of tissue inflammation and damage, is active at pH levels of 5 or greater. In addition, reflux-related damage has been noted for days after the inciting event. In the larynx, defenses against reflux are virtually nonexistent on a mucosal level. Therefore, negative probe results need to be interpreted carefully. There are also vagally mediated reflux reflexes eloquently described by Shaker,¹⁰⁷ such as the glottic closure reflex and the cricopharyngeal/upper esophageal sphincter contraction reflexes, which may cause globus and laryngospasm in the face of distal esophageal exposure to acid.^{107,108}

Wireless pH probe technology has been explored as an alternative to traditional pH probes. These probes consist of a transnasally or transpharyngeally placed capsule that may be attached to the mucosa of the esophagus; the sensor then detaches from the wall in about 3 days. A remote monitor on the waist records the data. These devices are capable of a longer recording time, providing more data for analysis. Their major limitation is that the proximal probe often cannot be placed close to the upper esophageal sphincter because of sensation at this area.^{109–112}

Mechanisms of Acidic and Nonacidic Refluxate Damage to the Mucosa

Recent work by Johnston colleagues¹¹³ has shown that pepsin exists in the laryngeal epithelium in reflux patients. When pepsin is incorporated into the cell via endocytosis, cellular cytotoxic events can occur. Pepsin does not require the presence of acid to remain active. Some investigators have suggested that pepsin may cause the depleted levels of carbonic anhydrase noted in the esophageal mucosa of LPR patients.^{114–116} Carbonic anhydrase (CA) and its related isoenzymes CA-I through

CA-IV are present in esophageal mucosa where they can convert carbon dioxide into bicarbonate, which can move into the extracellular space and neutralize the acid. Decreased levels of the isoenzyme CA-III were found in the vocal fold epithelium of LPR patients.

Bile salts and acids in nonacidic refluxate may also cause damage to the laryngeal mucosa. Sasaki and colleagues¹¹⁷ demonstrated that the bile salts taurocholic acid and chenodeoxycholic acid in an acidic and basic pH, respectively, produced laryngeal inflammation comparable to hydrochloric acid at a pH of 1.2. Localized inflammation clearly is the hallmark of this disease process, and needs to be reversed in order for healing to take place.

Monometry

Monometry is useful to assess for esophageal dysmotility and for weakness of the upper and lower esophageal sphincter contraction. Dysmotility is common in EER and can include ineffective motility, hypertensive lower esophageal sphincter, nutcracker esophagus (esophageal spasm), and achalasia.¹¹⁸ Monometry has not been considered a useful tool for diagnosing EER because of the short duration of testing, which may not accurately assess the transient relaxations of the lower esophagus that are thought to be important in the pathogenesis of EER.⁹⁵

Impedance Testing

The multichannel intraluminal impedance device uses a pH sensor to detect nonacidic gastroesophageal reflux. Using electrical conductivity of the bolus in the esophagus, the device is able to distinguish between solid or liquid as well as direction of flow, antegrade or retrograde. Using the pH sensor, acid events are delineated from nonacid events.^{119–123} Because persistent symptoms even after adequate acid-suppressive therapy have been attributed to nonacidic reflux events, impedance testing is likely to play a larger role in the diagnosis of this disease process in the future.

Transnasal Esophagoscopy

Further diagnostic testing may include transnasal esophagoscopy (TNE) with biopsy, which may show inflammatory changes to the esophageal mucosa. A diagnosis is made from looking at the amount of eosinophils per high-power field (HPF) that are present (in 5 or more fields). These histologic changes are felt to represent pathologic changes in the lining of the esophagus, even when the esophagus appears “normal.” TNE has been found to be more than adequate to evaluate the esophagus. Dickman and colleagues¹¹⁹ have demonstrated that the esophageal assessment is sufficient to diagnose reflux-related disease in patients with traditional esophageal reflux symptoms such as heartburn, regurgitation, and dysphagia, but who do not have gastric or duodenal symptoms such as abdominal pain, nausea, or a history of gastric or duodenal ulcer. Complete assessment of the stomach and duodenum is not necessary. TNE can be used to evaluate the esophagus in patients with suspected reflux disease to rule out Barrett esophagitis as well as adenocarcinoma. The presence of acid-induced reflux causes changes in the stratified squamous epithelium converting it to columnar epithelium normally present in the stomach mucosa. This condition is called Barrett esophagitis. Barrett esophagitis has been linked to adenocarcinoma.^{124–127} Because the incidence of adenocarcinoma has risen significantly in the United States and western Europe (in some studies: 175%), early diagnosis of Barrett esophagitis may prevent patients from progressing on to adenocarcinoma. Similarly, early adenocarcinoma lesions may be identified before they are far advanced and cause dysphagia. Five-year survival rates of early

