Evaluation of Recurrent Infections and Primary Antibody Deficiencies

Ewa Schafer, MD
October 1, 2016
Disclosure Information
Northshore Pediatric Specialty Symposium
Ewa Schafer, MD

I have no financial relationships to disclose.

I will not discuss off label use and/or investigational use in my presentation.
Learning Objectives

• Identify who should be screened for antibody disorders.
• Describe basic laboratory evaluation of the Immune system.
• Understand how to evaluate for qualitative antibody function.
• Describe treatments available for common antibody immunodeficiencies
Case Presentation

• 12 year old girl referred from ENT for recurrent sinus infections. She is treated for 4-5 sinus infections a year. She also had a history of recurrent ear infections as a young child. She was treated for a pneumonia once in the last year.
Case Presentation

• Medications:
  – Saline rinses rinses daily *
  – Nasonex 1 spray each nostril daily

*not using regularly
Case Presentation - PMH

• Born at 34 weeks gestation.
• Triplet birth
• History of wheezing
• Excision of skin tumor – granulomatous on pathology
Case Presentation- FH

• Paternal Uncles with recurrent sinus infections.
• Brother with autism
• No death from infections
• No lymphomas
• No autoimmune disease.
The patient underwent allergy testing which was negative.

Medications were adjusted.
- Rinses twice a day
- Nasonex 1 spray each nostril twice a day
- Need for compliance reviewed

Cough, nasal congestion, post nasal drip continued.

Need for antibiotics continued
Chronic Sinusitis: A Vicious Cycle of Mucosal Inflammation

Mucosal Swelling
(URI, allergy, environment, etc.)

Bacterial Infection

Ostial Obstruction

pH drops

Mucus Stasis
Chronic Rhinosinusitis - Pathophysiology

- ANATOMIC
- GENETIC/
- IMMUNOLOGIC
- ENVIRONMENTAL
- ANATOMIC
What is Comprehensive Medical Therapy?

- saline irrigations
- topical steroid sprays
- “rescue” systemic antibiotics and systemic corticosteroids for acute exacerbations.
- systemic antihistamines/leukotriene receptor antagonists
Which Antibiotic?

• First line: Amoxicillin +/- clavulanate
• Second line:
  • Doxycycline*
  • Fluoroquinolone*
  • Trimethoprim-sulfamethoxazole**
  • Macrolides**

• Duration: 10-14 days

*American Academy of Otolaryngology- Head and Neck Surgery, Infectious Diseases Society of America
**Canadian Clinical Practice Guidelines
Topical Antibiotics

- Particularly helpful after sinus ostia have been opened.
- Alternative for patients with poor tolerance for PO antibiotics.
- Multiple delivery methods
  - Dissolved in irrigation solution
  - Nebulized
  - Directly instilled under endoscopic guidance

Desrosiers et al., AJR 2007
Etiologies of Recurrent Infections

- Anatomic/Physiologic
- Secondary Immunodeficiency
- Primary Immunodeficiency
Etiologies of Recurrent Infections – Anatomic/Physiologic

- **Recurrent otitis**
  - Cholesteoma
  - TM perforation
  - ETD due to allergy or viral infection

- **Sinusitis**
  - OMU obstruction
  - Nasal polyps
  - Mucocoele
  - Allergic rhinitis
  - Viral infection
  - Inadequate therapy for acute sinusitis

- **Lung**
  - Smoking
  - Intrinsic airway disorders
  - Recurrent aspiration
  - Esophageal disease
  - Bronchial obstruction
  - Unrecognized CF or ciliary dyskinesia

- **GU tract**
  - Urinary stasis
  - Compromised hygiene
  - Diaphragm use
  - Instrumentation
  - Renal calculi, ureteral obstruction, ureteral reflux

- **Skin**
  - Trauma
  - Lymphedema, lymphatic dysfunction, venous insufficiency, chronic edema
  - Prior cellulitis
  - Obesity
  - Poor hygiene

- **Meningitis**
  - Cranial vault defects
  - Chronic mastoid/sinus infection
Conditions Associated with Secondary Immune deficiency

- Immunosuppressive therapy
  - Chemo
  - Pre and post transplant
  - Treatment of autoimmune disease
  - Steroids
- Infections
  - Viral (HIV, measles, HSV)
  - Bacterial infections
  - Mycobacterial infection
  - Parasitic infection
- Malignancy
  - Hodgkin's, CLL, MM
  - Solid tumors
- Homeostasis disorders
  - Diabetes
  - Renal insufficiency/ dialysis
  - Hepatic insufficiency
  - Malnutrition, poor nutrition
- Autoimmune disease (SLE, RA)
- Trauma
  - Burns
- Environmental exposure
  - Allergies
    - Especially in recurrent sinus disease and asthma
  - Radiation
  - Toxic chemicals
- Other
  - Nutritional deficiencies
  - Pregnancy
  - Stress, poor sleep
  - Asplenia
  - Aging
Primary Immunodeficiency

