Approach to the Patient with Suspected Immunodeficiency

Ray J. Rodríguez MD, MPH, MBA
FAAP, FACAAI
Allergy-Immunology
Clinical Laboratory Immunology
Overview

• Recognize history and physical findings suggestive of immunodeficiency
• Recognize most common types of immunodeficiency
• Evaluation of a patient with suspected immunodeficiency
• Recognize when to refer a patient
Immune System

• Host mechanisms for recognition of microbial structures
  – **Innate System**: hard-wired responses that are encoded by genes in the host’s germline and that recognize molecular patterns that are shared by many microbes but are not present in the mammalian host.
  – **Adaptative System**: responses that are encoded by gene elements that somatically rearrange to assemble antigen-binding molecules with high specificity for microbial structures.

• Self Tolerance
Innate System

- *Epithelial barriers* and the mucociliary blanket that sweeps inhaled or ingested particles
- Soluble proteins and bioactive small molecules (*Complement System and Defensins*)
- Substance released from cells as they are activated (cytokines, chemokines, lipid mediators of inflammation and bioactive amines and enzymes)
- **Toll-like receptors**: cell surface receptors that bind molecular patterns expressed on the surface of invading microbes.
Host Immune Defense Mechanisms

**Non-specific**

- Barriers
  - Skin
  - Secretions (mucous, tears, saliva)
  - Mucociliary clearance, peristalsis
- Phagocytes
  - Neutrophils
  - Macrophages
- Complement
- Cytokines

**Specific**

Humoral (antibodies)
Cellular (lymphocytes)
Neutrophils
APC
T-cells
B-cells
Bacterias, viruses
interleukins
complement
SKIN
Antibody
Immunodeficiency

- Healthy patients will have between 6-8 URI/”colds” per year
- Nurseries/Daycare
- Pt’s with allergic rhinitis can have an increase history of sinusitis & OM
- Poorly treated sinusitis
- Cystic Fibrosis, Alpha 1 antitrypsilin deficiency
Immunodeficiency

• Definition
  Immunodeficiency is the result of a diverse group of abnormalities of the immune system resulting primarily in an increased incidence of infection

• Primary Immunodeficiency
  Congenital and hereditary

• Secondary Immunodeficiency
  Acquired on a transient or permanent basis
Immunodeficiency

- The causes of primary & secondary immunodeficiencies are heterogenous
- Over 100 disorders of primary immunodeficiency and rising
- Secondary immunodeficiency: HIV, CMV, starvation, metabolic diseases, drugs, radiation therapy, etc...
  - Cunningham-Rundles et al*.: impairment of the immune response with micronutrient deficiencies: Zinc, Copper, Iron, Selenium, and antioxidant vitamins.

*J Allergy Clin Immunol 2005;115:1119-28
Primary Immunodeficiencies

• Primary immunodeficiencies occur in as many as 1 in 2,000 live births
• Male to female ratio: 5:1 in infants and children but changes to 1:1 in adults.
• Pathology:
  – Abnormal genes producing altered cell proteins
  – Defective synthesis of specific protein
  – Molecular lesions produce failure of cell differentiation
  – Enzyme deficiency
Primary Immunodeficiency

Frequency

- Italy: 1:77,000
- Japan: 1:200,000
- Switzerland: 1:54,000
- Sweden: 1:55,000
- United States: est. 1:100,000
- Puerto Rico: ??
Primary Immunodeficiency General Considerations

- 58% of cases diagnosed in children less than 15 years of age
- 83% of these are males
- X-linked recessive, autosomal recessive, autosomal dominant and sporadic inheritance patterns are observed
B-lymphocyte defects

- X-linked agammaglobulinemia (Bruton’s)
- Common Variable Immunodeficiency (CVID)
- Selective Ig-A Deficiency
- Transient Hypogammaglobulinemia of Infancy
- Functional Hypogammaglobulinemia
- IgG Subclasses deficiency
- Hyper Ig-M Syndrome
An eight-month-old boy was presented to a pediatrician with fever, aseptic meningitis, left ocular and facial palsy, and flaccid paralysis of the lower extremities. Two months earlier, the child had received an oral poliovirus immunization. A presumptive diagnosis of post-infectious polyneuritis was made, but, because of a serum IgG concentration of 9 ml/dl (extremely low).
Based upon the absence of mature B-cells in the circulation and a state of panhypogammaglobulinemia, a diagnosis of X-linked agammaglobulinemia was made.

