Immunology Update: Recurrent Infections, Vaccine Responses, and SCID

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Disclosures

• None
Outline

- Recurrent Infections—When to worry
- Diagnostic vaccination
- SCID updates

Overview

Immune System

Innate Immunity  Adaptive Immunity
The Innate Immune System

- Rapid response, first line defense
- Uses pattern recognition receptors to recognize components of microbes
- Elements
  - Skin and mucosal barriers
  - Enzymes
  - Receptors (Toll-like receptors)
  - Complement
  - Phagocytes
  - Natural Killer (NK) cells

The Adaptive Immune System

- Changed and adjusted throughout lifetime
- Extensive repertoire of unique receptors to identify pathogens
- Immunological memory
- Components
  - T cells (cellular response—cytotoxicity, T helper cells)
  - B cells (humoral response—immunoglobulins)
Overview

Innate Immunity

Barriers

Complement

Phagocytes

Immune System

Cellular Immunity

Humoral Immunity

Adaptive Immunity

Primary Immunodeficiencies

- Inherent defect in any aspect of the system
- >200 known PIDS with distinct genetic cause identified*
- Most common are ones that affect humoral immunity
  - Selective IgA deficiency
  - Common Variable Immunodeficiency
- Incidence 1/10,000 to 1/2000 live births*
- Prevalence 1/10,000 to 1/12,000*
- Average time to diagnosis is 12.4 years+
- Can be fatal, severely impact quality of life, cause permanent impairment, and be a large financial burden

* Immune Deficiency Foundation 2007 National Patient Survey
+ Immune Deficiency Foundation 2007 National Patient Survey
What are recurrent infections?

- Frequent
  - 2 or more severe respiratory or bacterial in one year
  - Three or more respiratory infections in one year
  - Need for antibiotics two months/year
- Severe
  - Failure to respond to oral antibiotics
  - Require IV antibiotics/hospitalization
  - Unusual pathogen
  - Unusual complications
  - Unusual site
  - Persistent abnormalities/fever
- Chronic or long lasting

http://www.uptodate.com

Concerning Clinical Features

- Family history of PID
- Unexplained early death
- Failure to thrive
- Chronic diarrhea
- Unexplained autoimmunity/fevers
- Syndromic features
- Complications from a live vaccine
- Skin lesions/nonhealing wounds
- Opportunistic infections

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Causes of RI other than PID

- Exposure—child or sibling in daycare, smoking
- Anatomic abnormalities
- Environmental allergies
- Passive smoke exposure
- Chronic disease—asthma, CF, atopic dermatitis, reflux, others
- Differential dx: malignancy, periodic fever syndrome, etc

Recurrent URIs in a “normal” child

- 10% of children can have 10 or more colds per year, each lasting 8-14 days*
- 50% of children with recurrent infections have no known cause+
- No risk factors
- Normal exam (presence of lymphoid tissue?)
- Growing appropriately
- Healthy in between episodes/recover completely

### Pathogens associated with PID

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<th>T cell</th>
<th>B cell</th>
<th>Granulocyte</th>
<th>Monocytes</th>
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<td>S. Pneumo</td>
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<td>Staph</td>
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<td>H. Flu</td>
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<td><strong>Virus</strong></td>
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<td>HSV, VZV, RSV</td>
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<td><strong>Fungus/Parasite</strong></td>
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<td>Giardia</td>
<td>Aspergillus</td>
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<td>Respiratory</td>
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<td>Autoimmunity</td>
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### Concerning RI—where to start?

- ~10% of children with RI will have an immune defect*  
- **H&P**
  - Birth hx, growth and development, immunizations, meds, illnesses and treatments (age of onset), **fam hx (consanguinity)**, social/environmental hx (exposures)  
- **PE**—thorough with special attention to:  
  - Signs of infection
  - Rashes
  - Lymphoid tissue (tonsils, spleen, LN)—absent or over abundant?  
  - Lung exam
  - Mouth—ulcers, poor dentition, gingivitis  
  - Physical findings associated with PID

Screening Tests—CBC with differential

• Absolute lymphocyte count
  - Lookup/ know normal values!
  - Newborn >2500/μL
  - Older children: age dependent
  - Normal value makes SCID/ T cell defect less likely
    - ~70% lymphocytes are T cells
    - Doesn’t rule it out

CBC

• Absolute neutrophil count
  - Generally elevated in Leukocyte Adhesion Disorder
  - Normal or elevated rules out congenital neutropenia
• Platelet count
  - Normal excludes Wiskott-Aldrich Syndrome
  - Thrombocytosis—possible inflammation
• Howell-Jolly bodies→suggest asplenia
• Any cytopenias concerning
Screening Tests

