Introduction

Allergic rhinitis, asthma, and chronic rhinosinusitis (CRS) are some of the most common conditions encountered in general otolaryngology practice. While many otolaryngologists do not directly manage asthma, its frequent coexistence and shared pathogenesis with allergic rhinitis and CRS make it a worthwhile inclusion in a discussion of the others. Indeed, as will be detailed below, some authors consider the three disorders to be different manifestations of the same underlying condition, i.e. pathologic inflammation of the airway.

Integrated Airway Hypothesis

Over the last few decades there has been a developing awareness of the interplay and frequent co-existence of allergic rhinitis, asthma, and CRS; this has led to the hypothesis that they are not three separate diseases but rather different manifestations of the same underlying pathogenic process.

There is extensive epidemiologic evidence to support this hypothesis. Asthma occurs in up to 40% of patients with allergic rhinitis, compared to the general population rate of ~10%. Conversely, allergic rhinitis occurs in 80-90% of patients with asthma, compared to the general population rate of 20%. Allergic rhinitis is present in 60-80% of patients with CRS, and among asthmatics, 40-60% have abnormal sinus radiographs, with the magnitude of the sinus abnormalities correlating with the severity of the patient’s asthma. Among patients with extensive sinus disease on computed tomography (CT) imaging, 78% have allergic rhinitis and 71% have asthma. Finally, patients with allergic rhinitis are three times more likely than normal controls to develop asthma later in life.
There is also experimental evidence to support the integrated airway hypothesis. Thickening of the bronchial reticular basement membrane, a feature of the airway remodeling seen in asthma, has been observed in patients with allergic rhinitis who did not have asthma. In two separate studies by Braunstahl et al, stimulation of the nasal mucosa of subjects with allergic rhinitis with an allergen to which subjects were sensitized resulted in increased bronchial symptoms compared to controls and infiltration of eosinophils into bronchial mucosa. When the allergen was introduced via bronchoscopy to the bronchial mucosa, an increase in nasal symptoms compared to controls and infiltration of eosinophils into the nasal mucosa were observed.

Several mechanisms have been proposed for interactions between the upper and lower airway in the context of an integrated airway:

- **Aspiration of nasal secretions**
  - disproven—Bardin and colleagues instilled radioactive markers in the nasal sinuses of patients with post-nasal drip and found no uptake in the lungs after 24 hours

- **Increased oral breathing**
  - proven—switching from nose breathing to mouth breathing of cold air produced a significant decrease in FEV1 in asthmatic patients

- **Nasobronchial reflex**
  - disproven—lidocaine instillation in the nasal cavity did not prevent development of bronchial symptoms with a nasal allergen challenge; however, phenylephrine instillation did prevent bronchial symptoms, suggesting that local vasoconstriction prevents systemic access to allergen and allergen-stimulated local mediators

- **Local response ➔ systemic response ➔ general airway inflammation**
  - current leading theory—local provocation leads to systemic inflammation response, with release of eosinophil upregulator IL-5; eosinophils then concentrate in both the upper and lower airways, regardless of the site of provocation

**Immunology**

One of the basic functions of the immune system is to distinguish self from non-self. This is referred to as self tolerance and is essential if the body is to successfully ward off invading microorganisms yet leave itself with minimal harm. The molecular basis for self tolerance is found in the major histocompatibility complex (MHC) located on the short arm of chromosome 6. Class I and Class II MHC molecules are produced from these genes. Class I molecules are present on nearly all nucleated somatic cells and interact with CD8\(^+\) (cytotoxic) T cells. Class II molecules are present on antigen-presenting cells (APCs), i.e. macrophages, monocytes, dendritic cells, and B cells, and interact with CD4\(^+\) (helper) T cells.
The immune system is divided into innate and adaptive systems. The innate system is non-specific but provides an immediate response to invading microorganisms. The components of this system include the skin and mucosa, antimicrobial substances such as lysozyme and lactoferrin, the complement system, and Toll-like receptors (TLRs) on phagocytic cells. The TLRs provide pattern recognition to the phagocytic cells. For example, TLR-2 binds lipoproteins found in the walls of many gram positive and gram negative bacteria, TLR-3 binds double-stranded RNA found in viruses, TLR-4 binds lipopolysaccharides (LPS) found in gram negative bacterial cell walls, and TLR-9 binds cytidine-phosphate-guanosine (CpG) dinucleotide sequences, which are twenty times more likely to be found in bacterial DNA than in human DNA.

The adaptive immune system is highly specific but provides a slower response to microorganisms compared to the innate immune system. A key aspect of the adaptive system is memory, which allows subsequent responses to be faster should a microorganism be encountered again. This system is composed of white blood cells, both of the lymphoid (T, B, and natural killer [NK]) and the myeloid (monocyte, macrophage, neutrophil, eosinophil, and basophil) cell lines.

**T cells**

T cells develop in the thymus and comprise 80% of circulating lymphocytes. They are defined by the presence of the surface T-cell receptor (TCR), and are further classified as CD8^+ and CD4^+. CD4^+CD8^- T cells do exist and appear to have a regulatory role, but their functions have not been fully elucidated and will not be discussed here. CD8^+ cells are the cytotoxic T cells, are involved in cell-mediated immune responses, and are highly active against virus-infected and tumor cells. CD4^+ cells are the helper T cells that work to augment humoral (B-cell) and cytotoxic immune responses.
• CD4⁺ T cells are further classified as follows:
  • TH1 cells
    o Produce IFN-γ essential to macrophage activation
    o Involved in intracellular pathogen clearance—viruses, mycobacteria, Listeria
    o Key players in delayed-type hypersensitivity
  • TH2 cells
    o Major role in B cell activation
    o Produce IL-4, IL-5, and IL-13—crucial role in allergy
    o Involved in extracellular pathogen clearance—parasites, bacteria, allergens
  • TH17 cells
    o Produce IL-17, a key neutrophil recruiter and eosinophil suppressor
  • Treg cells
    o These are Foxp3+ cells, which suppress T-cell responses and autoimmunity
    o Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)
      ▪ Caused by a loss of function mutation in the Foxp3 gene
      ▪ Spectrum of disease includes type-1 diabetes, autoimmune thyroiditis, eczema, bleeding abnormalities, and chronic wasting

