How to approach to patient with suspected Immunodeficiency

Dr. Amadia M. Alaki
KSMC, Pediatric Hospital
Pediatric Consultant Allergist & Immunologist

Common Risk Factors for Frequent Infections

- Day-care, school-aged siblings
- Second-hand smoke
- Atopy
- Anatomic abnormalities including ciliary defects
- Retained foreign body
- Gastroesophageal reflux

• Immuno-competent kids may have up to six URIs per year. Ten URIs per year if they attend daycare.
Secondary Immunodeficiencies

- Malnutrition
  - Vit. A deficiency - Infections of GI and resp. tract
  - Zinc deficiency – Acrodermatitis enteropathica, SCID-like syndrome
  - B12 deficiency – impaired immunoglobulin production
  - Protein and caloric deficiency – impaired immune response
  - Iron deficiency

- Frequent or recurrent sinopulmonary infections, malabsorption, nasal polyps…

- Cystic Fibrosis
  - 1:2500
  - More common than most of the immunodeficiencies

Secondary Immunodeficiency

Two most common •
- HIV infection – seventh leading cause of death in children 1-4 years in the US.
  - Third leading cause in black children 1-4 in the urban northeastern US.
  - Always think about it…

Primary Immunodeficiency

- A disorder in one or more components of the immune system.
Components of Immunity

• Humoral (B-cell) – quantitative or qualitative defects in antibody production account for more than 50% of defects.

• Cellular (T-cell) – usually combined with humoral; account for 20-30%.

• Phagocytic – defects in migration, or killing; account for ~18%.

• Complement – account for ~2%.

History Our Guide

• Age of onset

The 10 Warning Signs Of Primary Immunodeficiency

- Eight or more new ear infections within 1 year.
- Two or more serious sinus infections within 1 year.
- Two or more months on antibiotics with little effect.
- Two or more pneumonias within 1 year.
- Failure of an infant to gain weight or grow normally.
- Recurrent, deep skin or organ abscesses.
- Persistent thrush in mouth or elsewhere on skin, after age 1.
- Need for intravenous antibiotics to clear infections.
- Two or more deep-seated infections.
- A family history of Primary Immunodeficiency.
CRUISE
Important historical points

• CHRONIC
• RECURRENT
• UNUSUAL
• INVASIVE
• SEVERE

History Our Guide

Important historical points
– Frequency, duration, severity, complications, response to treatment
– Risk factors
– Family history
– Infection with low-virulence or unusual organisms

Physical Exam

• A benign physical exam does not rule out immunodeficiency.
• Look for:
  ✤ General appearance, weight, overall health
  ✤ Hair,
  ✤ Dysmorphic features
  ✤ Gingivitis, dental erosions, signs of sinusitis

• Tonsillar tissue, adenopathy, splenomegaly
• Arthritis, ataxia, neuro deficits
Disease Specific Skin Findings

- Eczema and petechiae – Wiskott-Aldrich Syndrome
- Telangiectasia – Ataxia-Telangiectasia

Laboratory Evaluation

- CBC with differential
  - Total WBC, ANC, ALC, AEC (age-appropriate values)
  - Lymphopenia = < 3,000 in infants, < 1500 in children and adults
  - Persistently high ANC occurs in LAD
- Hemolytic anemia, thrombocytopenia, leukopenia occurs in some B-Cell deficiencies.
Laboratory Evaluation

- Quantification of serum immunoglobulins
  - IgG, IgA, IgM is the first-step in evaluation for humoral immunity.
  - IgG subclasses do not need to be ordered as screening.
  - IgE only if severe atopy, or chronic dermatitis

Laboratory Evaluation

- Qualitative Evaluation of Antibodies
  - Isohemagglutins – Antibodies to ABO blood-group determinants
  - Antibodies to tetanus and diptheria glycoproteins and pneumococcal polysaccharides.
    - If low titers, give booster, then repeat titers 4 weeks later.
    - Children younger than 2 can not be tested for polysaccharide antigen antibody.

Laboratory Evaluation

- T-Cell Immunity
  - Delayed-hypersensitivity skin tests
    - Intradermal injection of antigens; Candida, tetanus, trichophyton.
    - Should produce redness and induration of > 5mm by 48-72 hours.
    - Severe illness, or steroids can cause diminished responses. (anergy)
  - Mitogen testing
    - In vitro proliferative responses to concanvalin A, phytohemagglutinin
    - Fast Immune
    - Blastogensis

Laboratory Evaluation

- Phagocytic Cell Function
  - Adhesion antigens by flow cytometry (CD11/CD18) – checks for adhesion defects
  - Chemiluminescence – phagocytic killing power
Laboratory Evaluation
• Complement function
  – Total hemolytic complement (CH50) – tests functional integrity of classic complement pathway.
  – AH50 – tests the functional integrity of alternate pathway.
  – The most common reason for an abnormal CH50 is improper handling of specimen.

