ALLERGY

DEFINITIONS

Allergy is a pathologically altered, enhanced immunological reactivity to antigens (allergens).

Atopy is a propensity to develop one or more IgE mediated diseases (bronchial asthma, allergic, rhinitis, eczema), often in familiar clustering. Atopy can be inherited (with the 11th chromosome)

Immune reactions involved in allergic diseases

Type I immunoreaction

1. Initial sensitization: first encounter of antigen → formation of specific IgE IL-4 → production of IgE

Binding of IgE to high affinity FceR of mast cells and basophils

2. Allergic phase: second and further encounters with the antigen → combination of antigen with IgE

→ degranulation of basophils and mast cells

→ release of mediators by IgE or other mechanisms (early, late phases)

Type III, IV immunoreactions

Mediators released during degranulation of mastocytes

<table>
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<tr>
<th>Chemotactic mediators</th>
<th>Neutrophil chemotactic factor (NCF)</th>
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<tr>
<td></td>
<td>Eosinophil chemotactic factor A (ECF-A)</td>
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<tr>
<td></td>
<td>Leukotriene B4 (LTB4)</td>
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<tr>
<th>Proteolytic enzymes</th>
<th>Histamine</th>
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<tr>
<td></td>
<td>Tryptase</td>
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<td>Kininogenase</td>
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<tr>
<th>Spasmogenic mediators</th>
<th>Histamine</th>
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<tr>
<td></td>
<td>Prostaglandin D2 (PGD2)</td>
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<td></td>
<td>Leukotriene C4 (LTC4)</td>
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<tr>
<td></td>
<td>Leukotriene D4 (LTD4)</td>
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<td></td>
<td>Platelet activating factor (PAF)</td>
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<th>Other mediators</th>
<th>Heparin</th>
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Preformed mediators

De novo synthetized mediators

LIST OF ALLERGIC DISEASES

Systemic: Anaphylaxis, serum sickness

Skin and mucous membranes: Atopic dermatitis, urticaria, angioedema, eczema, contact dermatitis, allergic vasculitis

Upper respiratory tract: Allergic rhinitis, nasal polyps, sinusitis

Lung: Bronchial asthma, hypersensitivity pneumonitis (extrinsic allergic alveolitis), allergic bronchopulmonary aspergillosis
**GI tract:** Food allergy

**Drug allergy** can be systemic or can involve several organs: skin, lung, liver, kidney, bone marrow and blood cells.

**The diagnosis of allergic diseases**

1. **History and physical examination**

2. **In vivo diagnostic procedures:**

   **Skin tests**
   - Immediate type: Prick test
   - Immediate type with late phase reaction: Arthus reaction
   - Late phase: epicutaneous, intracutaneous

   **Other provocation tests:**
   - Nasal, conjunctival provocation

   **Bronchial provocation tests:**
   - Aspecific (histamine, acetylcholine, KCl, adenosine), exercise-induced, Allergen-specific (occupational materials)
   - Broncholytic tests (with β-mimetics)

   **Food challenge:** DBPCFC: double blind placebo-controlled food challenge

3. **In vitro diagnostic procedures:**

   **Determination of IgE and IgG4 concentrations:**
   - Total and specific IgE, IgG4 - radio-allergosorbent test (RAST)
   - Determination of other mediators: ECP

   **Determination of immune activation in presence of allergen:**
   - Lymphoblastic transformation (LBT)
   - Chromatin activation method

   **Determination of mediators in body fluids**
   - Eosinophils, ECP, PAF in bronchoalveolar lavage (BAL), nasal and conjunctival fluids
   - Fecal IgE, allergen-specific IgE, IgG, ECP

**ANAPHYLAXIS**

**Definitions**

Anaphylaxis is a life-threatening response of a sensitized individual, which appears within minutes after administration of specific antigen which manifests by respiratory distress, vascular collapse or shock.
**Anaphylactoid reaction:** systemic reaction with the same symptoms as anaphylaxis, but are not due to an IgE-dependent mechanism and are usually not immune.

