Pulmonary Issues & Complications of Primary Immune Deficiency Disorders (PIDD)

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Disclosures and Conflict of Interest
- Disclosures: I'm not a pulmonologist!
- I'll be wearing my "Immunology hat.”
- Terminology
  - PID = Pelvic Inflammatory Disease
  - PIDD = Primary Immune Deficiency Disorders
- No conflict of interest

Objective:
- When should we think of PIDD in pts presenting with respiratory symptoms?
- Lung symptoms → Immune deficiency
- Who and how do we monitor pts with PIDD for lung complications?
- Immune Deficiency → Lung complications
- WHO: > 185 PIDD

Primary Care
- Pulm
- Derm
- ENT
- Allergy
- Surgeon

Immunol
- Pulm
- Path
- Genetics
Case Study:
- 38 year old surgeon
- In Residency: several bronchitis and recurrent sinusitis, self-treat with antibiotics
- Pneumonia twice
- Recurrent "pink eye" every few months
- PMHx: well child; immunizations up to date.
- FHx: negative for recurrent infections, autoimmune
- SHx: married, non-smoker
- Exam: Normal
- Next step?

PIDD: Epidemiology
Previously thought to be 'uncommon'; true incidence?
Est cases in the US: 500,000 (50,000 new cases/yr)
Gender predominance:
  - More males than females in childhood (5:1)
  - Nearly equal in adults (1:1.4)
Age of diagnosis:
  - Most commonly in infants/children (60%)
  - Need to remember about teens/adults (40%)

High Index of suspicion is needed!
Masked presentations: frequent use of antibiotics and intensive care

Immune Deficiency
Primary
- Humoral
  - IgA deficiency
  - Bruton’s X-linked
  - CVID
- Cellular
  - DiGeorge
- Mixed
- SCID
- Complement
  - Phagocytic disorders
    - CGD, LAD, Chediak-Higashi
Secondary
- HIV
- Drugs: chemo
- Burns
- Splenectomy
- Radiation therapy
- Nutritional deficiency
Relative Distribution of Primary Immunodeficiencies

- 50% antibody def.
- 20% antibody & cellular
- 18% phagocytic def.
- 10% cellular def.
- 2% complement def

Classified Immunodeficiencies - 1984 (N=19)

Antibody defects:
1. XLA
2. HIGM
3. IgA deficiency
4. Selective IgG isotypes
5. Transient hypogammaglobulinemia
6. CVID
7. Immunodeficiency with thymic atrophy
8. Antibody deficiency with normal IgG or hyper IgG

Cell-mediated defects:
1. PNP deficiency
2. ADA deficiency
3. Reticulocytosis syndromes
4. Low T and B cell numbers
5. Predominant T cell defect
6. Immunodeficiency with unusual response to EBV

Other defects:
1. Wiskott-Aldrich
2. Ataxia telangiectasia
3. DiGeorge
4. CGD

Classified Immunodeficiencies - 2005 (N > 150)

T and B cell immunodeficiencies:
1. T-B+ SCID:
   a. Gc
   b. Jak3
   c. IL-7R α
   d. CD45
   e. CD3 δ
2. T-B- SCID:
   a. Rag-1/-2
   b. Artemis
   c. ADA
   d. Reticulocytosis syndromes
3. T+B- SCID:
   a. Omenn's syndrome
4. DNA ligase IV
5. XHIGM (CD40L)
6. CD40
7. PNP
8. DNA ligase IV (X, Y, Z, H2AX, H2AF)
9. C2G
10. C1G
11. C2G deficiency (C2GNA)
12. ZAP-70
13. SH2D1A
14. Top-1
15. Top-2
16. WHN

Predominantly Ab deficiencies:
1. XLA (BTK)
2. AR agammaglobulinemia (µ, Igα, Igβ, BLNK, LIGM1)
3. Ig Heavy chain deletions (IgG1, IgG2, IgG4, IgE, IgA2, IgA1)
4. K chain
5. AID
6. UNG
7. ICOS
8. CVID
9. Selective Ig deficiency (IgG subclasses, IgA, not IgG)
10. Specific Ab deficiency
11. Transient hypogammaglobulinemia