T-cell immunity was normal. The spinal fluid subsequently grew the vaccine strain of poliovirus.
X-linked (Bruton’s) Agammaglobulinemia

- Gene defect chromosome location: Xq 21.3-22
- B-cell tyrosine kinase deficiency
- Pre-B cells present in reduced # in BM
- Absent circulating mature B-cells
- All major classes of immunoglobulin affected (IgG, IgM, IgA)
- Lack of ability to make an antibody response to antigen
- Sparse lymphoid tissue. High #’s T-cells (nl CD4:CD8)
B- Cell differentiation

- Stem Cell
- Pro B cell
- Early Pre B Cell
- Late Pre B Cell
- Immature B Cell
- Mature B Cell
- Plasma Cell

X-linked A
CVID
X-linked (Bruton’s) Agammaglobulinemia

- Infections begin at 4 - 6 months of life when maternal IgG wanes
- Infections with encapsulated organisms & mycoplasma organisms (Ureaplasma urolyticum)
- Sinusitis, otitis, pneumonia, osteo., septicemia
- Fungal & viral infections are handled well except enteroviruses
- Assoc. conditions: RA (20%) & lymphoreticular malignancies (5%)
The child has done well on monthly intravenous immunoglobulin replacement therapy, but is hemiplegic.

Individuals with a primary immunodeficiency should not be given live virus vaccines.
Case Presentation

• 4 y/o Hispanic male with a history of multiple episodes of cough & fever since his first year of life. Episodes associated with nasal secretions (yellowish-green).
• Multiple MD visits with multiple antibiotic use (x 5 2006).
• So far: x2 OM, x 3 pneumonia
• Cough is triggered by URI’s, exercise, weather changes and strong odors.
• Immunizations: up to date plus 3 doses of Prevnar
Case Presentation

- History of wheezing (on Pulmicort Respules)
- Family History: Mom and sister with asthma. Dad with allergic rhinitis
  - No family history of immunodeficiency
Physical

- Height: 3’ 9.75” (95%)  Weight 53 # (95%)
- HEENT: nose: swollen mucosal membranes with abundant yellowish secretions.
- Lungs: inspiratory and expiratory wheezing.
Assessment

- Asthma
- Rhinitis R/O allergic vs. chronic rhinosinusitis
Labs

• CBC-Diff
  – WBC: 10.7, HgB: 13 PLT 350 k
  – Polys: 39.9%, Lymph: 44.8%, Monos: 6.7%, Eos: 4.9%

• Sinus CT Scan: pansinusitis

• Ig’s
  – IgG: 726 mg/dl
  – IgM: 78.40 mg/dl
  – IgA: < 15 mg/dl
Selective IgA Deficiency

- Most frequently occurring immunodeficiency
- Incidence: 1: 400-700
- Can be caused by phenytoin, sulfasalazine, D-penicillamine, & hydrochloroquine
- Serum IgA concentration <10 mg / dL. No other isotype immunoglobulin deficiency
- 15% of cases associated with IgG subgroup deficiency (IgG2 & IgG4 subclass deficiency)
- Some patients with IgA deficiency are asymptomatic
Selective IgA Deficiency

- Associated with recurrent sinopulmonary infections and autoimmune, GI tract, and endocrine disorders
- GI: giardiasis, nodular lymphoid hyperplasia, Ulcerative Colitis, Cronh’s & Sprue-like syndrome
- Development of anti-IgA antibodies may lead to severe anaphylactic reactions with blood transfusions
- Precaution with IVIG & blood transfusions: anti-IgA Ab’s (no problem with partial deficiency > 5mg/dl)
- Associated with atopy
- Relationship with CVID
Selective IgA Deficiency

• Recently, mutation of \textit{TNFRSF13B} encoding the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) has been described in one patient with IgA deficiency (1/16)

• TACI is expressed on B cells and interacts with the ligands BAFF (B cell activating factor, TNFSF13B) and APRIL (a proliferation-inducing ligand, TNFSF13) expressed on macrophages and dendritic cells.