esophageal cancer are 80% to 90%; but 5-year survival for symptomatic esophageal cancer is less than 10%.¹²⁷ Because cough and hoarseness are better predictors for esophageal adenocarcinoma than heartburn or regurgitation, patients with persistent laryngopharyngeal symptoms despite antireflux treatment should have an esophageal endoscopy.¹²⁸ TNE is safer than a traditional endoscopy, and avoids the cardiac and pulmonary complications associated with this procedure.^{129,130}

ALLERGIC LARYNGITIS

Among voice specialists, it is well known that allergies play a significant role in patients with vocal complaints. Unfortunately, there have been few human or animal investigations that substantiate the current clinical findings. Chadwick¹³¹ suggested that both upper and lower airway allergic inflammation can cause primary and secondary biomolecular and biomechanical laryngeal disturbance. Corey and colleagues¹³² noted 2 types of allergic laryngitis: (1) acute, IgE-mediated (anaphylactic), (2) chronic, delayed, cyclic, non-IgE mediated. Research suggests that there are acute IgE-mediated laryngeal responses elicited by patients who were allergic to dust mites. Using antigen challenges, these patients were noted to have throat clearing, shortness of breath, bronchospasm, wheezing, coughing, and reduced FEV₁ (forced expiratory volume in 1 second) values.¹³³ The study was terminated prematurely, due to acute asthma exacerbation in 1 of 3 subjects studied and moderate side effects of wheezing and coughing in another of the 3. Chronic, non-IgE mediated reactions tended to be nonspecific and were difficult to differentiate from rhinitis, vocal abuse, lower airway reactions, and LPR.

The signs and symptoms that suggest allergic laryngitis are very similar to those seen in LPR: odynophagia, hoarseness, throat clearing, vocal cord edema, and coughing.^{134,135} The otolaryngologist needs to carefully attempt to differentiate between the two when possible. Naito and colleagues¹³⁶ studied 30 patients with chronic laryngeal allergy who tested positive on skin testing for inhalant allergies and had laryngeal examinations. A characteristic finding for laryngeal allergy in this study was pale, glistening, and edematous arytenoid mucosa. Corey¹³⁷ evaluated more than 200 videostroboscopic images in patients who complained of nasal allergies and dysphonia. Her patients noted limitations in pitch range, frequent throat clearing, postnasal drip, chronic cough, and globus sensation. Findings consistent with laryngeal allergy included mild vocal fold edema, sticky-thick endolaryngeal secretions bridging the larynx, mildly edematous arytenoids, and hyperactive laryngeal reflexes. The viscous, thick mucous secretions seemed to be the most noteworthy finding of laryngeal allergy. In another study in the voice laboratory at Wayne State University, investigators examined two groups of patients: control (nonallergic) and dust mite-allergic individuals with allergic symptoms.¹³⁸ In an attempt to eliminate bias from reflux findings, all patients with reflux histories (GERD or EER) were eliminated from the study. Results from 15 different comparative phonation and respiration subsystem analyses showed no significant differences between the two groups of subjects. It is clear that future research is needed to help delineate specific laryngeal allergic findings from other complex and closely related clinical conditions.