’Other well-defined immunodeficiencies’:
1. WAS (WASP)
2. DNA repair defects:
   a. AT (ATM)
   b. AT-like (MRE11)
   c. NBS (NBS1)
   d. Artemis (Artemis)
   e. DNA ligase IV
   f. Bloom (Helicase)
   g. Werner's (Helicase)
   h. Rothmund-Thomson (Helicase)
3. Thymic defects:
   a. DiGeorge
   b. WHN

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   h. Rothmund-Thomson (Helicase)
Diseases of Immune Dysregulation:

1. Immunodeficiency with albinism:
   a. CHS (LYST)
   b. Griscelli syndrome 2 (Rab27a)

2. HLH:
   a. Perforin
   b. Munc13-4
   c. XLP (SAP/SH2D1A)
   d. GST2

3. Syndromes with autoimmunity:
   a. ALPS:
      i. Type 1a (CD95)
      ii. Type 1b (CD95L)
      iii. Type 2a (caspase 10)
      iv. Type 2b (caspase 8)

Congenital defects of phagocytes:

1. SCN (ELA2)
2. SCN (GFI1)
3. Cyclic neutropenia (ELA2)
4. X-linked neutropenia (WASP)
5. LAD-1 (CD18)
6. LAD-2 (FUCT1)
7. LAD-3 (Rap-1)
8. Rac-2 (LAD-like)
9. β-actin
10. Localized juvenile periodonitis (FPR1)
11. Papillon-Lefevre syndrome (CTSC)
12. Specific granule deficiency (C/EBPα)
13. SDS (SBDS)

Congenital defects of phagocytes, cont.

14. CGD:
   a. X-linked (gp91phox)
   b. AR (p22phox, p47phox, p67phox)

15. G-6PD
16. MPO
17. IL-12/-23R β1/β2
18. IL-12p40
19. IFN-γ R1
20. IFN-γ R2
21. STAT1

Defects in innate immunity:

1. EDA-ID (NEMO)
2. EDA-ID (IκBα)
3. IRAK
4. WHIM (CXCR4)
5. Epidermodysplasia verruciformis (EVER1, EVER2)
6. Microasialoganglioside protein (MGP)
7. MBP associated serine protease 2 (MASP2)

Autoinflammatory Disorders:

1. Familial Mediterranean fever (MEFV)
2. TRAPS (TNFRSF1A)
3. Hyper-IgD (MVK)
4. Muckle-Wells (CIAS1)
5. Familial cold autoinflammatory syndrome (CIAS1)
6. Neonatal onset multisystem inflammatory disease (CIAS1)
7. PAPA (PSTPIP1)
8. Blau syndrome (NOD2)

Complement Deficiencies:

1. C1q
2. C1r
3. C4
4. C2
5. C3
6. C5
7. C6
8. C7
9. C8
10. C9
11. iC3b
12. CI inhibitor
13. FHL-1
14. Factor H
15. Factor D
16. MCP
17. MBP
18. MASP2
19. MCP

Who may have PIDD? History

- Age of onset: earlier age → more severe
- History of recurrent infections
  - Site: lung, otitis/mastoid/sinus, skin, blood, brain, gingivitis, abscess
  - Type (Pathogen): microbiology
- PMH: GI sxs, autoimmune diseases, reaction to vaccines, transfusion
- Family Hx: inheritable or X-linked, consanguinity, sib death

