Allergy and Immunology

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ALLERGY

Introduction

- Allergic disorders are very common in children and include a variety of conditions such as asthma, allergic rhinitis, atopic dermatitis, and food allergies
- There is a strong familial predisposition for allergic disease, but environmental exposures (i.e., air pollution, cigarette smoke), diet, and concomitant infection also play an important role in the incidence and severity of atopy in children
- Respiratory and food allergies are by far the most prevalent allergic disorders in the pediatric age, but children can also suffer from drug and insect venom hypersensitivity

Allergy or type 1 hypersensitivity is mediated by immunoglobulin E (IgE)

- Sensitization, that is, the ability to make IgE in response to a particular allergen, is the prerequisite for the development of allergic disease
- Yet, sensitization does not always lead to clinical manifestations. In other words, one may be able to detect IgE to peanuts in individuals who eat peanuts regularly with no problems

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Types of hypersensitivity (Table 11.1)

Allergic Rhinitis (AR)

Background

- Allergic rhinitis (AR) is the most common chronic disease in children
- Often mistaken for recurrent episodes of the common cold
- At difference to the common cold, AR usually does not present with low-grade fevers or malaise. Nasal and eye pruritus also distinguish AR from viral upper respiratory infections
- AR is one of the major reasons for visits to pediatricians and is associated with a number of significant comorbidities, including asthma, sinusitis, and ear infections

Implicated allergens

- Pollens, molds, dust mites, and animal dander are the most common causative allergens
- Tree pollens are highest in the spring, grass pollens in the early summer, and weeds in the fall—all important causes of seasonal or outdoor allergies.
- Molds are high all year round and may cause persistent allergies or indoor allergies, e.g., *Alternaria* and *Cladosporium* in warmer seasons and *Penicillium* and *Aspergillus* in the colder seasons. Molds are an important cause of asthma exacerbations

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_11

Table 11.1 Types of hypersensitivity

Types of hypersensitivity	Examples	Mediators	Description
Type I: allergy (immediate)	Anaphylaxis	IgE	Reaction occurs in minutes
	Allergic rhinoconjunctivitis		Antigens cross-link the IgE on mast cells and basophils → release of histamine and other mediators
			Testing: Skin test for specific IgE
Type II: cytotoxic, antibody-dependent	Drug-induced hemolytic anemia	IgM or IgG	Antibody (IgM or IgG) binds to cell surface antigens → complement fixation → cellular destruction via the MAC
		Complement	Testing: direct and indirect Coombs test
		MAC	
Type III: immune complex disease	Serum sickness	IgG	Circulating immune complexes → deposit in postcapillary venules → local inflammatory reaction
	Lupus	Complement	
	PSGN	Neutrophils	
Type IV: delayed-type hypersensitivity	Contact dermatitis	T-cell	Mediated by T-cells rather than by antibodies
	TB skin test		Cellular response usually appears 48–72 h after antigen exposure
	Chronic transplant rejection		

IgE immunoglobulin E, *MAC* membrane attack complex, *PSGN* poststreptococcal glomerulonephritis, *TB* tuberculosis

- Dog and cat dander are abundant in indoor settings and a common cause of perennial allergic rhinitis and asthma
- Dust mites are another prevalent indoor allergen, is a very important trigger of perennial asthma and allergies

Classification

- **Intermittent** disease with symptoms < 4 days/week or for a duration of < 4 weeks, usually related to outdoor allergens, e.g., pollens
- **Persistent** disease with symptoms > 4 days/week and are present for > 4 weeks, usually related to indoor allergens, e.g., molds

Clinical presentation

- Nasal congestion may be reported by parents as mouth breathing, snoring, or a nasal voice
- Paroxysmal sneezing, nasal and palatal pruritus, nose blowing, sniffing, snorting, and occasional coughing
- Nasal pruritus often produces the classic sign of the allergic salute
- Itchy eyes and postnasal drip
- Seasonality, progression of symptoms, identifiable triggers, alleviating factors, and responsiveness to allergy medication
- Comorbid conditions such as headaches, sleep disturbance, fatigue, and impaired concentration and attentiveness at school
- Nasal turbinates may appear edematous, with a pale to bluish hue
- Cobblestoning from lymphoid hyperplasia may be seen on the posterior oropharynx
- Dark discolorations underneath the eyes, "allergic shiners," are due to venous engorgement and suborbital edema
- Dennie–Morgan lines are folds under the eyes due to edema
- A transverse nasal crease is seen across the bridge of the nose in children who chronically push their palms upward under their noses ("allergic salute"; Fig. 11.1)
- Tonsils and adenoids are frequently enlarged in young patients with chronic rhinitis and can be an additional cause of mouth breathing, snoring, and, in severe cases, sleep apnea
- Chronic mouth breathing from nasal obstruction may cause allergic facies, with an open mouth, receding chin, overbite, elongated face, and arched hard palate
- Allergic conjunctivitis usually presents with excessive tearing, conjunctival injection, and rubbing of the eyes

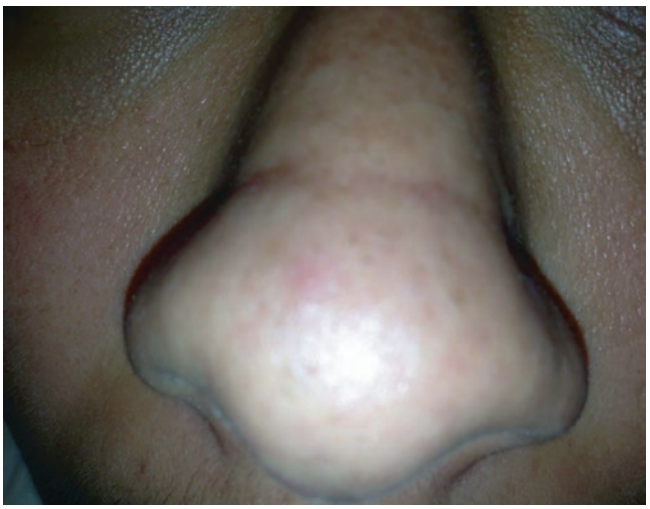

Fig. 11.1 Child with allergic rhinitis showing the transverse nasal crease across the bridge of the nose

Diagnosis

- History and physical examination are key to diagnosis
- Percutaneous (prick or puncture) skin testing remains the most specific and cost-effective diagnostic modality
- Serum detection of allergen-specific IgE by enzyme-linked immunosorbent assay (ELISA) also may be used
- These tests can help to identify the offending allergen, and specific avoidance can be recommended
- Nasal smear for eosinophils with eosinophil count of greater than 4% in children may help distinguish AR from viral infections and non-allergic rhinitis

Management

- Allergen avoidance, whenever possible
- Intermittent disease (outdoor environmental control)
  - Staying inside (5–10 a.m.)
  - Keep air-conditioning on during the spring, fall, and pollen seasons
- Persistent disease (indoor environmental control)
  - Avoiding molds includes humidity control < 51% in the home by using a dehumidifier
  - Use dust mite covers on the bed and pillows
  - Use hypoallergenic pillows and comforters
  - Wash linens in hot water to denature dust mite allergen
  - If allergic to pets, getting rid of them entirely or removing them from the bedroom may help decrease exposure to pet danders
  - A size-appropriate HEPA filter placed in the bedroom may also help decrease exposure to cat dander while removing indoor air pollutants
- Intranasal corticosteroids (INS)
  - The first-line treatment and most effective
  - Onset of action has been shown to be within 12 h
  - Can be used as needed, but far more effective if used long term
  - Epistaxis is the most common side effect
  - Generally have no effect on growth over 1 year of treatment in pediatric patients
- H1 antihistamine
  - The most popular
  - Decreases sneezing, itching, and rhinorrhea, but oral antihistamines are notoriously ineffective in treating nasal congestion
  - Adverse effects include sedation, which can lead to reduced school and cognitive performance
  - Sedation effect can be avoided by using second-generation antihistamines that have low or no sedation effect
- Decongestants
  - Long-term use of oral decongestants, in general, is not recommended because of potential side effects that include palpitations, tachycardia, and insomnia
  - Prolonged use of topical decongestant can lead to rhinitis medicamentosa (rebound nasal congestion)
- Leukotriene receptor antagonists (LTRA) such as montelukast can be used