EOSINOPHILIC ESOPHAGITIS

Eosinophilic esophagitis (EE) is a “new” disease identified in patients with esophageal eosinophilia unresponsive to the medical or surgical treatments of GERD. Confusion surrounding the diagnosis and management of these patients made it imperative that a precise definition and consensus statement be drafted. A multidisciplinary

task force developed a systemic review and consensus recommendation for diagnosis and treatment of EE.¹³⁹ This panel described EE as a clinicopathologic disease characterized by (1) symptoms including, but not restricted to, food impaction and dysphagia in adults, feeding intolerance and GERD symptoms in children; (2) greater than or equal to 15 eosinophils per HPF; (3) exclusion of other disorders associated with similar clinical, histologic, or endoscopic features (especially GERD). The other conditions associated with eosinophageal eosinophilia are eosinophilic gastroenteritis, Crohn's disease, connective tissue disease, hypereosinophilic syndrome, infection, and drug hypersensitivity response.¹⁴⁰

There has been a fourfold increase of disease prevalence in children with EE in the Midwest United States occurring from 2000 to 2003,¹⁴¹ with an incidence of 1:10,000 children per year. This number remained constant over a 4-year period in Cincinnati. The prevalence of EE in Switzerland is 1:4000 patients.¹⁴² EE occurs in 6% of the patients with esophagitis and in 6.5% of all adult patients undergoing endoscopy.^{139,143} EE is common in young males with atopy.¹³⁹ It is frequently found in younger patients, but may be found in patients older than 90 years.¹⁴⁴ EE is a chronic disease without spontaneous remission.¹⁴⁵ Seasonal variations are seen in the disease and in inhalant allergens.¹⁴⁶ It has been identified in all continents except Africa.

Signs and Symptoms, and Presentation of Eosinophilic Esophagitis

EE's variable disease presentation initially made the disease difficult to define and diagnose. EE may present differently in various age groups. Children may present with failure to thrive, emesis, abdominal pain, dysphagia, GERD-like symptoms (heartburn and regurgitation), and food intolerance.^{141,146–149} Adults tend to present with recurrent dysphagia and food impactions. These symptoms are usually refractory to antireflux treatment. The dysphagia is felt to be the result of impaired circular and longitudinal muscle function that occurs directly as a result of eosinophilic infiltration of the muscle. It improves once the condition has been adequately treated.^{149–151}

Diagnosis and Histopathology of Eosinophilic Esophagitis

As stated previously, there is no diagnostic test for EE. EE is a clinicopathologic diagnosis based on the amount of eosinophils per high power field (eos/HPF) noted in a biopsy specimen in patients with clinical signs and symptoms of the disease. The threshold for diagnosis is 15 eos/HPF. A lower level of eos/HPF (>6) indicates GERD, whereas higher levels, 20–24 eos/HPF, tend to indicate EE, especially when patients are on anti-GERD therapy.^{152,153} The number and location of the biopsies obtained is critical in making the diagnosis. At least 3 biopsies from the mid or distal esophagus are recommended, as the sensitivity for detecting EE is 97% when 3 or more biopsies are obtained.^{139,154} EE appears to affect the entire esophagus, whereas in GERD eosinophils may be localized in the distal esophagus. EE may also be associated with mucosal changes, such as: basal cell hyperplasia and papillary thickening, not seen in GERD.^{155,156} The diagnosis of EE is straightforward when endoscopic and radiographic findings of strictures, mucosal rings, ulcerations, whitish papules, and polyps are encountered (**Fig. 8**).^{148,157} Thirty percent of the patients with EE have a normal endoscopy,¹⁵⁸ which make biopsies essential in making the appropriate diagnosis.