Recurrent infection risk factors

- Atopy
- Smoke exposure
- Anatomic abnormality of airways
- CF

Day care, sibling
GER
FB
Ciliary abnormality
Who may have PIDD? Physical exam

- Normal exam (presence of lymphoid does not rule out)
- Absence of lymphoid tissue-suggestive
- Clues to specific immune deficiency
  - Growth failure: FTT
  - Dysmorphism:
    - Micrognathia, short philtrum, ear
      - Di George (22q11)
    - Short-limb dwarfism
      - Cartilage-Hair Hypoplasia
    - Course facies
      - Hyper-IgE
  - Skin/oral mucosa
    - Rash:
      - XLA, Omenn's, Wiskott-Aldrich, Hyper-IgE
    - Abscesses:
      - PMN, B cells
    - Poor wound healing:
      - Leukocyte adherence defect
    - Petechiae:
      - WAS
    - Candidiasis:
      - T cell, T/B cell, IPEX, CMCC
    - Telangiectasia:
      - Ataxia-Telangiectasia

Physical examination (cont)

- ENT
  - Chronic OM: B cell defect, Mannose Binding Protein
  - Sinusitis/mastoid: B cell defect
  - Dentition/gums/conical teeth: NEMO, LAD, neutropenia

- Respiratory:
  - Clubbing: Any immune component
  - Rales: Any immune component
  - Wheezing: IgA deficiency

- Cardiac:
  - Murmur: Di George

- Lymphatic
  - Absent tonsils: Brutons XLA
  - Hyperplasia: CGD, CVID, HIV, ALPS, XLP

Pulmonary Presentations of Primary Immune Deficiency

- Pneumonia
  - How many? Severity? Complications (empyema)
  - What kinds?
- Bronchiectasis
- Chronic cough
- Asthma
Children

Adults:
2 or more of these signs

Pneumonia

- **Bacterial:**
  - Encapsulated (B cell or complement deficiency)
  - Streptococcal pneumonia, non-typable H flu, Neisseria (rare)
  - Catalase +: (neutrophil or phagocyte defect [CGD])
    - Staph aureus, Burkholderia cepacia, Klebsiella, Serratia, Pseudomonas

- **Mycobacterial**
  - Mycobacterium avium intracellulare (MAI)
  - (T-cell deficiency, NK cell or IL-12/IFN-γ pathway defect)
**Pneumonia**
- **Viral**
  - Herpes, Varicella, CMV (T cell defect, IL-12/IFN-γ, NK cell)
- **Fungal**
  - Candida (T cell deficiency)
  - Nocardia (Phagocyte defect)
  - Aspergillus (T cell or phagocyte defect)
- **Parasites**
  - Giardia: diarrhea (B cell deficiency)
  - Toxoplasma gondii: usually encephalitis (T cell deficiency)
- **Opportunistic**
  - Pneumocystis jiroveci (formerly carinii) (T cell and HIV)
  - Cryptosporidium: usually GI (T cell deficiency)

**Bronchiectasis**
- **Symptoms:** Chronic cough, sputum, hemoptysis
- **Differential Dx**
  - ABPA
  - Viral or pyogenic
  - MAC (Mycobacterium avium complex)
  - CF and cilia (Kartagener’s)
  - Alpha-1 AT deficiency
  - TB
  - PIDD, bronchiolitis obliterans
- **Location**
  - ABPA: proximal/upper
  - Viral or pyogenic: bases
  - MAC: upper
  - CF and cilia: central/diffuse
  - Alpha-1 AT deficiency: lower lobes
  - TB: apices
  - PIDD, bronchiolitis obliterans: diffuse

**Chronic cough or wheezing**
- **Differential Diagnosis**
  - Asthma
  - ACE inhibitor
  - Post nasal drip syndrome from allergies or sinusitis
  - GERD/LPR
  - Bronchiectasis from PIDD
  - CF
  - Pulmonary hypertension from chronic lung disease from repeated infections
  - Exertional dyspnea
- **Evaluation**
  - Spirometry with SABA
  - Allergy testing and limited Sinus CT scan
  - pH probe
  - High Res chest CT; bronch.
  - Sweat test
  - ECG, ECHO, cardiac cath
Asthma and risk of IgA deficiency or CVID: population-based case-control study

**Aims**: To determine the association between history of asthma and a diagnosis of IgA deficiency and CVID. This association may account for increased risks of bacterial infections in some with asthma.

