Primary Immunodeficiency Disease: Underdiagnosed at any age

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Director of Scientific Affairs
The Binding Site, Inc.
Learning Objectives

• Identify the difference between primary and secondary immunodeficiency, and define categories of Primary Immunodeficiency Diseases (PID).

• Describe testing methodology for determining presence of a PID.

• Discuss potential economic impact of lack of diagnosis of a PID.
What is immuno-deficiency

Consequence of delayed diagnosis

Warning signs

Types of PID

Laboratory investigation

Immuno-deficiency
What is immunodeficiency?

Immune systems ability to fight infectious disease is compromised or entirely absent.
What is immunodeficiency?

- Primary
- Transient
- Secondary
Types of Immunodeficiency

Primary
- Born with defect
- Genetic mutation in an immune system protein

Transient
Characterised by:
- Recurrent infections
- Reduced serum IgGs
- Patients typically recover at around 30-40 months of life.

Secondary
- Born with normal immune system
- Caused by other factors
  - Malnutrition
  - Viruses (HIV)
  - Irradiation/chemotherapy
  - Corticosteroids
  - Leukemia
  - Metabolic disease (e.g. diabetes, liver disease)
What is immunodeficiency?

- Primary
- Transient
- Secondary

Immunodeficiency
What is primary immune deficiency (PID)?

- Over 250 types
- Genetic defects in ≥1 components of the immune system
- Incidence 1/1200
- Childhood or adulthood
- Increased infections:
  - Serious
  - Persistent
  - Unusual
  - Recurrent
- Increased rates of malignancies and autoimmunity
- Runs in family
First recorded history of PIDD – 1952 by Col. Ogden Bruton

- 8 year old boy with recurrent Pneumococcal sepsis
- ≥ 19 episodes in 4 years
- No gamma globulins by SPE
- Vaccination – no effect
- Transferred IgG antibodies - levels lasted for six weeks.
- Monthly intervals of Ig therapy – free from infection (1st recorded case of Ig replacement therapy for PID)
- Later identified as Bruton-type or X-linked agammaglobulinemia (XLA)
- Mutation in Btk gene

How common is PID?

The bar chart shows the percentage of patients diagnosed with PID at different age ranges. The age ranges are:
- 0 to 6
- 7 to 12
- 13 to 17
- 18 to 29
- 30 to 44
- 45 to 64
- 65+

The chart highlights 'Adult Onset' with a particular emphasis on the percentage of patients diagnosed after the age of 6.
Warning signs of immunodeficiency

1. Four or more new ear infections within one year.
2. Two or more serious sinus infections within one year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within one 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.

These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board. Consultation with Primary Immunodeficiency experts is strongly suggested. ©2013 Jeffrey Modell Foundation
Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Two or more new ear infections within 1 year.
2. Two or more new sinus infections within 1 year, in the absence of allergy.
3. One pneumonia per year for more than 1 year.
4. Chronic diarrhea with weight loss.
5. Recurrent viral infections (colds, herpes, warts, condyloma).
6. Recurrent need for intravenous antibiotics to clear infections.
7. Recurrent, deep abscesses of the skin or internal organs.
8. Persistent thrush or fungal infection on skin or elsewhere.
10. A family history of PI.

PID is not just a disease of children.
Severe Combined Immune Deficiency

- Most severe form of PID
- 1:100,000 births
- X-SCID, most common SCID (♂)
- Impaired development of T cells
- B cells present but non functional (no antibody)
- Recurrent infections develop in children <6 months.
- Failure to thrive
- Considered a “Pediatric Emergency”

States screening all newborns for SCID are: WI, MA, NY, CA, CT, MI, CO, MS, DE, FL, TX, MN, IA, PA, UT, OH, WY and KS.
Severe Combined Immune Deficiency

- Lack of T cell function
- Impaired B cell formation

David Vetter (1971-1984)
David Vetter, the Bubble Boy

- b1971 with SCID at Texas Children’s Hospital in Houston
- Infant older brother died of same thing so germ-free delivery arranged
- Lived in sterile plastic bubble until age 12
- Given imperfect match bone marrow transfusion at 12 from sister - became sick
- Lived for 15d out of bubble to get treatment – died from Burkitt’s lymphoma (latent EBV) in 1984, 4 mos after transfusion.
- Genetic defect in his cells that caused SCID was identified (Noguchi 1993 Cell)
- 8/9 children that received gene therapy for X-SCID (IL2R common \( \gamma \) chain receptor) are alive & living ‘outside’ (Dr. David Williams, Boston Childrens Hospital, ASH 2013).
Another notable: First Gene Therapy Recipient – Ashanthi DeSilva

