Allergic Rhinitis, Asthma, and Chronic Rhinosinusitis

Commonalities of etiology and management

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Overview

- Integrated airway hypothesis
- Review of immunology as it relates to allergy
- Allergic rhinitis
- Asthma
- Chronic rhinosinusitis
- Nasal polyposis
- Samter’s triad
- Churg-Strauss syndrome
Overview

- Therapeutics
  - Steroids
  - Medical therapy for allergic rhinitis
  - Medical therapy for asthma
  - Medical therapy for chronic rhinosinusitis
  - Surgical therapy for chronic rhinosinusitis
    - Functional endoscopic sinus surgery (FESS)
    - Balloon Sinuplasty
  - Therapy for Samter’s triad
  - Therapy for Churg-Strauss syndrome
Integrated Airway Hypothesis
Epidemiologic Evidence

- Extensive overlap among the diseases:
  - Asthma occurs in up to 40% of patients with allergic rhinitis (general population rate: 10%)
  - Allergic rhinitis occurs in 80-90% of patients with asthma (general population rate: 20%)
  - Allergic rhinitis is present in 60-80% of patients with chronic rhinosinusitis
  - Among asthmatics, 40-60% have abnormal sinus radiographs; magnitude of sinus abnormalities correlates with the severity of the patient’s asthma
  - Among patients with extensive sinus disease on CT imaging, there was associated allergic rhinitis in 78% of patients and asthma in 71% of patients
  - Patients with allergic rhinitis are three times more likely than normal controls to develop asthma later in life
Experimental Evidence

- Thickening of the bronchial basement membrane has been demonstrated in patients with allergic rhinitis who did not have asthma.
- Nasal provocation with grass allergen in allergic rhinitis patients increased bronchial symptoms and bronchial mucosa eosinophils, ICAM-1, E-selectin, and VCAM-1.
- Selective bronchial provocation with grass allergen in allergic rhinitis patients was shown to cause increased nasal symptoms and eosinophil infiltration of the nasal mucosa.
Proposed Mechanisms of Interaction in the 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
Basic foundations

- Self versus non-self
- Self tolerance
- Major histocompatibility complex (MHC)
  - Located on the short arm of chromosome 6
  - Class I molecules
    - Present on nearly all nucleated somatic cells
    - Interact with CD8⁺ (cytotoxic) T cells
  - Class II molecules
    - Present on antigen-presenting cells (APCs) — macrophages, monocytes, dendritic cells, and B cells
    - Interact with CD4⁺ (helper) T cells
Innate Immunity

- Immediate response
- Non-specific
- Components:
  - Skin, mucosa
  - Antimicrobial substances, e.g. lysozyme
  - Complement system
  - Toll-like receptors (TLRs)—pattern recognition
    - TLR-2: lipoproteins
    - TLR-3: double-stranded RNA
    - TLR-4: lipopolysaccharides (LPS)
    - TLR-9: cytidine-phosphate-guanosine (CpG) dinucleotide sequence
Adaptive Immunity

- Slow response
- Highly specific
- Memory
- Lymphoid cells
- Myeloid cells
- Role of cytokines in differentiation
T cells

- Develop in the thymus
- Comprise 80% of circulating lymphocytes
- Defined by the presence of surface T-cell receptor (TCR)
- Further classified by:
  - CD8+: cytotoxic, cell-mediated immunity, highly active against virus-infected and tumor cells
  - CD4+: “helper” cells, augment humoral (B-cell) and cytotoxic responses
CD4+ T cells

- **TH1**
  - Produce IFN-γ—macrophage activation
  - Intracellular pathogen clearance—viruses, mycobacteria, Listeria
  - Delayed-type hypersensitivity
- **TH2**
  - B cell activation
  - Produce IL-4, IL-5, and IL-13—crucial role in allergy
  - Extracellular pathogen clearance—parasites, bacteria, allergens
- **TH17**
  - Produce IL-17, a key neutrophil recruiter
  - IL-17 reduces pulmonary eosinophil recruitment
- **Treg**
  - Foxp3+ cells, suppress T-cell responses and autoimmunity
  - Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)
    - Loss of function mutation in Foxp3 gene
    - Spectrum of disease includes type-1 diabetes, autoimmune thyroiditis, eczema, bleeding abnormalities, and chronic wasting
TH cell Interactions