Prior to stimulation, a naïve TH cell has not yet become TH1 or TH2 and is termed TH0. After stimulation occurs, it begins to secrete IL-2 which begins an auto-stimulated process of differentiation. At this point, differentiation becomes dependent on the surrounding environment. If IL-12 produced by macrophages is present, the TH0 cell will be directed down the pathway to become a TH1 cell. Conversely, if IL-4 produced by mast cells, NK cells, and eosinophils is present, the TH0 cell will become a TH2 cell.

**B cells**

B cells develop in the bone marrow and comprise 10% of circulating lymphocytes. They are defined by the presence of surface IgM and IgD receptors which are analogous to the TCR for T cells. B cells provide humoral immunity via antibody production. Differentiation is promoted by T cells; as B-cells differentiate, they can form germinal centers, become plasma cells that produce large quantities of a specific antibody, or become memory cells that persist indefinitely in the circulation.

B cell activation can occur through both T-cell dependent and independent mechanisms. In T-cell dependent activation, the TCR of the T cell interacts with the MHC Class II molecule on the B cell; there is also interaction between the CD40 ligand on the T cell and CD40 receptor on the B cell. This process leads to IL-1 and IL-2 secretion by the T cell that further serves to activate the B cell. T-cell independent activation occurs primarily with large carbohydrate antigens with repeating antigenic determinants that cannot be presented on MHC Class II molecules; these antigens are usually components of bacterial capsules and cell walls. The
repeating antigenic determinants crosslink surface immunoglobulins on B cell, resulting in activation. This mechanism results in IgM class antibody production and is an essential defense against *Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis*.

**Antibodies**

There are five classes of immunoglobulin (Ig): G (75%), A (15%), M (10%), D (0.2%), E (0.004%). There are also four IgG subclasses (IgG1-IgG4) and two IgA subclasses (IgA1 and IgA2). Immunoglobulins are composed of two heavy and two light chains that combine to produce Fab and Fc regions (please see PowerPoint slides for figures). The Fab region binds antigen while the Fc region binds to Fc receptors on various white blood cells. Isotype switching (changing from one Ig class to another) is induced by cytokines. For example, IL-10 promotes switching to IgG1 and IgG3 production, IL-4 and IL-13 promote IgE production, TGF-β promotes IgA production, and INF-γ promotes IgG2 production. IgM is produced in the primary immune response, declines rapidly, and is replaced by IgG; it is the most efficient complement-fixing antibody due to its pentameric structure. IgG is produced in the late primary and secondary immune responses. It is the only Ig that crosses the placenta during pregnancy. IgG1, IgG3, and, to some extent, IgG2 fix complement. IgG1 and IgG3 bind protein antigens whereas IgG2 binds polysaccharide antigens. IgA is secreted on mucosal surfaces and is found in tears, saliva, and breast milk; it binds microorganisms to prevent them from crossing mucosal barriers. IgE binds to high-affinity Fc receptors on mast cells and basophils and to low-affinity receptors on neutrophils, eosinophils, macrophages, and platelets. IgD’s only known function is its role as a B-cell receptor.

**Natural Kill (NK) Cells**

NK cells comprise 10% of circulating lymphocytes and express CD16 (an Fc receptor) and CD56. Unlike T cells, NK cells are not restricted to interactions with cells bearing MHC molecules, which is essential to their function. Virus-infected and tumor cells frequently downregulate MHC Class I molecules to avoid T-cell mediated destruction. NK cells solve this problem. When an NK cells encounters a cell in the body, it attempts to interact with an MHC Class I molecule; if no MHC Class I molecule is found, the NK cell will destroy the cell.

**Neutrophils**

Neutrophils develop in the bone marrow and comprise 60-65% of circulating leukocytes. They accumulate at sites of bacterial infection or tissue injury, utilize oxygen radical production and phagocytosis to destroy microorganisms, and produce many cytokines, including IL-12 and TNF.
Monocytes/Macrophages

These cells comprise 10% of circulating leukocytes. Monocytes mature in the bone marrow, then enter tissues from the blood stream to become tissue macrophages, dendritic cells, Langerhans cells (epidermis), Kupffer cells (liver), and microglia (CNS). These cells possess both MHC Class I and Class II molecules and function as APCs. They also possess Fc receptors that facilitate phagocytosis of opsonized microorganisms. They produce many cytokines, including IL-12 and INF-γ.

Eosinophils

Eosinophils comprise 2-5% of circulating leukocytes and have a key role in combating parasite infestation. GM-CSF and IL-3 promote eosinophil growth and differentiation; IL-5 inhibits apoptosis, thereby maintaining viability. These cells have granules that contain major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and Charcot-Leyden crystal (CLC) protein.

Mast Cells and Basophils

Both of these cells originate from a common progenitor cell (CFU-BM); IL-3 and stem cell factor (SCF) are essential for growth and differentiation. Both cell types express high-affinity receptors (FcεRI) for the IgE Fc region. Crosslinking of these antibody/receptor complexes by antigens leads to degranulation, including histamine release.