**Pathomechanism**
Type I immunoreaction

**Agents causing anaphylaxis**

**Proteins**
- Heterologous proteins in the form of antiserum (mainly horse and rabbit serum): tetanus, diphtheria antitoxin, anti-lymphocyte globulin
- Venoms: Hymenoptera
- Pollens (ragweed, grass, etc.), pollen extracts
- Foods (eggs, seafood, nuts, grains, beans, cottonseed oil, chocolate)
- Human proteins: serum proteins, seminal fluid
- Hormones: insulin, ACTH, vasopressin, parathormone
- Enzymes: trypsin, penicillinase

**Haptens** and other low MWT substances
- Antibiotics: penicillins, sulfonamides, cephalosporins, tetracyclines, amphotericin B, nitrofurantoin, aminoglycosides
- Local anesthetics: lidocaine, procaine, etc.

**Polysaccharides:** Dextran, iron dextran.

**Other** drugs causing anaphylactoid reaction: NSAID-s, radiographic contrast materials.

**Clinical manifestations**

**Onset within seconds to minutes after induction of the antigen!**
- Circulatory system: skin erythema, feeling of warmth and/or impending doom, light-headedness, myocardial ischemia, ventricular arrhythmias, vascular collapse, shock.
- Upper and/or lower airway obstruction: Laryngeal edema: "lump" in the throat, hoarseness, stridor; Lung: tightness in the chest, shortness of breath, wheezing, pO2 ↓, pCO2 ↑
- Cutaneous: urticaria, angioedema. May coalesce to giant hives. Swelling of face, eyes, lips, tongue, pharynx or extremities.
- Gastrointestinal: nausea, vomiting, abdominal cramps, diarrhea.
- Central nervous: delirium, seizures.

**Diagnosis**
- Accurate history: timing, RAST.

**Differential diagnosis**
- Acute myocardial infarction, pulmonary embolism, acute asthma, hereditary angioedema, cold urticaria, seizure disorder, toxicologic response, vasovagal reaction.
- Anaphylactoid or idiosyncratic response, eg. chemical mast-cell degranulating agent (opiates, tubocurare, dextran, sulfobromophthalein), NSAID-s in asthma (PG/LT imbalance when COX is inhibited).
- Transfusion reaction (especially in IgA deficiency: IgG type anti-IgA antibody → complement activation → secondary mast cell degranulation)
TREATMENT
EARLY RECOGNITION IS MANDATORY!

- Mild symptoms - pruritus, urticaria: 0.2-0.5 mL (0.01 ml/kg) of 1:1000 epinephrine IM, if needed, repeat at 3-20 min intervals for severe reaction.
- If an extremity was injected - prompt application of a torquinet proximal to the reaction site, administration of 0.2 mL of 1:1000 epinephrine into the site; remove the insect sting without compression!
- If hypotension occurs - 5 mL of epinephrine 1:10,000 IV
- OR: infusion of epinephrine 1:50,000
  volume expanders, vasopressor agents (e.g. dopamine 2-20 mg/kg/min)

If epinephrine fails - consider hypoxia due to airway obstruction or cardiac arrhythmia

- oxygen via a nasal catheter
- intermittent positive pressure breathing of oxygen with 0.5 mL isoproterenol in 1:200 saline
- endotracheal intubation or tracheostomy is mandatory, if hypoxia is progressive!
- intravenous line, Swan-Ganz catheter
- The Epinephrine Auto-Injector (EpiPen)

Ancillary agents:

- antihistamines, eg. diphenhydramine 50-80 mg IM or IV (for urticaria-angioedema)
- methylxantines, eg. aminophylline 0.25-0.5 g (6 mg/kg loading dose, followed by 0.5-1 mg/kg/h) IV, inhaled b2 sympathomimetics (for bronchospasm)
- corticosteroids (eg. prednisolone 100 mg IV) - not effective for the acute event.

PREVENTION

- Avoidance of allergen (eg. food, drug, pollen)
- Medic-Alert bracelet
- Select an other agent or procedure
- Skin test - before the administration of highly allergenic materials: (eg. horse serum, allergenic extracts)
- Since even a skin or conjunctival test can produce a serious reaction, a scratch test should be done first!
- Hyposensitization is mandatory in case of the Hymenoptera venom.