**Methods**: Olmsted County, MN who met diagnostic criteria for IgAD/CVID from 1964 to 2008.

Each case had 4 matched controls (2 community, 2 from pt who had immune w/u).

**Results**: Of 39 cases, 26 (66.7%) had sIgAD and 13 (33.3%) had CVID.

Of the 39 cases, 51% were men (n=20) and 97% white (33 of 34 pts).

Mean age at index date (time when criteria were met) of IgAD/CVID was 34.2 yr.

Of 39 cases, 9 (23%) had history of asthma before index date of sIgAD/CVID; of 156 controls, 16 (10%) had history of asthma before index date (OR, 2.77; 95% CI, 1.09-7.06; P=.03).

**Conclusion**: A history of asthma was more prevalent in IgAD/CVID cases than matched controls.

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**Evaluation of PIDD: Tests**

**B cell Immunity**

- **Screening Tests**
  - CBC w/ diff
  - Quantitative serum immunoglobulins (IgM, G, A, E)
  - Specific antibody to vaccine response
    - Tetanus/Diphtheria: IgG1
    - Pneumococcal and meningococcal polysaccharides (IgG2)
    - Pneumococcal and meningococcal conjugated (IgG1)
    - Viral respiratory pathogens (IgG1 and IgG3)
  - Other vaccines: Hep B, Influenza, MMR, etc.
  - Isohemagglutinins: (IgM antibody to A and B blood group antigens)
  - Flow cytometry for B cell quantification (CD19, CD20)

- **Advanced Testing**
  - In vitro B cell Ig production
  - Regulation of Ig synthesis
  - CD40 ligand-CD40 interaction
  - Molecular analysis for gene deletions or mutations

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**Evaluation of PIDD: Tests**

**Innate Immunity**

- **Screening Tests**
  - CBC (PMN count, morphology)
  - CH50 and AP50
  - Dihydrorhodamine (CGD)
  - Flow cytometry (CD11b, CD15a)

- **Advanced Testing**
  - Phagocytic assays
  - Chemotaxis assays
  - Toll-like rec pathway analysis
  - Molecular analysis for specific defect

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**T cell Immunity**

- **Screening Tests**
  - CBC: ALC
  - Chest x-ray (thymic shadow)
  - OTH skin tests; recall Age

- **Advanced Testing**
  - Lymph proliferative response to mitogens and antigens
  - Lymph mediated cytotoxicity-NK
  - Cytokine production
  - Functional response to cytokines
  - Signal transduction studies
  - Molecular analysis for specific defects
Other Tests

- Cultures and sensitivity
- High resolution Chest CT scan
- ECG, ECHO
- Sweat chloride; gene mutations
- Biopsy for cilia morphology

Key points

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<tr>
<th>Site of Infection</th>
<th>Possible Cause</th>
<th>Screening Diagnostic Test</th>
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<tr>
<td>Upper Respiratory Tract</td>
<td>Ab or complement deficiency</td>
<td>Serum Ig levels, antibody titers to protein &amp; polysaccharide vaccines; isohemagglutinins; CH50</td>
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<tr>
<td>Lower Respiratory Tract</td>
<td>Ab, T cell or complement def phagocytic cell defects</td>
<td>Serum Ig levels; titers to protein and polysaccharide vaccines; isohemagglutinins; CH50; CBC with diff; Respiratory Burst Assay</td>
</tr>
<tr>
<td>Skin &amp; internal organs</td>
<td>phagocytic cell defects</td>
<td>Respiratory Burst Assay/CD11/CD18 Assay</td>
</tr>
<tr>
<td>Blood or CNS</td>
<td>Ab or Complement deficiency</td>
<td>Serum Ig levels, antibody titers to protein &amp; polysaccharide vaccines; CH50</td>
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Case (cont)