• Important role in B cell activation and Ig class switching.
Case Presentation

• 21-year-old referred to an AI clinic because of a 3-year history of recurrent pneumonia and recent weight loss.

• The patient related that his health had been perfect until 18 years of age. At that time he was noted to be cachectic and emaciated.

• CXR revealed severe restrictive and destructive lung disease.

• Serum immunoglobulin (IgG, IgA, IgM) were all severely depressed to less than 100 mg/dl each.

• *In vitro* proliferation of his peripheral blood lymphocytes revealed poor responses.
Common Variable Immunodeficiency (Late-Onset Hypogammaglobulinemia)

- Onset usually in 2nd or 3rd decade of life
- Slow decline in all classes of immunoglobulin
- Recurrent sinopulmonary infections (usually bacterial in origin)
- Gastrointestinal, endocrine, hematologic disorders can be associated
- May follow Epstein-Barr infection
B-Cell differentiation

Stem Cell

Pro B cell

Early Pre B Cell

Late Pre B Cell

Immature B Cell

Mature B Cell

Plasma Cell

X-linked A

CVID
Common Variable Immunodeficiency (CVID)

- Mutation of \textit{TNFRSF13B} encoding the transmembrane activator and calcium modulator and cyclophilin ligand interactor (\textbf{TACI}) has been described in a series of patients with CVID (17/181).

- TACI is expressed on B cells and interacts with the ligands BAFF (B cell activating factor, TNFSF13B) and APRIL (a proliferation-inducing ligan, TNFSF13) expressed on macrophages and dendritic cells.

- Important role in B cell activation and Ig class switching.
Common Variable Immunodeficiency (CVID)

- Mutations in the *inducible T-cell costimulator gene (ICOS)*
- ICOS is expressed on the surface of activated T-cells and interacts with ICOS ligand expressed on B-cells.
- Important role in the development of antibody response.
- Unknown why the onset of the clinical symptoms does not occur until late childhood or adulthood.
- Described in 9/226 patients (Black Forest in Germany)

Clin Immunol 2004;113:234-40
Case Presentation

- He was started on monthly IVIG therapy with improvement in his clinical condition.
Hyper IgM Syndrome

XL-EDA-ID  CD 40-ID  CD 40 L-ID

B cell

IKKγ

NFκB

AID, UNG

MHC II

TCR

CD 40

CD 40 L

B-cell proliferation

CSR

SHM

Long-lived PC generation

AID-ID, UNG-ID

B-cell proliferation

CSR

SHM

Long-lived PC generation

AID-ID, UNG-ID

CSR: Class Switching Recombination; SHM: Somatic Hypermutation; AID: Activation induced cytidine deaminase; UNG: uracil nucleoside glycosilade; NFκB: nuclear factor inducing kinase; IKKγ: known as NEMO; NFκB essential modulator; XL-EDA-ID: Ectodermal Dysplasia
## Hyper IgM Syndrome

<table>
<thead>
<tr>
<th></th>
<th>CD 40L defect</th>
<th>CE 40 defect</th>
<th>XL-EDA-ID</th>
<th>AR-AID</th>
<th>AIC-Case</th>
<th>AID</th>
<th>UNG defect</th>
<th>Upstream from DNA cleavage</th>
<th>Downstream from DNA cleavage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protein affected</strong></td>
<td>CD40L</td>
<td>CD 40 AR</td>
<td>NEMO</td>
<td>AID</td>
<td>AID</td>
<td>AID</td>
<td>UNG</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td><strong>Inheritance</strong></td>
<td>XL</td>
<td>AR</td>
<td>XL</td>
<td>AR</td>
<td>AR</td>
<td>AD</td>
<td>AR</td>
<td>AR</td>
<td>AR</td>
</tr>
<tr>
<td><strong>Bacterial infections</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Opportunistic infections</strong></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Lymphadenopathy</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Autoimmunity</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Tumors</strong></td>
<td>+</td>
<td>- (?)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>- (?)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Serum IgG</strong></td>
<td>D</td>
<td>D</td>
<td>Variable</td>
<td>D</td>
<td>D</td>
<td>N-D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td><strong>Serum IgA</strong></td>
<td>D</td>
<td>D</td>
<td>Variable</td>
<td>D</td>
<td>D</td>
<td>N-D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td><strong>Serum IgM</strong></td>
<td>N or E</td>
<td>N or E</td>
<td>N or E</td>
<td>EE</td>
<td>EE</td>
<td>E</td>
<td>EE</td>
<td>N - E</td>
<td>N - E</td>
</tr>
</tbody>
</table>
Hyper IgM Syndrome