- Allergy immunotherapy
  - It is not used routinely for management of mild-to-moderate AR that is responsive to medical treatment
  - Reserved for more severe cases and in those in which allergen avoidance is not desired or possible (e.g., pet ownership)
- Comorbidities
  - AR also is one of the risk factors associated with otitis media
  - 20% of children with AR have otitis media with effusion; 50% of the children who have chronic otitis media with effusion have AR
  - Poorly controlled rhinitis symptoms may exacerbate coexisting asthma and is an important cofactor in asthma exacerbations
  - AR may increase the risk of developing sinusitis

URTICARIA

Background

- Urticaria is a rash that consists of pruritic, blanching, erythematous, circumscribed, or (often) coalescent wheals
- Acute urticaria < 6 weeks
- Chronic urticaria 6 weeks or more

Causes

- Common allergens include food, medications, insects, pollens, and animal dander
- Physical factors such as cold, pressure, heat, and light can trigger urticaria
- Another common cause of urticaria in children is infectious illness, especially from viruses

Clinical presentation

- Wheals: Pruritic, blanching, erythematous, circumscribed, or (often) coalescent wheals (Fig. 11.2)

Differential diagnosis

- *Papular urticaria*
  - Common cause of papular, pruritic skin eruptions

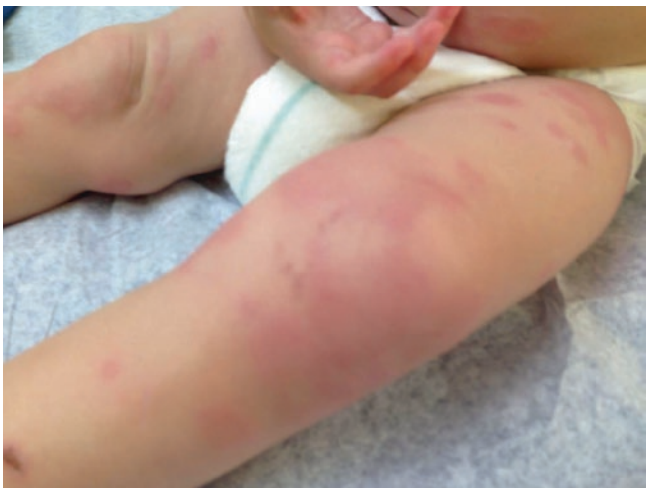

Fig. 11.2 18-month-old child with pruritic circumscribed and coalescent wheals

  - Caused primarily by insect bite-induced hypersensitivity
  - Clusters on exposed areas of skin, sparing the genital, perianal, and axillary regions
  - Prevalence of papular urticaria peaks in children from the ages of 2–10 years
- *Erythema multiforme*
  - Lesions may resemble urticaria and may be triggered by the same etiologic agents such as infections and medications
  - *Erythema multiforme is* distinguished from urticaria by the targetoid appearance of the lesions
  - Patients who have *erythema multiforme* are at risk for developing mucosal and systemic involvement
- *Urticaria pigmentosa* (UP)

Treatment

- Identify and avoid the offending agent
- First-generation antihistamines (diphenhydramine, hydroxyzine) are very effective but can lead to excessive sedation
- Second-generation antihistamines (loratadine, cetirizine, and fexofenadine) are also effective in controlling symptoms
- Use of glucocorticosteroids should be reserved for children not responsive to H1- and H2-antihistamines or children afflicted with severe cases that involve significant angioedema

- Another alternative medication for the treatment of acute urticaria is leukotriene modifiers such as montelukast, but with limited efficacy
- If anaphylaxis, such as laryngeal angioedema, respiratory, or gastrointestinal (GI) symptoms, a self-injectable epinephrine pen should be provided

Chronic Urticaria

Causes

- Defined by urticarial lesions persisting or recurring for more than 6 weeks
- Physical factors are common triggers for chronic urticaria and can act alone or with urticaria of other causes
- The main types of physical urticaria are dermatographic, cholinergic, cold, pressure, solar, vibratory, and exercise-induced
- Chronic infections, thyroid, and autoimmune disease are rare causes of chronic urticaria
- Allergies rarely play a causal role and allergy testing in general is not indicated

Differential diagnosis

- *Urticaria pigmentosa* (UP)
  - A form of cutaneous mastocytosis, usually benign; can be associated with systemic mast cell activation
  - Lesions of UP are reddish brown macules that wheal like a hive when stroked (positive Darier sign)
- Urticarial vasculitis
  - Rare in children but typically presents with fever, arthralgia, and painful fixed urticarial and petechial lesions that last longer than 24 h
  - Urticaria vasculitis is differentiated from typical chronic urticaria by the presence of nonpruritic, painful lesions with systemic symptoms

Diagnosis

- Infection may be the cause for the urticaria
- Positive serologic findings for *Chlamydia pneumoniae* and *Helicobacter pylori* can be found for these illnesses even in asymptomatic patients
- Other reported infectious causes are viral infections, urinary tract infections, and parasitic infections
- Autoimmune diseases that have been associated with chronic urticaria are thyroid disease, celiac disease, type 1 diabetes mellitus, inflammatory bowel disease, juvenile idiopathic arthritis, and systemic lupus erythematosus
- The most common specific autoimmune association with chronic urticaria is autoimmune thyroid disease
- If evidence of vasculitis, referral for skin biopsy may be indicated

Treatment

- Very similar to acute urticaria
- Specialists may use other therapies for children with chronic urticaria that has been refractory to standard therapies
- Examples of these medications include hydroxychloroquine, sulfasalazine, dapsone, omalizumab, colchicine, mycophenolate mofetil, and cyclosporine
- These medications require close monitoring for adverse effects and should be used only by specialists experienced in prescribing these immune-modulating medications

MASTOCYTOSIS

Background

- Disorder characterized by mast cell proliferation and accumulation within various organs, most commonly the skin
- **Cutaneous** mastocytosis
  - Urticaria pigmentosa
- **Systemic** mastocytosis

Clinical presentation

- Most patients have pruritic cutaneous lesions
- Macules, papules, nodules, plaques, blisters, and bullae (Fig. 11.3)

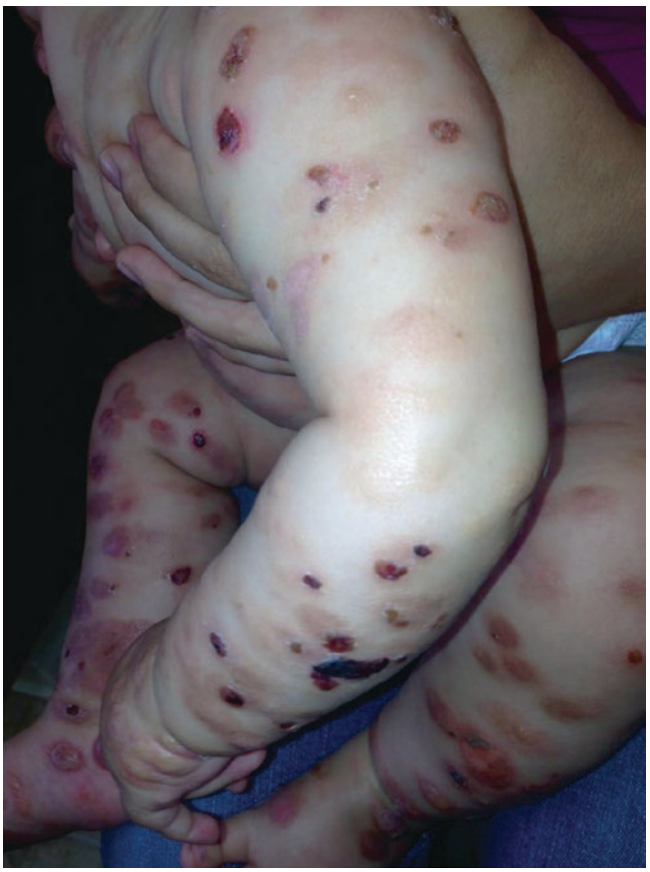

Fig. 11.3 8-month-old girl with severe mastocytosis cutaneous type (urticaria pigmentosa) showing pruritic macules, papules, blisters, and crusts all over the body