Pathogenesis of Eosinophilic Esophagitis

EE is significantly associated with atopy based on multiple co-occurrence studies, experimental animal studies, and the known success of avoidance-diets (allergen avoidance). Most patients are allergic to both food and aeroallergens, as determined

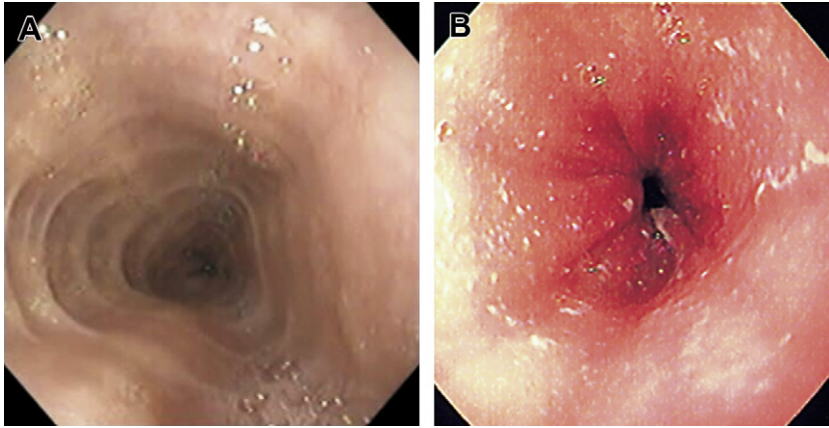


Fig. 8. Endoscopic findings associated with eosinophilic esophagitis (EE). (A) Mucosal rings representative of transient contractions or fixed strictures, also referred as trachealization or concentric rings. (B) Whitish exudates scattered across the mucosal surface; these represent rests of eosinophilic purulence bursting through the mucosa. (From Furata GT, Iacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systemic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;133(4): 1342–63; with permission.)

by skin testing for foods or inhalants.^{141,159} Multiple food allergies tend to be the rule rather than the exception. There are 6 major food groups that seem to be involved most commonly:

1. Wheat
2. Fish
3. Nuts
4. Bread
5. Milk
6. Eggs.

Avoidance, either by determining which foods the patient is allergic to (by skin-prick and patch testing) and removing them from the diet or complete removal of all 6 groups, has led to success in treatment.^{160,161} In severe, recalcitrant cases, an elemental diet is instituted. Unfortunately, in many cases patients may require an enteral feeding tube.

Skin allergy may also play a role in the development of EE. Atopic dermatitis is believed to “prime” the patient for the development of respiratory-induced EE.¹⁴⁷ Many of the patients with EE report having a preceding episode of atopic dermatitis. Aeroallergens or food allergens induce T-helper (Th) cells to secrete interleukin-13 (IL-13) (Fig. 9). IL-13 induces hyperplastic epithelial cells in the esophagus to produce eotaxin-3.¹⁶² Eotaxin-3 is a chemoattractant for the eosinophils in the bone marrow. IL-13 also induces overproduction of periostin.¹⁶³ Periostin is an extracellular matrix molecule that regulates eosinophil adhesion and assists in eotaxin-3 stimulated recruitment. IL-13 also downregulates flaggrin production. Flaggrin is a skin structure protein. Underexpression of this protein causes an increase in skin permeability and an increased susceptibility to atopic dermatitis. An increase in permeability results in further inflammation, which may enable acid to further erode the cell’s defenses, thus allowing more antigen uptake into the esophageal epithelial cell and activating