- Labs:
  - CBC normal
  - IgG 20, IgA 7, IgM 19, IgE 5
  - Tetanus, Diphtheria and HIB titers: borderline
  - Hepatitis B: low
  - Pneumococcal titer: 2 of 23 protective pre-; 4 of 23 post-
  - B cell markers:
    - Reduced class-switched CD27+IgM-IgD− memory B cells
- Radiology/Pulmonary
  - CXR: normal and Chest CT scan: normal
  - Spirometry: normal
  - Sinus CT: chronic changes
- What is his diagnosis?
CVID (Common Variable Immune Deficiency)

- Most common B cell PIDD in adults; 1 in 25,000 to 50,000
- Age > 4 yrs; delay in diagnosis: 5-7 years
- Common feature: recurrent sinopulmonary infections (73%)
- Lab:
  - low IgG, IgA, IgM (at least 2 < 2 SD) + poor/absent specific Ab
  - B cells: Low CD19+ (memory)
  - T cells: lower CD4+, esp CD45RA+ subset
- Co-morbid conditions:
  - Respiratory:
    - Bronchiectasis: 25%; higher risk if very low IgM and IgA at diagnosis
    - Granulomatous lung disease; (idiopathic-predates hypogammag); 8-12%
    - Granulomatous lymphocytic interstitial lung disease (GLILD): 5-15%
    - HHV-8
  - Lymphoid interstitial pneumonia → lymphoma
  - Autoimmune thrombocytopenia, hemolytic anemia, GI chronic diarrhea (21%)

PIDD Treatment:

- Avoid infections
  - Good hygiene-hand washing
  - Vaccines (not live for T cell defects)
  - Purified/washed blood transfusion
  - IgM-deficient donors
  - Pulmonary hygiene/toilet
- Antibiotics, Anti-viral, Anti-fungal
  - Episodic vs. prophylaxis
    - IV Ig or SC Ig, life-long
    - Antibody deficiencies
  - Other
    - Colony stimulating factors: Neutropenia
    - Stem cell/BM transplant: SCID, T cell
    - Gene therapy: ADA SCID
    - High-dose steroids, CSA, methotrexate: Granulomatous disease
    - Rituximab+azathioprine or mycophenolate: GLILD

Optimizing IVIG Therapy

- Starting dose: 400-600 mg/kg per month
- May take up to 3 months for levels to stabilize
- Need higher doses in pregnancy
- Trough levels >500 mg/dL; (>750 mg/dL)
- IVIG decreased pneumonia from 39% to 22% of CVID pts
- IVIG: 27% reduced risk of pneumonia for each 100 mg/dL increase of trough IgG serum level (up to 1000 mg/dL).
- If bronchiectasis, need higher doses of IVIG

Monitoring (CVID)
- Risks for chronic sinus and lung disease
- Spirometry: annually or 6-month intervals if appears to be progressing at a more rapid rate.
- Complete PFTs: periodically in pts who have interstitial lung disease in order to measure diffusion capacities.
- Chest x-ray: every 5 yrs
- High resolution Chest CT: baseline
- If bronchiectasis:
  - Sputum cultures, spiro w/DLCO
- If interstitial lung disease:
  - Biopsy: flow cytometry for clonal disease (malignancy)
- Labs: may indicate secondary complication or poor prognosis
  - Poor T cell function, decreased switch memory B cells, very low CD21+

Case: Conclusion
- Treatment
  - IVIG (tried SClg)
  - No further pneumonia
  - Less sinusitis
  - Less antibiotics
  - Changed his surgical practice
  - No respiratory complications

Summary
- History: Recurrent, severe, unusual or chronic infections
- Lung manifestations: common presentation of PIDD
  - Pneumonia, bronchiectasis
  - All that wheezes/coughs is not asthma
  - Early diagnosis and treatment of PIDD can prevent complications