The Immune System

What does it do?

- Recognizes pathogens (non-self)
- Organizes a defense response
- Facilitates pathogen destruction and elimination
The Immune System

1. Innate
   - Present from birth
   - Specificity is “pre-programmed”
     - Toll-like receptors – Pattern recognition
   - Includes “non-immunological” cells (e.g. skin and cilia)

2. Adaptive
   - Develops during life with exposure to infection (memory)
   - Increases affinity with experience (specificity)
   - Two compartments:
     - Cellular- Mediated by T-cells
     - Humoral-mediated by antibodies
   - Memory and Specificity are key features
Immune System Components

<table>
<thead>
<tr>
<th>Innate</th>
<th>Cellular</th>
<th>Humoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td></td>
<td>Complement</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Neutrophils, macrophages, NK cells</td>
<td></td>
</tr>
<tr>
<td>NK cells</td>
<td></td>
<td>Antibody</td>
</tr>
<tr>
<td>T cells</td>
<td></td>
<td>Antibody (B cells, plasma cells)</td>
</tr>
</tbody>
</table>

Adaptive
Molecular biology of PIDD

- Remarkable progress in understanding the genetic causes of PIDD
  - Over 350 genetic abnormalities described for primary immune deficiencies
Primary Immunodeficiencies

- Incidence: 1/1,200-20,000 (2:1,♂:♀)
- Distribution:

- Humoral/B cell deficiencies: 65%
- Combined/T-B deficiencies: 15%
- Celluar/T cell deficiencies: 10%
- Phagocyte/PMN- cell deficiencies: 5%
- Complement deficiencies: 5%
Average Number of Years to Diagnosis by Decade of Diagnosis

<table>
<thead>
<tr>
<th>Decade</th>
<th>Average Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N=1137)</td>
<td>12.35</td>
</tr>
<tr>
<td>Before 1970 (N=605)</td>
<td>14.0</td>
</tr>
<tr>
<td>1970's (N=480)</td>
<td>12.2</td>
</tr>
<tr>
<td>1980's (N=149)</td>
<td>8.4</td>
</tr>
<tr>
<td>1990's (N=56)</td>
<td>10.3</td>
</tr>
<tr>
<td>2000's (N=41)</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Q9. At what age was that person first diagnosed with a primary immunodeficiency disease? Q8. At what age (in years) did these repeated, serious or unusual infections begin? (Base: Infection prior to diagnosis- N = 1,218; 81 cases missing data to Q8 or Q9).
## 10 Warning Signs of PI

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 or more new ear infections within 1 year</td>
</tr>
<tr>
<td>2</td>
<td>2 or more serious sinus infections within 1 year</td>
</tr>
<tr>
<td>3</td>
<td>2 or more months on antibiotics with little effect</td>
</tr>
<tr>
<td>4</td>
<td>2 or more pneumonias within 1 year</td>
</tr>
<tr>
<td>5</td>
<td>Failure of an infant to gain weight or grow normally</td>
</tr>
<tr>
<td>6</td>
<td>Recurrent, deep skin or organ abscesses</td>
</tr>
<tr>
<td>7</td>
<td>Persistent thrush in mouth or fungal infection on skin</td>
</tr>
<tr>
<td>8</td>
<td>Need for intravenous antibiotics to clear infections</td>
</tr>
<tr>
<td>9</td>
<td>2 or more deep-seated infections including septicemia</td>
</tr>
<tr>
<td>10</td>
<td>A family history of PI</td>
</tr>
</tbody>
</table>

Sources:
Q9. At what age (in years) was that person first diagnosed with a primary immunodeficiency disease? (N=1,330 – excludes missing data)
Humoral Immune Evaluation

IMMUNE FUNCTION
1. ADAPTIVE IMMUNE SYSTEM

1st Stage
CBC with differential
Immunoglobulin production: IgG, IgA, IgM, IgE
   IgG subclasses (IgG 1, 2, 3, 4) - sometimes

2nd Stage
Isohemagglutinins – anti ABO red blood cell antigens
Vaccine response:
• Vaccine-specific antibody responses
   • tetanus, Hib, Prevnar/Pneumovax 23
   • Influenza A/B
IMMUNE EVALUATION

IMMUNE PHENOTYPING / CELL COUNTS

3\textsuperscript{st} Stage
• Lymphocyte subset counts
  T (CD3, CD4, CD8), B (CD19) and NK (CD16/56) cell: XLA, CVID
  naïve vs memory (CD45RA vs RO) CD4/CD8 T cells: CID