INSECT STING ALLERGY

Type I immunoreaction to venoms of insects in the Hymenoptera order:

- Bees: honeybees, bumblebees
- Vespids: yellow jackets, hornets, wasps

Epidemiology

- Incidence of immediate hypersensitivity: 3%.
- Positive skin test is present in more than 20%
- Familial clustering → inherited predisposition

Etiology: major allergen: phospholipase A
Pathogenesis
Venom → IgE (less than 3 months - 25 years) and
→ IgG (lasting only a few months, high titers in beekeepers, protective against anaphylaxis)

Sensitization can occur at any time in life, even after uneventful stings

Clinical manifestations
- Systemic sting reactions: anaphylaxis. Systemic reactions can be fatal!
- Urticaria-angioedema, dizziness-hypotension, dyspnea-wheezing, throat tightness-hoarseness, loss of consciousness
- Large local reactions: area of induration increasing (up to 24-48 hours), may lead to immobilization of limb

Diagnosis
- History
- Skin test: Prick 0.1-1-10-100 mg/ml, then IC 0.1-1-10-100 mg/ml,
- RAST: less sensitive, but equally accurate when positive

Treatment
- Epinephrine 1:1000, 0.3-0.5 ml sc, repeated twice at 10 min intervals, if necessary. Patients should always carry a kit with 1-2 loaded doses of epinephrine (Epi-pen)!
- Antihistamines and glucocorticoids are useful only for the cutaneous and the late phase reactions.
- Maintenance dose: 100 mg monthly for at least 6 months, than at 6-8 week intervals for 5 years.
- Hyposensitization is not indicated in the absence of a positive skin test or RAST

URTICARIA AND ANGIOEDEMA

Definitions
Urticaria is an itching, elevated, erythematous, well-circumscribed, pruritic wheals (hives), or serpiginous exanthem, usually surrounded by erythema. Its center blanches on pressure. It appears on any epidermal and mucosal surfaces, usually on the trunk, extremities, sparing the palms and soles. Caused by subcutaneous or intradermal leakage of fluid.

Angioedema is a brawny nonpitting edema, usually without well-defined margins, involving the epidermal and mucosal surfaces: lips, tongue, eyelids, genitals, dorsum of the hands. Caused by leakage of fluid in deeper (dermal, subdermal) layers.

Both are self-limited, evanescent in nature. Urticaria + angio-edema: 50%, urticaria alone: 40%, angioedema alone: 10%

Acute urticaria, angioedema: lasting < 6 weeks

Chronic urticaria, angioedema: > 6 weeks

Pathogenesis and pathology
- Type I immunoreaction: IgE → mast cell degranulation
• C3a, C4a, C5a, C2b \( \rightarrow \) PG, HETE, LTC, LTD, LTE, PAF
• bradykinin, SP
• Histology: subcutaneous edema, flattened rete pegs, widened dermal papillae, swollen collagen fibres, increased number of cutaneous mast cells.
• In chronic urticaria: ↑ CD4, ↑ Eo, few Mo/Mϕ
• In a minority: leukocytoclastic vasculitis

Classification of urticaria with angioedema

1 IgE-dependent
   a. Atopic diathesis
   b. Specific antigen sensitivity (pollens, foods, drugs, fungi, moulds, Hymenoptera venom, helminths)
   c. Physical: dermographism; cold; light; cholinergic; vibratory; exercise-related

2 Complement-mediated
   a. Hereditary angioedema: type 1; type 2
   b. Acquired angioedema: type 1; type 2
   c. Necrotizing vasculitis
   d. Serum sickness
   e. Reactions to blood products

3 Nonimmunologic
   a. Direct mast cell-releasing agents: opiates; antibiotics; curare, d-tubocurarine; radiocontrast media
   b. Agents which presumably alter arachidonic acid metabolism: aspirin and NSAID-s; azo dyes and benzoates

4 Idiopathic

Differential diagnosis
contact sensitivity, atopic dermatitis, erythrogenic porphyria, photoallergic reactions

Therapy
• Antihistamines, nifedipine, ketotifen, steroids,
• For management of acute very severe urticaria: epinephrine 1:10000, 0.2-0.3 ml SC
• Anti-IgE monoclonal antibody (omalizumab)

HEREDITARY ANGIOEDEMA (HAE)
Defect of C1-INH gene on chromosome 11. Inheritance: AD: affects 50% of offsprings, M/F=1:1

Symptoms
Can start at any age. Is mild in childhood, become more severe at the time of puberty.