• Born with ADA-SCID, adenosine deaminase def.
• At age 4, 9/14/90, her IV treatment at NIH marked first authorized test of gene therapy on a person in US.
• Dr. W. French Anderson, Dr. Michael Blaese, and Dr. Kenneth Culver performed historic & controversial experiment.
• Her T cell counts returned to normal within 6 mos.
• Treated cells did produce ADA, but did not grow. Consequence afterwards she had repeated gene therapy treatments & enzyme replacement (PEG-ADA) therapy. But considered a success.
Case study: Patient P

<table>
<thead>
<tr>
<th>Time</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td>Weight 3.1 kg (~25th centile)</td>
</tr>
<tr>
<td>3 months</td>
<td>Otitis media</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>5 months</td>
<td>Haemophilus influenzae pneumonia</td>
</tr>
<tr>
<td>11 months</td>
<td>Haemophilus influenzae pneumonia</td>
</tr>
<tr>
<td>16 months</td>
<td>Balanitis</td>
</tr>
<tr>
<td>18 months</td>
<td>Pale and thin</td>
</tr>
<tr>
<td></td>
<td>Weight below 3rd centile</td>
</tr>
<tr>
<td></td>
<td>No family history</td>
</tr>
</tbody>
</table>

Is this normal?
Warning signs of immunodeficiency

1. Four or more new ear infections within one year.
2. Two or more serious sinus infections within one year.
3. Two or more months on antibiotics with little effect.
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## Case study: Patient P

### Serum immunoglobulins

<table>
<thead>
<tr>
<th>Immunoglobulin</th>
<th>Normal range</th>
<th>Value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG (g/L)</td>
<td>5.5 – 10.0</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>IgA (g/L)</td>
<td>0.3 – 0.8</td>
<td>Not detected</td>
<td></td>
</tr>
<tr>
<td>IgM (g/L)</td>
<td>0.4 – 1.8</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Anti-Tetanus toxoid IgG</td>
<td>Not detectable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Diphtheria toxoid IgG</td>
<td>Not detectable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Blood lymphocyte subpopulations (x10^9/L)

<table>
<thead>
<tr>
<th>Lymphocyte subpopulation</th>
<th>Normal range</th>
<th>Value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lymphocyte count</td>
<td>2.5 – 5.0</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>T cells (CD3)</td>
<td>1.5 – 3.0</td>
<td>3.02</td>
<td></td>
</tr>
<tr>
<td>B cells (CD23)</td>
<td>0.1 – 0.4</td>
<td>&lt;0.03</td>
<td></td>
</tr>
<tr>
<td>(CD19)</td>
<td>0.3 – 1.0</td>
<td>&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>(CD20)</td>
<td>0.3 – 1.0</td>
<td>&lt;0.1</td>
<td></td>
</tr>
</tbody>
</table>

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**X-linked agammaglobulinaemia (XLA)**
Case study: Patient P

Primary Immuno-deficiency

Transient Secondary

BTK gene

X-linked agammaglobulinaemia (XLA)
Stem cell → Early pro-B cell → Late pro-B cell → Large pre-B cell → Small pre-B cell

- Heavy chain
- Light chain
- Surrogate light chain

Immature B cell → B-cell receptor

X-linked agammaglobulinaemia (XLA)
Stem cell → Early pro-B cell → Late pro-B cell → Large pre-B cell → Small pre-B cell

Heavy chain

Surrogate light chain

Immature B cell → B-cell receptor

X-linked agammaglobulinaemia (XLA)
Case study: Patient P

Treatment

• 2-weekly intravenous infusions of human normal IgG (IvIg).

| 4 years | Weight now on the 10th centile
|         | Only one episode of otitis media in the past 18 months |
Types of primary immunodeficiency (PID)

- Predominantly Antibody Disorders (PAD)
- Predominantly T-Cell Deficiencies
- Phagocytic Disorders
- Complement Deficiencies
- Other well defined PIDs
- Autoimmune & immunedysregulation syndromes
- Autoinflammatory syndromes
- Defects in innate immunity
- Unclassified PIDs

56.7%

Adapted from Mahlaoui, Rare Diseases and Orphan Drugs 2014;1:25-7
Review: Structure & Function of Antibodies

**Long-term secondary immunity.** Most common. Provides majority of Ab-based immunity against pathogens. Memory Abs. Only Ab capable of crossing placenta.

