

Atopy

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Continuing Education Activity

Atopy is a predisposition to immunological responses against a range of antigens or allergens, leading to CD4⁺ Th2 differentiation and overproduction of immunoglobulin E (IgE). These mechanisms drive hypersensitivity reactions to diverse allergens. The primary clinical manifestations of atopy include allergic bronchial **asthma** and allergic rhinitis, often accompanied by atopic dermatitis and food allergies. Patients may exhibit 2 or more of these conditions simultaneously or sequentially. The broad clinical spectrum of atopy includes allergic conjunctivitis, IgE-mediated drug reactions, sensitivities to insect bites, urticaria, angioedema, and anaphylactic shock.

In addition, genetic factors have a significant role in atopy, with specific genes associated with increased IgE synthesis. Due to the overlapping symptoms and diverse presentations, effective evaluation and management are crucial for optimizing care in affected patients. Evaluation typically involves a thorough examination and diagnostic tests such as complete blood cell count, IgE levels, and skin prick tests. Effective management strategies are crucial due to the complexity and prevalence of atopy, aiming to optimize care for affected individuals. This activity aims to provide healthcare professionals with critical insights into the epidemiology, genetics, clinical features, and management strategies for atopy, thus enhancing the quality of care for individuals grappling with this prevalent and complex condition.

Objectives:

- Identify patients presenting with symptoms suggestive of atopy, including allergic bronchial **asthma**, allergic rhinitis, atopic dermatitis, and food allergies, through comprehensive history-taking and physical examination.
- Implement evidence-based treatment modalities for atopy, including environmental control measures, pharmacotherapy, and immunotherapy, tailored to individual patient needs and preferences.
- Select appropriate pharmacological agents, including antihistamines, corticosteroids, and monoclonal antibodies, based on the severity and clinical manifestations of atopy in each patient.
- Collaborate with multidisciplinary healthcare professionals to ensure continuity of care and comprehensive management of atopic conditions.

Introduction

Atopy is a predisposition to respond immunologically to diverse antigens or allergens, leading to CD4⁺ Th2 differentiation and overproduction of immunoglobulin E (IgE). The consequence of these cellular processes is the development of hypersensitivity reactions to allergens. The most common

manifestations of atopy include allergic bronchial **asthma**, allergic rhinitis, atopic dermatitis, and food allergies. Two or more of these clinical conditions can coexist simultaneously in an individual or at different times. Other conditions involved in atopy include allergic conjunctivitis, IgE-mediated drug allergy, insect bites, urticaria, angioedema, and anaphylactic shock.[\[1\]\[2\]\[3\]\[4\]](#)

Etiology

The etiology of atopy is unknown. Twin and epidemiological studies, along with family and animal experiments, have demonstrated that genetic factors play a crucial role in atopy by regulating IgE synthesis and its specificity to different epitopes. The inheritance of several genes results in the overproduction of IgE. Although the concept of allergies running in families is partially demonstrated in the autosomal transmission of allergies, the full inheritance pattern is believed to be multigenic.[\[5\]](#)

One theory that explains the genesis of atopy suggests the involvement of abnormal regulation by T-helper cells and suppressor T lymphocytes, which facilitate the production of IgE by plasma cells.[\[6\]\[7\]](#) Examples of genes associated with atopy are associated with chromosome 5q and cytokine gene clusters and include several interleukins (such as IL-3, IL-4, IL-5, and IL-13), CD14, granulocyte-macrophage colony-stimulating factor (GM-CSF), and β 2-adrenergic receptors.

IL-4 and IL-13 promote IgE switching, whereas IL-5 stimulates eosinophil growth and activation. β 2-adrenergic receptors regulate the contraction of bronchial smooth muscles. Chromosome 6p contains genes that code for major histocompatibility complex (MHC) class II proteins, and some of these alleles regulate T-cell responses to environmental antigens or allergens. A gene in chromosome 11q, which codes for the high-affinity IgE receptor β -subunit, mediates mast cell activation. Chromosome 12q houses genes that code for stem cell factor (affects mast cell growth and differentiation), interferon- γ (IFN- γ ; inhibits IL-4 synthesis), and STAT6 (mediates IL-4 signal transduction).