Angioedema on extremities and genitalia, severe abdominal pain, respiratory obstruction \( \rightarrow \) asphyxiation. Attacks are sporadic: local trauma, pressure (50%), emotional stress (50%), erythema marginatum (33%). Progressively more severe symptoms over 1.5 days, then regression over a similar time period. High incidence of autoimmune diseases, endocrinopathies, granulomatous bowel disease, arthritides, SLE.

Pathogenesis
• HAE type I (80%): ↓ C1-INH level
• HAE type II (15%): C1-INH is present, but is non-functional
• Loss of control of 1) complement activation, 2) kinin, 3) fibrinolytic, 4) intrinsic clotting pathways.

Diagnosis
Low levels of C1-INH, ↓ C4/C2 (both during and between attacks), C3 is normal; C1 can also be normal

Treatment
In acute attacks:
• Purified C1-INH (Berinert H)
• Epinephrine 1:1000 in nebulizer, 0.2-0.3 ml sc, repeated 3 times in q 20-30 mins.
• Endotracheal intubation, tracheostomy.

For long-term therapy:
• Fresh frozen plasma.
• Acetylated androgens: danasol (200-400/d), stanozol, methyltestosterone (10-30 mg/d)
• ε-aminocapric acid

ECZEMA (DERMATITIS)

Definition
Eczema is an inflammatory response of the skin to multiple exogenous and endogenous agents.

Clinical forms
Known causes: Contact dermatitis (irritant, allergic contact), photodermatitis (allergic, contact), drug-induced, infectious, infectious, dermatophytid, autosensitization, xerotic eczema.

Unknown causes: Atopic, stasis dermatitis, lichen simplex chronicum (neurodermatitis), nummular, seborrheic, dyshidrotic, nonspecific eczema.

Allergic contact dermatitis: Caused by chemical agents that elicit type IV DTH on skin. Contact precedes rash by 2 or more days; site and configuration of eczema reaction conforms to site of contact with exogenous substances (plants, medicaments, cosmetics, metals).

Photoallergic dermatitis: UV light exposure plus topical or systemic substances induce type IV DTH. Eczematous reaction in sun-exposed areas of skin with sharp "cut-off" borders.

Atopic eczema: Hereditary disposition in association with familial tendency for asthma and allergic rhinitis. Eczematous reaction often localized to face, neck, antecubital and popliteal areas.

Diagnosis
History, epicutaneous (patch), intracutaneous skin tests, IgE, RAST

Therapy
Avoidance of allergen, wet dressings, topical steroids, emollients, systemic antihistamines
ALLERGIC RHINITIS AND CONJUNCTIVITIS

Definition
Allergic rhinitis is an IgE-mediated inflammatory disease of the nasal mucous membranes. Frequently associated with bronchial asthma and eczema. Incidence: 5-10%

Etiology
- **Seasonal**: tree, grass pollens, ragweed.
- **Perennial**: mites (Dermatophagoides pteronyssimus, D. farinae), animals (danders, saliva, urine), mould spores

Symptoms
- Rhinitis: nasal stuffiness, paroxysms of sneezing, profuse mucous secretion, frequent itching of the nose, eyes, posterior pharynx, periorbital swelling.
- Conjunctivitis: excessive tearing, mucoid discharge, itching
- Constitutional: fatigue, malaise, anorexia, irritability.
- Allergic "shiners", allergic "saluting".

Complications
Nasal polyps, serous otitis (hearing loss), chronic sinusitis (nocturnal cough, fever, headache)

Diagnosis
History, nasal examination, skin test, RAST, FAST, ELISA.

Differential diagnosis
Infectious, eosinophilic non-allergic, drug-induced, vasomotor rhinitides.