Hypersensitivity Reactions

- Type I (immediate)
  - Mast cell/basophil/IgE mediated
  - Example: anaphylaxis
- Type II (cytotoxic, antibody-mediated)
  - Antibodies bind to antigens on target cells
  - Example: penicillin-induced autoimmune hemolytic anemia
- Type III (immune complex-mediated)
  - Antigen-antibody complexes deposit in normal tissues
  - Examples: serum sickness, lupus
- Type IV (delayed hypersensitivity, cell mediated)
  - Antibody independent, mediated by T or NK cells
  - Example: positive PPD test

Allergic Rhinitis

Allergic rhinitis is an IgE-mediated hypersensitivity of the nasal mucosa to foreign substances that affects 20% of the United States population. It rarely occurs before 2 years of age and is almost always present in affected individuals by 20 years of age. There is a male predominance in childhood that equalizes in adulthood. Allergic rhinitis is frequently associated
with atopy, which is the genetic predisposition to respond to environmental allergens with the production of specific IgE antibodies to those allergens.

**Hygiene Hypothesis**

The hygiene hypothesis states that the decrease in infectious diseases during the past four decades is causally related to the concomitant increase in the incidence of allergic diseases. Several epidemiological observations support this hypothesis: (1) Children raised on a farm are less likely to develop allergic rhinitis than those not raised on a farm. (2) The risk of allergic rhinitis is inversely linked to birth order and family size. (3) Children with older siblings at home and those who attended daycare during the first six months of life have a lower incidence of asthma. Finally, (4) there is a higher prevalence of atopy and asthma in industrialized countries compared to undeveloped and poorer countries.

The following are some of the proposed mechanisms of hygiene hypothesis, and are not mutually exclusive:

- **TH1/TH2 regulation**
  - Cytokines of one TH cell type down-regulate the activation of the other
  - TH1 responses are activated by extracellular pathogens
  - TH2-produced cytokines IL-4 and IL-5 promote allergic diseases

- **Tregs**
  - Activity of these cells is up-regulated by infections
  - These cells produce IL-10 and TGF-β, which down-regulate both TH1 and TH2 mediated responses

- **Toll-like receptor interactions**
  - Activation of TLRs in dendritic cells promotes TH1 responses critical for cell-mediated immunity, thereby affecting the TH1/TH2 balance in favor of TH1

**Pathophysiology of Allergic Rhinitis**

The first phase in the pathogenesis of allergic rhinitis is sensitization. APCs in the nasal mucosa process and present antigen to T cells. Activated TH2 cells secrete IL-4, IL-5, and IL-13; these cytokines promote isotype switching to IgE and eosinophil recruitment and survival. The IgE produced attaches to high-affinity receptors on the mast cells and basophils in the nasal mucosa.

The second phase is marked by the appearance of clinical disease and is divided into early and late responses. The early response occurs within minutes of antigen exposure. IgE on mast cells is crosslinked, leading to degranulation. Both preformed (histamine, kinins, tryptase) and rapidly synthesized (prostaglandin D2, leukotriene C4, leukotriene B4, major basic protein, and platelet activating factor) mediators are released, leading to the symptoms of sneezing,
rhinorrhea, and nasal congestion. There is also a likely neuronal component to this early response, mediated by histamine acting on nasal afferent nerves, as evidenced by unilateral nasal challenge leading to bilateral symptoms and the concomitant ocular symptoms that occur with nasal antigen provocation. The late response occurs hours after exposure, usually peaking at 6 hours post-exposure and resolving by 24 hours post-exposure. The predominant symptom of the late response is nasal congestion. During this period, there is an increase in histamine, kinins, and numerous cytokines (IL-5, IL-6, IL-8, GM-CSF, TNF, and soluble ICAM-1) with a concomitant influx of inflammatory cells. Eosinophils, basophils, and neutrophils increase in nasal secretions while a mononuclear and mast cell infiltration occurs in the nasal mucosa. Most specifically, the increase in basophils correlates with the late rise in histamine, implying that basophil infiltration and subsequent histamine release is a key component of the late response.

**Diagnosis of Allergic Rhinitis**

- **History**
  - Recurrent episodes of sneezing, rhinorrhea, nasal congestion, and lacrimation
  - Pruritis (nasal, ocular, oral, pharyngeal) is highly suggestive of allergy
  - Post-nasal drip, throat clearing
  - Eustachian tube dysfunction—ear popping and clicking,
  - Systemic symptoms: fatigue, irritability, sleep disturbance
  - Personal or family history asthma, eczema, atopic dermatitis, allergic rhinitis
  - Exposure to exacerbating substances—tobacco smoke, smog

- **Timing of symptoms and definitions**
  - Traditionally allergic rhinitis has been classified as seasonal versus perennial
    - Seasonal—due to tree pollen, ragweed, grasses, outdoor molds
    - Perennial (symptoms for \( \geq 2 \text{ hours/day for } \geq 9 \text{ months/year} \))—due to dust mites, pet dander, cockroaches, indoor molds
  - Allergic Rhinitis and its Impact on Asthma (ARIA) classification (1999) provides a more formal nomenclature:
    - Intermittent allergic rhinitis
      - Symptoms <4 days/week or <4 consecutive weeks/year
    - Persistent allergic rhinitis
      - Symptoms >4 days/week and for >4 consecutive weeks/year
    - Mild, moderate, and severe modifiers
• **Physical Exam Findings**
  - Head: adenoid facies—elongated face, open mouth, retracted mandible, flattened malar eminences, pinched nostrils, raised upper lip
  - Ears: middle ear effusion or retraction
  - Eyes: allergic shiners (venous stasis from chronic nasal congestion)
  - Nose
    - External: supratip crease (allergic salute)
    - Internal: pale, boggy, edematous mucosa; inferior turbinate hypertrophy; polyps
  - Throat: cobblestoning of the posterior pharyngeal wall

• **Testing**
  - Skin testing
    - Antigen introduced via skin puncture versus intradermal injection
    - Advantages: rapid, inexpensive, more sensitive
    - Disadvantages: affected by antihistamine therapy, cannot be used if patient has dermatographism, potential for systemic reaction
  - In vitro testing—radioallergosorbent testing (RAST) and enzyme-linked immunosorbent testing (ELISA)
    - Identify antigen-specific IgE in the patient’s serum
    - Advantages: No needles, can be used for patients with dermatographism, no potential for systemic reaction
    - Disadvantages: longer turnaround time, more expensive, less sensitive

**Asthma**

Asthma is a clinic syndrome characterized by variable airflow obstruction, airway hyperreactivity, and cellular inflammation of the lower airway. It affects 10% of adults and 15% of children in the United States; most patients have atopy, which is the major risk factor. There is a 2:1 male to female ratio in childhood that equalizes in adulthood. The pathogenesis is very similar to allergic rhinitis, with a key difference being that capacitance vessels are affected in allergic rhinitis, leading to rhinorrhea and nasal congestion, whereas in asthma, bronchial smooth muscle is simulated, leading to constriction and airway narrowing.

