Evaluation and Treatment of Immune Deficiency in Adults

Tolly Epstein, MD, MS
Adjunct Assistant Professor of Clinical Medicine
Division of Immunology, Allergy, & Rheumatology

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Disclosures

• None
Learning Objectives

#1: Identify clinical findings that warrant further investigation for primary or secondary immune deficiency in adults.

#2: Formulate a differential diagnosis for suspected immune deficiency in adults, and initiate appropriate testing and sub-specialty referral.

#3: Summarize evidence-based treatment algorithms for immune deficiency in adults, and gain expertise regarding the risks and benefits of treatment.
Case

• 70 year old female admitted to University of Cincinnati Hospital with fever, fatigue, cough
  – Found to have left upper lobe pneumonia on chest X-ray
  – Blood cultures positive for *S. pneumococcus*
  – Improving with IV antibiotics, ready to go home, but the resident notices that the patient has been admitted several times for pneumonia in the past
Case #1

- Further history and review of records reveals 11 lobar pneumonias in the last 20 years
  - Also at least 5-6 episodes of sinusitis per year, and ear pain
  - Minimal infectious history prior to age 50
- Non-smoker
- No history of environmental allergies
- No lymphadenopathy on exam, no chronic night sweats or weight loss
- Outpatient pulmonary function tests were normal 1 and 3 years ago
An impairment in what type of immune response is most likely in an adult presenting with recurrent lobar pneumonias, sinusitis, and/or otitis media?

A. Cell-mediated immunity
B. Humoral immunity
C. Combined immunity (both cell-mediated and humoral)
D. Innate immunity
Innate immunity provides initial defense against infections.

Adaptive immunity develops later and involves greater specificity in terms of recognition and response.
Humoral versus Cell-mediated Immunity

Humoral immunity

- Microbe: Extracellular microbes
- Responding lymphocytes: B lymphocyte
- Effector mechanism: Secreted antibody
- Transferred by: Serum (antibodies)
- Functions: Block infections and eliminate extracellular microbes

Cell-mediated immunity

- Microbe: Phagocytosed microbes in macrophage
- Responding lymphocytes: Helper T lymphocyte
- Effector mechanism: Activate macrophages to kill phagocytosed microbes
- Transferred by: Cells (T lymphocytes)
- Functions: Kill infected cells and eliminate reservoirs of infection
Cellular Immunity is also important for Humoral response to protein antigens
# Pathogens associated with Deficiencies of Innate Immune System

<table>
<thead>
<tr>
<th>Type of immune deficiency</th>
<th>Pathogens involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia/ Phagocytic cell deficiencies e.g. Chronic Granulomatous Disease</td>
<td><em>Staph aureus</em>, Coag negative Staph, oral <em>Streptococci</em>, <em>Enterococcus</em>, <em>Enterobacteriacea</em>, <em>Pseudomonas aeruginosa</em>, <em>Candida</em>, <em>Aspergillus</em></td>
</tr>
<tr>
<td>Complement deficiency</td>
<td><em>Neisseria</em> species (need membrane attack complex), <em>Strep pneumococcus</em></td>
</tr>
<tr>
<td>NK cell deficiency</td>
<td>Viral infections, particularly herpes viruses</td>
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</table>
### Pathogens associated with Deficiencies of Adaptive Immune System

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<tbody>
<tr>
<td>Humoral (B cell/ antibodies)</td>
<td>Extracellular: <em>S. pneumococcus</em>, <em>H. influenza</em>, Giardia, Cryptosporidium</td>
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<tr>
<td>T cell deficiency</td>
<td>Intracellular: including <em>Herpes simplex virus</em> (HSV), <em>Mycobacterium</em>, <em>Listeria</em>, and intracellular fungi (<em>Histoplasma</em>), <em>P. jirovecii</em></td>
</tr>
</tbody>
</table>
• Suspected Humoral immune deficiency
  – Recurrent pneumonias, sinusitis, otitis media
    • Extracellular, common pathogen (S. pneumococcus)
Categories of Immune Deficiency in Adults

1) Secondary immune deficiency due to underlying disease, or due to complication of therapy

2) Known inherited genetic disorder resulting in primary immune deficiency that was diagnosed in childhood (>200 defined so far)

3) Late-onset primary immune disorder presenting in adulthood
Secondary Immune Deficiency in Adults

• Much more common than primary immune deficiency

• HIV infection

• Metabolic disorders
  – Diabetes (neutrophil dysfunction, cardiovascular compromise)
  – Uremia (impaired T,B, and phagocytic cells)
  – Liver failure (leukopenia, neutropenia due to splenomegaly with splenic margination)
Secondary Immune Deficiency in Adults

• Malignancy
  – Chronic lymphocytic leukemia
    • Abnormal cellular and humoral immune responses
    • Up to 50% die from infection
  – Lymphoma
    • Generally humoral immune deficiency unless T cells involved
  – Multiple myeloma
    • May have high IgG but ineffective since mostly from over-producing clone
    • Some may have low B cells and hypogammaglobulinemia
  – Thymoma with hypogammaglobulinemia, and sometimes cellular immune deficiency=
    Good’s syndrome