- Most patients present in infancy (CD 40 L: X-linked)
- Recurrent bacterial or opportunistic infections (*Pneumocystis jiroveci*-induced pneumonia and diarrhea caused by *Cryptosporidium*)
- Neutropenia
- Severe liver-biliary tract disease progressing to sclerosing cholangitis
- High proportion of patients die before the fourth decade of life
T-cell Immunodeficiency
T-cell Dysfunction : Clinical Characteristics

- **Infections with intracellular microorganisms**
  - Viruses (HSV, V-Z, CMV, EBV)
  - Protozoa (Cryptosporidium, toxoplasma)
  - Mycobacteria
  - Fungal (Candida, \textit{P. carinii})
  - Bacteria, gram negative enteric (T-cell)
  - Bacteria, polysaccharide encapsulated (B-cell)
T-cell Dysfunction: Clinical Characteristics

- Anergy to recall antigens
- Graft versus host disease
- Failure to thrive (especially with diarrhea)
- Increased B-cell malignancies
- Eosinophilia, thrombocytopenia
- Eczema, alopecia
Mutations in several distinct genes SCID

- **Defects in cytokine receptors & signaling**
  - $\gamma_c$ deficiency, X-linked SCID
  - JAK3 deficiency
  - IL-7 receptor $\alpha$ chain deficiency
  - CD 45 deficiency
  - CD 3 $\delta$ chain deficiency

- **Defects in the purine pathway enzymes**
  - ADA deficiency
  - Purine nucleoside phosphorylase deficiency

- **Defects in recombination of the antigen receptor genes of B & T cells**
  - Recombinant Activating gene 1 (RAG 1)
  - Recombinant Activating gene 2 (RAG 2)
  - Artemis deficiency

- **Defects in modifiers of gene expression underlying multisystem disorders:**
  - Cartilage Hair Hypoplasia
  - SCID with alopecia and nail dystrophy
# Lymphocyte Phenotypes in SCID

<table>
<thead>
<tr>
<th>Form of SCID</th>
<th>CD 3</th>
<th>CD 4</th>
<th>CD 8</th>
<th>B cells</th>
<th>NK cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common γ chain, JAK 3, IL-2R α chain, CD 45</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>NL</td>
<td>↓</td>
</tr>
<tr>
<td>IL-7R α chain, CD 3δ</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>NL</td>
<td>NL</td>
</tr>
<tr>
<td>RAG 1, RAG 2</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>NL</td>
</tr>
<tr>
<td>ADA</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>MHC class II</td>
<td>NL</td>
<td>↓</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
</tr>
<tr>
<td>ZAP 70, MHC Class I</td>
<td>NL</td>
<td>NL</td>
<td>↓</td>
<td>NL</td>
<td>NL</td>
</tr>
</tbody>
</table>
Case Presentation

• A 4 month-old infant was noted to have persistent oral thrush due to *Candida albicans*. Barium swallow x-ray, and ulcer craters due to this same organism were observed throughout the esophagus.

• IgG was normal (maternal IgG) but the IgA and IgM were virtually absent.

• Few mature T-cells could be detected by examination of surface antigen phenotypes by flow cytometry, and there was no response of peripheral blood lymphocytes to stimulation by mitogens. *(SCID)*

• The child survived with a bone marrow transplantation from his HLA- and MLC-compatible sister.
Wiskott-Aldrich Syndrome

- Rare X-linked recessive with variable clinical phenotypes (mutation in the WAS protein (WASP) gene (mutations: WAS, XLT, IXLT & XLN)
- Incidence of classic WAS: 1 and 10 in 1 million individuals
- WASP:
  - Key regulator of actin polymerization in hematopoietic cells
  - Has a 5 well defined domains that are involved in signaling, cell locomotion and immune synapse formation
  - Plays an important role in lymphoid development and in the maturation and function of myeloid monocytic cells.
Wiskott-Aldrich Syndrome