- Face tends to be less affected
- Darier sign: Wheal and surrounding erythema develop in a lesion after rubbing it
- Some patients, especially those with extensive cutaneous disease, experience acute systemic symptoms exacerbated by certain activities or ingestion of certain drugs or foods
- Possible systemic symptoms include flushing, headache, dyspnea, wheezing, rhinorrhea, nausea, vomiting, diarrhea, and syncope
- Anaphylactic reactions to Hymenoptera stings may be the first sign of mastocytosis

Diagnosis

- Complete blood count (CBC) in systemic mastocytosis may reveal anemia, thrombocytopenia, thrombocytosis, leukocytosis, and eosinophilia
- Plasma or urinary histamine level
- Elevated tryptase level

Treatment

- H1 and H2 antihistamines decrease pruritus, flushing, and GI symptoms
- Cromolyn is a mast cell stabilizer that improves diarrhea, flushing, headaches, vomiting, urticaria, abdominal pain, nausea, and itching in some patients
- Epinephrine pens for cases of anaphylaxis
- Avoid triggers

Prognosis

- Most patients with urticaria pigmentosa (UP) exhibit onset before age 2 years, which is associated with an excellent prognosis, often resolved by puberty
- Cutaneous mastocytosis onset after age 10 years portends a poorer prognosis, which is associated more often with systemic disease, and carries a higher risk of malignant transformation

HEREDITARY ANGIOEDEMA (HAE)

Background

- HAE usually presents in childhood or adolescence with a mean age at onset between 8 and 12 years
- Type 1 is secondary to insufficient levels of C1 inhibitor
- Type 2 is associated with normal levels but dysfunctional C1 inhibitor
- Type 3 has normal functional levels of C1 inhibitor; this type is nonexistent in children and adolescents

Clinical presentation

- Recurrent, episodic, nonpruritic swelling of the skin and mucosal tissues

- Laryngeal edema that may lead to death by asphyxiation
- Severe abdominal attacks manifested by intestinal edema
- The swelling can occur anywhere on the body, including lips, eyelids, hands, feet, and genitals
- The swelling usually develops over the course of 24 h and then resolves spontaneously in the next 24–36 h
- Can be triggered by minor injury, dental work, infection, stress, or menstruation
- The frequency of the swelling is patient-specific, occurring as frequently as once per week or as rarely as once per year
- The disease is inherited, commonly in an autosomal-dominant fashion
- If a diagnosis of HAE is made, testing of first-degree relatives is recommended

Diagnosis

- The abdominal attacks may be mistaken for an acute abdominal condition such as appendicitis or mechanical obstruction
- The angioedema of HAE occurs without pruritus or urticaria, develops more gradually over several hours, and is poorly responsive to antihistamines, corticosteroids, or epinephrine
- The diagnosis of HAE is made by confirming a deficiency in the C1 inhibitor, either quantitatively or qualitatively

Treatment

- Begins with immediate management of the patient's airway if compromised
- Intubation may be necessary for the protection of the airway if laryngeal edema is present
- In children with severe or frequent attacks occurring more than once per month, long-term prophylaxis should be considered
  - Complement C1 esterase inhibitor can be used as an acute treatment, short or long-term prophylaxis
  - Attenuated androgens, such as danazol or oxandrolone, and antifibrinolytics, such as tranexamic acid

ANAPHYLAXIS

Background

- Anaphylaxis is an acute, life-threatening systemic reaction that results from the sudden release of mediators from mast cells and basophils
- Prompt recognition of the signs and symptoms of anaphylaxis is critical to providing rapid and effective treatment
- Epinephrine is the most important medication for treating anaphylaxis, and earlier administration portends a better prognosis

Causes

- Food
  - The most common cause of anaphylaxis in the outpatient setting is food
  - Foods most commonly implicated are peanuts, tree nuts, fish, shellfish, cow's milk, soy, egg, soy, and seeds
- Medications
  - Medications are the second most common cause of anaphylaxis in children
  - The two most frequent culprits are antibiotics, particularly β-lactam antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs)
- Radiographic contrast
  - Anaphylactoid reactions associated with radiographic contrast material occur in approximately 1% of patients
  - Pretreatment with oral corticosteroids and antihistamines can reduce the risk of anaphylactoid reactions from radiographic contrast material
- Stinging insects
  - Hymenoptera: Stings by bees, vespids (yellow jackets, hornets, and wasps), and

stinging fire ants can cause anaphylaxis and can be fatal
  - Cutaneous symptoms can be treated symptomatically with cold compresses, oral antihistamines, and oral analgesics
  - Systemic symptoms should prompt immediate administration of epinephrine and immediate evaluation in a local emergency department
- Latex
  - Natural rubber latex is an emerging cause of anaphylaxis
  - Common in certain patients, e.g., patients with spina bifida and bladder exstrophy due to frequent exposure and sensitization
- Vaccination
  - Anaphylaxis to vaccines is an exceedingly rare but important cause of a life-threatening allergic reaction
  - A vaccine containing gelatin, egg, chicken, yeast, and neomycin can cause anaphylaxis
  - Patients can undergo skin testing to the components of the vaccine, such as gelatin, and to the vaccine itself
- Exercise
  - Exercise and physical exertion can lead to systemic mast cell mediator release, resulting in anaphylaxis
  - A few minutes of exercise can cause flushing, pruritus, diffuse warmth, urticaria, and fatigue
  - It may progress to angioedema, laryngeal edema, GI symptoms, hypotension, or collapse if exercise is continued
  - Eating specific food 4–6 h before exercise is a common co-trigger, as are alcohol or NSAIDs
  - Taking medication before exercise by up to 24 h may prevent food-exercise-induced anaphylaxis or medication-exercise-induced anaphylaxis
- Immunotherapy
  - Subcutaneous allergen immunotherapy (allergy shots) is another potential cause of anaphylaxis
- Idiopathic

Clinical presentation

- Flushing, urticaria, pruritus, angioedema, cough, wheezing, stridor, dyspnea, abdominal cramping, vomiting, diarrhea, dizziness, and syncope
- Absence of cutaneous symptoms argues against anaphylaxis but cannot completely rule it out
- IgE-mediated allergic reactions triggered by foods typically occur rapidly and usually within 1 h of ingestion
- Other adverse food reactions, such as food poisoning, occur more slowly and may be delayed by as much as 24 h from ingestion
- 80% to 90% of cases of food-induced anaphylaxis present with cutaneous findings of hives, angioedema, or both
- Cutaneous findings are uncommon in food poisoning
- A careful history from the patient, parent, caregiver, or other witness is helpful in determining a potential trigger

Differential diagnosis

- Vasovagal or neurogenic syncope
- Vocal cord dysfunction
- Asthma exacerbation
- Panic attack
- Isolated angioedema
- Food poisoning and other causes of shock
- Sepsis
- Cardiogenic shock

Management

- A serum tryptase level taken within 6 h of a suspected anaphylactic reaction may help confirm the diagnosis in many cases

- Referral to an allergist is warranted so that skin tests, specific IgE in vitro testing, can be done
- Challenge tests may be considered for more definitive diagnosis, especially in difficult cases
- Epinephrine
  - The mainstay of short-term treatment for anaphylaxis
  - Aqueous epinephrine in a 1:1000 dilution (0.01 mg/kg in children; maximum, 0.3 mg)
  - Should be administered intramuscularly in the outer aspect of the thigh every 5 min as needed to control symptoms
- Epinephrine pens
  - Self-administration epinephrine pens must be carried for all patients at risk for anaphylaxis
  - For children under 30 kg, the dose is 0.15 mg
  - For children greater than or equal to 30 kg, the dose is 0.3 mg
- Diphenhydramine
  - Second-line therapy
  - 1 to 2 mg/kg every 6 h as needed
- Ranitidine
  - Histamine-2 (H2)-receptor antagonists may be considered
  - 1 to 2 mg/kg
- Inhaled beta-2 agonist, e.g., albuterol if bronchospasm
- Glucocorticosteroids
  - It may not be helpful for short-term treatment but can be considered for prevention of recurrent or protracted anaphylaxis
  - Oxygen therapy and intravenous (IV) fluid
  - If hypoxia or hypotension
- Prevention
  - Avoid triggers or allergens
  - Penicillin reaction non-IgE-mediated
    - For example, vomiting, diarrhea, headache, or a nonurticarial, nonpruritic rash
    - These cases can be given cephalosporin with no problem
  - Penicillin reaction IgE-mediated
    - Anaphylaxis
    - Urticarial rash
    - First-generation cephalosporins in penicillin-allergic patients is 3–7%, whereas the increased risk is negligible for third-generation cephalosporins
  - Stevens–Johnson syndrome or toxic epidermal necrolysis associated with a particular medication
    - Same drug and structurally related drugs should be strictly avoided in the future