**Pathogenesis of Asthma**

Allergens, sensitizers, viruses, and air pollutants lead to lower airway inflammation with a chronic eosinophilic bronchitis. This leads to airway hyperresponsiveness. The hyperresponsiveness combined with triggers leads to symptoms—coughing, wheezing, chest tightness, and dyspnea. Over time airway remodeling occurs, which is characterized by smooth muscle hyperplasia and hypertrophy, fibroblast activation with subsequent collagen deposition, and mucous gland hyperplasia.
Triggers

There are numerous triggers for asthma exacerbation. These include indoor allergens such as dust mites, pet dander, and cockroaches and outdoor allergens such as trees, grasses, and weeds. Beta-blockers, ACE inhibitors, and aspirin are the most common medication triggers. In women, hormone changes can cause premenstrual worsening of asthma symptoms; if severe, treatment with high doses of progesterone can be used. Other triggers include viral infections, exercise, cold air, hot air, fog, and air pollution.

Diagnosis of Asthma

- **History**
  - Wheezing
  - Dyspnea
  - Coughing
  - Increased mucous production
- **Physical Exam Findings**
  - Wheezing, rhonchi—expiratory>inspiratory
  - Non-productive cough
  - However, examination usually is normal
- **Pulmonary Function Tests (PFTs)**
  - Gold standard for the diagnosis of asthma
  - Simple spirometry is sufficient in evaluation of asthma
    - **Definitions:**
      - FVC—forced vital capacity
      - FEV1—forced expiratory volume during the first one second
      - FEV1/FVC ratio—normal ratio is between 80-120% of predicted; 70-79%—mild airflow obstruction; 51-69%—moderate airflow obstruction; <50%—severe airflow obstruction
    - **Reversibility**—indicator of asthma
      - Increase in FEV1 by >12% and at least 200 mL after administration of a short-acting beta-agonist
      - Must stop long-acting beta-agonists, ipratropium, and cromolyn 12 hours prior to testing and short-acting beta-agonists 4-6 hours prior to testing
  - Other components of full PFTs, i.e., lung volumes and diffusion capacities, are not particularly helpful in the diagnosis of asthma but are useful for evaluation of other lung diseases, especially restrictive diseases.
  - Please see PowerPoint slides for diagrams of PFTs.
• **Bronchial provocation testing**
  - Can be used in rare cases when PFTs are inconclusive
  - Exercise
    - FEV1 measured at 1, 3, 5, 10, 15, and 20 minutes after exercise
    - Exercise-induced bronchoconstriction present if FEV1 decreases by >15% from baseline
  - Methacholine challenge
    - Cholinergic agonist
    - Positive test if FEV1 decreases >20% from baseline at a methacholine concentration <8 mg/mL

**Chronic Rhinosinusitis**

Chronic rhinosinusitis (CRS) is a complex group of disorders with inflammation as the major universal finding. It affects approximately 15% of the adult population in the United States. The term rhinosinusitis is preferred over the term sinusitis because the nose is almost always involved at the same time as the paranasal sinuses. Several other important definitions are worthwhile to consider. Acute rhinosinusitis occurs with sudden onset and has a duration <4 weeks. Subacute rhinosinusitis has a duration of 4-12 weeks. Recurrent rhinosinusitis is defined as >3 episodes of rhinosinusitis in one year. Chronic rhinosinusitis is defined as having a duration >12 weeks and is further classified as with or without nasal polyposis (CRSwNP and CRSsNP, respectively). Acute exacerbation of chronic rhinosinusitis (AECRS) is used to describe the acute flares of disease that frequently occur in patients with CRS.

**Pathogenic factors in CRS**

There are many factors that have been found to play a role in the development and maintenance of CRS. Bacterial superantigens, such as enterotoxins and toxic shock toxins produced by *Staphylococcus aureus*, can lead to extensive inflammation due to interaction of the toxins outside of the normal TCR and MHC Class II molecule binding sites, which results in polyclonal activation of T-cells.

Biofilms are polymicrobial ecosystems within a polymeric matrix that become irreversibly associated with an inert or living surface; they are much akin to coral reefs. Biofilms are found in up to 80% of patients undergoing surgery for CRS and are particularly difficult to treat due to the pronounced antibiotic resistance provided to the bacteria species living in the biofilm; indeed, antibiotic concentrations greater than 1,000 times therapeutic serum levels can be required to eradicate the bacteria within the biofilm. This high dose requirement usually makes medical therapy impossible, necessitating removal of affected surface, be it an inert medical device or living tissue.

Fungi can contribute to CRS through non-invasive colonization that leads to obstruction of the sinus ostia or through allergic fungal sinusitis which is an IgE-mediated hypersensitivity.
Allergic rhinitis is present in 40-84% of patients with CRS; it is thought to contribute to CRS by inducing mucosal swelling that obstructs the sinus ostia.

Genetic factors can also play a role in CRS. Seven percent of patients with CRS are cystic fibrosis (CF) carriers, compared to the general population rate of 2%. Furthermore, 36% of CF patients have CRS, compared to the 15% general population rate.