- TH cell after stimulation produces IL-2, begins to differentiate, initially termed TH0
- From there, differentiation to TH1 or TH2 depends on environment
- IL-12 from macrophages leads to TH1 cells
- IL-4 from mast cells, NK cells, or eosinophils leads to TH2 cells

Photo source: Cummings Otolaryngology: Head & Neck Surgery
B cells

- Develop in the bone marrow
- Comprise 10% of circulating lymphocytes
- Defined by presence of surface IgM and IgD receptors (analogous to TCR)
- Provide humoral immunity via antibody production
- Differentiation promoted by T cells
  - Germinal center formation
  - Plasma cells
  - Memory B cells
B cells

- **T-cell dependent activation**
  - TCR:MHC class 2 interaction
  - CD40:CD40 ligand interaction
  - T-cell produced IL-1 and IL-2
  - Cytokine mediated isotype switching

- **T-cell independent activation**
  - Occurs with large carbohydrate antigens that cannot be presented on MHC class 2 molecules (capsule, cell wall)
  - Repeating antigenic determinate cross-links surface immunoglobulins, resulting in B cell activation
  - Primarily results in IgM antibody production
  - Essential defense against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*
Antibodies

- Five classes: G(75%), A(15%), M(10%), D(0.2%), E(0.004%)
  - Four IgG subclasses (IgG1-IgG4)
  - Two IgA subclasses (IgA1 and IgA2)
- Heavy and light chains
- Fab and Fc regions
- Isotype switching induced by cytokines:
  - IL-10: IgG1 and IgG3
  - IL-4 and IL-13: IgE
  - TGF-β: IgA
  - INF-γ: IgG2
- **IgM**: primary immune response, declines rapidly, replaced with IgG; most efficient complement-fixing antibody

- **IgG**: secondary immune response and later primary response, IgG1&3, and to some extent, IgG2, fix complement; only Ig to cross placenta; IgG1&3—protein antigens; IgG2—polysaccharide antigens

- **IgA**: secretory, prevents microbes from crossing mucosal barriers

- **IgD**: only functions as B-cell receptor

- **IgE**: High-affinity receptors on mast cells and basophils; low-affinity receptors on neutrophils, eosinophils, macrophages, and platelets
Natural Killer (NK) Cells

- Comprise 10% of circulating lymphocytes
- Unlike T cells, NK cells are not MHC restricted
- Express CD16 (Fc receptor) and CD56
- Virus-infected and tumor cells frequently down-regulate class I MHC molecules to avoid T-cell mediated destruction
- NK cells are the solution to this:
  - Interact with class I MHC on cells encountered
  - If no class I MHC molecules present, the cell is destroyed
Neutrophils

- Comprise 60-65% of circulating leukocytes
- Develop in the bone marrow
- Accumulate at sites of bacterial infection or tissue injury
- Utilize oxygen radicle production and phagocytosis
- Produce cytokines, including IL-12 and TNF
Monocytes/Macrophages

- Comprise 10% of circulating leukocytes
- Monocytes mature in the bone marrow
- Enter tissues from the blood stream to become macrophages, dendritic cells, Langerhans cells (epidermis), Kupffer cells (liver), microglia (CNS)
- Possess both class I and class II MHC molecules
- Function as APCs
- Fc receptor facilitates phagocytosis of opsonized microbes
- Produce many cytokines, including IL-12 and INF-γ
Eosinophils