- Petechiae, bloody diarrhea, recurrent infections and eczema
- Excessive hemorrhage after circumcision is an early diagnostic sign
- Megakaryocytes in BM, thrombocytopenia due to defective PLT production (PLT’s are small & malfunctional)
Wiskott-Aldrich Syndrome

- Infections with both high & opportunistic org.
- Frequently Coomb’s (+) hemolytic anemia
- High incidence of malignancy (EBV)
- Variable Ig’s (low IgM, elevated IgA & IgE & slightly low IgG)
- Poor Ab response to polysaccharide & some protein Ag’s
- Moderately low T-cells
IFN-γ / IL-12 Pathway Defects

INF-γR1, INF-γR2, IL-12Rβ1, IL-12 p40 & STAT1

T-cells & NK cells

Lymphocyte

IL-12R

STAT 4

INFγ

INFγR

STAT 1

IL-12

IL-12

STAT: Signal Transducer and activator of transcription 1

Mycobacteria

Macrophage

TNFα

STAT: Signal Transducer and activator of transcription 1
IFN-γ / IL-12 Pathway Defects
INF-γR1, INF-γR2, IL-12Rβ1, IL-12 p40 & STAT1

• Patients with the AR mutation leading to complete loss of INF-γR1, INF-γR2 are the most severe
  – Present early in life with disseminated infections
  – Infections with Salmonella and viral (herpes, CMV, parainfluenza and RSV)
  – Treatment: Bone Marrow Transplantation

• Patients with AD mutation in INF-γR1
  – Pathognomonic: multifocal mycobacterial osteomyelitis
  – Treatment: subcutaneous INF-γ
Case Presentation

• On day one of life, a newborn baby sustained a generalized seizure which responded to calcium infusions.

• He was noted to have a systolic heart murmur and a lateral chest x-ray revealed no thymic shadow under the sternum.

• The child was noted to have unusual facies: frontal bossing, saddle-bridge nose, widened epicanthal folds, fish-shaped mouth, shortened upper lip, and small low-set ears.
DiGeorge Syndrome

- Dysmorphogenesis of structures arising from the 3rd & 4th pouches
- Hypertelorism, short philtrum upper lip, low-set ears
- Thymic shadow absent or reduced at birth
- Hypocalcemic tetany (parathyroid)
- Congenital Heart Disease (VSD, conotruncal/atrial)
- Early appearance of mucocutaneous candidiasis
- Mildly lymphopenic but low T-cell function
- Normal B-cells, NI Ig’s (± IgA) with high IgE
## DiGeorge Anomaly: Partial vs Complete

### Partial DGA
- Most frequent
- Thymic hypoplasia
- Normal corticomedullary differentiation
- Presence of Hassall’s corpuscles
- Normal thymic function
- CD4 cells > 400/mm³
- T-cell function adequate
- B-cell numbers and function normal
- Usually free of infections

### Complete DGA
- Uncommon
- Thymic aplasia
- CD4 cells < 400/mm³
- B-cell numbers normal
- Antibody response decreased
- Susceptible to infections
- Susceptible to GVHD
Case Presentation

• An 8-year-old boy was evaluated by a hematologist-oncologist for a suspected diagnosis of leukemia secondary to a greatly enlarged spleen noticed on chest x-ray and a total white blood cell count of 30,000.

• In retrospect, this child has suffered not only repeated bouts of pneumonia but also hard-to-treat cellulitis of the neck and groin.
Chronic Granulomatous Disease

- Recurrent bacterial infection (catalase positive organisms)
  - *Staphylococcus aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Nocardia* species, and *Aspergillus* species
- Granulomas of skin, liver, lungs, lymph nodes observed
  - Staphylococcal liver abscesses: pathognomonic of CGD.
NADPH Oxidase

- Gene defect chromosome location:
  - gp91 phox (XL) (65%)  
  - p22 phox (AR)  
  - p47 phox (AR)  
  - p67 phox (AR)

O_2^- : Superoxide  
SOD: Superoxide dismutase  
H_2O_2 : Hydrogen Peroxide  
MPO: myeloperoxidase

O_2^- : Superoxide  
SOD: Superoxide dismutase  
H_2O_2 : Hydrogen Peroxide  
MPO: myeloperoxidase