Tsiodras Mayo Clin Proc 2000
Secondary immune deficiency in Adults

• Medications
  – Immunosuppressives: cytotoxic drugs, glucocorticoids, chemotherapy
  – Monoclonal antibodies, including Rituximab
  – Anti-epileptic drugs

• Radiation---leukopenia, immune cell dysfunction

¹Cooper, B J Hematology 2009
Secondary Immune Deficiency in Adults

- Malnutrition, and vitamin/mineral deficiency (Zinc)
- Protein loss (nephropathy, GI losses, burns)
- Aging
- Asplenia---susceptible to polysaccharide encapsulated bacteria
- Autoimmune diseases associated with complement consumption (Systemic Lupus)
Back to our case of suspected humoral immune deficiency in an adult…

- CBC with differential, liver function tests, renal panel, blood glucose were normal
- HIV negative, Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) negative
- No other signs/symptoms or history consistent with other causes of secondary immune deficiency

Consider a primary immune deficiency
Why should we learn about rare diseases like primary immune deficiencies?

• A disease is no longer rare when it affects our loved ones or ourselves

• Rare diseases often teach us mechanistic lessons that impact the evaluation and treatment of common ones

• Primary immune deficiencies are frequently unrecognized in both adults and children
  – Diagnosis delayed by 12.4 years, on average

Most Patients with Primary Immunodeficiency are Diagnosed in Adulthood

N=1030 patients on immunoglobulin replacement therapy for primary immune deficiency; Immune Deficiency Foundation Survey 2008
Primary Immune Deficiency in Adults

• 1:1200 adults in the US have a primary immune deficiency
  – More common among genetically isolated or consanguineous populations
  – IgA deficiency = most common (1:300-1:600 Caucasians), but usually asymptomatic

  – Common variable immune deficiency (CVID) = 1:25,000 Caucasians
    • Most common clinically important primary immune deficiency in adults

Types of Primary Immune Deficiency Diagnosed in Adulthood

- Common variable immune deficiency: 58%
- Undefined or novel humoral immune deficiency: 13%
- T-cell immune deficiency: 20%
- Combined cellular and humoral immune deficiency: 5%
- Natural killer cell deficiency: 1%
- Phagocytic deficiency: 0%

n=210 patients diagnosed with primary immune deficiency in adulthood;
Excludes IgA deficiency

Srinavasa Am J Med 2012
Which of the following are the most appropriate initial tests for suspected humoral immune deficiency, as in our Case?

A) Lymphocyte subpopulation studies
B) Quantitative IgG, IgM, and IgA subclasses
C) Total IgE level
D) Quantitative IgG, IgM, and IgA levels (total)
Case - Initial testing

- Total IgG=22 (normal= 602-1406)
- Total IgM=20 (normal= 63-263)
- Total IgA=7 (normal= 48-345)

- Lymphocyte subpopulation studies were normal
  - Normal T, B and NK cell numbers
  - Normal CD4/CD8 ratio
In a stable patient with low immunoglobulins, a normal CBC, and recurrent infections, the most appropriate next step is to:

A) Begin Immunoglobulin replacement therapy (IVIG)
B) Perform bone marrow biopsy
C) Check specific vaccine titers
D) Begin prophylactic antibiotics
Diagnostic Criteria for Common Variable Immune Deficiency (CVID)

- IgG levels <2 standard deviations below the mean
- Most patients have low IgA, and many have low IgM
- ***Must document impaired production of specific antibodies= surrogate functional study***
  - Isohemagglutinins= IgM antibodies against blood cell antigens
  - Poor responses to one or more vaccines
- T cell abnormalities are not uncommon

Cunningham-Rundles *Hematology* 2012
Evaluating response to vaccines in adults

1) Check IgG to **Pneumococcus**
   - Polysaccharide antigen (T cell independent)
Check IgG to **Diphtheria and Tetanus**
   - Protein antigens (T cell dependent)

2) Vaccinate with pneumococcus (PPV-23);
   vaccinate with tetanus and diphtheria if low titers

3) Repeat vaccine titers 4-8 weeks later
   - For ages 6-65 years, a normal response to PPV=
     conversion of 70% of serotypes tested with 2-4 fold increase in titers
   - May see less response in adults >65 years

Cunningham-Rundles *Hematology* 2012
Case - Diagnosis

- Inadequate response to pneumococcus, tetanus, and diphtheria vaccines

- Diagnosis = CVID
At what age are most individuals with CVID diagnosed?

(A) Less than age 1 year
(B) Ages 1-4 years
(C) Ages 4-20 years
(D) Ages 20-40 years
(E) Greater than age 40 years
Molecular basis for CVID

• Largely unknown
  – Likely many different diseases grouped together

• Rare autosomal-recessive mutations in B-cell function genes

• 8-10% have mutations in B-cell receptor transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI)
  – Can see same mutations in non-immunodeficient individuals
Pathologic hallmarks of CVID

• A relative or complete loss of plasma cells in the bone marrow and other tissues such as the lamina propria of the GI tract

• Generally have normal total B cell count, but reduced numbers of isotype switched memory B cells (IgG-IgM-CD27+)
Which of the following are not typically considered manifestations of CVID?