**Primary.** Eliminates pathogens in early humoral response (before there is enough IgG). On surface of B cells.

**Allergy.** Binds to allergens and triggers histamine release. Also anti-parasitic.

**Antigen receptor on B cells that have not been exposed to antigens. Activates basophils and mast cells.**

**Secretory.** Found in mucosal areas (gut, respiratory tract) to prevent colonization by pathogens. Also found in saliva, tears, and breast milk.
Tests to investigate Immunodeficiency

IgG, IgA, IgM

SPE and sFLC

IgG subclasses

Lymphocyte/Phagocyte count & function

Specific antibodies

Complement

# Total Immunoglobulins (Ig)

**Why test?**
- Dysgammaglobulinemia is a major hallmark of a PAD
- Levels of IgG, IgA, IgM and IgD
- Compare to age specific normal ranges

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Specific Disease</th>
<th>Gene Defect</th>
<th>Ig Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent B cells</td>
<td>XLA</td>
<td><em>BTK</em></td>
<td>↓ IgG, IgA, IgM and IgD</td>
</tr>
<tr>
<td>Normal/Low B cells</td>
<td>CVID e.g. TACI deficiency</td>
<td><em>TACI</em></td>
<td>↓ IgG, IgA but IgM variable</td>
</tr>
<tr>
<td>CSR deficiencies (normal/high B cells)</td>
<td>e.g. Uracil-DNA Glycosylase deficiency</td>
<td><em>UNG</em></td>
<td>↓ IgG, IgA but IgM normal or elevated (Class switching requires recombination)</td>
</tr>
<tr>
<td>Selective IgA deficiency</td>
<td></td>
<td>Unknown</td>
<td>↓ IgA but IgG and IgM normal</td>
</tr>
<tr>
<td>SAD with normal Igs (normal B cells)</td>
<td></td>
<td>Unknown</td>
<td>IgG, IgA, IgM all normal IgG Sc normal</td>
</tr>
<tr>
<td>Periodic Fever Syndromes</td>
<td></td>
<td><em>MVK</em></td>
<td>IgG and IgM can be normal IgD may be elevated</td>
</tr>
</tbody>
</table>
**Properties of IgG Subclasses**

*Why test IgG subclasses?*
- PAD may occur even with *normal* IgG level
- 4 subclasses of IgG with different serum range

<table>
<thead>
<tr>
<th></th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult Serum Range (g/L)</strong></td>
<td>4.9 – 11.4</td>
<td>1.5 – 6.4</td>
<td>0.20 – 1.10</td>
<td>0.08 – 1.40</td>
</tr>
<tr>
<td><strong>% Total IgG</strong></td>
<td>43-75</td>
<td>16-48</td>
<td>1.7 – 7.5</td>
<td>0.8 – 11.7</td>
</tr>
<tr>
<td><strong>Half-life (days)</strong></td>
<td>21</td>
<td>21</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td><strong>Ab response to:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>proteins</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>polysaccharides</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>allergens</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement activation:</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
</tr>
</tbody>
</table>
Vaccine Response assays and response to normally encountered pathogens

Why test?

- Measure ability of immune system to produce functionally active specific antibodies towards specific vaccines.
- Deficiencies can occur with normal IgG and IgG subclass levels.
  - *e.g.* Specific Antibody Deficiency (SAD).
- Examine T-cell dependent and T-cell independent responses
- **Poor response indicates immunodeficiency**

Tests should include responses to:

- **Protein**
  - Tetanus toxoid
  - Diphtheria toxoid
  - Varicella Zoster Virus (glycoprotein)

- **Protein-Polysaccharide conjugate**
  - Hib
    - Haemophilus influenzae type b (behaves like a protein antigen)

- **Polysaccharide (carb)**
  - PCP
  - Pneumococcal capsular polysaccharide
  - Typhi Vi
  - Salmonella typhi vi
Types of antibody deficiency

Common Variable Immune Deficiency
- Low/absent IgG & Low/absent IgA
- Low/normal IgM
- Poor response to vaccines
- >4 years of age (20-40 years)

IgA Deficiency
- Low serum IgA
- Normal serum IgG and IgM
- Normal IgG Ab response to vaccines
- >4 years of age
Types of antibody deficiency