4\textsuperscript{nd} Stage (immunology specialist)
• B cell panel: B cell compartments (naïve, switched memory, plasma cells)
• T cell panel: Naïve/ memory/ effector/ activated T cells
  Naïve recent immigrant T cells
  Regulatory T cells
• Lymphocyte proliferative responses to mitogens/antigens
Common Variable Immunodeficiency (CVID)

- Recurrent sinopulmonary infections with encapsulated organisms
- Most common B-cell immune deficiency
  - 1:25,000 to 1:50,000
- Variable onset of clinical findings
  - Often delayed diagnosis by 6-8 yrs
  - More commonly diagnosed in the 3rd/4th decade of life or later
- Low serum IgG, and IgA, and sometimes IgM
  - At least 2 Ig isotypes (one of which is IgG) that are >2 SD below normal for age
  - Poor or absent specific antibody production
  - Diagnosis after age 4 to exclude transient delayed hypogammaglobulinemia of infancy (THI)

Diagnostic Criteria for CVID – ESID 2014

- At least one of the following
  - Increased susceptibility to infection
  - **Autoimmune disease**
  - Granulomatous disease
  - Unexplained polyclonal lymphoproliferation
  - Affected family member with antibody deficiency

- **AND** marked decrease in serum IgG and decrease IgA with or without a low IgM

- **AND** at least one of the following
  - Poor antibody response to vaccines (and/or absent isohemagglutinins)
  - Low switched memory B-cells

- **AND** secondary causes of hypogammaglobulinemia have been excluded

- **AND** diagnosis after age 4

- **AND** no evidence of profound T-cell deficiency
When to Suspect Antibody Deficiency

Signs and Symptoms

- Allergic conditions
- Meningitis and/or sepsis
- Recurrent sinopulmonary infections
- Lymphopenia, absent or enlarged lymph nodes
- Autoimmune disorders
- Skin infections
- Gastrointestinal infections

Complications

- Hearing impairment
- Neurological deficit
- Bronchiectasis
- Impaired digestive function

Clinical Phenotypes and Prognosis
Common variable immunodeficiency (CVID)

Definition:
Recurrent infections
Low vaccine titers
Low immunoglobulin levels (IgG from 2SD of normal with low IgA or IgM)

Standard of care:
Tx: Immunoglobulin (IVIG) replacement / antibiotics

Mortality of 473 CVID patients

Patients with **CVID and autoimmunity**: Diagnostic and clinical challenge

**CVID with non-infectious phenotype**: Less favorable outcome
May be undertreated/misdiagnosed
Increased mortality and morbidity

- Risk of morbidity and mortality 11 fold higher in patients with complications
- Increased mortality associated with:
  - lymphoma
  - hepatitis
  - lung disease
  - GI disease

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Q13. Does the PIDD patient suffer from any other serious, chronic disease (not counting immune deficiency)? (N=1,314 – excludes missing data)
Clinical spectrum of PID in adults

- Infections
- Autoimmunity
- Inflammation
- Allergies
- Malignancy
- Lymphoproliferation
**Autoimmune Complications in CVID**

- Autoimmunity is the second most common complication of CVID (29%)
- Cytopenias as the most common autoimmune complications

**Study of 902 CVID patients from 6 countries, 28 medical centers in Europe**

<table>
<thead>
<tr>
<th>Condition</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune thrombocytopenia</td>
<td>34</td>
</tr>
<tr>
<td>Evans syndrome</td>
<td>12</td>
</tr>
<tr>
<td>Autoimmune haemolytic anaemia</td>
<td>10</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>7</td>
</tr>
<tr>
<td>Anti-IgA</td>
<td>5</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>4</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>3</td>
</tr>
<tr>
<td>Pernicious anaemia</td>
<td>3</td>
</tr>
<tr>
<td>Myasthenia gravid</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>3</td>
</tr>
<tr>
<td>Immune urticaria</td>
<td>3</td>
</tr>
<tr>
<td>Anti-cardiolipin</td>
<td>2</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>2</td>
</tr>
<tr>
<td>Uveitis</td>
<td>2</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>2</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>1</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>1</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>1</td>
</tr>
</tbody>
</table>


Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies

Alain Fischer, MD, PhD, a,b,c,d,e Johan Provot, MSc, a Jean-Philippe Jais, MD, PhD, a,c,f
Alexandre Alcais, MD, PhD, a,c,g Nizar Mahlaoui, MD, MSc, MPH, a,b,c,g and the members of the CEREDIH French PID study group*  Paris, France
French National PIDD registry – 2183 consecutive PI cases
One or more autoimmune and inflammatory complications were noted in 26% of patients
Risk of autoimmune cytopenia – 120 times general population
Risk of inflammatory bowel disease in children – 80 times general population