(A) Noncaseating granulomatous lung disease
(B) Disseminated histoplasmosis
(C) Chronic diarrhea and malabsorption
(D) Lymphoma
(E) Thrombocytopenia
Manifestations of CVID

N=473 patients followed for 4 years

- Infections only: 32%
- Chronic lung disease: 28%
- Autoimmunity: 28%
- Gastrointestinal disease: 16%
- Granulomatous disease: 14%
- Liver disease/hepatitis: 10%
- Lymphoid malignancies: 8%
- Splenectomy: 7%
- Other cancers: 5%
Morbidity/Mortality from CVID

- Most patients with CVID do not die from infections, if they are treated with immune globulin replacement.

![Graph showing survival rates with and without complications](Image)

- Most common cause of death = Autoimmune conditions or Malignancy (54% lymphoma).

Resnick *Blood* 2012; Cunningham-Rundles *Hematology* 2012
Autoimmune conditions in CVID

- Idiopathic thrombocytopenia purpura (ITP) (44%)
- Autoimmune hemolytic anemia (AIHA) (22%)
- Evans syndrome (ITP + AIHA) (13%)
- Rheumatoid arthritis (10%)
- Anti-IgA antibody (5%)
- Alopecia (3%)
- Others (13%)

Resnick *Blood* 2012
Treatment= Immunoglobulin Replacement Therapy

- Pooled immunoglobulin (95% IgG) from >1,000 donors

- Treat to patient’s “biological” IgG level
  - Evidence that IgG>800 is generally better than IgG>500

Bonagura JCI 2012
FDA approved indications for IVIG

- Allogeneic bone marrow transplant
- Chronic lymphocytic leukemia (CLL)
- Primary immune deficiencies
- Idiopathic thrombocytopenic purpura (ITP)
- Pediatric HIV
- Kawasaki disease
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Kidney transplant with a high antibody recipient or ABO incompatible donor
Potential adverse effects of Immune Globulin Replacement Therapy

- Most common= Headaches
- Aseptic Meningitis/Encephalitis
- Arthralgia/myalgia
- Nephritis/renal failure (*much lower with lower osmotic and low sucrose preparations*)
- Dermatitis
- Venous thrombosis

Bonagura JCI 2012
Potential adverse effects of Immune Globulin Replacement Therapy

• Viral infection (HCV, HBV, HIV)
• Anaphylaxis in IgA deficient patients
• Infusion related and Anaphylactoid reactions (due to immune precipitates)
  – 5-14% of patients on IVIG
  – Pre-medication can help
IV vs SubQ Immunoglobulin Therapy

**Intravenous (IVIG)**

- **Advantages:**
  - Rapid peak for severely ill
  - Dose every 4 weeks
- **Disadvantages:**
  - Rapid loss of IgG after infusion with GI or renal losses
  - Less efficacious at trough level
  - Greater potential for severe adverse events

**Subcutaneous (SCIG)**

- **Advantages:**
  - Stable IgG level
  - Patients can infuse themselves
  - Lower risk of severe reactions
  - Does not require IV access
- **Disadvantages:**
  - Must be given 1X per week
  - High risk of local infusion site reactions (up to 49%)
  - Need highly motivated patient

Bonagura JCI 2012; Moore Ann of Allergy 2008
Resolution- Case

• Patient started IVIG q month, ultimately transitioned to SubQ immunoglobulin replacement due to convenience

• Tolerated very well with no re-admissions and minimal infections
6 Warning Signs for Immune Deficiency in an Adult

(1) ≥ 4 infections requiring antibiotics within 1 year

(2) Recurring infections or infection requiring prolonged antibiotic therapy

(3) ≥ 2 severe bacterial infections (osteomyelitis, meningitis, septicemia, cellulitis)

European Society for Immunodeficiencies 2013
6 Warning Signs for Immune Deficiency in an Adult

(4) Two or more radiologically proven pneumonias within 3 years

(5) Infection with unusual localization or unusual pathogen

(6) Primary immune deficiency in the family

- Early deaths, consanguinity, autoimmune disease

European Society for Immunodeficiencies 2013
Non-infectious clues to Immune Deficiency

- ~6% of patients with primary immune deficiency do not present with infections
- Premature loss of dentition
- Recurrent aphthous ulcers
- Poor/delayed wound healing
- Multiple autoimmune disorders
- Extensive skin warts
- Chronic diarrhea
- Bronchiectasis
Summary

• Suspect immune deficiency in patients with:
  – Recurrent or persistent infections
  – Infections from unusual or less virulent infectious agents
  – Low blood cell counts

• Secondary immune deficiency is more common in adults, but the majority of patients with primary immune deficiency are diagnosed in adulthood
Summary

• Consider pathogen and most likely component of the immune system (innate versus adaptive, humoral versus cellular) when initiating work-up

• Functional studies (vaccine responses) should be conducted prior to making a diagnosis of and initiating treatment for a suspected humoral immune deficiency

• Most primary immune deficiencies in adults can be managed with favorable outcomes, but frequently require life-long replacement therapy
Thank you!

• What questions do you have?