Additional genes associated with atopy include the IL-4 receptor α -chain, DPP10 (regulates chemokine and cytokine activity), ADAM33 metalloproteinase (involved in airway remodeling), and CD80/CD86 (located in 3q) and RANTES (in 17q) are genes thought to be involved in atopy. Finally, PHF11 in 13q encodes for a transcriptional regulator involved in the clonal expansion of B cells and immunoglobulin expression.[\[8\]\[9\]\[10\]\[11\]](#) Nonspecific triggers of **asthma** include infections (such as viral respiratory infections), climatic factors (such as ozone, cold air, and SO₂), physiological factors (such as exercise and hyperventilation), and ingestants (such as aspirin and nonsteroidal anti-inflammatory drugs [NSAIDs]).

The list of occupational allergens causing IgE-mediated allergic **asthma** includes animal products (obtained from cows, pigs, mice, dogs, cats, and horses), insect dust (from mealworms, storage mites, cockroaches, bees, and flies), plant products (such as fruits, vegetables, seeds, leaves, pollens, flours, plant, grain, and cotton dust, castor beans, tobacco, and weeping fig). Other allergens include gums and extracts (such as western red, California redwood, and exotic woods), microbial agents (fungal allergens, alginates, protozoa, bacteria, and fungi), enzymes (such as papain, hog trypsin, pancreatic extracts, subtilisin, and pineapple bromelain), therapeutic agents (such as penicillins, tetracycline, cephalosporins, sulfonamides, and spiramycin), sterilizing agents (such as chloramides), inorganic chemicals (such as metal fumes and salts, aluminum, cobalt, fluoride,

nickel, platinum, vanadium, and zinc) and organic chemicals (such as amines, anhydrides, and azodicarbonamide).[10]

Epidemiology

Atopy affects a significant portion of the global population, with a prevalence estimated between 10% and 30% in developed countries. Approximately 80% of atopic individuals have a family history of allergies, indicating a genetic component to the susceptibility to atopic diseases. However, research suggests that atopy results from the interaction of multiple genes with moderate effects rather than 1 or 2 dominant causative genes.[12] Additionally, monozygotic twin studies have demonstrated only a 50% concordance rate.

Allergic rhinitis affects 10% to 12% of Americans. The prevalence and morbidity rates vary across the country due to the geographic distribution of allergens, the most common being dust mites and allergenic plants. Both sexes are equally affected.

The prevalence of bronchial **asthma** varies worldwide. This condition affects 5% of the population in Western countries and causes over 3,000 deaths annually in the United States. Mortality and morbidity rates are increasing despite substantial advances in immunotherapy.[13][14] In 2014, 8.4 million children in the United States were living with **asthma**, with 11.1% of these children residing in low-income, urban areas.[15]

Pathophysiology

The pathophysiology of atopy characteristically involves mast cell activation. Antigen binding to IgE causes cross-linking of Fc epsilon RI proteins on mast cells. This cross-linking activates protein tyrosine kinases (Lyn and Syk), which, in turn, cause activation of a mitogen-activated protein kinase (MAPK) cascade and phosphatidylinositol-specific phospholipase C. This enzyme catalyzes the cleavage of PIP₂ into IP₃ and DAG. Inositol trisphosphate (IP₃) causes the release of intracellular calcium from the endoplasmic reticulum. DAG and calcium activate protein kinase C (PKC), which phosphorylates substrates such as myosin light chain molecules, thereby leading to degradation and release of preformed mediators.

MAPKs and calcium activate the cytosolic enzyme phospholipase A₂, which stimulates the synthesis of lipid mediators, including PGD₂, LTC₄, LTD₄, and LTE₄. Ras/MAPKs trigger cytokine gene expression in the presence of calcium and PKC, leading to the release of tumor necrosis factor (TNF) and other cytokines such as IL-4, IL-5, IL-6, and IL-13. The release of lipid mediators, cytokines, and histamine induces an inflammatory response.[16][17][18]