Immunodeficiency should be considered as a possible contributor to CRS when aggressive therapy has failed. In patients with refractory CRS, the rates of immunodeficiency range from 3-10%. The most common disorders seen in this group are selective IgA deficiency, common variable immunodeficiency, and hypogammaglobulinemia.

Finally, environmental irritants such as tobacco smoke and industrial pollution can contribute to the development and persistence of CRS.

**Diagnosis of CRS**

- **Major symptoms and signs**
  - Nasal obstruction (81-95%)
  - Facial congestion/pressure/fullness (70-85%)
  - Nasal discharge/purulence (51-83%)
  - Hyposmia/anosmia (61-69%)

- **Minor symptoms and signs**
  - Headache
  - Fever
  - Fatigue
  - Dental pain
  - Cough
  - Ear pain/pressure/fullness

- **Nasal endoscopy**
  - To evaluate for:
    - Anatomic abnormalities
    - Neoplasms
    - Polyps
    - Rhinorrhea
    - Turbinate hypertrophy
    - Adenoid hypertrophy
  - Can obtain middle meatal cultures to direct antibiotic therapy
Imaging
- Computed tomography (CT) without intravenous contrast is the gold standard for imaging of the paranasal sinuses
- Recommended in the evaluation of CRS (in contrast to acute sinusitis, in which imaging is not recommended)
- Excludes aggressive infections or neoplastic disease that can mimic CRS
- Can establish the presence of and monitor the course of inflammation
- Also identifies sinus ostial obstruction, anatomic variants, and polyposis
- Findings should be interpreted in the context of clinical examination and/or nasal endoscopy

Nasal Polyps

Nasal polyps are edematous, semitranslucent masses that most commonly arise from the middle meatus and ethmoid sinuses. Nasal polyps are present in 19-36% of patients with CRS. Interestingly, eosinophils are abundantly present in 80% of polyps in United States patients, whereas in Asian patients, neutrophils predominant in nasal polyps. The presence of nasal polyps is linked to CF in children and aspirin sensitivity in young adults. In patients with CF, 37-48% have nasal polyps, which underscores the importance of testing all children with nasal polyps for CF.

The following is a common classification system for nasal polyps:
1. The antrochoanal polyp, mostly arising from the maxillary sinus and prolapsing into the choana, a commonly large isolated unilateral cyst-like non-eosinophilic formation
2. Idiopathic unilateral or bilateral, mostly eosinophilic polyps without involvement of the lower airways
3. Bilateral eosinophilic polyposis with concomitant asthma and/or aspirin sensitivity
4. Polyposis with underlying systemic disease such as cystic fibrosis, primary ciliary dyskinesia, Churg-Strauss syndrome, or Kartagener's syndrome

The following is the endoscopic staging system for nasal polyps:
0  No polyps present
1  Polyps confined to the middle meatus
2  Polyps beyond the middle meatus (reaching the inferior turbinate or medial to the middle turbinate)
3  Polyps almost or completely obstructing the nasal cavity

Samter’s Triad

Samter’s triad is characterized by nasal polyposis, asthma, and aspirin sensitivity. In patients with nasal polyps, 15% have aspirin sensitivity and 20-70% have asthma. In patients with aspirin sensitivity, 40-80% have nasal polyps. Symptoms of the triad usually develop following a prolonged upper respiratory infection in the third or fourth decade of life. Initially, the patient suffers from nasal congestion, rhinorrhea, post-nasal drip, and hyposmia; within a few
years, bronchial asthma and nasal polyposis develop. The asthma is usually severe, with 50% of patients requiring chronic burst or daily oral steroid therapy. Asthma and rhinitis attacks are triggered by ingestion of aspirin and non-selective non-steroidal anti-inflammatory drugs (NSAIDs); however, the progression of the disease is not affected by aspirin ingestion.

**Pathogenesis of Samter’s Triad**

The pathogenesis of Samter’s triad is not completely understood; however, unlike asthma and allergic rhinitis, atopy and IgE do not appear to play a role. Peripheral blood and local mucosal eosinophilia are characteristic, as are elevated tissue and urine cysteinyl-leukotrienes (cys-LTs) concentrations, which increase with aspirin exposure. The latter findings provide a potential mechanism for the disease. Because aspirin inhibits COX 1 and 2 in the arachidonic acid metabolism pathway, production equilibrium is shifted toward leukotriene formation. In eosinophils of aspirin sensitive patients, there is a several-fold elevation of LTC4 synthase, which is the terminal enzyme in cys-LT production; therefore, polymorphisms in the LTC4 synthase gene are suspected to contribute to the development of Samter’s triad.

**Diagnosis of Samter’s Triad**

No validated laboratory testing available
Oral aspirin provocation in a controlled setting is the current gold standard in the U.S.

- Asthma medications are discontinued prior to the testing
- Aspirin is dosed TID, with increasing amount of aspirin in each dose
- FEV1 is measured every 30 minutes
- Positive test:
  - Decrease in FEV1 by 20% or more from baseline
  - Severe nasal congestion and/or rhinorrhea occur
- Negative test:
  - Cumulative dose of 1000 mg of aspirin is reached without either of the positive test criteria occurring

**Churg-Strauss Syndrome**

Churg-Strauss syndrome is a clinical syndrome characterized by asthma, eosinophilia, and vasculitis. In 1990, the American College of Rheumatology established the follow six diagnostic criteria, at least four of which must be present:

- Asthma
- Eosinophilia (>10% of total white blood cell count)
- Mononeuropathy or polyneuropathy
- Migratory or transient infiltrates on chest x-ray
- Paranasal sinus abnormality (pain, tenderness, or radiographic opacification)
- Biopsy of a vessel demonstrating extravascular eosinophils
Churg-Strauss syndrome usually has a tri-phasic progression. First, the patient develops allergic rhinitis, rhinosinusitis, and asthma of variable severity. Next, blood eosinophilia and eosinophilic tissue infiltration occurs. Finally, the patient develops life-threatening, multi-organ vasculitis involving the cardiac, pulmonary, gastrointestinal, and central nervous systems.