- Comprise 2-5% of circulating leukocytes
- Combat parasite infestation
- GM-CSF and IL-3 promote growth and differentiation
- IL-5 inhibits apoptosis, maintaining viability
- Granule contents:
  - Major basic protein (MBP)
  - Eosinophil peroxidase (EPO)
  - Eosinophil cationic protein (ECP)
  - Eosinophil-derived neurotoxin (EDN)
  - Charcot-Leyden crystal (CLC) protein
Mast Cells and Basophils

- Both 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 IgE
  - Crosslinking 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
Background

- IgE-mediated hypersensitivity of the nasal mucosa to foreign substances
- Affects 20% of the United States population
- Rarely occurs before 2 years of age, almost always present by 20 years of age
- Male predominance in children, equalizes in adults
- Atopy: genetic predisposition to respond to environmental allergens with the production of specific IgE antibodies
Hygiene Hypothesis

- Decrease in infectious diseases during the past four decades is causally related to the concomitant increase in the incidence of allergic diseases

Evidence

- Children raised on a farm were found to be less likely to develop allergic rhinitis than those not raised on a farm
- Risk of allergic rhinitis inversely linked to birth order and family size
- Children with older brothers and sisters at home and those who attended daycare during the first six months of life have a lower incidence of asthma
- Higher prevalence of atopy and asthma in industrialized countries compared to undeveloped and poorer countries
Hygiene Hypothesis

- Proposed Mechanisms:
  - TH₁/TH₂ regulation
    - Cytokines of one down-regulate the activation of the other
    - TH₁ responses activated by extracellular pathogens
  - Tregs
    - Activity of these cells is up-regulated by infections
    - 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

NOTES:
TH1 cytokines IL-2 and INF gamma—autoimmune diseases
TH2 cytokines IL-4 and IL-5—allergic diseases
Pathophysiology of Allergic Rhinitis

Source: Cumming's Otolaryngology: Head & Neck Surgery
Sensitization

- APCs in nasal mucosa process and present antigen to T cells
- Activated TH2 cells secrete IL-4, IL-5, and IL-13
  - IgE isotype switching in B cells
  - Eosinophil recruitment and survival
- IgE produced attaches to high-affinity receptors on mast cells and basophils in the nasal mucosa
Early Response

- Occurs within minutes of antigen exposure
- IgE on mast cells cross-linked, leading to degranulation
  - Preformed: Histamine, kinins, tryptase
  - Rapidly synthesized: PGD₂, LTC₄, LTB₄, MBP, and PAF*  
- Symptoms: sneezing, rhinorrhea, nasal congestion
- Neuronal component
  - Unilateral challenge leads to bilateral response
  - Concomitant ocular symptoms
  - Likely mediated by histamine on nasal afferent nerves

*PG: prostaglandin, LT: leukotriene, MBP: major basic protein, PAF: platelet activating factor
Late Response

- Occurs hours after antigen exposure
  - Peak at 6 hours, resolution by 24 hours
- Symptoms: predominately nasal congestion
- Increase in histamine, kinins, and numerous cytokines:
  - IL-5, IL-6, IL-8, GM-CSF, TNF, and soluble ICAM-1
- Influx of inflammatory cells
  - Eosinophils, basophils, and PMN in secretions
  - Mononuclear infiltrate and mast cells in the mucosa
  - Increase in basophils correlates with late rise in histamine
Diagnosis

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
- Inquire about personal or family history asthma, eczema, atopic dermatitis, allergic rhinitis
- Exposure to exacerbating substances—tobacco smoke, smog
Diagnosis

• Timing of symptoms and definitions
  • Traditionally classified as seasonal versus perennial
    • Seasonal—due to tree pollen, ragweed, grasses, outdoor molds
    • Perennial (symptoms for $\geq 2$ hours/day for $\geq 9$ months/year)—due to dust mites, pet dander, cockroaches, indoor molds
  • Allergic Rhinitis and its Impact on Asthma (ARIA) classification (1999)
    • 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
Diagnosis

- Physical Exam
  - 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
Diagnosis

