Immune Deficiencies
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Disclosures

• No relevant disclosures to this topic
• No mention of any products or medications other than FDA-approved vaccines
• Information on PID sourced from non-for-profit foundation websites (Immune Deficiency Foundation and Jeffrey Modell Foundation)
• Research funding of the PIDTC from NIAID, NIH
Is it just an infection?
You should be suspicious if you have an infection that is...

Severe
requires hospitalization or intravenous antibiotics

Persistent
won’t completely clear up or clears very slowly

Unusual
caused by an uncommon organism

Recurrent
keeps coming back

Runs in the Family
others in your family have had a similar susceptibility to infection

If any of these words describe your infection, the Immune Deficiency Foundation (IDF) recommends that you ask your physician to check for the possibility of a primary immunodeficiency disease. These diseases are caused by genetic defects and can affect anyone, regardless of age or gender. People with primary immunodeficiencies are more susceptible to infections and health problems that lead to serious and debilitating diseases. It is critical to get an early diagnosis and proper medical care.

As the national patient organization dedicated to persons living with primary immunodeficiency diseases, IDF says THINK ZEBRA!

In medical school, many doctors learn the saying, “When you hear hoof beats, think horses, not zebras!” and are taught to focus on the likeliest possibilities when making a diagnosis, not the unusual ones. However, sometimes physicians need to look for a zebra. Patients with primary immunodeficiency diseases are the zebras of the medical world.

If you have an infection with any of these characteristics, ask your physician to THINK ZEBRA!
Introduction
Primary Immunodeficiencies (PIDs)

- PIDs are caused by germline mutations resulting in loss of (or occasionally, gain of) function of a gene involvement in immunologic development, maintenance, and/or function

- PIDs manifest as increased susceptibility to:
  - Infection (often from ‘opportunistic’ organisms)
  - Autoimmunity / autoinflammation
  - Occasionally, malignancy
Introduction

Primary Immunodeficiencies (PIDs)

• PIDs were once thought to be rare, but as a group are increasingly recognized (1 in 1000-5000 births)
Introduction
Primary Immunodeficiencies (PIDs)

- PIDs are categorized as those affecting primarily:
  - Cellular (T-cell) and humoral (B-cell) immunity
    - E.g. Severe Combined Immunodeficiency (SCID)
  - Combined immunodeficiencies with associated or syndromic features
    - E.g. Wiskott-Aldrich Syndrome (WAS)
  - Diseases of immune dysregulation (aka ‘PIRD’)
    - E.g. Hemophagocytic Lymphohistiocytosis (HLH) or Immune Polyendocrinopathy and Enteritis X-Linked (IPEX)
Introduction
Primary Immunodeficiencies (PIIDs)

• PIDs are categorized as those affecting primarily:
  – Phagocyte (neutrophil) number or function
    • E.g. Chronic Granulomatous Disease (CGD)
  – Intrinsic and innate immunity (monocytes and/or NK cells)
    • E.g. Interferon-gamma Receptor 1 Deficiency
  – Predominately antibody production
    • E.g. X-linked agammaglobulinemia
Introduction

Primary Immunodeficiencies (PIDs)

• PIDs are primarily, but not exclusively, caused by defects in cells derived from hematopoietic stem cells (HSCs) and are therefore amenable to being cured by a HCT
  – Rare PIDs are due to defects in:
    • Thymic function: e.g. DiGeorge
    • Secondary lymphoid organs: e.g. NEMO (IKBKG Deficiency)
  – These don’t respond as well (or at all!) to HCT

• Major problem: Although we have traditionally lumped them into the basket term “PID,” each genetic mutation behaves slightly differently
Management

Primary Immunodeficiencies (PIDs)

• After diagnosis, PIDs are managed by:
  – Infection prophylaxis tailored to the individual disease
  – Immunosuppression, if needed
  – Transplant, either allogeneic, or increasing autologous gene-corrected (gene therapy)

• The severity of PIDs varies greatly:
  – Very mild: Most antibody-only defects can live normal life-spans with minimal medical therapy and will not be transplanted
  – Very severe: Typical SCID patients will generally die within a year of birth and require prompt and early HCT
  – Everything in between
Transplant
Primary Immunodeficiencies (PIDs)

• PIDs were first transplanted in 1968!
• Many unique features to PID transplant approaches
  – SCID patients can have GVHD before transplant!
  – Some SCID patients receive no conditioning regimen!
• Because these patients don’t experience relapse of a malignant disease, they only die from:
  – Progression of preexisting infection / autoimmunity
  – Incomplete correction of immunodeficiency
  – Transplant-related complications
Transplant Indication

PID vs. Lymphoma? This can be a very difficult question!