CGD

CYTOPLASM

NADPH

NADP+

Rac
Chronic Granulomatous Disease

- Phagocytic cells ingest but do not kill bacteria due to failure to form oxygen radicals
- Diagnosed by:
  - Nitroblue tetrazolium dye test (NBT)
  - Superoxide radical formation (chemiluminescence test)
  - Flow cytometry (dihydrorhodamine 123 assay)
Case Presentation

• An 8-year-old boy was evaluated by a hematologist-oncologist for a suspected diagnosis of leukemia secondary to a greatly enlarged spleen noticed on chest x-ray and a total white blood cell count of 30,000.

• In retrospect, this child has suffered not only repeated bouts of pneumonia but also hard-to-treat cellulitis of the neck and groin.

• All of the tests ordered proved normal except the nitroblue tetrazolium dye reduction by polymorphonuclear leukocytes.

• Flow cytometry (dihydrorhodamine 123 assay)
Case Presentation

• After being seen by six physicians for repeated herpetic lesions of the lips and mouth, misshapen and discolored teeth and severe slow-to-heal skin sores, a three-year-old boy was referred to an allergist-immunology clinic.

• Tests of antibody, complement, and lymphocyte function were normal, but the total white blood cell count was 60,000.

• Moreover, assays of the chemotaxis and random motility of isolated polymorphonuclear leukocytes were remarkably abnormal.
Leukocyte Adhesion Deficiency  LAD 1

• Absent beta subunit β2 integrin (CD18) of 3 cell surface glycoproteins (CD11 family)
• Gene defect chromosome location: 21q22.3; gene product: CD18
• Neutrophils cannot migrate toward inflammatory stimuli or adhere to vascular endothelium
• Diagnosis suggested by:
  – Recurrent soft tissue infections
  – Delayed umbilical cord separation >30 days
  – Severe peridontal disease
  – No pus formation despite high white blood cell counts
Case Presentation

- After being seen by six physicians for repeated herpetic lesions of the lips and mouth, misshapen and discolored teeth and severe slow-to-heal skin sores, a three-year-old boy was referred to an allergist-immunology clinic.

- Tests of antibody, complement, and lymphocyte function were normal, but the total white blood cell count was 60,000.

- Moreover, assays of the chemotaxis and random motility of isolated polymorphonuclear leukocytes were remarkably abnormal.

- There was no surface expression of MAC-1, LFA-1, and P150, 95 glycoproteins on these isolated white blood cells.
Complement Component Deficiency

- Deficiency of most all complement components reported, but still an uncommon immunodeficiency in the population
- C2 deficiency most commonly reported
- Most abnormal genes for complement component deficiencies now isolated
Complement Component Deficiency

• Complement deficiency associated with recurrent pyogenic infection and also connective tissue disease (especially C2 and C4)

• Complement deficiency of components 5 through 8 associated with recurrent Neisseria species infection
Diagnosis of Primary Immunodeficiency

• Medical history
• Physical examination
• Laboratory testing
Medical History in Immunodeficiency

• Thorough history !!!

• **Recurrent** and/or **chronic nature** of the infection

• Infections do not occur only in a single anatomic site, but usually involves **multiple organs** or **multiple sites** within the same organ
Diagnosis of Primary Immunodeficiency

History

Onset of Symptoms

• Birth to 3 months
  – Phagocytic cell defects
  – Complement defects
  – DiGeorge syndrome

• 3 to 6 months
  – Severe combined immunodeficiency (SCID)

• 6 to 18 months
  – X-linked agammaglobulinemia

• 18 months through adulthood
  – Common variable immunodeficiency
  – Complement defects
Primary Immunodeficiency: *Infections*

- Family history of IDS
  - ≥ 8 new ear infections within 1 year
  - ≥ 2 serious sinus infections within 1 year
  - ≥ 2 months on antibiotics with little effect
  - ≥ 2 pneumonias within 1 year

- Need for IV antibiotics to clear infections
- Recurrent, deep skin or organ abscesses
- Reaction to live vaccines
- FTT
- Persistent thrush

