Disclosures

- None
Objectives

- Categorize primary immunodeficiencies by presenting symptoms and results of testing
- Recognize oral allergy syndrome
- Recognize and advise patients with food allergies
- Understand the current evaluation and treatment of patients with allergic reactions to medication
Primary Immunodeficiencies

- First recognized in 1952
- Over 200 genetically determined immunodeficiency diseases recognized
  - Molecular basis known for 80%
- Patient usually looks overtly normal
  - So when there is a visible abnormality, it is a great test question.
Immune System

- Self Defense and Surveillance
  - Innate
    - Non specific
    - Reacts quickly
  - Specific
    - Use recognition and receptors
    - Can clonally expand
Immune system Components

- Non specific
  - Complement
    - Critical role against bacteria, fungi and virus
  - Phagocytes
    - Macrophages, neutrophils, NK cells
Specific Immune system Components

- Lymphocytes
  - Recognition: Antigen Specific
    - B-cell
    - T-cell
  - Each receptor on cell is identical
  - Need 10-100 million different and unique lymphocytes
Primary Immunodeficiencies
Relative Distribution

Antibody | Combined | Phagocytic | Cellular | Complement
---|---|---|---|---
50 | 20 | 15 | 10 | 5
Clues to the type of Immunodeficiency

- Features associated with specific immunodeficiency disorders
- Recurrent bacterial otitis media and pneumonia: Hypogammaglobulinemia
- Fungal, protozoal and viral infections: defective cell mediated immunity
- Uncommon bacteria, typically of low virulence: chronic granulomatous disease
Primary Immunodeficiencies
Relative Distribution

- Antibody
- Combined
- Phagocytic
- Cellular
- Complement

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Complement Deficiency

- Role of Complement
  - Critical role in defense against bacteria, fungi and virus
  - Most important in early stage of infection
  - Critical in limiting infection to original site and preventing dissemination
  - Helps clear microorganism from blood stream
Deficiency of early components

- C3 deficiency
  - C3b is opsonic ligand when bound to bacteria
  - increased susceptibility to bacteria for which opsonization is primary defense mechanism
    - Streptococcus pneumoniae
    - Haemophilus influenzae
Deficiency of early components

- C1, C4 or C2 deficiencies
  - Similar to C3 deficiency, as these components are necessary for activation of C3 via classical pathway
  - Not as susceptible as those with C3 deficiency
- Most common inherited complement deficiency is C2
  - Approximately 1 in 10,000
Terminal Component Deficiency

- C5, C6, C7, C8 or C9
- Terminal components assembled into membrane attack complex (MAC)
- Only gram-negative bacteria are susceptible to its bactericidal effects
- Patients susceptible to gram-negative bacteria such as Neisseria meningitidis
Phagocytic Disorders

- Neutropenia
  - Not enough
- Leukocyte Adhesion Deficiency (LAD)
  - Lots, but can’t get where needed
- Disorder of microbicidal activity
  - Enough, but they don’t work
    - CGD
Leukocyte Adhesion Deficiency (LAD)

- Disorder of migration and/or adhesion
- Extreme leukocytosis
  - 15,000-70,000 consistently
  - >100,000 in face of infection
- Abnormal inflammatory response: no pus
- Recurrent bacterial infections
- Delayed separation of the umbilical cord
LAD I

- Lack the leukocyte integrin CD11/CD18 complex
  - CD 18 defect (common beta-chain of beta-2 integrin family)
- CELL SURFACE integrins LFA-1, CR3, p150,95 are deficient
- May be partial (2-8%) or complete
- Autosomal recessive: chromosome 21q22.3 (codes CD18)
LAD II

- Defect is on the endothelial cells, not leukocytes
- Normal levels of CD18
- Defective expression of glycans such as sialyl-Lewis X (SLex) and the H antigen (Bombay)
- Very rare
LAD III