Management Issues
• Prompt recognition of infection and aggressive treatment
  Obtain cultures, and initiate early empiric therapy for suspected pathogens
• Prophylactic antibiotics for patients with significant T-cell defects. (trimethoprim-sulfamethoxazole)
• Live vaccines should not be given to children with T-cell defects
• Only irradiated, leukocyte reduced, virus-free blood products should be given.
• Monitor growth and weight gain diligently.

Treatment for Primary Immune Deficiencies
• Bone marrow transplantation
• Immunoglobulin replacement
• Enzyme replacement
• Gene therapy
Specific Diseases

History Our Guide

PREDOMINANT T-CELL DEFECTS

- Early onset, usually 2-6 mos
- Bacteria, mycobacteria, viruses: CMV, EBV, varicella; fungi, parasites, PCP, mycobacterium avium-intracellulare
FTT, protracted diarrhea, extensive
Mucocutaneous candidiasis
GVHD caused by maternal engraftment, nonirradiated blood
Hypocalcemic tetany in infancy

Severe Combined Immunodeficiency
- Recurrent infections by three months. Can be life-threatening.
- Candida, PCP, cryptosporidiosis, HSV, RSV, rotavirus, adenovirus, enterovirus, EBV, CMV.
- Absence of lymphoid tissue, lymphopenia, no thymic shadow.
- Anergy, abnormal T-Cell proliferation, +/- B-Cell dysfunction.
- Absence of adaptive immunity.

DiGeorge Anomaly
Variable hypoplasia of thymus and parathyroid.
Hypocalcemia → seizures
- Susceptability to fungi, viruses, PCP.
- T-Cells variable in number, abnormal mitogen studies
- Normal to increased B-Cells, normal antibody levels.
- Microdeletion of 22q11.2
- Associated heart defects, facial anomalies, esophageal atresia.

Ataxia-Telangiectasia
- Recurrent sinopulmonary disease.
- Telangiectasias between 3-6 years.
- Ataxia soon after learning to walk, in wheelchair by 10-12 years.
- Often low or absent IgA.
- Variable depressions of other immunoglobulins.
- Anergy and depressed mitogen studies.
- Risk for lymphoreticular malignancy.
Ataxia-Telangiectasia

- AR, chromosome 11
- 1 case in 100,000 births

- Single gene mutation results in impaired repair of DNA damage = cancer in 1/4 (lymphoma)
- Usually presents in the 2-3 year of life as a lack of balance and slurred speech.
- Ocular telactasia before age of 6. Mild MR in 1/3

Hyper-IgE Syndrome

- Chronic pruritic dermatitis.
- Recurrent staph infections of skin, lungs, joints, and dental infections.
- Course facial features.
- Markedly elevated IgE and eosinophilia.

Hyper-E syndrome

- Pruritic dermatitis (eczema)
- Recurrent staphylococcal abscesses of skin, lung, joints, etc.
- Eosinophilia of blood and sputum
- Ig G, M, A usually normal
- Extremely high Ig E > 1000, high Ig D
- Diminished response to immunization
- Poor cellular and humoral response to neoantigens

Tx: IVIG, BMT

Wiskott-Aldrich Syndrome

- Atopic dermatitis
- Microcytic thrombocytopenia → bleeding
- Recurrent infections with encapsulated bacteria: pneumococcus esp.
- Variable antibody levels. Often low IgM, high IgA and IgE. Poor antibody formation.
- Low to low-normal T-Cells.
- WASPy boys.
Onset after maternal antibodies diminish, usually after 5-7 months, later childhood to adulthood.

**B cell disorders**

- **B cell disorders**
  - X-linked Agammaglobulinemia
    - **Bruton’s X-linked**
      - Well for first 6-9 months
      - Recurrent infections with pneumococcus, H.Flu, Giardia.
      - Minimal tonsillar tissue, and no palpable lymph nodes.
      - <2SD below normal levels of IgG, IgA, IgM, IgE
      - Defect in Btk gene (Bruton tyrosine kinase) → abnormal B-Cells
Recurrent sinopulmonary infections,
- Chronic GI symptoms, malabsorption,
- Arthritis,
- Viral meningoencephalitis
- Autoimmunity,
- lymphoreticular malignancy; thymoma,
- lymphoma

Bacteria: strep, staph, H.flu; Campylobacter, enteroviruses, giardia, cryptosporidia

IgA Deficiency
- 1:400 to 1:800
- Symptoms: GI, GU, RTI infections. Many asymptomatic patients.
- Normal IgG and IgM response to pathogens and vaccines.
- Role in diagnosis of Celiac disease.
- May evolve into CVID.
- Be very careful if pt. develops Kawasaki...