- ESR/CRP
  - Nonspecific for infection/autoimmune process
- Imaging as indicated
  - CXR
  - sinus films
- Infection evaluation as indicated
- CH50 (total hemolytic complement)
  - Excludes most complement deficiencies

Screening Tests--Immunoglobulins

- IgA, IgM, IgG, IgE
- Low IgA only—Selective IgA deficiency
- Low IgG +/- low A/M
  - Transient hypogammaglobulinemia of infancy
- Low IgG + A/M
  - CVID
  - CD40L (Hyper IgM)
- High IgE
  - Hyper IgE (Job's), Omenn Syndrome, Wiskott-Aldrich, IPEX, allergy, atopic dermatitis
- IgG subclasses generally not helpful—questionable diagnoses
Addional testing by PCP

- HIV
- Testing to r/o other causes of secondary immunodeficiency or underlying disease if warranted

Diagnostic Immunization

- Common method of assessing humoral function
- Pre and post titers should ideally be run in same lab
- Tetanus, Diphtheria, Hib, PCV 7 or PCV13
  - T cell dependent (T and B cells work together)
  - Protein response
- Pneumovax (PPV23)
  - T cell independent polysaccharide response
  - Not approved for under age 2
  - T cell independent responses should not be a part of evaluating young children
Immunogenicity

- Tetanus
  - No significant immunogenic variability
- Protein conjugated Hib and Pneumococcal
  - Variability in immunogenicity
  - Based on protein carrier and antigen

Pneumococcal titers

- Protective defined as 1.3 µg/mL or greater
- Measurement should be done 4-8 weeks after vaccination
- Normal response is conversion from nonprotective to protective
- Most patients with titer >1.3 can mount two fold increase
- Certain strains are more reliably antigenic
- A patient can receive PPV23 if they have received PCV 7 or PCV13
- Specific Antibody Deficiency
  - Intact protein response but deficiency polysaccharide response
- Titers vary with time (2-5 years) in healthy subjects

Pneumococcal titers

- Children 24 months-5 years
  - Conversion of 50% of titers with protective levels/2 fold increase
- People 6-65 years
  - Conversion of 70% to protective/2 fold increase
- Based on limited evidence


When to refer?

- Abnormalities in the screening tests/poor vaccine titers
- Normal work up but clinically worsening patient
- If you feel uncomfortable with the initial workup or patient’s presentation
- Positive family history of PID
- Parent strongly feels that something is wrong and is requesting further evaluation
Severe Combined Immunodeficiency (SCID)

- Absent T cells, impaired humoral function, potentially absent B or NK cells
  - Many genetic causes known
- Pediatric Emergency! Must be referred immediately
  - Transplant before 3.5 months of age, 96% survival
  - After 3.5 months: 70% survival*
- Important to avoid live vaccines (rotavirus)
- Confirmatory test is flow cytometry—not necessary to immediately send genetic testing

* Railey M, Lokhorstins Y, Buckley R. Long-term Clinical Outcome of Patients with Severe Combined Immunodeficiency Who Received Related Donor Bone Marrow Transplants without Pretransplant Chemotherapy or Post-transplant GVHD Prophylaxis. *The Journal of Pediatrics. 2009 Dec; 155(6); 834-840.*
I am not sure who your audience is but you might want to tell them where your lab sends flow (Duke?).
Virginia NBS for SCID

- Started July 2015
- Testing evaluates TREC (T Cell Receptor Excision Circles) as a biomarker for naïve T cells
- Reported as Ct count ("cycle threshold")
  - Higher number is bad
- Can be affected by inadequate DNA, PCR inhibitors like heparin
- RNase P or Beta actin genes used as control DNA

Virginia Results

- One abnormal screen OR one inconclusive → to PCP for repeat
- Two abnormal screens OR one critical screen (including zero) OR two inconclusive screen
  - Consider critical value → called to PCP and immunologist
  - We will see these patients urgently
- NICU babies are a different story
SCID Screening Questions

- What about a normal screen followed by an abnormal/critical??
  - There have been a few reports of PNP or Zap70 (SCID variants) presenting with normal screen followed by abnormal
  - Would suggest at least repeating the screen if it’s critical
  - Other centers and MD call it normal if there is a normal screen
  - Normal followed by critical—concern for ADA
- Validity in older babies?
  - Should still have adequate TREC until 6 months of age

What to tell families?

- This is a screening test and try not to worry because chances are it’s fine
- Ok to continue breastfeeding
- Avoid sick contacts, crowded situations (church, grocery store, etc)
- Good handwashing before touching baby
- No live vaccines until cleared
Where does VA Stand

- Awaiting yearly review of data to determine changes
- Will discuss changing “critical” value from “unsat x 2” to “unsat x 3”
- At least one SCID identified, other variants and lymphopenia

- Please contact us with any concerns

Thank you!