- **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
Background

- Clinic syndrome of variable airflow obstruction, airway hyper-reactivity, and cellular inflammation
- Affects 10% of adults and 15% of children
- Most patients have atopy, which is the major risk factor
- 2:1 male:female ratio in childhood, equalizes in adults
- Very similar pathogenesis to allergic rhinitis
  - Capacitance vessels versus bronchial smooth muscle
  - Hygiene hypothesis
NOTES: Association between RSV infection in infancy and development of asthma
Pathogenesis of Asthma

NOTES:
- Basement membrane thickening a characteristic, likely caused by eosinophil mediators
- Airway smooth muscle hypertrophy and hyperplasia
Asthma Triggers

- Allergens
  - Dust mites, pet dander, cockroaches
  - Trees, grasses, weeds
- Viral infections
- Medications
  - Beta-blockers
  - ACE inhibitors
  - Aspirin
- Exercise
- Cold air, hot air, fog
- Air pollution
- Hormone changes
  - Premenstrual worsening of asthma symptoms
  - Treated with high doses of progesterone
Diagnosis

- History
  - Wheezing
  - Dyspnea
  - Coughing
  - Increased mucous production
- Physical Exam
  - Wheezing, rhonchi—expiratory > inspiratory
  - Non-productive cough
  - Frequently examination is normal
Diagnosis

- Pulmonary Function Tests (PFTs)
  - 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—l lung volumes, diffusion capacities—are not particularly helpful in the diagnosis of asthma but are useful for evaluation of other lung diseases, especially restrictive diseases.
Diagnosis

**Diagrams**

1. **Expiratory flow volume loop**
   - Peak flow graph showing different curves labeled A to E.
   - Curves A to E represent different conditions.
   - Curves A and B are labeled as non-asthmatic.
   - Curves C to E are labeled as asthmatic.

2. **Inspiratory flow volume loop**
   - Vital capacity graph showing curves A to E.
   - Curves A and B are labeled as non-asthmatic.
   - Curves C to E are labeled as asthmatic.

**Subject 1:** A non-asthmatic child
- FEV\(_1\) = 3.4 (100% of predicted)
- FVC = 3.8 (100% of predicted)
- FEV\(_1\)/FVC = 0.86

**Subject 2:** An asthmatic child
- FEV\(_1\) = 2.1 (62% of predicted)
- FVC = 3.7 (97% of predicted)
- FEV\(_1\)/FVC = 0.57

**Photo source:** Nelson’s Textbook of Pediatrics
Diagnosis

- Bronchial provocation testing
  - 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
Background

- Complex group of disorders with inflammation as the major universal finding
- Affects approximately 15% of the adult population in the United States

Definitions

- **Rhinosinusitis**
  - Term now preferred over “sinusitis” since the nose is almost always involved at the same time as the sinuses

- **Acute rhinosinusitis**
  - Sudden onset
  - Duration <4 weeks

- **Subacute rhinosinusitis**
  - Duration 4-12 weeks

- **Recurrent rhinosinusitis**
  - >3 episodes of rhinosinusitis in one year

- **Chronic rhinosinusitis (CRS)**
  - Duration >12 consecutive weeks
  - Commonly associated with flares: Acute exacerbation of chronic rhinosinusitis (AECRS)
  - Further classified as with or without nasal polyposis (CRSwNP and CRSsNP, respectively)
Pathogenesis

- Bacterial
  - Superantigens
    - Staphylococcus aureus
      - Enterotoxins A and B
      - Toxic shock toxins
    - Interaction with MHC molecules and TCR
  - Biofilms
    - Found in up 80% of patients undergoing surgery for CRS
    - Polymicrobial ecosystem within a polymeric matrix that becomes irreversibly associated with an inert or living surface
Pathogenesis

- **Fungi**
  - Non-invasive colonization—obstruction of sinus ostia
  - Allergic fungal sinusitis—IgE mediated hypersensitivity

- **Allergic Rhinitis**
  - Present in up to 40-84% of patients with CRS
  - Proposed mechanism:
    - Allergy-induced inflammation leads to mucosa swelling and obstruction of the sinus ostia
Pathogenesis