Treatment
1. **Avoidance of offending allergens**
2. **Symptomatic treatment**
   - antihistamines (1st, 2nd generation drugs)
   - nasal decongestants (α-agonists) - only for a few days!
   - cromolyn sodium
   - topical corticosteroids
3. **Immunotherapy (hyposensitization)**

BRONCHIAL ASTHMA

Definition
Asthma is a syndrome characterized by airflow obstruction that varies both spontaneously and with specific treatment. Chronic airway inflammation causes airway hyperresponsiveness to a variety of triggers, leading to airflow obstruction and respiratory symptoms including dyspnea and wheezing.

Prevalence
The prevalence of asthma has increased markedly over the past 30 years. In developed countries, approximately 10% of adults and 15% of children have asthma. Considerable overlap with allergic rhinitis
Common airways - ARIA

Types of asthma

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<tr>
<th>EXTRINSIC</th>
<th>INTRINSIC</th>
<th>OCCUPATIONAL</th>
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<tr>
<td>Atopy</td>
<td>No atopy</td>
<td>Adult-onset</td>
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<tr>
<td>Childhood-onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic rhinitis and/or eczema</td>
<td>Allergen tests are negative</td>
<td>Chemicals: toluene diisocyanate, trimellitic anhydride</td>
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<tr>
<td>Elevated IgE</td>
<td>Normal IgE</td>
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Triggers of asthma

- Inhaled allergens
- Viral upper respiratory tract infections
- Drugs: β-adrenergic blocking agents, NSAIDs (salicylates)
- Physical exercise
- Other: air pollution, occupational exposures, and stress

Symptoms

- Wheezing, dyspnea, and cough.
- These symptoms often vary widely within a particular individual, and they can change spontaneously or with age, season of the year, and treatment.
- Symptoms may be worse at night

Indicators of inadequate asthma control:

- Nocturnal awakenings, need for systemic steroid treatment, hospitalization, and intensive care treatment

Physical examination

- Wheezing and rhonchi throughout the chest, more prominent in expiration
- In severe cases respiratory distress: tachypnea, use of accessory respiratory muscles, and cyanosis.
- Evidence of allergic nasal, sinus, or skin disease should be assessed.
- When asthma is adequately controlled, the physical exam may be normal.

Pulmonary function tests

- Spirometry often shows airflow obstruction, with a reduction in the FEV1 and FEV1/FVC ratio.
- However, spirometry may be normal, especially if asthma symptoms are adequately treated.
- Bronchodilator reversibility is demonstrated by an increase in FEV1 by ≥200 mL and ≥12% from baseline FEV1 15–20 min after a short-acting β agonist (often albuterol MDI two puffs or 180 μg).
- Many but not all asthmatics will demonstrate significant bronchodilator reversibility; optimal pharmacologic treatment may reduce bronchodilator reversibility.
- The peak expiratory flow rate (PEF) can be used by the patient to track asthma control objectively at home.
- Increases in total lung capacity and residual volume may be observed.
- The diffusing capacity for carbon monoxide is usually normal.
Other tests
- CBC may demonstrate eosinophilia.
- Specific IgE measurements for inhaled allergens (RAST) or allergy skin testing may assist in determining allergic triggers.
- Total serum IgE is markedly elevated in allergic bronchopulmonary aspergillosis (ABPA).

Radiologic findings
- Chest x-ray is usually normal. In acute exacerbations pneumothorax may be identified.
- In ABPA, eosinophilic pulmonary infiltrates may be observed.
- Chest CT scan is not typically performed in routine asthma but may show central bronchiectasis in ABPA.

Differential diagnosis
- Upper airway obstruction by tumor or laryngeal edema (stritor)
- Endobronchial tumor or foreign body (localized wheezing in the chest)
- Chronic heart failure (bubisilar crackles)
- Eosinophilic pneumonias and Churg-Strauss syndrome
- Vocal cord dysfunction
- COPD

Step-wise approach to asthma therapy according to the severity of asthma and ability to control symptoms

ICS, inhaled corticosteroid; LABA, long-acting β2-agonists; OCS, oral corticosteroid.