Basophils and mast cell mediators include biogenic amines, enzymes (preformed and stored in granules), cytokines, and lipid mediators, primarily newly synthesized after cell activation. Histamine, other biogenic amines, and lipid mediators induce vascular leakage and intestinal hypermotility, which are components of immediate allergic responses. Cytokines and lipid mediators increase inflammation as part of a late-phase reaction. Activated eosinophils release enzymes and toxic cationic proteins that damage parasites and host cells. Some eosinophil granule enzymes are theorized to cause tissue damage in chronic allergic disorders.[19][20][21]

Defective lymphocyte regulation is a possible explanation for allergic dermatitis. Delayed hypersensitivity skin test responses to allergens, in vitro lymphocyte responses to mitogens or allergens, and autologous mixed lymphocyte reactions are associated with allergic dermatitis. Concurrently, increased susceptibility to the vaccinia virus, molluscum contagiosum, warts, herpes simplex virus, and dermatophyte skin infections can occur due to a defect in the T-lymphocyte effector mechanism, contributing to the pathophysiology of atopic dermatitis. Furthermore, it is suggested that an abnormal or defective CD4⁺ helper T-cell population may be responsible for the failure of CD8⁺ T cells to function as immunosuppressors of IgE production.[\[22\]](#)[\[23\]](#)

Histopathology

Atopy presents with a characteristic "wheal-and-flare" skin reaction, which is a response to an allergen-stimulated release of mediators from mast cells. This reaction involves local blood vessels dilating and becoming leaky to proteins and fluids, resulting in localized swelling and redness.[\[24\]](#)

Histologically, bronchial **asthma** is characterized by excessive mucus production, increased submucosal inflammation (involving lymphocytes and eosinophils), a thickened basement membrane, and smooth muscle hypertrophy.

History and Physical

The following atopic diseases involve a history of atopy (hypersensitivity to numerous allergens and elevated IgE serum levels). Patients are typically symptom-free in the absence of exposure. Some critical factors associated with these conditions are listed below.

Atopic Rhinitis

- Nasal congestion
- Rhinorrhea
- Sneezing
- Nasal itching
- Post-nasal drainage
- Dry cough
- Ocular symptoms
- Rhinoscopy, showing a pale, swollen nasal mucosa with watery secretions
- Hyperemic and edematous conjunctivae

Allergic Asthma

- Allergic **asthma** may begin at any age
- Frequent episodes of wheezing and dyspnea
- Chest tightness

- Coughing, especially nocturnal in children, with thick and tenacious sputum
- Fatigue
- Malaise
- Increased use of accessory muscles
- Lung fields may produce hyper-resonant sounds
- Diminished breath sounds may be heard
- Rhonchi sounds
- Wheezing
- Prolonged expiratory phase

Atopic Dermatitis

- Atopic dermatitis usually begins in infancy
- Pruritus is more pronounced at night and exacerbated by irritants such as wool
- Often has a strong family history of atopy
- Scratching and rubbing cause the typical eczematous skin eruption to flare
- Exacerbations may occur following ingestion of allergenic foods
- Dry and scaly skin
- Active skin lesions present with prurigo and erythema
- Chronic lesions become thickened and lichenified
- Distribution of lesions varies with age, with the forehead and cheeks commonly affected during childhood

Food Allergies

- Rhinoconjunctivitis
- **Asthma**
- Hypotension
- Arrhythmias
- Nausea and vomiting
- Abdominal cramping
- Diarrhea
- Usually causes systemic anaphylaxis
- Respiratory symptoms alone are rare

Evaluation

The evaluation of immediate hypersensitivity includes obtaining a complete blood cell count, an IgE level, and a skin prick test.[\[25\]](#)

Quantitative Serum Immunoglobulins

- Immunoglobulins such as IgM, IgG, and IgA.

Total Leukocyte Count and Differential

- Hemoglobin levels, which may be decreased in autoimmune hemolytic anemia.
- Eosinophilia.
- Lymphocyte studies, including CD4/CD8 count and suppressor T-cell count, which may be lower than the standard value.

Allergic Tests

- Skin prick tests that utilize various allergens from animals, plants, food, pathogens, and environmental pollutants.
- A radioallergosorbent test (RAST) to determine specific IgE antibodies.

Other Tests

- Serum protein electrophoresis to rule out IgE myeloma.
- Stool examination to assess for intestinal parasitism.
- Appropriate exclusion diet and blinded provocations for diagnostic clarification of food allergies.
- Chest x-ray to evaluate for bronchial **asthma**.