*adapted from Jeffrey Modell Foundation*
Medical History in Immunodeficiency

• Sites of Infection
  – Respiratory Tract Infections: B-cell deficiency
  – Gingiva: neutrophil or phagocyte deficiency
  – Recalcitrant thrush: T-cell defect or SCID
  – Skin: neutrophil/phagocyte deficiency or B-cell deficiency
  – Recurrent septicemia: opsonic defect (lack of IgG or Complement Defect)
Medical History in Immunodeficiency

• Sites of Infection:
  – Organ abscesses: neutrophil/phagocyte defects
  – Lymphadenitis: neutrophil/phagocyte defects

• Delayed separation of the umbilical cord >6 weeks: Leukocyte Adhesion Deficiency
Medical History in Immunodeficiency

• Type of organism:
  – Recurrent viral, fungal, mycobacterial, or protozoal infections suggest T-cell defect
  – Repeated infections of invasive encapsulated bacteria: B-cell defect
  – SCID can have all of the above
Medical History in Immunodeficiency

• Type of organism:
  – *Giardia lamblia*: IgA deficiency & CVID
  – Enteroviruses (Echo. & Cocksackie virus): X-linked hypogammaglobulinemia
  – *P. carinii* & *M. avium intracellulare*: T-cell defect
  – Recurrent *S. aureus* skin infections: neutrophil defect
Medical History in Immunodeficiency

• Type of organism:
  – Lymphadenitis (E. coli, Serratia, or Klebsiella): neutrophil/phagocytic defect
  – Recurrent Neisseria infections: late complement defect (C₅-C₈)

• GI disturbances
  – CVID: Yersinia, Campylobacter & Giardia
  – B & T-cell defect: Enteroviruses & CMV
  – Increase incidence of lactose intolerance
Medical History in Immunodeficiency

- Autoimmune/Rheumatic diseases
  - IgA, CVID & Complement Deficiency
- Hematological
  - Anemia, thrombocytopenia, or leukopenia: WAS
  - Autoimmune hemolytic anemia or ITP: CVID, IgA deficiency or Hyper IgM
Physical Exam in Immunodeficiency

- Growth Chart (growth delay, FTT)
- Dysmorphisms:
  - DiGeorge’s & Cartilage-Hair Hypoplasia
- Skin:
  - Eczema: Wiskott-Aldrich, Hyper Ig-E
  - Petechiae: Wiskott-Aldrich
  - Abscesses/Scars: neutrophil, Hyper IgE
  - Telangiectasia: Ataxia-Telangiectasia
Physical Exam in Immunodeficiency

• **EENT:**
  – Absence of tonsillar tissue: X-linked Agammaglobulinemia
  – Periodontitis/Dental erosions: LAD-1

• **Pulmonary:** (Rales/rhonchi, Clubbing)

• **Cardiovascular:** pulmonary hypertension & cardiac anomalies (DiGeorge’s)
Physical Exam in Immunodeficiency

• Others:
  – Hepatosplenomegaly & diffuse adenopathy: HIV infection
Value of Screening Tests

- CBC-Diff
- Serum Ig’s (age)
- Isohemagglutinins
- CXR
- DTH skin test (Anergy Panel)
- C3, C4, CH 50

- Functional Ab levels (pre & post)
- High Resolution Chest CT scan

- Disorder screened by the panel:
  - X-linked Agamm.
  - CVID
  - Selective IgA deficiency
  - SCID
  - Wiskott-Aldrich
  - Neutropenia
  - Complement Deficiencies
  - IgG subclasses
  - Transient Hypogammaglobulinemia of Infancy
Laboratory Evaluation

- Immunoglobulin levels
  - Low IgA is seen in all agammaglobulinemic pts and in selective IgA deficiency
  - Low IgG & its subclasses (IgA deficiency may be associated with low IgG₂)
  - Elevated IgM and low IgA & G
  - Normal ranges of serum immunoglobulins vary with age
Laboratory Evaluation

- Isohemagglutinins
  - Natural IgM antibodies to polysaccharide blood group antigens A and/or B
  - Titers: > 1:10 (children > 1 year old)

- Antibody response to protein (Dipht-Tet.) and polysaccharide (pneumococcus) vaccines
  - Rise in specific Ab’s levels 3 weeks post-vaccine
  - Poor response in children < 2 years of age
  - Response: Polysaccharide: >2-fold; Protein: >4-fold
  - Immunized with polysaccharide vaccines (not with protein based vaccines: newer HIB or Prevnar)
Laboratory Evaluation