FOOD ALLERGIES

Mechanism of food allergies

- IgE-mediated
  - The most common form, affecting about 8% of children in the United States
- Non-IgE-mediated
  - Not so rare, includes disorders such as eosinophilic esophagitis (EoE), cow's milk protein allergy, and food protein-induced enterocolitis (FPIES)
- Most common triggers
  - Eggs, cow's milk, peanuts, tree nuts, fish, shellfish, soy, and wheat

Clinical presentation

- Skin reactions, urticaria, or angioedema (80%)
- Atopic dermatitis (AD) is a frequent comorbidity in patients with IgE-mediated food allergy
- Nasal congestion, rhinorrhea, cough, wheeze
- Abdominal pain, emesis, diarrhea
- Anaphylaxis
- In IgE-mediated food allergy, the onset of reaction is usually quick, from minutes to up to 2 h

- Non-IgE-mediated reactions develop over time and can present as dysphagia (EoE), delayed and protracted emesis (FPIES), and failure to thrive
- Cow's milk protein allergy characteristically presents in breastfed infants with bloody stools, fussiness, and occasionally failure to thrive

Diagnosis
- Skin testing
- ELISA
- Oral food challenge (the gold standard)
- Food allergy may play a causative role in a select group of children with severe atopic dermatitis; diagnosis in these cases may require the implementation of an elimination diet with the subsequent monitoring of skin manifestations

Treatment
- Avoidance is the mainstay of treatment
- Oral and epicutaneous immunotherapy are novel therapeutic modalities in development

Prognosis
- Allergies to peanuts, tree nuts, fish, and shellfish tend to be lifelong
- Most infants and children outgrow allergies to egg, milk, and soy protein
- Cow's milk protein allergy usually resolves in the second year of life

ADVERSE DRUG REACTIONS

- Many drug reactions are idiosyncratic (nonimmune)
- Drug overdose
- Drug-drug interaction
- Drug side effects
- Some drug reactions are triggered by an immune response to the drug. All types of hypersensitivity (Table 11.1) have been implicated in these immune-mediated drug reactions

Immune responses
- Specific IgE hypersensitivity
- IgG-predominant response resulting in serum sickness
- Antibody-mediated hemolysis by binding of the drug to the surface of red blood cells
- Drug-induced, delayed-type hypersensitivity reaction mediated by T-lymphocyte and monocytes

Timing of reaction
- If the drug given IV and an immediate reaction occurs within an hour, an IgE-mediated (type 1) process is likely
- If the reaction is delayed up to 72 h, a non-IgE-mediated reaction is more likely
- Steven–Johnson syndrome, toxic epidermal necrolysis, fixed drug reactions, and photosensitivity usually appear more than 72 h after exposure to drugs

Specific drug reaction
- Penicillin is composed of benzylpenicillin, which is the major determinant of penicillin allergies
- Minor determinants, e.g., benzylpenicilloate, are responsible for most anaphylaxis

Cross-reactivity
- Penicillin cross-reacts with cephalosporin at a rate of 3–7%
- Penicillin has a high rate of cross-reactivity with imipenem
- Penicillin has no cross-reactivity with aztreonam, per current reporting

Desensitization
- Desensitization is necessary if the medication is the only clinically effective therapy
- For example, a pregnant woman with syphilis or a person with neurosyphilis requiring definitive penicillin therapy; both require desensitization and use of IV penicillin
- Subsequent administration down the road may require repeat desensitization

SERUM SICKNESS

Background

- Serum sickness is a type III hypersensitivity reaction that results from the injection of heterologous or foreign protein or serum
- Immune complex causes vascular injury and influx of neutrophils and eventual tissue injury or death
- Reactions secondary to the administration of nonprotein drugs are clinically similar to serum sickness reactions
- Serum sickness does not require prior exposure to an antigen (prior sensitization) and can occur on initial exposure
- The most common cause of serum sickness today is antibiotics, e.g., cefaclor and penicillin
- Stings from Hymenoptera (bees, wasps, and some ants) can induce serum sickness

Clinical presentation

- It may take 6–12 days for the reaction to develop, but can take up to 3 weeks
- If previous exposure has occurred, a reaction may occur as quickly as 1–3 days post-exposure
- Fever/malaise
- Skin rash: Urticarial (92%) and/or serpiginous, the rash typically starts on the anterior lower trunk or the periumbilical or axillary regions and spreads to the back, upper trunk, and extremities
- Arthritis is usually in the metacarpophalangeal and knee joints and usually symmetrical
- Edema may occur, particularly the face and neck
- Renal manifestations include proteinuria, microscopic hematuria, and oliguria
- GI complaints
- Headaches
- Myalgias
- Blurred vision
- Dyspnea/wheezing
- Lymphadenopathy
- Neurologic manifestation, e.g., peripheral neuropathy

Management

- Stop the offending agent
- NSAIDs can help for fever and muscle/bone pain
- Diphenhydramine or hydroxyzine will help to relieve urticaria and itching
- Prednisone 1–2 mg/kg/day can be given if other interventions are not helpful

ALLERGIC REACTIONS TO INSECTS

- Insect stings usually result in site-limited transient pain, itching, and swelling
- Allergic reactions of varying severity can occur in previously sensitized patients and can be life-threatening
- Recurrent systemic reactions to venom tend to be similar in severity to the initial reaction in an individual patient

Clinical presentation

- There are three common types of allergic reactions to the venom of Hymenoptera (includes bees, yellow jackets, wasps, hornets, and fire ants):
  1. **Anaphylactic reactions** (i.e., involving multiple organ systems)
  2. **Systemic cutaneous reactions** (widespread) include widespread pruritus, hives, erythema, and/or angioedema developing shortly after the sting. Can be dangerous if they involve edema of the lips, tongue, or structures near the airway. They may take several days to resolve fully
  3. **Large local reactions** (contiguous to the site) usually result in delayed and prolonged local inflammation that

increases over 24–48 h. Take 3–4 days to resolve

Diagnosis

- History of insect sting and symptoms consistent with an allergic reaction
- Presence of positive skin test and/or elevated serum levels of venom-specific immunoglobulin
- Testing can be done as soon as 1 week following the sting, but if negative and the history is convincing, it should be repeated 5–6 weeks later (transient anergy)

Management

- **Anaphylactic reactions**
  - Epinephrine
  - Other medications as per standard management of anaphylaxis
  - Prescribe epinephrine autoinjector
  - Refer to an allergist for venom immunotherapy
- **Systemic cutaneous reactions**
  - Antihistamines
  - Consider corticosteroids
  - Consider prescribing an epinephrine autoinjector to patients with a history of moderate-to-severe systemic cutaneous reactions
  - Consider referral to an allergist for venom immunotherapy
- **Large local reactions**
  - Ice pack
  - NSAIDs
  - Antihistamines
  - Consider corticosteroids
- **Venom immunotherapy**
  - Effective in reducing the severity of allergic reactions
  - Minimum 5-year duration
  - Indicated in all patients with a history of anaphylactic reaction to an insect sting and positive venom skin test or elevated serum levels of venom-specific IgE
  - Considered in selected patients with a history of moderate-to-severe cutaneous systemic reaction
  - Offered to very selected patients with a history of repeated large local reactions

SKIN TESTING

Background

- Skin prick tests are the most common screening tests for patients suspected to have allergies. Both environmental and food allergies can be tested this way
- Skin testing is highly sensitive and safe even in very young children
- These tests provide useful and reproducible clinical information in a short period (i.e., 15–20 min), with minimal expense and negligible risk to the patient