- Doubt this will be tested
- Previously considered LAD I variant
- Affects beta-1, beta-2 and beta-3 integrin families
  - Both leukocytes and platelets affected
- LAD + bleeding complications
- Poor prognosis without BM transplantation
Phagocytic Dysfunction

- Chronic Granulomatous Disease
- Glucose-6 phosphate dehydrogenase deficiency
- Chediak-Higashi Syndrome
- Job’s Syndrome
Phagocytic Dysfunction

Clinical Characteristics

- Range from mild skin infections to severe systemic infections
- Mainly susceptible to low grade virulent bacterial infections
- Skin infections, furunculosis, organ abscess, lymphadenitis
- Delayed separation of the umbilical cord
Chronic Granulomatous Disease

- Most cases are X-linked
  - Affected gene codes for gp91
  - 2006: 2 cases treated with gene therapy and stem cell transplant
    - Bone marrow transplants have had good results
    - Guarded outlook for gene therapy
- Autosomal recessive similar treatment and prognosis
Screening Tests: Phagocytosis

- Leukocyte count with differential: measures total number of neutrophils
- Nitro Blue Tetrazolium (NBT), chemiluminescence: measures neutrophil metabolic function
  - Blue is good: Normal neutrophils turn NBT to blue
- Dihydrorhodamine 123 (DHR) is a newer test
  - Dihydrorhodamine is reduced to rhodamine by normal cells
- Cytochrome c reduction assay
Chronic Granulomatous Disease

- Nitroblue tetrazolium test, quantitative killing curve, superoxide generation or chemiluminescence
  - Functional defect in respiratory burst
- X-linked (autosomal variant)
- Symptoms by 2 years of age
- May survive into second decade and beyond with TMP-SMX prophylaxis
Chediak-Higashi Syndrome

- Phagocytic Dysfunction
- Characteristic abnormality: Giant cytoplasmic granular inclusions in leukocytes and platelets on routine peripheral blood smears.
- Autosomal recessive
- Poor prognosis, but may live into 3rd decade
Primary Immunodeficiencies
Relative Distribution
Antibody (B-Cell) Immunodeficiency Disorders

- Transient hypogammaglobulinemia of infancy
- Common Variable immunodeficiency
- X-linked (congenital) hypogammaglobulinemia
- Immunodeficiency with hyper-IgM
- Selective deficiencies
  - IgA; IgM; IgG subclasses
- X-linked lymphoproliferative disease
- Duncan’s Syndrome: X-linked lymphoproliferative syndrome
- Secondary (drugs, protein losing states)
B-Cell Deficiencies
Clinical Characteristics

- Onset of symptoms: 7-9 months
- Recurrent infections--high grade bacterial pathogens
- Chronic sinopulmonary infections
- Few problems with fungal or viral pathogens
- No growth failure, survival with treatment
- May or may not lack palpable lymph nodes/lymphoid tissues
- Increased allergy/autoimmune diseases
Antibody-mediated Immunity Tests

- Quantitative Immunoglobulins
  - IgG, IgM, IgA

- Isohemagglutinin titer (anti-A and Anti-B): measure IgM antibody function primarily

- Specific antibody levels following immunization
  - Look for 4 fold increase in titer
Common Variable Immunodeficiency

- Onset at any age: Usually become symptomatic at age 15-35
- Recurrent pyogenic infections
- Autoimmune diseases
- Recurrent sinopulmonary infections
- Total Ig and IgG low, B cell #’s NORMAL
- Defect in Toll like receptor signaling
  - TLR 7 and TLR 9
- Normal life span possible
Common Variable Immunodeficiency

- **Diagnostic:** Failure to produce Ab following specific immunization
- **Major complication:** Chronic lung disease that may develop in spite of adequate therapy
- **Increased prevalence of malignant disease:** leukemia, lymphoma and gastric carcinoma
- **RX:** IVIG 100-200mg/kg per month
Selective IgA deficiency