**Diagnosis of Churg-Strauss Syndrome**

- **Physical Exam Findings:**
  - Nose: nasal polyps, nasal mucosal congestion, rhinorrhea
  - Cardiovascular: heart failure
  - Lungs: wheezes, rhonchi, decreased breath sounds
  - Neurologic: Mononeuritis multiplex—sensory and motor neuropathy in the distribution of one nerve, polyneuropathy
  - Skin: palpable purpura, papules, ulcers, bullae, and “Churg-Strauss granulomas”—cutaneous extravascular necrotizing granulomas on extensor surfaces and pressure points (elbow)

- **Laboratory:**
  - White blood cell
    - Marked eosinophilia (up to 60%)
  - Antineutrophil antibodies (ANCA)—present in 50% of patients
  - Erythrocyte sedimentation rate (ESR)—elevated in most cases

- **Imaging:**
  - CT thorax—best to demonstrate pulmonary infiltrates
  - Echocardiogram
  - Heart failure
  - Dysfunction from regional fibrosis

- **Biopsy Findings:**
  - Skin lesions: extravascular granulomas with eosinophilic infiltrate
  - Lung: massive alveolar and interstitial infiltrates (eosinophilic)
  - Blood vessel: necrotizing fibrinoid eosinophilic vasculitis of small to medium-sized vessels

- **Distinguishing Churg-Strauss from Asthma:**
  - Degree of eosinophilia
    - Churg-Strauss: blood eosinophil counts usually >1500/μL
    - Asthma: blood eosinophil counts usually <1500/μL
  - ESR
    - Positive in Churg-Strauss
    - Negative in asthma
  - ANCA
    - Positive in 50% of patients with Churg-Strauss
    - Negative in patients with “regular” asthma
Therapeutics

Steroids

Steroids (glucocorticoids) are potent anti-inflammatory and immunosuppressant medications with many formulations—intranasal, inhaled, oral, intramuscular, and intravenous. These agents are used extensively in the treatment of allergic rhinitis, asthma, chronic rhinosinusitis, nasal polyposis, Samter’s triad, and Churg-Strauss disease.

A brief review of steroid pharmacology follows. The glucocorticoid receptor (GR) resides in the cytoplasm of cells; after binding of a glucocorticoid molecule, the complex translocates to the cell nucleus. Once in the nucleus, GR and other factors modify gene transcription, downregulating some genes while upregulating other genes. The downregulated genes include mediators of inflammation—cyclooxygenase-2, numerous cytokines, and inducible nitric oxide synthase. The upregulated genes are metabolic regulators—enzymes involved in gluconeogenesis, amino acid metabolism, etc.

Despite their great usefulness in treating all of the diseases discussed in this presentation, steroids are not without side effects. The side effects of prolonged, systemic, supra-physiologic exposure to glucocorticoids include hyperglycemia, hypertension, peptic ulcers, myopathy, behavior changes ranging from nervousness and anxiety to full psychosis, osteoporosis, osteonecrosis, growth retardation in children, and cataracts. The risk for cataract development is dose-dependent; therefore, if a patient is taking prednisone 10-15 mg/day or equivalent on a chronic basis, slit-lamp examination should be performed periodically.

Therapeutic Options for Allergic Rhinitis

The therapeutic options for the treatment of allergic rhinitis include avoidance of the offending allergen(s), intranasal steroids, antihistamines, decongestants, anticholinergics, cromolyn, leukotriene modifiers, systemic steroids, and immunotherapy. Each of these is discussed below.

- **Avoidance**
  - Remove offending pet from the home
  - Hypoallergenic mattress covers and pillow cases
  - Washing bedding in hot water
  - In general, hard to accomplish

- **Intranasal steroids**
  - Reduce number of inflammatory cells and TH2 cytokines in the nasal mucosa
  - Result in significant inhibition of early and late phase reactants
  - Effective in both seasonal and perennial allergic rhinitis
  - Superior efficacy compared to both antihistamines and leukotriene modifiers
  - **First-line therapy**, except for mildest forms of allergic rhinitis
- Continuous use is best; however, as-needed use has been proven superior to placebo
- Side effects
  - Local irritation (10%)
  - Epistaxis (4-8%)
  - Nasal septal perforation (very rare)
- Pediatric consideration: regular growth monitoring every 3-6 months

- **Antihistamines**
  - H1 blockers
  - First generation (diphenhydramine) more lipophilic, cross CNS, lead to sedation
  - Second generation (cetirizine, loratadine, fexofenadine) are less lipophilic, much less sedating
  - Effective at controlling sneezing, itching, rhinorrhea, and watery eyes; not as effective at controlling nasal congestion
  - Topical preparation available
    - Azelastine
  - Side effects
    - Sedation (20%, first generation)
    - Altered sense of smell immediately after use (azelastine)

- **Decongestants**
  - Oral
    - Pseudoephedrine
    - Phenylephrine—lack of efficacy compared to placebo
  - Topical
    - More effective than systemic
    - Oxymetazoline (0.05%)
    - Phenylephrine (1%)
  - Mechanism: alpha-agonist mediated vasoconstriction
  - Side effects:
    - Rhinitis medicamentosa (topical)
    - Insomnia, irritability (systemic)
    - HTN (systemic)
    - Seizures in children (systemic)

- **Anticholinergics**
  - Intranasal ipratropium bromide
  - Useful when rhinorrhea is the predominant symptom
  - No effect on sneezing or nasal congestion
  - Minimal side effects
• **Cromolyn**
  - Cromolyn sodium intranasal (4%)
  - Mast cell stabilizer
  - Most effective when started prior to onset of symptoms
  - Effective for sneezing, rhinorrhea, and itching
  - Must be dosed 4-6 times per day
  - Useful for known upcoming exposures to allergen and in pregnancy
  - Minimal side effects