Treatment / Management

Allergic Rhinitis

Treating allergic rhinitis involves environmental measures to prevent allergen exposure, drugs, and desensitization. As with other allergic diseases, prophylactic treatment by avoiding allergens is the most effective means of management. However, avoidance is not always feasible, so medications are often necessary for symptom control.

Environmental measures involve avoiding an allergen based on clinical history. A positive skin test or RAST alone is not sufficient. Environmental control also involves removing household pets, frequent dusting to minimize house dust, and avoiding toys and other objects that collect dust. Using air-cleaning devices to reduce airborne allergens may be helpful. Pollen and outdoor mold growth must be prevented.

Antihistamines are the most commonly used drugs in allergic rhinitis and should be administered cautiously to avoid adverse effects. Newer nonsedating antihistamines are available that cause fewer adverse effects. Orally administered nasal decongestants may be helpful in

combination with antihistamines. Antihistaminic eye drops are commonly used for treating allergic conjunctivitis. Treatment with nasal cromolyn spray 4 times daily is beneficial and causes no immediate or long-term toxicity. Systemic corticosteroids effectively reduce allergic rhinitis symptoms but should only be used in the short term. Allergic rhinitis is a chronic and benign condition. Desensitization (allergen injection therapy) is recommended for patients whose symptoms are uncontrolled despite appropriate previous therapeutic measures.[\[26\]](#)

Allergic Asthma

This condition manifests as atopy localized to the bronchus, where mediators such as histamines, leukotrienes, and cytokines (IL-4, IL-5, IL-13, and TNF), as well as eosinophil chemotactic factors are released. Symptomatic **asthma** treatment aims to control the hyperirritable bronchial mucosa using environmental measures, drugs, and other therapies. Treatment of bronchial **asthma** includes environmental control similar to atopic rhinitis management.

Sympathomimetic β -adrenergic bronchodilators are used to abort acute attacks and for long-term management. Albuterol, metaproterenol, pirbuterol, and isoetharine are selective β -adrenergic bronchodilators administered via aerosol inhalation. Theophylline is a potent bronchodilator combined with sympathomimetic medication and can be administered 250 to 500 mg during an acute **asthma** attack. Epinephrine can be given subcutaneously in a 0.2 to 0.5 mL dose.

Glucocorticoids are effective in treating allergic **asthma**; a typical dose is 30 to 60 mg. However, glucocorticoids should be reserved for **asthma** refractory to other therapies.[\[15\]](#)

Cromolyn sodium can be administered using a 20-mg (metered-dose) inhaler for long-term prophylactic therapy, although it cannot abort an acute attack. Antibiotics may be prescribed if secondary bacterial bronchitis or bronchopneumonia is present. Hydration and expectorants are effective for clearing thick sputum.

Desensitization is equally effective for allergic rhinitis and allergic **asthma**. One example is an injection treatment for pollen hay fever. Antileukotrienes, such as montelukast and zafirlukast, can be administered in allergic **asthma** and atopic rhinitis.

Atopic Dermatitis

Atopic dermatitis is a chronic skin disease requiring proper skin care, environmental control, drugs, and allergen avoidance. The most effective preventive measure for pruritis is non-irritating topical lubricants. Topical steroids are effective for milder skin involvement. For eczema, systemic corticosteroids are initiated at a high dose and tapered until a therapeutic effect is achieved. Oral antihistamines can control itching. Frequent bathing and the use of irritating fabrics and detergents are discouraged. If infection occurs, an appropriate antibiotic is necessary.[\[27\]](#)

Food Allergies

Treating a food allergy requires strict elimination of the offending allergen. Having an emergency care plan and a written anaphylaxis action plan is paramount. Carrying a form of self-injectable epinephrine and wearing a medical alert bracelet aids healthcare professionals during an acute attack. The most common pediatric allergens include cow's milk, soy, wheat, eggs, and peanuts, accounting for 91% of reactions. The most common allergens for adults include fish, shellfish, peanuts, tree nuts, eggs, fruits, and vegetables.[\[28\]](#)

Immunotherapy for atopic conditions such as allergic rhinitis, **asthma**, and atopic dermatitis has seen significant advancements in recent years, with monoclonal antibodies and cytokines playing crucial roles.