- Genetic factors
  - Cystic fibrosis (CF) carrier state
    - 36% of CF patients have CRS (compared to 15% in the general population)
    - 7% of patients with CRS are CF carriers (compared to 2% in the general population)
  - Primary ciliary dyskinesia
    - Risk factor for CRSsNP but not CRSwNP

- Immunodeficiency
  - Should be considered when aggressive therapy for CRS has failed
  - In patients with refractory CRS, rates of immunodeficiency range from 3-10%
  - Most common disorders are selective IgA deficiency, common variable immunodeficiency, and hypogammaglobulinemia

- Environment irritants
  - Tobacco smoke
  - Industrial pollution
  - Also associated with allergic rhinitis and asthma
Diagnosis

- 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
Diagnosis

- Nasal endoscopy
  - Evaluate for:
    - Anatomic abnormalities
    - Neoplasms
    - Polyps
    - Rhinorrhea
    - Turbinate hypertrophy
    - Adenoid hypertrophy
  - Can obtain middle meatal cultures to direct antibiotic therapy
Diagnosis

- 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

- Edematous, semitranslucent masses
- Most polyps arise from the middle meatus and ethmoid sinuses
- Present in 19-36% of patients with CRS
- Eosinophils are abundantly present in 80% of polyps in U.S. patients (in contrast to Asian patients, in whom neutrophils predominate in nasal polyps)
- Presence linked to CF in children and asthma and aspirin sensitivity (Samter’s triad) in young adults
  - 37-48% of patients with CF have polyps

Photo source: Middleton’s Allergy: Principles and Practice
Nasal Polyps

CLASSIFICATION OF 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
Nasal Polyps

Endoscopic staging

- 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

- Nasal polyposis, asthma, and aspirin sensitivity
  - 15% of patients with polyps have aspirin sensitivity
  - 20-70% of patients with polyps have asthma
  - 40-80% of patients with aspirin sensitivity have polyps
- Symptoms usually develop following a prolonged upper respiratory infection in the third or fourth decade of life
  - Initially nasal congestion, rhinorrhea, PND, and hyposmia
  - Within a few years, bronchial asthma and nasal polyposis develop
  - Asthma and rhinitis attacks triggered by ingestion of aspirin and non-selective nonsteroidal anti-inflammatory drugs (NSAIDS)
  - Asthma is usually severe, with 50% of patients requiring chronic burst or daily oral steroid therapy
  - Course of the disease is not affected by aspirin ingestion
Samter’s Triad

- Pathogenesis
  - Not completely elucidated
  - Atopy and IgE do not appear to play a role
  - Peripheral blood and local mucosal eosinophilia
  - Elevated tissue and urine cysteinyll-leukotrienes (cys-LTs), concentrations of which increase with aspirin exposure
    - Aspirin inhibits COX 1 & 2, funneling arachidonic acid metabolism toward leukotrienes
    - Several-fold elevation of LTC4 synthase (terminal enzyme in cys-LT production) found in eosinophils of aspirin sensitive patients
    - Polymorphisms in the LTC4 synthase gene suggested as a possible etiology
Samter’s Triad

- **Diagnosis**
  - 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

- Clinical syndrome of asthma, eosinophilia, and vasculitis
- American College of Rheumatology criteria (1990)
  - Must have at least four of the six following criteria:
    - 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 tri-phasic progression
  - First: allergic rhinitis, rhinosinusitis, and asthma of variable severity
  - Second: blood eosinophilia and eosinophilic tissue infiltrates occurs
  - Third: Life-threatening, multi-organ vasculitis—cardiac, pulmonary, GI, and central nervous systems
Churg-Strauss Syndrome

- Diagnostic findings:
  - Physical exam
    - 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)
Churg-Strauss Syndrome

- **Diagnosis**
  - **Laboratory**
    - White blood cell count
      - 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
Churg-Strauss Syndrome