• **Leukotriene modifiers**
  - 5-lipoxygenase pathway inhibitor (zileuton)
  - Leukotriene receptor antagonists (monteleukast, zafirlukast)
  - Monteleukast
    - Most commonly used in the United States
    - Equal in effectiveness to antihistamines
      - Combination of monteleukast and an antihistamine superior to each agent alone
  - Side effects
    - Headache
    - Dyspepsia

• **Systemic corticosteroids**
  - Best reserved for patients who present with complete nasal obstruction
    - Uncontrolled allergic rhinitis
    - Rhinitis medicamentosa

• **Immunotherapy**
  - Reserved for unavoidable allergens and inadequate response to standard therapies
  - Effects
    - Rise in serum-specific IgG
    - Suppression of IgE
    - Shift from TH2 to TH1 profile
    - Reduction of inflammatory cells in the nasal mucosa and secretions
  - Onset of action 12 weeks after starting therapy, increases slowly over 1-2 years
  - Subcutaneous (SCIT)
    - Antigen extract is injected into the skin
  - Sublingual (SLIT)
    - Antigen is applied under the tongue
    - Widely used in Europe
    - Not FDA approved, but trials underway
    - Primary benefits are avoiding frequent office visits for therapy and no needles
**General Therapeutic Approach for Allergic Rhinitis:**
- For mild disease
  - As-needed intranasal corticosteroid
- For moderate to severe disease
  - Regular intranasal corticosteroid
- Reassess two weeks after starting therapy
  - If ocular symptoms persist: intraocular antihistamine
  - If nasal congestion persists: antihistamine/decongestant combination or monteleukast
  - If rhinorrhea persists: ipratropium bromide
- Perennial disease and inadequate response with maximal medical management—immunotherapy

**Therapeutic Options for Asthma**

The therapeutic options for the treatment of asthma include bronchodilators—short and long-acting β2-agonists and anticholinergics—and controller therapies—inhaled and systemic corticosteroids, leukotriene modifiers, cromolyn, immunotherapy, and anti-IgE. Each of these is discussed below.

**β2-agonists**
- Short-acting: albuterol, terbutaline—PRN symptom relief
- Long-acting: salmeterol, formoterol—steroid-sparing
- Relax airway smooth muscle
- Inhibit mast cell degranulation
- No effect on inflammation or airway hyperreactivity
- Side effects:
  - Palpitations
  - Muscle tremor

**Anticholinergics**
- Ipratropium bromide
- Inhibit cholinergic-mediated bronchoconstriction and mucus secretion
- Much less effective than β2-agonists
- Used only in combination with β2-agonists
- Side effects:
  - Dry mouth
  - Urinary retention
  - Glaucoma

**Inhaled corticosteroids**
- Most effective anti-inflammatory agents used in asthma
- Reduce eosinophils in secretions and T cells and mast cells in the mucosa
- Reduce airway hyperreactivity
- **First-line therapy for persistent asthma**
- Side effects:
• Oral candidiasis (prevent with oral rinse and spacer)
• Hoarseness

**Systemic corticosteroids**
• Used for acute asthma exacerbations
• Necessary for maintenance therapy in 1% of patients
• Side effects
  • See previous section on supra-physiologic effects of steroids

**Leukotriene modifiers**
• Less effective than inhaled corticosteroids
• May be used instead of a long-acting beta agonist (LABA) if an inhaled corticosteroid does not completely control symptoms

**Cromolyn sodium (and nedocromil sodium)**
• Safe and effective but limited by minimum 4 times per day dosing that is required

**Immunotherapy**
• Not recommended in most asthma treatment guidelines due to lack of clinical efficacy in asthma
• However, immunotherapy appears to have a preventative effect against future development of asthma in patients with allergic rhinitis

**Anti-IgE**
• Omalizumab
• Neutralizes circulating IgE
• Reduces number of exacerbation in patients with severe asthma and improves overall control
• Minimal side effects
• Drawback—very expensive

A stepwise approach is taken for asthma therapy (please see PowerPoint slides for figure). For mild intermittent disease, a short-acting β2-agonist alone is used. For mild persistent disease, a low-dose inhaled corticosteroid (ICS) is added. If disease progresses to moderate persistent, a long-acting β2-agonist is added. For severe persistent disease, the ICS is increased to high-dose. Finally, for very severe persistent disease, an oral corticosteroid is added.

**Medical Therapeutic Options for CRS**

The medical therapeutic options for the treatment of CRS include nasal saline lavage, systemic and topical antibiotics, topical and systemic antifungals, intranasal and systemic corticosteroids, leukotriene modifiers, decongestants, antihistamines, anti-IgE, and intravenous immunoglobulin (IVIG). Each of these is discussed below.
• **Nasal saline lavage**
  • Study results range from showing no benefit at all to more benefit than standard medical therapy
  • Cochrane review in 2007 concluded that it does have benefit as an adjunctive treatment in CRS
  • Irrigation has shown more benefit than spray

• **Oral antibiotics**
  • In CRS, no randomized placebo-controlled trial has demonstrated efficacy of short courses of oral antibiotics
  • Long-term macrolide therapy has been shown to be effective in CRS
    • Anti-inflammatory mechanism separate from antimicrobial effects
    • Possibly decreases biofilm formation and bacterial virulence
    • Recommended as part of primary therapy for non-atopic patients with bilateral disease

• **Topical antibiotic therapy**
  • Less need for surgery demonstrated for patients with cystic fibrosis who were treated with tobramycin in saline nasal rinses than in patients with cystic fibrosis who did not undergo any rinses
  • However, similar benefited noted in this study and another between antibiotic plus saline and saline alone

• **Topical antifungal therapy**
  • Similar findings as with topical antibiotic therapy—saline alone appears to be equally effective