Monoclonal antibodies are laboratory-produced molecules designed to mimic the natural immune mediators that aid the body in fighting off harmful pathogens. In atopic conditions, these antibodies target specific proteins or cells involved in the allergic response, as mentioned below.

- **Omalizumab:** This monoclonal antibody targets IgE—a key mediator in allergic reactions. By binding to IgE, omalizumab prevents it from triggering the release of inflammatory chemicals, thereby reducing allergic symptoms.
- **Dupilumab:** This drug targets IL-4 receptor-alpha (IL-4Rα), which is involved in the signaling pathway responsible for allergic inflammation. Dupilumab is approved for the treatment of moderate-to-severe **asthma** and atopic dermatitis.
- **Mepolizumab, reslizumab, and benralizumab:** These monoclonal antibodies target IL-5, a cytokine involved in the production and activation of eosinophils, which contribute to allergic inflammation. These medications are indicated for the treatment of severe eosinophilic **asthma**.

Cytokines are small proteins secreted by various cells in the immune system to regulate immune responses. Several cytokines are involved in the pathogenesis of atopic conditions:

- **Interleukins:** IL-4, IL-5, IL-13 are key cytokines involved in allergic inflammation. IL-4 promotes IgE production, IL-5 is crucial for eosinophil activation, and IL-13 contributes to airway hyperreactivity and mucus production.
- **Tumor necrosis factor-α:** Although primarily associated with inflammatory conditions such as rheumatoid arthritis, TNF-α has also been implicated in the pathogenesis of severe **asthma**.
- **Interferon-γ:** IFN-γ plays a role in regulating the balance between Th1 and Th2 responses. Dysregulation of this balance is implicated in allergic diseases.

Immunotherapy

Allergy immunotherapy, often called desensitization or allergy shots, involves administering progressively increasing doses of allergens to reduce the allergic response over time and induce immune tolerance to specific allergens. This therapy can be administered via subcutaneous injections or sublingual tablets or drops.

Overall, monoclonal antibodies targeting specific cytokines or cells involved in allergic inflammation have shown promise in treating atopic conditions, offering new avenues for personalized and targeted therapy. Additionally, allergy immunotherapy remains essential for long-term management, particularly in cases where allergen avoidance or conventional pharmacotherapy is insufficient. [\[29\]](#)[\[30\]](#)[\[31\]](#)

Differential Diagnosis

Differential Diagnoses of Diseases Associated with Elevated Serum IgE

- Allergic bronchopulmonary aspergillosis
- Parasitic diseases
- Immunodeficiency with ataxia-telangiectasia
- Hyper-IgE syndrome
- Wiskott-Aldrich syndrome
- IgE myeloma
- Thymic aplasia
- Graft-versus-host reaction

Differential Diagnoses of Atopic Rhinitis

- Chronic nonallergic (vasomotor) rhinitis
- Rhinitis medicamentosa
- Infectious rhinitis
- Vernal keratoconjunctivitis

Differential Diagnoses of Allergic Bronchial Asthma

- Pulmonary emphysema
- Acute bronchiolitis
- Cystic fibrosis
- Foreign body aspiration
- Airway obstruction caused by a congenital vascular anomaly
- Cardiac **asthma** caused by left ventricular failure
- Carcinoid tumors

Differential Diagnoses of Atopic Dermatitis

- Localized neurodermatitis (lichen simplex chronicus)
- Allergic or irritant contact dermatitis
- Seborrhea and dermatophytoses
- Pompholyx (dyshidrosis)

Pertinent Studies and Ongoing Trials

Research relevant to atopy includes:

- A recent meta-analysis demonstrated that multiple-strain probiotics are particularly effective for preventing eczema in children.[\[32\]](#)
- A study indicated that the subcutaneous administration of a single dose of tralokinumab (150-600 mg), a human monoclonal antibody in clinical development for atopic dermatitis and **asthma**, was well tolerated in healthy Japanese volunteers. This phase I trial, conducted on healthy Japanese volunteers, used a single-blind, randomized, placebo-controlled, and single ascending-dose design. The findings demonstrated the well-tolerated nature of tralokinumab, supporting the selection of a 300-mg dose for Japanese patients with **asthma**.[\[33\]](#)
- Epicutaneous immunotherapy (EPIT) has emerged as an effective treatment for food allergies. By activating the skin's natural desensitization pathway, EPIT elicits a progressive and sustained response. This form of immunotherapy offers promising alternatives to traditional atopic immunotherapy methods, as it is less invasive and associated with a reduced risk of systemic reactions compared to oral immunotherapy.[\[34\]](#)
- Oral immunotherapy involves the gradual administration of escalating doses of a food antigen to individuals with food allergies, aiming to induce a state of desensitization. However, concerns persist regarding its tolerability, efficacy, and safety, prompting ongoing evaluation.[\[35\]](#)
- Randomized placebo-controlled studies have demonstrated that ciclesonide, an inhaled corticosteroid, is effective in initiating and maintaining disease control in individuals with persistent **asthma** across all disease severities.[\[36\]](#)
- Randomized controlled trials investigating the use of vitamin D as a treatment for acute respiratory infections have shown promising outcomes. Vitamin D supplementation is safe and effective in preventing acute respiratory infections, particularly in individuals who are initially deficient in vitamin D.[\[37\]](#)

Prognosis

Individuals with atopy typically have a lifelong predisposition to allergic reactions, as the condition is incurable. However, the specific manifestations of atopy often evolve over time. Atopic dermatitis generally has a more favorable prognosis, with immunotherapy showing moderate effectiveness in managing symptoms. The prognosis for allergic **asthma** can vary based on factors such as the persistence of the allergen triggering the condition, levels of IgE in the blood or tissues, and the patient's genetic predisposition.

Systemic anaphylaxis arises from an IgE-mediated reaction that affects multiple tissues simultaneously. The causative allergen triggering this reaction can be insect venom, food, or medication. Anaphylaxis can be life-threatening and can be evoked by even a tiny amount of allergen. Prompt medical attention is crucial, as the prognosis for anaphylaxis is often very poor.

Complications

Complications of Allergic Rhinitis

- Sinusitis
- Otitis media
- Nasal polyps
- Apnea

Complications of Allergic Bronchial Asthma

- Pneumothorax
- Subcutaneous emphysema

Complications of Atopic Dermatitis

- Secondary infections caused by *Staphylococcus*
- Eczema herpeticum
- Secondary contact dermatitis (due to antibiotics)
- Hand dermatitis (excessive hand washing)
- Ophthalmic complications (including atopic keratoconjunctivitis, keratoconus, and atopic cataracts)

Anaphylaxis

- Anaphylaxis is a medical emergency that can lead to acute, life-threatening respiratory failure.
- This is an IgE-mediated reaction with massive and rapid release of histamines and leukotrienes from mast cells.
- In severe cases, acute laryngeal edema, bronchospasm, hypotension, cyanosis, and shock are present.
- Drugs and additives known to cause anaphylactoid reactions include NSAIDs (such as aspirin, aminopyrine, fenoprofen, flufenamic acid, ibuprofen, indomethacin, and naproxen), opioids (such as morphine, codeine, and meperidine), mannitol, radiographic iodinated contrast media, dextran, curare, and d-tubocurarine.
- Anaphylactoid reactions should be treated similarly to anaphylaxis.[\[38\]](#)[\[39\]](#)[\[40\]](#)

Consultations

The following specialists should be consulted for atopic cases:

- Allergy specialist
- Dermatologist

- Pulmonary physician
- Immunologist

Deterrence and Patient Education

Patient education is crucial. For pediatric patients, this involves educating parents, especially to identify and remove triggers. Patients should also receive education on managing these reactions initially and when to seek medical aid.

Enhancing Healthcare Team Outcomes

Atopy should be recognized early; it often requires early identification by the pediatrician and early referral to an allergy specialist for disease confirmation and management. Consultation with pulmonology and dermatology may be considered. The primary care provider, specialty-trained nurses, and pharmacists should educate the patient on keeping records of allergens and carrying an epinephrine injector with them. All healthcare professionals must collaborate as an interprofessional team to guide cases to the best possible outcome. Patients who have experienced an anaphylactic reaction should also be advised to wear an ID bracelet.

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