IgG Subclass Deficiency

- Normal levels of IgG, IgA and IgM
- Two of IgG\textsubscript{1-3} subclasses low or deficient
- Poor response to some vaccines

Specific Antibody Deficiency

- Normal levels of IgG, IgM and IgA
- Normal IgG subclass levels
- Poor response to most polysaccharide vaccines
## Types of antibody deficiency

<table>
<thead>
<tr>
<th></th>
<th>Laboratory investigations</th>
<th></th>
<th></th>
<th></th>
<th>Vaccination response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG</td>
<td>IgG subclass</td>
<td>IgA</td>
<td>IgM</td>
<td></td>
</tr>
<tr>
<td><strong>CVID</strong></td>
<td>Low</td>
<td>Abnormal</td>
<td>Low</td>
<td>Normal/low</td>
<td>Poor</td>
</tr>
<tr>
<td><strong>IgA deficiency</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Absent</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>IgG subclass deficiency</strong></td>
<td>Normal</td>
<td>Two of IgG1/G2/G3 low</td>
<td>Normal</td>
<td>Normal</td>
<td>May be poor</td>
</tr>
<tr>
<td><strong>Specific antibody deficiency</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Poor (mostly polysaccharide)</td>
</tr>
</tbody>
</table>
Antibiotics

IVIG

Treatment

Stem cell transplant
Case Study 1

- 48 year-old man – admitted for weight loss associated with intermittent diarrhea
- History of pneumonia as a child and once as a young man
- At age 33 years – chronic sinusitis, persistent headaches, under-weight

Investigations
1. Total serum IgG and IgM – normal but IgA - very low.
2. IgG1/3 – very low         IgG2 – normal         IgG4 – high
3. Immunization responses –
   T.tox, Diphtheria – poor response,
   Pneumovax – normal response

Diagnosis  IgA and IgG SUBCLASS DEFICIENCIES (with chronic sinusitis)

Essentials of Clinical Immunology.
H. Chapel et al.
Case Study 2

- 35 year old woman
- History of recurrent respiratory tract infections, candidiasis and urinary tract infections
- No underlying cause – symptoms possible psychosomatic!
  - Treated for depression

Investigations (Referred to hospital immunology department)
1. Total serum IgG, IgM and IgA normal
2. IgG1 – normal  IgG2 – normal  IgG4 – normal
3. IgG3 – greatly reduced

Diagnosis

IgG SUBCLASS DEFICIENCY
(recurrent infections reduced with subsequent IVIG therapy)
Snowden, et al 1984
Case Study 3

- 3 mos old - developed otitis media and an upper respiratory tract infection
- 5 mos and 11 months – *Haemophilus influenzae* pneumonia
- 16 mos – Candida infection
- 18 mos – failure to thrive
- Fully immunized – tetanus/diphtheria toxoids, pneumococcal, pertussis, Hib vaccine and oral polio

**Immunological investigations**
1. Total serum IgG/A/M – very low IgG and IgM, no detectable IgA
2. Immunization responses – no IgG antibodies detected

**Diagnosis**

*X-LINKED AGAMMAGLOBULINAEMIA (XLA)*
*(confirmed by detection of mutated Btk gene)*
Antibody deficiency and diagnostic delay

Median delay

<table>
<thead>
<tr>
<th>Hospital stay?</th>
<th>Major infection</th>
<th>Minor infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>10 points</td>
<td>5 points</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Examples
- Pneumonia
- Meningitis
- Osteomyelitis
- Septic arthritis
- Septicaemia
- Chest infection (requiring antibiotics)
- Sinusitis
- Otitis
- Gastroenteritis
- Skin sepsis

Accumulated morbidity 25 points

2 years
Complement Deficiencies

- Rare – only 2% of all PIDs
- Deficiency of any component of complement cascade (or regulatory proteins)
- Clinical indications: recurrent mild or serious bacterial infections, autoimmune disease or episodes of angioedema
- Two categories:
  - Disorders of proteins that *inhibit* complement system → Overactive immune response
    - Hereditary angioedema and hemolytic-uremic syndrome
  - Disorders of proteins that *activate* complement system → Underactive immune response
    - Susceptibility to infections
- No supplemental therapy available
Complement Deficiency

Why test?

(1) Even with normal IgG and normal vaccine responses the patient may present with symptoms of PID.
(2) Some specific clinical presentations raise the possibility of complement deficiency.
    Includes: >1 episode of invasive meningococcal infection or other *Neisserial* bacteria.