<table>
<thead>
<tr>
<th>TABLE I. Categorization of the 852 autoimmune or inflammatory manifestations observed in 571 patients with PID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manifestation</td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Autoimmune cytopenia</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Skin</td>
</tr>
<tr>
<td>Rheumatologic disorders</td>
</tr>
<tr>
<td>Endocrine disorders</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Eye</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>Vasculitis and other systemic disorders</td>
</tr>
<tr>
<td>Neurologic disorders</td>
</tr>
<tr>
<td>Urologic disorders</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE II. Number of patients with the most common autoimmune and/or inflammatory manifestations as a function of the type of PID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manifestation</td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>B-cell CVIDs</td>
</tr>
<tr>
<td>Other B-cell deficiencies</td>
</tr>
<tr>
<td>T-cell deficiencies</td>
</tr>
<tr>
<td>Innate deficiencies</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Note: Some patients had more than 1 type of autoimmune or inflammatory manifestation, and therefore the total number might exceed the total number of patients. Likewise, the sum of the percentages can exceed 100%.
*Based on the total number of patients with at least 1 autoimmune or inflammatory manifestation (n = 571).
FIG 2. Cumulative incidence of autoimmunity/inflammatory manifestations in patients with PIDs as a function of the PID disease group.
50 CVID patients with either:
- early onset
- autoimmune/inflammatory manifestations
- low B lymphocytes
- and/or familial history of hypogammaglobulinemia
- average age 36 yr.

Targeted gene screening (269 genes): 40% of patients with genetic diagnosis
Know Gene Mutations in Primary Immune Deficiencies

Data from IUIS
When do you obtain genetic testing?

Enteropathy in PIDD
- Chronic diarrhea and weight loss
- Failure to thrive
- Celiac like
- Autoimmune enteropathy
- Granulomas
- Lymphocytic infiltrate

Endocrinopathy in PIDD
- Type 1 diabetes mellitus
- Thyroid disease
- Addison’s disease
- Hyperparathyroidism
- Gonadal failure
- Growth hormone deficiency

Autoimmune Cytopenias in PIDD
CTLA-4 deficiency (Cytotoxic T Lymphocyte Associated Protein 4)

- Brain, GI, lung, lymphocytic infiltrates.
- Autoimmune thrombocytopenia and other cytopenias,
- Hypogammaglobulinemia
- Clonally expanded gd-CD8+ T cells
- CD4 T cell lymphopenia.
- Low circulating mature B cells
- Reduced expression of FOXP3 Treg cells

CTLA-4

• Inhibitory receptor expressed on activated T cells
Treatment of this patient

- Steroids
- Rituximab

Abatacept alleviates severe autoimmune symptoms in a patient carrying a de novo variant in CTLA-4

Lee et al. JACI. 2016
LRBA-deficient Patients and Clinical Course with Abatacept

Bernice Lo et al. Science 2015;349:436-440
LRBA-deficient Patients and Clinical Course with Abatacept

Bernice Lo et al. Science 2015;349:436-440
Alopecia areata reversed by JAK inhibition

- Alopecia areata (AA) mediated by T-cell autoimmune process
- In a mouse model giving anti-IFN-γ antibodies prevented AA
- Intervene downstream using small molecule inhibitor of JAK kinases
- Ruxolitinib (FDA approved - myelofibrosis)
  - Inhibitor of JAK1/2
  - 20 mg PO twice daily

Xing L et al Nature Med 2014
STAT1 Immune Deficiencies

- Hypermorphic- Gain-of-Function (GOF)
  - Autosomal dominant
  - Chronic mucocutaneous candidiasis
    - CMC – more than 50% of the cases
  - Other fungal and bacterial infections
  - Autoimmune disorders (1/3 patients)
  - CNS vascular lesions
Ruxolitinib successfully treats chronic mucocutaneous candidiasis in GOF STAT1

- 28 yr old female with GOF STAT1
- Alopecia, recalcitrant CMCC
- Prior history autoimmune hepatitis
- Two weeks Rx with ruxolitinib
  - dramatic hair growth
  - Resolution of the oral candidiasis
Survival in Patients With CVID

Survival (as %) of patients with CVIDs, with or without disease related complications, compared with UK general population controls.

- Bone marrow Tx
- Gene therapy
- Biologics

“…the greatest teachers of modern immunology: patients with immunodeficiency diseases.”

Robert A. Good, M.D., D.Sc., Ph.D.