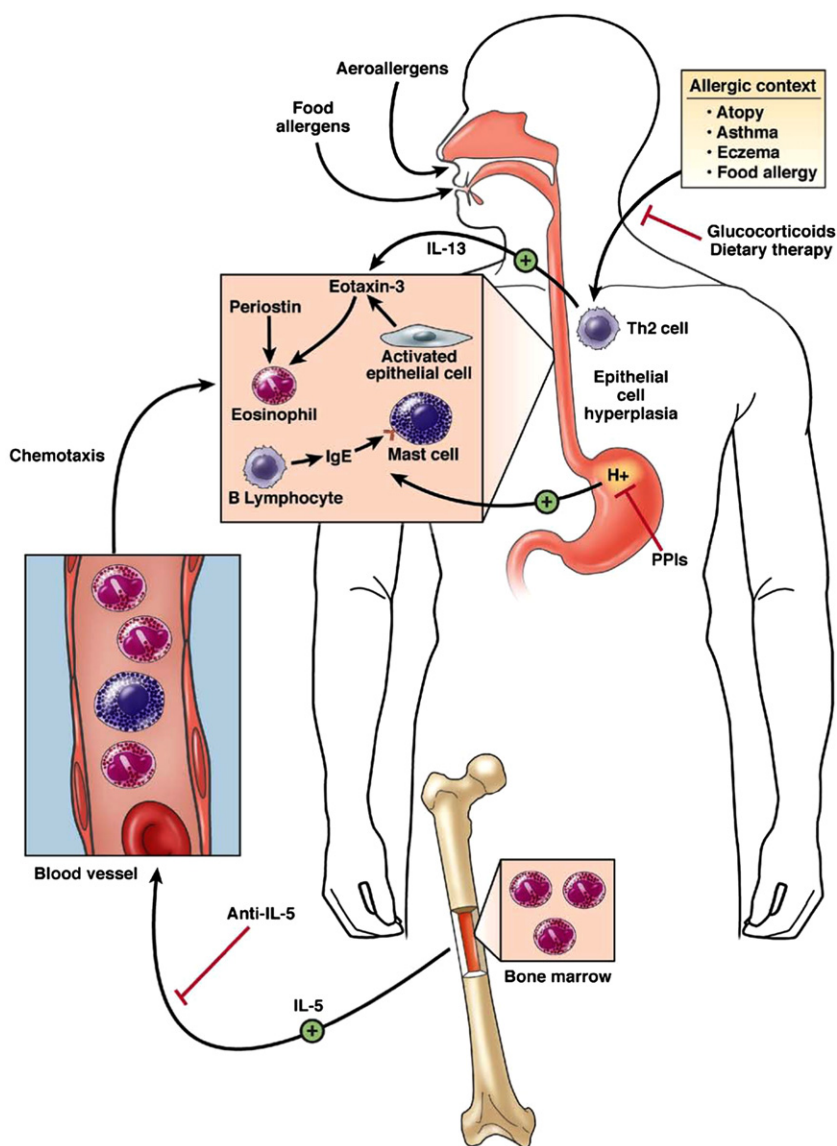


Fig. 9. Pathogenesis and treatment of EE. Aeroallergens, food allergens, and skin sensitization have been implicated in the pathogenesis of EE. Therapies such as an elemental diet, systemic glucocorticoids, and anti-interleukin-5 (IL-5) improve the microscopic features of EE, acting at different steps of pathogenesis. Determining the response to proton pump inhibitors (PPIs), which reduce gastric acidity, is important in the diagnosis of EE; inflammation is still present in patients following administration of these drugs. Allergens induce Th2 cells to produce interleukin-13 (IL-13), which can cause hyperplastic epithelial cells of the esophagus to overexpress eotaxin-3, and fibroblasts to overexpress periostin and downregulate filaggrin. Eotaxin-3 and periostin overexpression cooperatively chemoattract CCR3⁺ cells (Th2 cells). Activated Th2 cells also produce IL-5, which regulates eosinophil numbers and their response to eotaxin-3. Inheritance studies indicate that there is a genetic component to EE; a single-nucleotide polymorphism in *eotaxin-3* has been associated with the disease. In addition to eosinophils, mast cells and lymphocytes (including B cells) accumulate in the esophagus to contribute to the local inflammatory responses observed in patients with EE. (From Rothenberg M. Biology and treatment of eosinophilic esophagitis. *Gastroenterology* 2009;137(4):1238–49; with permission.)

the B cells and mast cells. In situ production of immunoglobulins has been noted in EE patients.^{164–167}

Th2 cells also express interleukin-5 (IL-5), which has been implicated in the pathogenesis of EE. IL-5 helps to regulate the eosinophil and increase its sensitivity to eotaxin-3. In animal experiments, overproduction or added IL-5 causes EE. Blocking IL-5 eliminates allergen, and IL-13 experimentally induced EE in mice. Anti-IL-5 medications have shown some promise in treating EE.^{168–171}

Genetic Predislection for Eosinophilic Esophagitis

There are numerous studies that have shown EE to have a familial relationship.¹⁴¹ Some pediatric studies have shown up to a 25% incidence of EE in a sibling or a parent with eosinophilic esophagitis. Three generations of EE have been reported in some studies.¹⁷² Three affected brothers were reported in another.¹⁷³ Blanchard and colleagues¹⁶⁴ have reported a single-nucleotide polymorphism of eotaxin-3 in patients with EE, but this allele is present in only 14% of the patients with EE. Much more research needs to be conducted on the genetics of this disease process.