Guidelines – if all antibody responses are normal and patient has recurrent meningococcal disease test for complement deficiency.
Serum Proteins in the Complement Pathway

- Serum proteins (C1-C9)
- Lysis of foreign cells (C5-C9 form Membrane Attack Complex MAC)
- Inflammation (C5a, C3a) via release of histamine, which increases vascular permeability
- Phagocytosis (C3b) via opsonization
- MAC complex formation (CH50)
Three mechanisms of complement activation

“starting the complement cascade”

1. Classical Pathway: Initiated by Antibody-Antigen complexes


3. Lectin Pathway: Initiated by lectin binding to mannose on pathogen
Activation of Complement Pathway

Adaptive

CLASSICAL PATHWAY

C1
Ag-Ab complex
C4
C4a
C4b2b (C3 convertase)
C2
C2a

LECTIN PATHWAY

Mannan-binding Lectin binds to mannose on pathogen surface
C4
C2
C4b2b (C3 convertase)
C3

ALTERNATIVE PATHWAY

C3b
Initiation factor C3a
C3b
Factor B
C3bBb (C3 convertase)
Ba
Factor D

All 3 pathways converge

Lead to formation of MAC

C5b6789 (Membrane Attack Complex)
C5a
C5b
C6
C7
C8
CYTOLYSIS
Complement Function I: Activation of the Membrane Attack Complex

1. Antibody molecules attach to antigens on pathogen’s plasma membrane.
2. Complement proteins link two antibody molecules.
4. MAC pores in the membrane causes cell lysis.

MAC: hole punched in bacterial cell membrane
Complement Function II: Opsonization
If one of the complement factors (C1 – C9) is missing or dysfunctional, the cascade slows down or stops.

The main tests that measure total complement activity are CH50 and CH100.
CH50 Clinical Significance

• Low CH50 levels suggest possibility of complement component deficiency (C3, C4, C1, etc.)

• National (IDF) and International (ESID) Guidelines for Primary Immunodeficiency recommend screening with CH50 in diagnostic workup of complement deficiency\(^1,2\)

1. Immune Deficiency Foundation (IDF) Diagnostic Care and Clinical Care Guidelines, 2008
2. European Society for Immunodeficiencies (ESID) www.esid.org
Assays that Measure Complement

- **Classical Complement CH50**
  - Screening test – measures total classical complement activity via MAC Complex Formation
  - Recommended as part of diagnostic protocol for Primary Immunodeficiency.

- **Total Hemolytic Complement Kit**
  - Detects deficiencies of Classical Complement Pathway and terminal sequence (C3-C9) components

- **Alternative Pathway Hemolytic Complement kit**
  - Designed to measure activity of Alternative Complement Pathway (AR50 or AR100)

- **Individual Complement Components**
Diagnosis of Complement Deficiencies

Ear infections, Pneumonia, Bacteremia, Meningitis, System Neisserial infection

Laboratory tests

Complement Component or Inhibitor defects

Angioedema, laryngeal edema, abdominal pain

Laboratory tests

Complement Screening assays:
CH50, AH50
Specific assays:
Complement components
(C1, C2, C3, C4, etc)

If abnormal, refer to immunologist for further evaluation, diagnosis and treatment

C1 Esterase Inhibitor
Case Study 4

- 26 yr old male. Extreme headache, vomiting.
- Lumbar puncture: *N. meningitidis* cultured from CSF.
- Immediate family no history of PID

**Investigations**
1. Total serum IgG, IgA, IgM all normal.
2. Immunization responses to T.tox, Diphtheria and Pneumovax all normal.
3. Detectable responses to varicella zoster
4. CH50 no detectable activity.

**Diagnosis**

**COMPLEMENT DEFICIENCY**
(C6 deficiency)

*Essentials of Clinical Immunology. H. Chapel et al.*
Case Study 5

- 56 year old male previous history of meningitis (purulent meningitis at age 23)
- Presented with acute meningococcal meningitis (recurrent)

Investigations
- Full lymphocyte count - normal
- Antibody and subclass levels - normal
- CH50 and APH50 assays reduced
- C9 completely absent

Diagnosis

COMPLEMENT DEFICIENCY
(C9 deficiency)

Review of the Problem

• PIDs are under diagnosed
• Diagnosis is delayed by average of 5 years
• Impact to health and healthcare resources to underdiagnose
  • Frequent doctor/hospital visits, intensive care
  • Long term morbidity
  • Months off work/school
  • Impact on healthcare resources
• Economic impact
Improvement after Diagnosis of PID