- **Diagnosis**
  - **Biopsies**
    - 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
Churg-Strauss Syndrome

- 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 (Glucocorticoids)

- Potent anti-inflammatory and immunosuppressant medications with many formulations—intranasal, inhaled, oral, intravenous
- Used extensively in the treatment of allergic rhinitis, asthma, chronic rhinosinusitis, nasal polyposis, Samter’s triad, and Churg-Strauss disease
Steroids (Glucocorticoids)

- Pharmacology
  - Glucocorticoid receptor (GR) resides in the cytoplasm of cells
  - After binding of glucocorticoid molecule, the complex translocates to the nucleus
  - Once in the nucleus GR and other factors modify gene transcription
    - Downregulated genes
      - Mediators of inflammation—cyclooxygenase-2, numerous cytokines, inducible nitric oxide synthase
    - Upregulated genes
      - Metabolic regulators—enzymes involved in gluconeogenesis, amino acid metabolism, etc.
<table>
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<tr>
<th><strong>CELL TYPE</strong></th>
<th><strong>FACTOR</strong></th>
<th><strong>COMMENTS</strong></th>
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<tbody>
<tr>
<td>Macrophages and monocytes</td>
<td>Arachidonic acid and its metabolites (prostaglandins and leukotrienes)</td>
<td>Mediated by glucocorticoid inhibition of COX-2 and PLA₂.</td>
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<td>Cytokines, including: interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α)</td>
<td>Production and release are blocked. The cytokines exert multiple effects on inflammation (e.g., activation of T cells, stimulation of fibroblast proliferation).</td>
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<td>Acute phase reactants</td>
<td>These include the third component of complement.</td>
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<td>ELAM-1 and ICAM-1</td>
<td>ELAM-1 and ICAM-1: critical for leukocyte localization.</td>
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<td>Endothelial cells</td>
<td>Acute phase reactants</td>
<td>Same as above, for macrophages and monocytes.</td>
</tr>
<tr>
<td></td>
<td>Cytokines (e.g., IL-1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arachidonic acid derivatives</td>
<td></td>
</tr>
<tr>
<td>Basophils</td>
<td>Histamine, LTC₄</td>
<td>IgE-dependent release inhibited by glucocorticoids.</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>Arachidonic acid metabolites</td>
<td>Same as above for macrophages and monocytes. Glucocorticoids also suppress growth factor–induced DNA synthesis and fibroblast proliferation.</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Cytokines (IL-1, IL-2, IL-3, IL-6, TNF-α, GM-CSF, interferon-γ)</td>
<td>Same as above for macrophages and monocytes.</td>
</tr>
</tbody>
</table>

ELAM-1, endothelial-leukocyte adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1.
Steroids (Glucocorticoids)

- Side effects of prolonged supra-physiologic exposure
  - Hyperglycemia
  - Hypertension
  - Peptic ulcers
  - Myopathy
  - Behavior change
    - Nervousness, anxiety
    - Psychosis
  - Cataracts
    - Dose-dependent—if taking prednisone 10-15 mg/day chronically, periodic slit-lamp exam should be performed
    - Children more at risk than adults
  - Osteoporosis
  - Osteonecrosis
  - Growth retardation in children
Allergic Rhinitis

- Therapeutic options
  - Avoidance
  - Intranasal steroids
  - Antihistamines
  - Decongestants
  - Anticholinergics
  - Cromolyn
  - Leukotriene modifiers
  - Systemic steroids
  - Immunotherapy
Allergic Rhinitis

- Therapeutic options
  - Avoidance
    - Removing offending pet from the home
    - Hypoallergenic mattress covers and pillow cases
    - Washing bedding in hot water
    - In general, hard to accomplish
Allergic Rhinitis

- Therapeutic options
  - 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
Allergic Rhinitis

- Therapeutic options
  - 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)
Allergic Rhinitis

- Therapeutic options
  - 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)
Allergic Rhinitis

- Therapeutic options
  - 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
Allergic Rhinitis