- antibody deficiencies 65%
- phagocytic deficiencies 10%
- complement deficiencies 5%
- cellular deficiencies 5%
- combined cellular and antibody deficiencies 15%
Warning Signs of Primary Immunodeficiency

*The Jeffrey Modell Foundation Medical Advisory Board*

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.
Immune effector mechanisms

- Antibody production
- T cell help
- Intracellular killing
- Antibody
- Complement
- Extracellular killing
- Cytotoxicity
Laboratory Evaluation of the Immune System

• Screening:
  – CBC with diff
  – Comprehensive Chemistry
  – IgG, IgM, IgA, IgE
  – HIV (consider)
  – CH50 (consider)
Laboratory Evaluation of the Immune System

• More specific testing
  – Pneumococcal, Hib, Tetanus titers (i.e. specific antibody titers)
  – Flow cytometry for B/T cells
  – Antigen/mitogen stimulation studies
  – +/- IgG subclasses (consider)
Case Presentation- Evaluation

- An Immune workup was ordered.
Clinical Course – Laboratory evaluation

<table>
<thead>
<tr>
<th>Component</th>
<th>Latest Ref Rng</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGG QUANT</td>
<td>669 - 1529 MG/DL</td>
<td>11/16/2009</td>
</tr>
<tr>
<td>IGA QUANT</td>
<td>51 - 190 MG/DL</td>
<td></td>
</tr>
<tr>
<td>IGM QUANT</td>
<td>37 - 314 MG/DL</td>
<td></td>
</tr>
<tr>
<td>IMMUNOGLOBULIN E, S (IGE)</td>
<td>kU/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>230 (L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 (L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;2.0</td>
<td></td>
</tr>
</tbody>
</table>

Repeat Testing confirmed abnormal values.
## Clinical Course – Laboratory evaluation

<table>
<thead>
<tr>
<th>Component</th>
<th>Latest Ref Rng</th>
<th>11/16/2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>% CD20 B CELL</td>
<td>8 - 24 %</td>
<td>5 (L)</td>
</tr>
<tr>
<td>CD20 CELL NUMBER</td>
<td>200 - 600 CELLS/MCL</td>
<td>80 (L)</td>
</tr>
<tr>
<td>% CD56 NK CELL</td>
<td>6 - 27 %</td>
<td>6</td>
</tr>
<tr>
<td>CD56 CELL NUMBER</td>
<td>70 - 1200 CELLS/MCL</td>
<td>102</td>
</tr>
<tr>
<td>% CD3 TOTAL T CELL</td>
<td>52 - 78 %</td>
<td>87 (H)</td>
</tr>
<tr>
<td>CD3 CELL NUMBER</td>
<td>800 - 3500 CELLS/MCL</td>
<td>1395</td>
</tr>
<tr>
<td>% CD4 T HELPER CELL</td>
<td>25 - 48 %</td>
<td>66 (H)</td>
</tr>
<tr>
<td>CD4 CELL NUMBER</td>
<td>400 - 2100 CELLS/MCL</td>
<td>1059</td>
</tr>
<tr>
<td>% CD8 T SUPPRESSOR</td>
<td>9 - 35 %</td>
<td>19</td>
</tr>
<tr>
<td>CD8 CELL NUMBER</td>
<td>200 - 1200 CELLS/MCL</td>
<td>298</td>
</tr>
<tr>
<td>CD4/CD8 RATIO</td>
<td>1.0 - 3.0</td>
<td>3.5 (H)</td>
</tr>
</tbody>
</table>
Clinical Course – Laboratory evaluation

- Pneumococcal titers 0/23 protective
Primary Antibody Immunodeficiency

- IgA deficiency
- IgG subclass Deficiency
- Specific antibody Deficiency
- Common Variable Immune deficiency

Others:
- Good’s syndrome (adult onset hypogammaglobulinemia with thymoma)
- Hyper IgM – Low IgA, IgG and Normal to Elevated IgM
- Selective IgM deficiency
- Transient hypogammaglobulinemia of infancy
- Hypogammaglobulinemia, unspecified
Clinical Presentation
Antibody Deficiency

Increased susceptibility to infections:

- Encapsulated bacterial organisms
  - H. influenzae
  - S. pneumoniae
- Infection with GNR (pseudomonas and others) may occur especially in patients treated repeatedly with broad spectrum antibiotics
- Mycoplasm, Ureaplasma
- Viruses (enteroviruses)
- Protozoa (giardia, cryptosporidium)
Clinical Presentation
Antibody Deficiency

- Recurrent upper/lower respiratory tract infections are the most common presenting symptom
  - Think about antibody deficiency in patients with > 1 pneumonia, intractable sinusitis, recurrent otitis media
- GI tract infections also common
  - Intractable or recurrent giardia, enteroviruses
- Less common
  - Meningitis, septicemia, osteomyelitis
Laboratory Evaluation of the Immune System

IgA

- Secretory component
- Found in saliva, colostrum and breast milk, tears, mucosal secretions from the respiratory tract, GU tract and prostate

Low IgA leads to more infections in the sinuses, lungs and gut
Laboratory Evaluation of the Immune System