- Comparing quality of life data per year for undiagnosed vs. diagnosed patients with PID
### Yearly cost of Undiagnosed PID

#### III. Economic Impact Study
Comparing Undiagnosed and Diagnosed Patients with Primary Immunodeficiencies

[Based on data collected pre and post Dx]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cost per episode/ per day</th>
<th># of episodes pre-period</th>
<th>Cost prior to diagnosis</th>
<th># of episodes post-period</th>
<th>Costs After diagnosis</th>
<th>Annual Savings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Infections</td>
<td>$2,950 (per episode)</td>
<td>6.4</td>
<td>$18,880</td>
<td>1.8</td>
<td>$5,310</td>
<td>$13,570</td>
</tr>
<tr>
<td>Severe Infections</td>
<td>$5,708 (per episode)</td>
<td>4.3</td>
<td>$24,544</td>
<td>0.6</td>
<td>$3,424</td>
<td>$21,119</td>
</tr>
<tr>
<td>Bacterial Pneumonia</td>
<td>$7,529 (per episode)</td>
<td>2.8</td>
<td>$21,081</td>
<td>0.6</td>
<td>$4,517</td>
<td>$16,564</td>
</tr>
<tr>
<td>Chronic Infection</td>
<td>$36.33 (per day)</td>
<td>44.7</td>
<td>$1,623</td>
<td>12.6</td>
<td>$457</td>
<td>$1,166</td>
</tr>
<tr>
<td>Physician/Hospital/ ER Visits</td>
<td>$125 (per visit)</td>
<td>70.9</td>
<td>$8,862</td>
<td>11.8</td>
<td>$1,475</td>
<td>$7,387</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>$1,158 (per day)</td>
<td>19.2</td>
<td>$22,233</td>
<td>5.1</td>
<td>$5,905</td>
<td>$16,328</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>$4.25 (per day)</td>
<td>166.2</td>
<td>$706</td>
<td>72.9</td>
<td>$309</td>
<td>$397</td>
</tr>
<tr>
<td>School/Work Days missed</td>
<td>$136.40 (per day)</td>
<td>33.9</td>
<td>$4,623</td>
<td>8.9</td>
<td>$1,213</td>
<td>$3,410</td>
</tr>
</tbody>
</table>

**Totals per patient:**

$102,552

**Costs After diagnosis:**

$22,610

**Annual Savings:**

$79,942

Overall Economic impact

- Undiagnosed PID patient = \( \sim \$102,736 / \text{year} \)
- Diagnosed PID patient = \( \sim \$22,794 / \text{year} \)
- Savings by diagnosing PID = \( \$79,942 / \text{year} \)
- According to NIH and phone survey, 150,000-500,000 cases of PID undiagnosed in the US.
- Economic impact of undiagnosed PID patients to healthcare system in US could total over \$40 billion annually

Conclusion

- Primary Immunodeficiency Disease occurs in both children and adults
- Lack of awareness and education – widely underdiagnosed conditions
- Many tests aid the diagnosis of a number of PIDS
  - Immunoglobulins
    - Ig subclasses
    - Levels of Igs that recognize specific antigens after vaccination
  - Classical complement pathway
  - Alternative complement pathway
  - Individual complement components
- New products may make this process easier for clinician and provide prognostic information to determine patient management.
Summary

- Immunodeficiency – immune systems ability to fight infectious disease is compromised
- Warning signs can help to identify PID
- 55-60% of PIDs are antibody deficiencies
- Laboratory investigations include; Immunoglobulins, IgG subclass, vaccine response
- Delays in diagnosis are associated with increased morbidity
Resources for Immunodeficiencies

- International Union of Immunological Sciences (IUIS)  
  Primary Immunodeficiency Expert Committee
- European Society for Immunodeficiencies (www.esid.org)
- Immune Deficiency Foundation (http://primaryimmune.org/)
  - Jeffrey Model Foundation (http://www.info4pi.org/)
Advertisements in airports

When I grow up, I want to be a chef!

Last year Sarah was too sick to dream. She has Primary Immunodeficiency or PI. Thanks to the Jeffrey Modell Foundation, she was properly diagnosed and treated... Now her future is sweet.

Jeffrey Modell Foundation
info4pi.org
25 years of helping children reach for their dreams

Because of the Jeffrey Modell Foundation I have a chance.
QUESTIONS?

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