- Therapeutic options
  - 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
Allergic Rhinitis

- Therapeutic options
  - Systemic corticosteroids
    - Best reserved for patient who present with complete nasal obstruction
      - Uncontrolled allergic rhinitis
      - Rhinitis medicamentosa
Allergic Rhinitis

- Therapeutic options
  - 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
Allergic Rhinitis

- General therapeutic approach
  - 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
Asthma

- Therapeutic options
  - Bronchodilators
    - B2-agonists
    - Anticholinergics
  - Controller therapies
    - Inhaled corticosteroids
    - Systemic corticosteroids
    - Leukotriene modifiers
    - Cromolyn
    - Immunotherapy
    - Anti-IgE
Asthma

- Therapeutic options
  - B2-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
Asthma

- Therapeutic options
  - 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
Asthma

- Therapeutic options
  - 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
Asthma

- Therapeutic options
  - 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
Asthma

- Therapeutic options
  - 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
Asthma

- Therapeutic options
  - 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
Asthma

- Stepwise approach to therapy
Chronic Rhinosinusitis

- Therapeutic options—medical
  - Nasal saline lavage
  - Oral antibiotics
    - Organism-directed
    - Long-term macrolide therapy
  - Topical antibiotics
  - Topical antifungals
  - Systemic antifungals
  - Intranasal corticosteroids
  - Systemic corticosteroids
  - Leukotriene modifiers
  - Decongestants
  - Antihistamines
  - Anti-IgE
  - IVIG
Chronic Rhinosinusitis

- Therapeutic options—medical
  - 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
Chronic Rhinosinusitis

- Therapeutic options—medical
  - 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
Chronic Rhinosinusitis

- Therapeutic options—medical
  - Topical antibiotic therapy
    - Less need for surgery in 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 benefits 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
Chronic Rhinosinusitis

- Therapeutic options—medical
  - Intranasal corticosteroids
    - Effective in both CRSsNP and CRSwNP
  - Systemic corticosteroids
    - Effective in CRSsNP
    - Strong effective in CRSwNP
    - Particularly useful in short bursts for complete nasal obstruction to increase nasal patency to allow for penetration of nasal corticosteroid sprays
Chronic Rhinosinusitis

- Therapeutic options—medical
  - 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
Chronic Rhinosinusitis

- Therapeutic options—surgical
  - Functional endoscopic sinus surgery (FESS)
    - In CRS, inflammation from viral, bacterial, and fungal infections and from allergies leads to mucosal edema—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 natural ostia
Chronic Rhinosinusitis

Therapeutic options—surgical

- Functional endoscopic sinus surgery (FESS)
  - Common steps
    - 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
Chronic Rhinosinusitis

- Therapeutic options—surgical
  - 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 initially confirmed with fluoroscopy
      - A lighted guide wire 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
Chronic Rhinosinusitis

• Therapeutic options—surgical
  • Balloon Sinuplasty
    • 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, disease tissue is not removed
  • Balanced view—a good tool when used in appropriately selected patient populations
Chronic Rhinosinusitis

- Approach to therapy
  - 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
Chronic Rhinosinusitis

- Approach to therapy
  - CRSwNP
    - Similar 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
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**
  - FESS necessary in some patients due to burden of nasal polyps and inadequate response to medical treatment
Churg-Strauss Syndrome

- Therapeutic options
  - 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

- Key themes among all of these disorders
  - Inciting event that stimulates the immune system
  - Inflammation
    - TH2, IgE, eosinophil mediated
    - Atopy
    - Hygiene hypothesis
- The integrated airway hypothesis highlights the interplay among, and the interdependence of, allergic rhinitis, asthma, and chronic rhinosinusitis
- Given the inflammatory nature of these disorders, it is not surprising that corticosteroids constitute the most effective medical therapy
- Sublingual immunotherapy and balloon sinuplasty are two treatment modalities that are poised to become convenient, less painful alternatives to current therapy for patients with allergic rhinitis and chronic rhinosinusitis, respectively
References