Transient Hypogammaglobulinemia of Infancy
- Decreased IgG beyond 6 months.
- Normal IgA, and variable IgM.
- Able to synthesize antibodies to blood type, diphtheria, and tetanus antigens normally.
- May have increase otitis and sinusitis.
- Usually resolves by 4 years of age.
Common Variable Immunodeficiency
- Recurrent sinopulmonary infections with usual pathogens.
- Low IgG and poor antibody responses to immunizations.
- Variable levels of IgM and IgA.
- Increased risk for autoimmune diseases and malignancy.
- B-Cells phenotypically normal.

Selective IgG Subclass Deficiencies
- Unsure of clinical relevance.
- May be evolving form of CVID.
- May be normal variation.
- Does not need treatment or evaluation unless there is an impaired ability to form antibodies to protein and polysaccharide antigens.

X-linked Lymphoproliferative Syndrome
- Initially asymptomatic.
- Defective response to EBV.
- Fulminant often fatal mono, lymphomas, acquired hypogammaglobulinemia.
- 70% of boys die by 10.
- Impairment of antibody to EBNA
- Viral capsid antigen antibody titers may be absent to exaggerated.

Phagocytic disorders
"Indigestion" = CGD, Chediak-Higashi
**GRANULOCYTE DEFECTS**

- Early onset, delayed separation of cord (>8 weeks), poor wound healing

**Chronic Granulomatous Disease**

- Recurrent abscesses, lymphadenitis, or osteomyelitis at multiple sites.
- Unusual infections with catalase positive organisms: Staph, Serratia, Aspergillus, Candida, Salmonella, gram-enterics.
- Defect in NADPH oxidase enzyme → leading to the inability to produce H2O2.
- No problem with streprococci.
- Chemiluminescence (DHR test)

---

**Phagocytic disorders**

1. NADPH oxidase catalyzes reduction of O₂ to superoxide anion (O₂⁻)
2. Superoxide dismutase converts it to H₂O₂
3. Neutrophil-derived myeloperoxidase (MPO) converts H₂O₂ into HOCl-bleach

- Staph, Pseudomonas, Serratia, Klebsiella;
- Fungi: Candida, Nocardia, Aspergillus

- Dermatitis, impetigo, cellulitis, abscesses, suppurativelymphadenitis, periodontitis, osteomyelitis
Phagocytic disorders

A. Normal peripheral blood smear

B. Peripheral blood smear from a patient with the Chédiak-Higashi syndrome: large perinuclear granules.

C. Peripheral blood smear from a patient with agranulocytosis: the cytoplasm is pale, no granules are present, and nuclei are notched and hyposegmented.

D. Nitroblue tetrazolium test (NBT) in normal neutrophils: phagocytosis results in dark-blue staining of the cytoplasm.

E. NBT in neutrophils from a patient with CGD: there is no phagocytosis = no dark-blue cytoplasmic staining.

F. A hair from a patient with the Chédiak–Higashi syndrome in which giant granules are present, (normal hair on the right).

Leukocyte Adhesion Defect

- 1:10 million
- Striking neutrophilia.
- Recurrent bacterial and fungal infections without pus.
- Severe gingivitis, periodontitis, alveolar bone loss.
- Decreased or absent CD18/CD11 by flow.
- Delayed separation of umbilical cord.

Phagocytic Disorders 1. “commuting”

LAD:
- the defect is a lack of a neutrophil adhesion molecule = no emigration into tissues.
- presents with delayed separation of the umbilical cord, recurrent SBIs, leukemoid reactions

Chediak-Higashi Syndrome

Partial oculocutaneous albinism.
Frequent infections of skin, mucous membranes, respiratory tract. Gram -, Gram +, and fungi.
Large inclusions in all nucleated blood cells.
Accelerated lymphoma-like syndrome; non-neoplastic infiltration of liver, spleen, and lymph nodes associated with recurrent infections and death.
History Our Guide

Complement Defects

- Late (C5-C9) –
- Neisserial infections:
  - meningitis, septic arthritis from gonorrhoeae.

Complement Defects

- Early (C1, C4, and C2) – autoimmune disease
- C3 deficiency – overwhelming sepsis, especially with gram negative organisms

“Twenty years from now you will be more disappointed by the things you didn’t do than by those you did.”

— Mark Twain

...Catch the trade winds in your sails, explore, dream, discover & live...."
Monocytes and macrophages bind
IFN-γ activation:
1. production of hydrogen peroxide (H₂O₂)
2. synthesis & release of IL-12 & tumor necrosis factor (TNF)

A. Resolving mycobacterial infection with normal granuloma formation
B. An AR mutation of the IFN-γ receptor: mycobacteria survive in macrophages
C. Same patient: no granuloma

IL-12 produced by macrophages and dendritic cells in the presence of a pathogen, binds to its receptors on T cells and NK cells, inducing the release of IFN-γ.

Please nooo questions.