Indications

- Identification of aeroallergen triggers in patients who have asthma
- AR not controlled with usual medications, specific avoidance is desired in such cases, e.g., pet dander
- Food allergy
- Insect sting allergy
- Vaccine, drug, or latex allergy
- Evaluation for moderate-to-severe atopic dermatitis
- Other conditions, including allergic fungal sinusitis, allergic bronchopulmonary aspergillosis, and eosinophilic esophagitis

Medication that alters the result of skin test

- First-generation nonselective antihistamines, e.g., diphenhydramine, suppress skin reactivity for 3 days
- Second-generation antihistamines (e.g., cetirizine, loratadine) may blunt skin test for up to 7 days

- Ranitidine and famotidine may blunt the skin test for up to 7 days
- Tricyclic antidepressants and phenothiazines may block skin reactivity for 2 weeks

Medications do not interfere with allergy skin test

- Corticosteroids
- Asthma medications, e.g., albuterol and montelukast

Method of testing

- A small amount of concentrated allergen is deposited on the skin and a tiny puncture is made with a plastic device
- IgE receptors undergo cross-linking and activate mast cells, causing a release of histamine and other products leading to local vasodilatation and increased vascular permeability, resulting in wheals

In Vitro Allergy Testing

Enzyme-linked immunosorbent assay (ELISA)

- Radioallergosorbent (RAST) testing is outdated because of radiation and is rarely used today
- ELISA, which uses antibodies linked to enzymes, as well as fluorescent enzyme immunoassay (EIA) and chemiluminescent immunoassays
- The accuracy of immunoassays varies with the system being used and the quality of the allergen
- There is a good predictive value (> 90%) for pollens of grass, trees, dust mites, and cats, whereas less accurate results may be obtained from venoms, weeds, latex, dogs, and molds
- If testing is equivocal, it can be further evaluated by skin testing and, if indicated, a challenge to the allergen
- Both skin and ELISA are evidence of sensitization but not necessarily of clinical reactivity to a particular allergen. In contrast, a negative skin-prick test is strong evidence against clinically relevant allergy to the tested allergen

General Rules in the Management of Allergies

Avoidance of specific triggers

- Exposure to indoor allergens can be minimized with relatively simple measures
- Outdoor allergens are usually more difficult to avoid
- Strict avoidance of food allergens, including hidden sources and restaurant meals
- Selection of alternative medications in the case of drug allergies
- Latex-free materials during procedures for patients with latex allergies

Medications

- **First-generation** antihistamine: Diphenhydramine, chlorpheniramine, and hydroxyzine
  - Adverse effects of first-generation antihistamines:
    - Sedation
    - Interaction with acetylcholine receptors and can cause dry mouth, blurry vision
- **Second-generation** antihistamine: Cetirizine, fexofenadine, loratadine, and desloratadine
  - Does not cross the blood–brain barrier and are more specifically aimed at H1 receptor and not the other receptors
- **Steroid**
  - Intranasal corticosteroids are the most effective agents for nasal allergy and do not have the systemic effects seen with oral steroids
  - Inhaled corticosteroids are important treatment measure in the patient with persistent asthma

Immunotherapy

- Only therapy capable of changing the course of allergic disease

- The goal is to decrease the severity of reaction upon exposure
- Permanent cure (tolerance) can be achieved in some cases
  - Involves giving increasing doses of allergens via the subcutaneous, sublingual, or oral route to induce an alteration in the immune response to the allergen
  - Usually takes 1–2 years before beneficial effect occurs. Minimum length of therapy estimated around 5 years
  - Effective in the treatment of venom allergy, pollen allergies, dust mites, and animal dander allergies
  - Efficacy currently being tested for the treatment of IgE-mediated food allergies
  - Local reactions are common, but systemic (anaphylactic) reactions can occur during allergen immunotherapy

IMMUNOLOGY

Overview of the Immune System

Two main arms of vertebrate immunity

- **Innate immune system** (rapid and always available)
  - Physical barriers—skin, hair, cilia, mucous membranes, mucous and chemical secretions, digestive enzymes, stomach acid, etc.
  - Internal defenses—inflammatory responses, complement proteins, phagocytic cells, natural killer (NK) cells
  - NK cells: Do not require antigen to be presented with HLA antigen
    - Produce large quantities of interferon-gamma, IL-4, and granulocyte-macrophage colony-stimulating factor, and multiple other cytokines and chemokines (IL-2, IL-13, IL-17, IL-21, and TNF-alpha)
- **Adaptive immune system** (recognizes "self" versus "non-self," tailors immune response for specific pathogens/infected cells, possesses immunologic memory)
  - Humoral immunity (antibodies)
  - Cell-mediated immunity
  - Memory response

T-Lymphocytes

Characteristics

- **T**-cells mature in the **t**hymus
- Play a central role in cell-mediated immunity
- Cell surface marker: CD3+

Subtypes of T-lymphocytes

- Helper T-cells (CD4+ T-cells)
  - Promote maturation of B-cells and interact with B-cells to allow antibody production
  - Interact with cells that express class II major histocompatibility complex (MHC), which is loaded with extracellular proteins
- Cytotoxic T-cells (CD8+ T-cells)
  - Kill cells infected by intracellular bacteria/virus/cancer
  - Recognize their targets by binding to an antigen associated with MHC class I molecules, which are present on the surface of all nucleated cells

B-Cells

Background

- **B**-cells mature in the **b**one marrow
- B-cells are surface membrane immunoglobulin-positive. B-cell receptor composed of membrane-bound IgG, IgA, IgM, IgE, or IgD
- Cell surface marker: CD19+/CD20+

Antibodies (IgG, IgA, IgM, IgE, and IgD)

- **IgG:** In its four forms (IgG1, IgG2, IgG3, and IgG4) provides the majority of antibody-based immunity against invading pathogens. The only antibody capable of crossing the placenta to give passive immunity to the fetus
- **IgM:** Expressed on the surface of B-cells (monomer) and in a secreted form (pentamer) with very high avidity. Eliminates pathogens

in the early stages of disease before class switching to other immunoglobulin isotypes. Good at activating complement
- **IgA:** Main immunoglobulin in mucosal secretions. Found in mucosal areas such as the gut, respiratory tract, and urogenital tract and prevents colonization by pathogens. Also found in saliva, tears, and breast milk
- **IgD:** Functions mainly as an antigen receptor on B-cells that have not been exposed to antigen. Has been shown to activate basophils and mast cells to produce antimicrobial factors
- **IgE:** Binds to allergens and triggers histamine release from mast cells and basophils and is involved in allergy. Also protects against parasites

Initial Immunologic Testing of a Child with Recurrent Infections

CBC with manual differential and erythrocyte sedimentation rate (ESR)
- Normal absolute lymphocyte count rules against T-cell defect
- Normal absolute neutrophil count rules against congenital or acquired neutropenia
- Normal platelet count excludes Wiskott–Aldrich syndrome
- Absence of Howell–Jolly bodies rules against asplenia
- Normal ESR makes chronic bacterial and fungal infection unlikely

Additional testing for B-cell defects
- Quantitative immunoglobulins (IgG, IgA, and IgM)
- Antibody titers to vaccines (e.g., tetanus, diphtheria, *Haemophilus influenzae* type B, and pneumococcus)
- Isohemagglutinins

Additional testing for T-cell defects
- T-cell quantification
- T-cell functional studies: Lymphocyte proliferation assay to mitogens (phytohemagglutinin, concanavalin A, pokeweed mitogen) and/or to antigens (candida, tetanus)
- T-cell receptor excision circles (TREC); newborn screening (as of December 2018, all newborns in the United States are screened for severe combined immunodeficiency (SCID))

Additional testing for phagocyte defects
- Absolute neutrophil count
- Neutrophil oxidative burst assay (dihydrorhodamine [DHR] assay)

Additional testing for complement deficiencies
- CH50

Clinical patterns in some of the primary immunodeficiencies (Table 11.2)