Therapeutic agents used in asthma

β2-adrenergic agonists
- Short-acting (SABA): salbutamol, albuterol. Rapid onset of action and last for up to 6 h. SABAs are effective rescue medications but excessive use indicates inadequate asthma control. SABAs can prevent exercise-induced asthma if administered before exercise.
• Long-acting (LABA): salmeterol and formoterol, have a slower onset of action but last for >12 h.
• Common side effects of β2-adrenergic agonists include muscle tremor and palpitations, arrhythmias

Anticholinergics: ipratropium bromide

Theophylline

Controller therapies

• Inhaled corticosteroids (ICS): fluticasone, triamcinolone, budesonide, flunisolide, beclomethasone
• Systemic corticosteroids: prednisolone, methylprednisolone POS or IV should be avoided if at all possible in the chronic management of asthma due to multiple potential side effects.
• Antileukotrienes: montelukast, zafirlukast
• Cromolyn sodium, nedocromil sodium: brief durations of action and typically modest effects.
• Anti-IgE antibody (omalizumab): given SC.

Hyposensibilisation

Acute exacerbations - Acute severe asthma – Status asthmaticus

Definition

Periods of acute worsening of asthma symptoms that may be life-threatening.

Etiology

Viral upper respiratory tract infections

Symptoms

• Increased dyspnea, wheezing, pulsat paradoxicus, tachypnea, tachycardia, and lung hyperinflation.
• Pulmonary function testing
• Reduction in FEV1 and PEF, hypoxemia can result. PCO2 is usually reduced due to hyperventilation.
• Normal or rising PCO2 can signal impending respiratory failure.

Treatment

• High doses of SABA (by nebulizer or metered-dose inhaler with a spacer)
• IV or POS corticosteroids, such as methylprednisolone (e.g., 80 mg IV q8h)
• Supplemental oxygen should be provided to maintain adequate oxygen saturation (>90%).
• If respiratory failure occurs, mechanical ventilation
• Antibiotics only if bacterial infection is present (rarely)

OCCUPATIONAL ASTHMA

Definition: Asthma that occurs in a previously healthy individual as a result of occupational exposure.

Common causes of occupational asthma

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<th>Agents</th>
<th>Occupational exposure</th>
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**Low molecular weight chemicals**

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<th>Industries/Products</th>
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<td>Isocyanates</td>
<td>Plastics, varnishing, spray painting, foundries</td>
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<tr>
<td>Anhydrides: phthalic, trimellitic, tetrachlorophthalic</td>
<td>Plastics, epoxy resins</td>
</tr>
<tr>
<td>Soldering fluxes</td>
<td>Electronic, aluminum plants</td>
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<tr>
<td>Metal salts: Pt, Cr, Ni</td>
<td>Metal planting, refining, tanning</td>
</tr>
<tr>
<td>Wood dusts: red cedar, redwood, zebrawood</td>
<td>Sawmills, carpentry</td>
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<tr>
<td><strong>Complex organic materials</strong></td>
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<tr>
<td>Plant dusts: grain, coffee bean, castor bean</td>
<td>Grain handlers, bakers, agricultural workers</td>
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<tr>
<td>Laboratory animals</td>
<td>Laboratory workers, animal handlers</td>
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<tr>
<td>Shellfish: crab, prawn, oyster</td>
<td>Shellfish processors</td>
</tr>
<tr>
<td>Biologic enzymes</td>
<td>Detergents, pharmaceuticals, chemical industry</td>
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**DRUG ALLERGIES**

Most commonly:

**Antibiotics:** all, esp. penicillin, amoxicillin, sulphonamides,

**Radiographic contrast media:** Mostly pharmacological actions caused by hyperosmolarity → activation of complement, release of histamine

**Local anesthetics:** Toxic, psychophysiologic reactions, contact dermatitis

**Aspirin and other NSAID-s:** Asthma, rhinorrhea, urticaria

**ACE inhibitors:** Prolong the effect of bradykinin. Cough, severity of asthma, angioedema ↑

**Source**

Harrison’s Principles of Internal Medicine