- Most common immunodeficiency
  - 1:600-1:800 prevalence
  - IgA < 5 mg/dl, other Ig levels normal

- Associated with allergies, recurrent sinopulmonary infections, GI tract disease and autoimmune disease

- In atopic population prevalence is 1:200-1:400
Primary Immunodeficiencies
Relative Distribution

- Antibody
- Combined
- Phagocytic
- Cellular
- Complement
T-cell Immunodeficiency Disorders

- DiGeorge’s Syndrome: Congenital Thymic Aplasia
- Chronic Mucocutaneous Candidiasis
  - CMCC
Chronic Mucocutaneous Candidiasis

- Selective T cell defect: B cell immunity intact
- Associated with idiopathic endocrinopathies; hypoparathyroidism is most common
- May appear as late as second decade
- Candidal infections of mucous membranes, skin, nails, vagina: usually NOT systemic candidiasis
- May survive into 3rd decade
- Multiple phenotypes/genotypes
Primary Immunodeficiencies
Relative Distribution

Antibody  Combined  Phagocytic  Cellular  Complement
T-Cell Deficiencies
Clinical Characteristics

- Onset frequently early infancy (4-5 months)
- Recurrent infections
- Opportunistic infections
- Failure to thrive, often fatal in childhood
- Fatal infections -- Live virus vaccines or BCG vaccination
- Graft vs. Host disease following blood transfusions
- Increased incidence of malignancy
T-cell Immunity Screening Tests

- Absolute lymphocyte count
- Chest x-ray for thymus shadow in the newborn period
- Delayed skin hypersensitivity to recall antigens
- Quantitation of T-cell subsets
Combined B and T cell Immunodeficiency disorders

- **SCID**: Severe Combined Immunodeficiency Disease
- **Nezelof’s Syndrome**: Cellular Immunodeficiency with abnormal immunoglobulin deficiency
- **Immunodeficiency with Ataxia-Telangiectasia**
- **Wiskott-Aldrich Syndrome**: Immunodeficiency with Thrombocytopenia, Eczema and Recurrent Infection
- **Graft vs Host**
Immunodeficiency with Ataxia-Telangiectasia

- May reach 5th decade of life
- Predisposition to malignancies
- Autosomal recessive
- Progressive deterioration of neurologic and immunologic functions
- Cerebellar ataxia, oculocutaneous telangiectasias
Oculocutaneous Telangiectasia: Immunodeficiency with Ataxia-Telangiectasia
Wiskott Aldrich Syndrome

- Immunodeficiency with Thrombocytopenia, eczema and recurrent infection
- Thrombocytopenia characterized by small platelets
- X-linked inheritance
  - WASp gene
- Increased incidence of lymphoid malignancies
- IgM is usually low with elevated IgA & IgE
Graft vs Host

- **Hyperacute**
  - maculopapular rash with rapid progression to that resembling toxic epidermal necrolysis, associated with severe diarrhea: Death shortly after reaction

- **Acute** (<100 days)
  - Initial maculopapular rash
  - Diarrhea, hepatosplenomegaly, jaundice, cardiac irregularity, CNS irritability, pulmonary infiltrates

- **Chronic** (>100 days)
  - Chronic desquamation of skin, dysplastic nail growth, hepatosplenomegaly, chronic diarrhea
Immunodeficiencies: Treatment

- **Gamma globulin**
  - B-cell disorders
    - DO NOT use in selective IgA deficiency
  - T-cell disorders only when absent antibody response is demonstrated
- **Hyperimmune Gamma Globulin**
  - Used when specific exposure has occurred
Immunodeficiencies: Treatment

- Fetal thymus transplant
  - DiGeorge’s syndrome
- Adenosine deaminase polyethylene glycol
  - Adenosine deaminase deficiency
- Bone Marrow Transplant
  - Used when T cell function is impaired
- Infusion of erythrocytes
  - Possible benefit in enzyme deficiencies associated with immunodeficiency
Adverse Food Reactions