Table 11.2 Clinical patterns in some of the primary immunodeficiencies

Clinical features	Diagnosis
0–6 months of age	
Unusual facial features, hypocalcemia, heart disease (conotruncal)	22q11.2 deletion syndrome (DiGeorge syndrome)
Delayed umbilical cord detachment, leukocytosis, recurrent infection	Leukocyte adhesion defect
Persistent thrush, pneumonia, failure to thrive, diarrhea, small tonsils, nonpalpable lymph nodes, profound lymphopenia, usually present in the first few months of life	Severe combined immunodeficiency
Bloody stools, draining ears, small platelets, atopic eczema	Wiskott–Aldrich syndrome
4- to 9-month-old with recurrent mild infections, but appropriately makes antibodies to diphtheria and tetanus toxoids	Transient hypogammaglobulinemia of infancy (THI)
6 months to 5 years	
Boy presents between 6 and 9 months with severe and recurrent infection, absent antibodies and absent tonsils	X-linked agammaglobulinemia

(continued)

Table 11.2 (continued)

Clinical features	Diagnosis
Severe progressive infectious mononucleosis	X-linked lymphoproliferative syndrome
Recurrent staphylococcal abscesses, staphylococcal pneumonia with pneumatocele formation, coarse facial features, pruritic dermatitis	Hyper-IgE syndrome
Persistent thrush, nail dystrophy, endocrinopathies	Chronic mucocutaneous candidiasis
Short stature, fine hair, severe varicella	Cartilage–hair hypoplasia with short-limbed dwarfism
Oculocutaneous albinism, recurrent infections, silvery hair	Chediak–Higashi syndrome
Boy with liver abscesses, suppurative lymphadenopathy, antral outlet obstruction, pneumonia, osteomyelitis, nitroblue tetrazolium (NBT) or dihydrorhodamine assay reduced or no color change	Chronic granulomatous disease
Recurrent respiratory, gastrointestinal, and genitourinary tract infections, many patients are asymptomatic, risk of anaphylaxis with blood products	IgA deficiency
Older than 5 and adults	
Healthy male until acquires fulminant often fatal infectious mononucleosis or EBV infection (mean age of presentation is < 5 years)	X-linked lymphoproliferative syndrome
Sinopulmonary infections, neurologic deterioration, telangiectasia	Ataxia–telangiectasia
Recurrent *Neisseria* infections	Terminal complement defect
Sinopulmonary infections, normal B-cell counts, hypogammaglobulinemia, autoimmune cytopenias	Common variable immunodeficiency

EBV Epstein–Barr virus

DISORDERS OF PHAGOCYTE FUNCTION

Chronic Granulomatous Disease (CGD)

Background

- Defect in NADPH oxidase complex
- Neutrophils unable to generate hydrogen peroxide or hydroxyl radicals (superoxides) to kill phagocytosed organisms
- X-linked form most common; AR disease also occurs

Clinical presentation

- Pyogenic infections of the skin, lungs, bones, liver, and GI tract
- Characteristic infections with
  - *Aspergillus* spp.
  - *Staphylococcus aureus*
  - *Burkholderia (Pseudomonas) cepacia*
  - *Serratia marcescens*
  - *Nocardia* spp.
  - Outside of the United States: *Salmonella* and bacillus Calmette–Guérin (BCG)
- Most common sites of disease: Lung, skin, lymph nodes, GI, liver, urinary tract
- Autoimmune/inflammatory complications

Diagnosis

- DHR assay: Functional neutrophils take up DHR and oxidize it to a green fluorescent compound detectable by flow cytometry
- Nitroblue tetrazolium (NBT): An older method that is now less used due to operator subjectivity and higher false-negative rate
  - **Normal:** NBT oxidized to purple/blue color
  - **CGD:** Reduced or no color change

Treatment
- Prophylactic antibiotics (antibacterial and antifungal)
- Interferon (IFN)-gamma can be added
- Aggressive treatment of infections
- Definitive therapy:
  - Hematopoietic cell transplant
  - Gene therapy

Leukocyte Adhesion Defect

Background
- Defect in adhesion molecules that allow neutrophils to leave circulation in response to infection
- Keywords: *Delayed umbilical cord separation, leukocytosis*

Clinical presentation
- **Delayed umbilical** cord separation > 1 month
- **Leukocytosis** with average white blood cell (WBC) count (45×10^9/L)
- Recurrent bacterial infections, especially staphylococcal infections (recurrent skin abscess)
- Absence of pus and neutrophils at the wound site
- Poor wound healing

Diagnosis
- Delayed separation of an umbilical cord and persistent high WBC count is highly suggestive
- Flow cytometric measurements of surface glycoprotein (CD18 or CD11) expression

Treatment
- Prophylactic antibiotics
- Definitive therapy with hematopoietic cell transplant

Chediak–Higashi Syndrome

Background
- Autosomal recessive
- Mutation in *CHS1/LYST* gene on chromosome 1q42.1-2
- Disease characterized by abnormal lysosomes/granules in all cell types

Clinical presentation
- Partial oculocutaneous albinism due to improper transfer of melanosomes to epithelial cells (fair skin, light blond/gray/white hair)
- Neutrophil abnormalities (impaired chemotaxis and dysfunction)
  - Contains giant azurophilic granules that do not release contents with infection
  - Recurrent pyogenic infections (mostly skin and respiratory tract)
- Coagulation defects due to decreased platelet stores
- Progressive neurologic abnormalities
- "Accelerated phase"—massive systemic lymphohistiocytosis

Risk of malignancy
- Life-threatening lymphoma-like syndrome
- Leukemia and lymphoma
- Lymphohistiocytic infiltration of the liver, spleen, and lymph nodes
- Pancytopenia
- Fulminant Epstein–Barr virus (EBV) infections

Diagnosis
- Classic giant azurophilic granules (peroxidase positive) in neutrophils, eosinophils, and granulocytes
- Neutropenia
- Poor NK-cell cytotoxicity
- B-cell function usually normal

Treatment
- Prophylactic antibiotics/aggressive treatment of infections
- Hematopoietic cell transplantation (but does not correct neurologic decline or oculocutaneous albinism)

ANTIBODY DEFICIENCY SYNDROMES

Transient Hypogammaglobulinemia of Infancy (THI)

Background

- Maternal IgG traverses placenta to the fetus throughout gestation; most pronounced during the latter half of the third trimester
- After birth, IgG levels in the infant fall as newborn IgG contribution is still catching up, resulting in a physiologic IgG nadir
- THI results from a prolongation of the physiologic hypogammaglobulinemia that usually occurs around age 3–6 months
- Most common age of developing symptoms is 6–12 months

Clinical presentation

- Most infants are asymptomatic, but some can develop recurrent respiratory infections (otitis media and bronchial infections)
- Life-threatening infections (cellulitis, bacteremia, meningitis) are unusual but may occur
- T-cell immunity is intact
- By definition, a self-limited disorder
  - Recurrent infections usually resolve by 9–15 months of age
  - IgG normalizes by 2–4 years of age (but can take up to 10 years)

Diagnosis

- Low serum IgG levels
- Antibody titers to protein immunizations (e.g., tetanus toxoid, diphtheria toxoid, polio) are at normal or near-normal concentrations

Treatment

- Supportive
- Antibiotic prophylaxis
- IgG replacement can be considered in severe cases

X-Linked Agammaglobulinemia

Background

- Defect in Bruton tyrosine kinase (BTK) causing arrest in B-lymphocyte development
- Almost no circulating B-cells → panhypogammaglobulinemia

Clinical presentation

- Presents at 3–9 months of age when maternally transferred antibodies disappear
- Unusually severe or recurrent bacterial respiratory tract infections
  - Sequelae of infections include chronic cough, rhinitis, digital clubbing, and failure to thrive
- Absence or near absence of B-cell-rich tonsils and adenoids
- Episodes of sepsis with encapsulated bacteria
- Increased susceptibility to certain infections such as enterovirus (echovirus, coxsackie), causing meningoencephalitis or hepatitis, even with adequate IgG replacement

Diagnosis

- Absent circulating CD19+/CD20+ B-cells by flow cytometry
- Very low serum IgG, IgA, IgM
- Deficient antibody responses to immunizations
- Neutropenia in ~20% of patients
- Absent *BTK* expression by flow cytometry
- Abnormal *BTK* gene sequencing

Treatment

- IgG replacement
- Aggressive treatment of infections

Common Variable Immune Deficiency (CVID)