• **Systemic antifungal therapy**
  • No strong evidence to date that this is useful in the treatment of CRS

• **Intranasal corticosteroids**
  • Effective in both CRSsNP and CRSwNP

• **Systemic corticosteroids**
  • Effective in CRSsNP
  • Strongly effective in CRSwNP
  • Particularly useful in short bursts for complete nasal obstruction to increase nasal patency to allow for penetration of nasal corticosteroid sprays

• **Leukotriene modifiers**
  • Limited studies for use in CRS
  • Some benefit has been seen in patients with CRSwNP

• **Decongestants**
  • Best used for short-term relief of nasal congestion (exacerbations)
- **Antihistamines**
  - No controlled studies showing effectiveness in CRS

- **Anti-IgE**
  - No studies for its use in CRS

- **Intravenous immune globulin (IVIG)**
  - Significant improvement in immunodeficient patients

### Surgical Therapeutic Options for CRS

The standard surgical option for CRS refractory to medical therapy is functional endoscopic sinus surgery (FESS). In the past few years, balloon sinuplasty has become a viable alternative for certain subsets of patients. Both of these options are discussed below.

- **Functional endoscopic sinus surgery (FESS)**
  - In CRS, inflammation from viral, bacterial, and fungal infections and from allergies causes mucosal edema, which leads to obstruction of the natural sinus ostia
  - Anatomic abnormalities—septal deviation, concha bullosa, paradoxical middle turbinate, Haller cells, agger nasi cells, and nasal polyps—can obstruct natural sinus ostia
  - Principles of FESS
    - First maximize medical therapy
    - Restore sinus function by re-establishing the physiologic pattern of ventilation and mucociliary clearance
    - Remove diseased mucosa and bone, preserve normal tissue, and widen natural ostia

- **Common steps of the surgery**
  - Resection of the uncinate process
  - Maxillary antrostomy
  - Anterior ethmoidectomy
  - Posterior ethmoidectomy
  - Sphenoid sinusotomy
  - Ethmoidectomy completed superiorly

- **Additional steps as needed**
  - Frontal sinusotomy
  - Septoplasty
  - Conchal bullosa resection
  - Removal of polyps
  - Marsupialization of mucoceles
• **Balloon Sinuplasty**
  - Recently developed, with first clinical outcomes published by Bolger in 2007
  - Guide catheter positioned near sinus to be dilated under endoscopic guidance
  - Guide wire is passed into sinus cavity
    - Position was initially confirmed with fluoroscopy
    - A lighted guide wire is now available to confirm position without radiation exposure to the patient
  - Balloon passed over guide wire and inflated while within the sinus ostium
  - Used for maxillary, frontal, and sphenoid sinus
  - Initially confined to the operating room, now also being performed in the clinic setting
  - Results from Bolger’s initial study of 115 patients and follow up:
    - Patency at 6 months and 1 year were >80% by endoscopy
      - 18% indeterminate
      - 1% non-patency rate
    - Revision rate of 1%, 2%, and 3.6% at 6 months, 1 year, and 2 years, respectively
  - **Caveats**
    - Original study by Bolger excluded patient with nasal polyposis
    - If balloon sinuplasty is performed instead of FESS, diseased tissue is not removed
  - **Balanced view** of balloon sinuplasty—a good tool when used in appropriately selected patient populations

**General Approach to Therapy for CRS**

• **CRSsNP**
  - Mild symptoms
    - Intranasal corticosteroids and nasal saline lavage
    - Reassess after three months
      - If no improvement, culture and start long-term macrolide
      - Consider CT scan
    - Reassess after another three months
      - If no improvement, CT scan and consider sinus surgery
  - Moderate/severe symptoms
    - Start with intranasal steroids, nasal saline lavage, culture, and macrolide; if no response in three months, CT scan and consider sinus surgery

• **CRSwNP**
  - Similar approach to CRSsNP, except antibiotics are not recommended
  - Mild/moderate symptoms
    - Intranasal corticosteroid and nasal saline lavage
    - Reassess in three months
      - If no improvement, oral corticosteroids for one month
    - If symptoms persist, CT scan and consider sinus surgery
  - Severe symptoms
• Start with both intranasal corticosteroids and one month of oral steroids
• Reassess in three months
  • If no improvement, CT scan and consider sinus surgery

**Therapeutic Options for Samter’s Triad**

• **Medical Therapy**
  • Avoidance of aspirin and non-specific NSAIDs
  • Acetaminophen and celecoxib are tolerated in most patients
  • Treatment of asthma symptoms as per asthma guidelines
  • Leukotriene modifiers
    • Somewhat effective, though no more so than in regular asthma
  • Aspirin desensitization

• **Surgical Therapy**
  o FESS necessary in some patients due to burden of nasal polyps and inadequate response to medical treatment

**Therapeutic Options for Churg-Strauss Syndrome**

• **Oral corticosteroids**
  • Frequently only therapy needed

• **Immunosuppressants**
  • Milder disease
    • Azathioprine
    • Methotrexate
    • Mycophenolate
  • Severe disease (involvement of the heart, glomerulonephritis, or vasculitic neuropathy)
    • Cyclophosphamide

• **Bronchodilators**—as needed for bronchial hyperreactivity

**Summary**

The integrated airway hypothesis highlights the similarities and interplay among allergic rhinitis, asthma, and CRS. In these three diseases there is an inciting event that stimulates the immune system, leading to inflammation that is predominantly TH2 and IgE mediated and eosinophilic in nature. Atopy is therefore a major risk factor for the development of these diseases. Given that inflammation is central to each of these diseases, it is not surprising that corticosteroids constitute the most effective medical therapy for each one. Continued research
for better, more lasting solutions to these diseases has led to the development of sublingual immunotherapy and balloon sinuplasty, two treatment modalities that are poised to become convenient, less painful alternatives to current therapy for patients with allergic rhinitis and CRS, respectively.

References


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