- Hypersensitivity
  - IgE mediated

- Intolerances:
  - Non IgE mediated
  - Host factors
    - Metabolic
    - Psychologic
  - Food Factors
    - Pharmacologic
    - Toxic
Pathogenesis: Food Allergens

- Glycoproteins
  - Molecular weight: 10-80 Kilodaltons
  - Stable to heat, acid, enzyme
- Children
  - Egg, milk, peanut, soy, fish, wheat
- Adults
  - Peanuts, tree nuts, shellfish, fish, eggs
Food Hypersensitivity

- Anaphylaxis: potentially fatal
- Urticaria/Angioedema
  - Acute (common)
  - Chronic (rare)
  - Exercise-Associated (rare)
- Atopic Dermatitis (pediatric)
Oral Allergy Syndrome

- Oropharyngeal symptoms
  - Primarily itch
- May occur in absence of systemic symptoms
- Fruits and vegetables
- Resolves soon after food exposure ends
Food Allergies: Therapy

- Avoidance
- Preparation for reaction to accidental exposure
  - Patient education
  - Self-administered epinephrine
  - Antihistamines
- No FDA approved desensitization
Unapproved Therapies

- Not FDA approved for FOOD allergy (but being used by some)
  - Subcutaneous immunotherapy
  - Sublingual immunotherapy
  - Oral immunotherapy
- The treatment for food allergies is avoidance and preparation
Drug Reactions

- Common; estimated in 2% - 3% hospitalized patients
- Not all drug reactions are “allergic” there are other types of drug reactions
  - Vancomycin: Red man syndrome
  - Radiocontrast dye: anaphylactoid reaction
Types of Drug Reactions

- Allergic
  - IgE mediated Immunologic response
- Idiosyncratic
- Intolerance
- Side Effects
- Secondary Effects
- Drug-Drug Interactions
- Fixation or phobic reaction
Allergic vs Pseudoallergic Reaction
(anaphylactic vs anaphylactoid reaction)

Pseudoallergic reactions
- closely resemble allergic reactions
- First dose phenomenon: sensitization not required
- premedication can reliably suppress reaction
  - Not necessarily true of allergic reaction
DRESS Syndrome

- Drug rash with Eosinophilia and Systemic Symptoms (DRESS)
  - AKA: Drug Induced hypersensitivity syndrome (DiHS)
- Systemic drug reaction beginning 1-12 weeks into continuous treatment.
- Fever, rash and multi-organ involvement
- Name under debate: eosinophilia not universally present
- Critical point: These patients should not receive drug again: desensitization is not indicated
Penicillin

- Skin testing available
- Penicilloyl: Major determinant
  - most abundant
  - shared by all antibiotics with beta-lactam ring
- minor determinants:
  - more likely cause anaphylaxis
- Cross reactivity with cephalosporins continues to be debated
Patient Risk Factors

- HIV Infection
- Cystic Fibrosis
- Multiple Drug Allergy
- Familial Drug Allergy
Risk Factors: Drug Allergy

- Topical administration > parenteral administration > oral administration
- Prolonged high dose > single dose
- Frequent courses > courses separated by yrs
- Adults with atopic disease *DO NOT* have increased incidence of drug allergy
Management: Drug Allergy

- Careful History of Patient and Drug Allergies
- Ensure drug is indicated
  - Apply knowledge of Infectious Diseases
  - Apply knowledge of Immunochemistry and Immunodiagnostic Screening
- Assess for resensitization: Tolerating one course of therapy does not assure tolerance of another course
- Management plan must be highly individualized
Desensitization

- Alternative medicine where possible
- Desensitization if there is no alternative
- Administer gradually increasing doses
  - Treat through selected reactions
  - Follow patient closely during therapy
- Desensitized state requires continuous presence of drug (not curative)
- Stevens-Johnson syndrome, etc are nearly absolute contraindications to desensitization
Questions?