IgM - i.e. “The first responder”

- First antibody to appear in response to the initial exposure to antigen
- Spleen is the major site of specific IgM production
- Large antibody that cannot diffuse well and is found primarily in the serum. Contributes to but by itself is ineffective at opsonization.
Laboratory Evaluation of the Immune System

• IgG
  – Represents 75% of serum immunoglobulins in humans
  – Crosses the placenta, secreted in breast milk, high percentage found in colostrum
  – Involved in many pathways (opsonization, complement pathway, antibody dependent cell-mediated toxicity (ADCC), Type II and III hypersensitivity
Laboratory Evaluation of the Immune System

IgG

- Appears 24-48 hours after antigenic stimulation
- On repeat exposure to the antigen, IgG will proliferate
  - I.e. MEMORY
  - Induced by vaccines
Laboratory Evaluation of the Immune System - Qualitative

- Look at specific antibodies to evaluate B cell function
  - Tetanus (protein function)
  - H. influenzae
  - S. pneumoniae (polysaccharide function)
If levels are low (nonprotective) then vaccinate and assess response to vaccination.

- T cell function
  - Antigen/mitogen stimulation
Laboratory Evaluation of the Immune System - Qualitative

Interpretation of S. pneumoniae titers

- A minimum of 14 pneumococcal serotypes should be assessed (At Northshore we check 23)

- A titer of 1.3 mcg/ml or greater is protective, regardless of prevaccination titer.

- A normal response is defined as the generation of protective titers in more than 70% of serotypes (50% in those age 5 and younger)
Common Variable Immune Deficiency (CVID)

- Most prevalent severe antibody deficiency affecting children and adults
- Incidence: 1:25,000
- Onset: typically after puberty and before 30 years of age, but delay in diagnosis is common
- T cell abnormalities common
  - up to 40%
- Most cases are NOT inherited 80%
  - Family member with IgA deficiency in 8-10%
- Not a single disease
  - Collection of hypogammaglobulinemia syndromes resulting from many genetic defects
CVID

• Age of onset and clinical course is variable
• Delay in diagnosis is common
• Usual presenting symptoms:
  – Recurrent/ chronic upper and lower respiratory tract infections
  – GI infections
• With the use of high dose IgG replacement therapy invasive infections have decreased
• Causes of death
  – Pulmonary disease
  – Malignancy (B cell lymphomas > gastric cancer)
  – Autoimmune complications
  – Liver disease
  – Infection
CVID - diagnosis

- Low IgG AND low IgA and/or IgM
  - > 2 SD below the mean
- Poor response to vaccines
- Exclusion of other causes of hypogammaglobulinemia
  - Medications (rituximab, steroids)
  - Protein loss (GI, lymphatics, renal, burns)
  - Malignancies (B cell lymphomas, myeloma)
  - Bone marrow failure
CVID Noninfectious Complications

• Lung Disease (29%)
  – Diffuse (restrictive)
    • Granulomatous lymphocytic ILD
    • Bronchiolitis obliterans organizing pneumonia (BOOP)
    • Malignancy
  – Obstructive
    • Bronchiectasis
    • Asthma
    • Bronchiolitis obliterans

• Autoimmunity (29%)
  – Hematologic most common (ITP, hemolytic anemia, Evan’s syndrome)
  – RA or RA like
  – Thyroid disease
  – vitiligo
CVID Noninfectious Complications

- **GI disease (15%)**
  - Enteropathy
  - IBD
  - Focal nodular hyperplasia
  - Atrophic gastritis

- **Granulomatous disease (8-20%)**
  - Noncaseating
  - Lymphoid or solid organs

- **Liver disease (9%)**
  - Nodular regenerative hyperplasia
  - Autoimmune hepatitis

- **Neoplasia**
  - Lymphoma (8.2%)
    - Non-Hodgkin’s more common
  - Other (7%)
    - Gastric more common
Treatment of CVID

- **IgG replacement therapy**
  - IV every 4 weeks (400mg/kg)
    - At infusion center or at home with home health
  - SQ every week
    - can be given by the patient

- **Early evaluation and recognition of infections**
Effects of Ig Replacement

• Decreased infections
  – Still have susceptible to sinopulmonary and gut infections
  – Decreased antibiotic use

• Decreased hospitalizations

• May slow the progression of chronic lung disease in patients with CVID
Risks of IVIG

• Chills/fever/flushing/myalgias/malaise/nausea and vomiting (often related to rate)
• Neurologic
  – Headache (common)
  – Migraine and aseptic meningitis
• Renal injury (more so in older preparations in sucrose)
• Hematologic complications (hemolysis, neutropenia)
• Thrombotic complications including CVA, MI, DVT/PE (increased risk with higher doses > 1g/kg)
• Anaphylaxis
• Transmission of blood borne pathogens *
Clinical Course

- Patient was started on IVIG replacement therapy with marked improvement for several years.
- Sinus infections returned.
- Patient underwent limited ESSS
- Compliance with topical therapy addressed.
- Sinus infections now occurring 1-2 times per year at age 18.
Questions?