Background

- Markedly reduced serum IgG in combination with low IgA and/or IgM

  - Poor or absent response to immunizations
  - Absence of other defined immunodeficiencies
- Genetics: Most cases are sporadic and likely due to multiple genes, but more monogenic causes are being identified
- Usually in the second and third decades and very rare before the age of 6 years

Clinical presentation

- Recurrent infections—Permanent damage to the bronchi may occur, resulting in bronchiectasis
- As many as 20% of patients with CVID develop autoimmune complications:
  - Immune thrombocytopenia (ITP)
  - Autoimmune hemolytic anemia (AIHA)
  - Evans syndrome
  - Rheumatoid arthritis
  - Systemic lupus erythematosus (SLE)
  - Autoimmune thyroid disease
- GI diseases also commonly associated (malabsorption, chronic diarrhea, inflammatory bowel disease)

Risk of malignancy

- Increased risk of malignancy, particularly non-Hodgkin lymphomas

Diagnosis

- Quantitative immunoglobulins (IgG, IgA, IgM)
- Evaluation of antibody responses after immunization with polysaccharide and protein conjugate antigens

Treatment

- IgG replacement
- Antibiotics for bacterial infections
- Treatment of autoimmunity. (Note: autoimmunity needs to be diagnosed clinically, since patients may not have detectable autoantibody production)
- Monitoring for malignancy

Selective IgA Deficiency (sIgAD)

Background

- sIgAD is the most common immunologic defect in humans
- Deficiency of serum IgA in the setting of normal IgG and IgM in an individual > 4 years of age

Clinical presentation

- Majority are asymptomatic
- Various GI tract infections with viruses and bacteria
- *Giardia* manifests as chronic diarrhea with or without malabsorption
- Recurrent sinopulmonary infections can occur
- Increased incidence of autoimmunity and atopy

Diagnosis

- Very low or absent IgA
- Low serum IgA levels in children aged 6 months to 4 years should be confirmed to be persistently low at age 4 years before making a lifetime diagnosis of sIgAD

Treatment

- Antibiotics
- Clean drinking water due to increased risk of *Giardia*

DEFECTS OF CELLULAR IMMUNITY

22q11.2 Microdeletion Syndrome/DiGeorge Syndrome (see Table 11.2)

Background

- Microdeletion at 22q11.2 → disorder of third and fourth pharyngeal pouches
- CATCH 22
  - **C**ardiac (conotruncal: tetralogy of Fallot, truncus arteriosus, interrupted aortic arch)

  - **A**bnormal facies (short philtrum, low-set ears, hypertelorism, antimongoloid slant)
  - **T**hymic hypoplasia
  - **C**left palate (palate anomalies, speech delay, learning disability)
  - **H**ypoparathyroidism with hypocalcemia and tetany
  - Chromosome **22**
- Types
  - Partial DiGeorge syndrome (most common)
  - Complete DiGeorge syndrome (< 1% of cases); association with CHARGE (**C**oloboma [eye]; **H**eart defects of any type; Atresia [choanal]; **R**etardation [of growth and/or development]; **G**enital anomaly; **E**ar anomaly) syndrome

Clinical presentation

- Cardiac abnormalities (ranges from asymptomatic to cyanotic)
- Neonatal hypocalcemia
- Immunodeficiency: Ranges from asymptomatic to recurrent sinopulmonary infections to severe combined immunodeficiency, depending on the degree of thymic hypoplasia
- Intellectual disability

Diagnosis

- Serum calcium and phosphorus
- Lymphocyte count (SCID workup if there is evidence of complete DiGeorge syndrome)
- Chest radiograph to evaluate for thymic shadow
- Immunoglobulin levels +/− vaccine antibody titers if indicated
- Renal ultrasound to rule out genitourinary tract abnormalities
- Genetic analysis (FISH, now being replaced by microarray)

Treatment for complete DiGeorge syndrome

- Thymus transplant
- Hematopoietic cell transplant

Prognosis

- Varies significantly—depends on the nature and degree of involvement of different organs
- Many live long productive lives

Chronic Mucocutaneous Candidiasis (CMC)

Background

- The unifying feature of these heterogeneous disorders is impaired cell-mediated immunity against *Candida* species
- Classic forms are due to mutations in the autoimmune regulator gene (*AIRE*) and signal transducer and activator of transcription 1 gene (*STAT1*)

Clinical presentation

- Endocrinopathies
- Autoimmunity: AIHA, ITP, autoimmune neutropenia
- Immunodeficiency
  - Abnormal T-cell proliferation to *Candida* antigen
  - Increased bacterial and viral infections

Diagnosis

- Evaluation for immunodeficiency (CBC, quantitative immunoglobulins, vaccine antibody titers, lymphocyte subsets, lymphocyte proliferation studies)
- *STAT1* function can be evaluated by flow cytometry
- The definitive test is a genetic analysis
- Endocrine evaluation

Treatment

- Systemic antifungal therapy
- Treatment of associated endocrinopathies and autoimmunity
- IgG replacement if indicated

X-Linked Lymphoproliferative (XLP) Syndrome

Background
- Mutation in signaling lymphocyte activation molecule (SLAM)-associated protein (*SAP*) gene

Clinical presentation
- Healthy male until EBV infection
- Average of presentation is 2.5 years
- Fulminant, often fatal **infectious mononucleosis causing** multi-organ failure
  - Can result in secondary hemophagocytic lymphohistiocytosis (HLH)
- Dysgammaglobulinemia
- Lymphoproliferative disease, predominantly non-Hodgkin B-cell lymphomas
- 70% of affected boys die by age 10

Diagnosis
- EBV studies
- Peripheral blood smears will show atypical lymphocytosis, particularly CD8+ T cells
- Hypogammaglobulinemia is common
- NK-cell activity often reduced
- Chemistry profiles will show transaminitis and other findings of acute hepatitis/liver failure
- HLH labs if indicated, including bone marrow biopsy
- Mutation analysis for the *SAP* gene mutation

Treatment
- Rituximab to ablate B-cells
- IgG replacement
- Definitive therapy—hematopoietic cell transplantation

Hyper-IgE Syndrome (HIES)

Background
- Autosomal dominant (AD) (*STAT3*) is more common
- Autosomal recessive (*DOCK8*) also occurs but more rare

Clinical presentation
- AD HIES
  - Recurrent skin abscesses
  - Eczema
  - Recurrent pneumonia with pneumatoceles (staphylococcal infections)
  - Mucocutaneous candidiasis
  - Coarse facial features
  - Bone fractures, scoliosis

Diagnosis
- Elevated serum IgE levels (does not correlate with disease severity)
- Eosinophilia
- Some have decreased IgG levels and poor vaccine antibody responses

Treatment
- Skin care (hydration and control of itch)
- Prophylactic antibiotics to prevent cutaneous and respiratory infections
- Aggressive treatment of infections
- Monitor/treat skeletal abnormalities
- Hematopoietic cell transplantation addresses immunodeficiency but not somatic abnormalities

COMBINED ANTIBODY AND CELLULAR IMMUNODEFICIENCY

Severe Combined Immunodeficiency (SCID)

Background
- Caused by multiple mutations (X-linked, AR, or sporadic) that affect T- and B-cell development
- CD3 T-cell count typically < 300/μL

- CD19/CD20 B-cells and CD16/56 NK-cells may or may not be present, depending on the genetic defect
- Keywords: *Lymphopenia, chronic diarrhea, thrush, failure to thrive, absent thymus, severe recurrent infections, bone abnormalities*

Clinical presentation

- Sibling death in infancy (e.g., multiple deaths during infancy due to infection or unexplained deaths) or previous miscarriages in the mother
- Family history of SCID or other primary immunodeficiency
- Family history of consanguinity
- Most patients present before 3 months of age
- Poor feeding
- Failure to thrive
- Chronic diarrhea
- Recurrent infections, especially pneumonia
- Very small/absent thymus

Diagnosis

- Low CD3 T-cell count, usually < 300/μL. (Note that the normal lymphocyte count in a newborn is ~2500/μL)
- Flow cytometry for lymphocyte subsets to quantify CD3/4/8 T-cells, CD19 B-cells, and CD16/56 NK-cells
- Abnormal lymphocyte proliferation studies to mitogens
- Low quantitative immunoglobulins (initially normal due to maternal transfer of IgG)
- No antibody response to vaccination
- Newborn screening for T-cell receptor excision circles (TREC)