• CXR (PA & Lateral views)
  – Look for thymic shadow (DiGeorge or T-cell defect/SCID)
  – Thymus may shrink with stresses, surgery & infection

• DTH Skin Test (Candida, Tetanus & Tricophyton)
  – Check response in 48 hrs
  – Should respond to at least one (>6-12 m)

• Complement
  – \( \text{CH}_{50} \): reflects the activity of \( C_1 - C_9 \) (Classical)
  – C3 & C4
Leukocyte Evaluation

- PMN’s <1500/μL: increased susceptibility for infection
- Adhesion Molecules
  - CD 18, CD 11 a-c: Leukocyte Adhesion Deficiency
- Killing of ingested material
  - Respiratory Burst Activity
    - NBT Test (nitroblue tetrazolium test): changes to a blue color (CGD)
    - Flow cytometry (dihydrorhodamine 123 assay)
Laboratory Evaluation

• Flow Cytometry
  – Fluorescent monoclonal Ab
  – Identification of T & B cells subsets, NK cells, adhesion molecules, cytokines (IL-2R)
  – Separate ranges should be used in children
  – Can be affected by age, gender & adrenocorticoid levels
# CD designations

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Target Cell Recognized</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD 3</td>
<td>Pan T Helper Cell</td>
</tr>
<tr>
<td>CD 3 + CD 4</td>
<td>T helper cells</td>
</tr>
<tr>
<td>CD 3 + CD 8</td>
<td>T cytotoxic cells</td>
</tr>
<tr>
<td>CD 16 + CD 56</td>
<td>NK cells</td>
</tr>
<tr>
<td>CD 19 + CD 20</td>
<td>B cells</td>
</tr>
<tr>
<td>CD 25</td>
<td>Activated cells</td>
</tr>
<tr>
<td>CD 38</td>
<td>Activated cells</td>
</tr>
<tr>
<td>CD 45</td>
<td>Pan leukocyte</td>
</tr>
<tr>
<td>CD 45 RO + CD 4 or CD 8</td>
<td>Memory T cells</td>
</tr>
<tr>
<td>CD 45 RA + CD 62L + CD 4 or CD 8</td>
<td>Naïve T cells</td>
</tr>
</tbody>
</table>
Flow Cytometry

- CD 2  
  Pan T cells
- CD3  
  T-cells
- CD4  
  MHC II
- CD8/CD3  
  MHC I
- CD 19/20  
  B cells
- CD45  
  Leukocytes
- CD 11  
  Adhesion Molecule
- CD 18  
  Adhesion Molecule
PROMPT EARLY DIAGNOSIS IS IMPORTANT
Consult to Allergy-Immunology

- Abnormal screening tests
- Recurrent infections
- Diagnosis and Treatment
- Follow up of immunodeficiency patients who needs special infusions (IVIG)
TREATMENT OPTIONS

• IVIG
• BMT
• Avoidance live viral vaccines (BCG, MMR, oral typhoid and Yellow Fever)
• Irradiation blood products
  – Irradiated, CMV-negative, lymphocyte depleted cellular blood (Graft-Host Disease)
• Prophylactic antibiotics
• Education: Immune Deficiency Foundation (www.primary immune.org) & Jeffrey Model Foundation (www.jmfworld.org)
An infant with SCID who had lethal GVHD from a nonirradiated packed RBC transfusion. Photograph courtesy of Dr Fred Rosen.
Suspected Primary Immunodeficiency

- Are there:
  1. Neisserial infections?
  2. Abscesses and/or fungi
  3. Atypical mycobacteria, Disseminated infection or Opportunistic infection

- Sinopulmonary Bacterial infections only
  - Yes
  - No

- Is there an antibody deficiency
  - Yes
  - No

- Is there a complement deficiency
  - Yes
  - No

- Is there a phagocyte defect
  - Yes
  - No

- Is there a cellular or combined defect
  - Yes
  - No

- SCID a possibility
  - Yes
  - No

- Undefined immunodeficiency or other problem
  - Proceed to referral/therapy

- Emergency! Proceed immediately to referral