Eosinophil Function in Eosinophilic Esophagitis

Eosinophils are pleiotropic cells that participate in the adaptive immune response and propagate the inflammatory reaction.¹⁷⁴ The eosinophil contains secretory granules that contain 4 primary cationic proteins: EDN (eosinophil derived neurotoxin), major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophilic derived peroxidase (EPO).¹⁷⁵ Eosinophils secrete cytokines (many interleukins), chemokines, lipid mediators, and neuromodulators. Eosinophils can directly present antigen to and regulate T-cell activities by modulating the release of its chemokines. Eosinophils can release mitochondrial traps for bacteria and can release tumor growth factor- β , which causes fibrosis.^{176–178} The end result of eosinophil activity is epithelial cell hyperplasia, cell cytotoxicity, muscle dysmotility, and fibrosis of the tissue.

Treatment of Eosinophilic Esophagitis

Avoidance diets, anti-inflammatory medications, and surgical dilation are the mainstay of treatment. Patients are usually placed on anti-GERD medications. If they do not improve with these medications (histologically), patients are placed on selective diets to avoid the specific allergens that affect them. An elemental (amino acid based) diet can be used as well. Unfortunately, these diets are not very palatable and often require feeding-tube placement to comply with the nutritional needs of the patient. Selective diets may be difficult to determine because of the many food groups that patients may be sensitive to. Patch testing and skin-prick testing are used to make the allergic diagnosis.¹³⁹ Spergel and colleagues^{160,179} demonstrated 77% resolution of the disease in their biopsy specimens after treatment with diets determined by both tests. A resolution of 98% was achieved in patients treated with an elemental diet.¹⁴⁸

Corticosteroids, both systemic and topical, have been used to treat EE. Systemic steroid therapy is only necessary when urgent relief of symptoms is required. Severe dysphagia, dehydration, weight loss, or strictures are conditions that may warrant treatment. In 1998 Liacouras and colleagues¹⁸⁰ presented findings of clinical symptom relief (in 7 days) and histologic improvement (in 4 weeks) in 20 of 21 children with EE. Reported doses are 1 to 2 mg/kg/d (maximum 60 mg/d). Typically when the medicine was discontinued, the disease returned. Because of the long-term side effects and risk factors, systemic steroid treatment is not recommended unless deemed absolutely necessary.

Faubion and colleagues¹⁸¹ were the first to describe the use of topical steroids to treat EE. Other studies showed improvement with topical steroid treatment. Complete resolution occurred in 75% of the patients. About 25% recurred after discontinuation of the treatment.^{156,165,182,183} Reported doses are 440 to 880 μg fluticasone per day in children and 880 to 1760 μg in adults, in divided dosing 2 to 4 times a day for 4 to 6 weeks.

Dilation of the esophagus in these patients is tricky and is associated with mucosal tears, significant pain, and rare perforation.^{184–187} A 7% to 50% recurrence rate was noted 2 to 24 months later.^{184,185,188,189}

Antibody therapy, such as anti-IL-5, and anti-IL-13, has promising results for treating experimental EE.^{162,169,190–192} Anti-IgE therapy may also be of benefit to reduce inflammation.¹⁹³ Human studies are ongoing, and future research will determine their effectiveness.

SUMMARY

There are many different diagnostic mimics of allergy. A thorough history and physical examination usually enables the clinician to avoid the various pitfalls that may complicate making an accurate diagnosis. An allergic diagnosis is made after ruling out a vast myriad of conditions. This article presents some of the most common conditions encountered in clinical practice.

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