Treatment

- Initial management: Protective isolation, intravenous immunoglobulin (IVIG), *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis, fungal prophylaxis, no live vaccines, palivizumab, cytomegalovirus (CMV) negative blood products, discontinue breastfeeding if mother is CMV positive
- Adenosine deaminase (ADA) enzyme replacement for ADA-deficient SCID
- Definitive: Stem cell transplant, preferably before the onset of severe persistent opportunistic infections and with a matched sibling donor
  - Gene therapy available for some forms of SCID (ADA, X-linked, Artemis)
  - Good survival with early transplant

Complications

- Early graft-versus-host disease (GVHD) from maternal cells crossing the placenta (maternal engraftment)
- Without intervention, SCID usually results in severe infection and death in children by 2 years of age

Wiskott–Aldrich Syndrome

Background

- Genetics: X-linked recessive (Xp11.22–23)
- Results from mutations in Wiskott–Aldrich syndrome protein (WASp) (important in actin cytoskeleton remodeling and impacts interactions between T-cells and APCs, B-cells, etc.)
- Keywords: *Eczema, small platelet, bleeding, recurrent infection*

Clinical presentation

- Classic triad
  - Thrombocytopenia (small platelets)
  - Increased susceptibility to infections
  - Eczema
- Prolonged bleeding from the umbilical stump or circumcision site
- Eczema is often seen during the first year of life
- Recurrent infections (sinopulmonary infections, meningitis, and sepsis) with encapsulated bacteria including *Streptococcus pneumoniae, Neisseria meningitidis, H. influenzae*

- Hepatosplenomegaly
- Autoimmunity: Cytopenias, vasculitis
- Increased risk of lymphoma associated with EBV infection and increased risk of leukemia
- Bleeding is the main cause of death

Diagnosis

- Early onset thrombocytopenia with small platelets
- Screening for WASp by flow cytometry
- Gene sequencing
- Other lab findings:
  - T-cell lymphopenia
  - Abnormal lymphocyte proliferation
  - Abnormal immunoglobulin isotypes
  - Poor vaccine response

Treatment

- Supportive care
  - IgG replacement
  - Prophylactic antibiotics
  - Platelet transfusions
  - Skin care
  - Splenectomy to increase circulating platelets. Not routinely recommended given the increased risk of septicemia with asplenia
- Definitive care
  - Hematopoietic cell transplantation
  - Gene therapy

Ataxia-Telangiectasia

Background

- Affected gene: Ataxia–telangiectasia mutated (*ATM*) at 11q22.3
- *ATM* is expressed in all tissues in the body. Involved in DNA repair and recombination

Clinical presentation

- Progressive ataxia
  - Usual presenting symptom
  - Often appears healthy during the first year and begins to walk, but with slow progression
  - Usually reliant on a wheelchair by 10 years of age. Also, develop dysarthria around this time
- Telangiectasia
  - Conjunctiva (3–5 years of age)
  - Cutaneous (on exposed areas such as pinnae, nose, face, neck)
- Immunodeficiency
  - Humoral and cellular immunodeficiency
  - Recurrent sinopulmonary infections
  - Infections outside of the respiratory tract are not increased

Risk of malignancy

- Lymphoma and leukemia most common
- AT cells are susceptible to ionizing radiation and chemotherapeutic drugs due to defective DNA repair making treatment more difficult and late complications more common

Diagnosis

- Elevated alpha-fetoprotein level (AFP) in children > 8 months of age
  - Level does not correlate with disease severity
- Wide range of immune laboratory abnormalities
  - Immunoglobulin deficiency (often IgA and/or IgG subclasses)
  - Poor antibody response to polysaccharide vaccines
  - Lymphopenia, predominantly of T-cells
- Brain imaging: Cerebral atrophy and ventricular enlargement

Treatment

- IgG replacement
- Antibiotics
- Close monitoring of chronic lung disease
- Swallow evaluation

- Physical and occupational therapy
- Minimize tests with ionizing radiation
- Close monitoring for malignancy

X-Linked Hyper-IgM Syndrome (XHIM)

Background

- Rare primary immunodeficiency caused by mutations in CD40 ligand (CD40L)
  - CD40L (on T-cells) interacts with CD40 (on B-cells) to induce class switching of IgM to other immunoglobulin isotypes
- Considered a combined immune deficiency because dendritic cells and monocytes/macrophages also express CD40 and require CD40L stimulation

Clinical presentation

- Recurrent sinopulmonary infections (primarily encapsulated bacteria)
- Opportunistic infection (PJP pneumonia) is often the presenting symptom
- *Cryptosporidium* infection is common and causes biliary tract disease
  - Common cause of chronic diarrhea that is present in a large percentage of patients
- Increased risk of malignancy

Laboratory findings

- Normal or elevated serum IgM levels associated with low or absent IgG, IgA, and IgE serum levels
- Lack of antibody response to vaccines
- Approximately two-thirds of patients have neutropenia

Diagnosis

- Lack of CD40L expression on T-cells by flow cytometry
- Absent CD40L function as measured by binding to CD40 by flow cytometry
- Confirmatory gene sequencing

Treatment

- Immunoglobulin replacement
- Prompt treatment of infections
- Prevention of *Cryptosporidium* infection by using boiled or filtered water
- Patients with neutropenia may benefit from treatment with granulocyte colony-stimulating factor (G-CSF)
- Definitive: Hematopoietic cell transplantation

DISORDERS OF THE COMPLEMENT SYSTEM

Complement Defect

Background

- Initial defect: Associated with autoimmune diseases
- Terminal defect: Increased risk of infection

Clinical presentation

- Genetic deficiency of C1q, C1r/s, C2, C4, and C3 is associated with autoimmune inflammatory diseases (SLE) and recurrent pyogenic bacterial infections
- Genetic deficiency of C5, C6, C7, C8, and C9 is associated with increased susceptibility to *Neisseria* infections (also some association with rheumatic diseases)

Diagnosis

- Complement (CH50) test: Screen for deficiencies in complement by performing the total serum classic hemolytic complement (CH50) test
  - Note that complement hemolytic activity is unstable and temperature sensitive → CH50 can be reduced if left only a few hours at room temperature
- Direct measurement of individual serum complement proteins, such as C3 and C4, can

also be performed and is helpful in determining the diagnosis

Treatment

- Watch closely for meningococcal disease and treat early
- Vaccination (especially meningococcal and pneumococcal vaccines)
- Antibiotic prophylaxis is not routinely done, but may be needed in some
- Plasma infusions (to replace complement factors) done very rarely

PEARLS AND PITFALLS

- Environmental allergies are responsible for a large proportion of asthma exacerbations in children 5 years and older.
- A positive skin test or an elevated IgE to a particular allergen does not always translate into clinical reactivity.
- Atopic dermatitis developing the first few months of life is an important risk factor for food allergies.
- Allergen immunotherapy has been proven to be effective for treating environmental and insect venom allergy. A similar approach is now being evaluated for the treatment of food allergies.
- Mastocytosis in children is usually limited to the skin and follows a benign course.
- Functional neutrophil disorders include the inability to generate superoxides to kill phagocytosed organisms (CGD) or the inability to properly adhere to blood vessels and leave the circulation to sites of infection (LAD).
- Most of a newborn's IgG is received through the placenta from the mother during the last trimester. There is a physiologic nadir that occurs around 3–6 months of age.
- Normal T-lymphocyte counts in a newborn are usually around 2500/μL. In SCID, CD3 T-cell counts are usually < 300/μL and must be accompanied by poor T-cell function via lymphocyte proliferation assays.
- Newborn screening for SCID is now performed in every state in the United States.
- Terminal complement defects are associated with recurrent *Neisseria* infections, while early complement defects are associated with autoimmunity.
- Hematopoietic stem cell transplant has the potential to cure many immunodeficiencies by using healthy donor stem cells that are capable of producing functional blood immune cells. However, this will not address somatic features of diseases such as ataxia telangiectasia, Chediak–Higashi syndrome, etc.

Suggested Reading

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