• Case example: 12 yo girl presented with an EBV+ DLCBL and treated on COG Protocol ANHL1131.
  – After completion of chemotherapy, her lymphoma recurred.
  – Additional workup at that time demonstrated abnormalities in her immune system, prompting genetic testing, which demonstrated homozygous mutations in *CECR1*, diagnostic of ADA2 Deficiency, a recognized PID.

• Form 2034: XLP (Not asked on any other PID form!)
  – Q17: Was lymphoma present at diagnosis?
  – Q95: Did the recipient develop lymphoma between diagnosis and start of conditioning?
  – If yes – Also complete Form 2018: Lymphoma

**CECR1**

**ADA2 Deficiency**
Donor Issues

Like other genetic diseases, close attention must be paid to related donors.

• Related donors can:
  – Have the same disease that is not yet clinically apparent (esp. younger siblings)
  – Have a partial form of the disease (esp. females in X-linked diseases, due to extreme lyonization / inactivation)

• Form 2034: XLP
  – Q129: Was donor testing for XLP done prior to HCT?

• Not asked for WAS or CGD or any other X-linked disease
Transplant Changes Over Time

SCID

**TABLE I. Patient transplant characteristics – SCID**

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>93</td>
<td>215</td>
<td>321</td>
<td>352</td>
</tr>
<tr>
<td>Age at transplant (y), median (interquartile range)</td>
<td>0.55 (0.37-0.78)</td>
<td>0.55 (0.29-0.89)</td>
<td>0.55 (0.34-0.94)</td>
<td>0.38 (0.20-0.99)</td>
</tr>
<tr>
<td><strong>Donor type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA identical sibling</td>
<td>15 (16)</td>
<td>46 (21)</td>
<td>51 (16)</td>
<td>62 (38)</td>
</tr>
<tr>
<td>Other relative</td>
<td>71 (76)</td>
<td>119 (55)</td>
<td>95 (30)</td>
<td>68 (19)</td>
</tr>
<tr>
<td>Matched other relative</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Mismatched other relative</td>
<td>0</td>
<td>0</td>
<td>81</td>
<td>58</td>
</tr>
<tr>
<td>HLA match not reported</td>
<td>71 (7)</td>
<td>50 (23)</td>
<td>175 (55)</td>
<td>222 (63)</td>
</tr>
<tr>
<td><strong>Unrelated donor</strong></td>
<td>7 (8)</td>
<td>50 (23)</td>
<td>175 (55)</td>
<td>222 (63)</td>
</tr>
<tr>
<td><strong>Graft type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>93 (91)</td>
<td>196 (91)</td>
<td>161 (59)</td>
<td>211 (60)</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>0</td>
<td>5 (2)</td>
<td>50 (16)</td>
<td>38 (11)</td>
</tr>
<tr>
<td>Cord blood</td>
<td>0</td>
<td>14 (7)</td>
<td>110 (34)</td>
<td>103 (29)</td>
</tr>
<tr>
<td><strong>Conditioning intensity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No conditioning regimen</td>
<td>71 (76)</td>
<td>96 (45)</td>
<td>61 (19)</td>
<td>66 (19)</td>
</tr>
<tr>
<td>Myeloablative</td>
<td>12 (13)</td>
<td>81 (38)</td>
<td>147 (46)</td>
<td>166 (47)</td>
</tr>
<tr>
<td>Reduced intensity</td>
<td>10 (11)</td>
<td>38 (18)</td>
<td>113 (35)</td>
<td>120 (34)</td>
</tr>
<tr>
<td><strong>In vivo T-cell depletion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>83 (89)</td>
<td>153 (71)</td>
<td>141 (44)</td>
<td>124 (35)</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (11)</td>
<td>62 (29)</td>
<td>180 (56)</td>
<td>238 (65)</td>
</tr>
<tr>
<td><strong>GvHD prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No GvHD prophylaxis</td>
<td>17 (18)</td>
<td>9 (4)</td>
<td>16 (5)</td>
<td>13 (4)</td>
</tr>
<tr>
<td><strong>Ex vivo T-cell depletion</strong></td>
<td>63 (68)</td>
<td>69 (32)</td>
<td>40 (12)</td>
<td>44 (13)</td>
</tr>
<tr>
<td>CD34+ selection</td>
<td>0</td>
<td>0</td>
<td>29 (9)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>Cyclosporine ± MMF/MTX</td>
<td>5 (5)</td>
<td>108 (50)</td>
<td>171 (54)</td>
<td>172 (49)</td>
</tr>
<tr>
<td>Tacrolimus ± MMF/MTX</td>
<td>0</td>
<td>0</td>
<td>38 (13)</td>
<td>76 (22)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (9)</td>
<td>29 (13)</td>
<td>27 (8)</td>
<td>18 (5)</td>
</tr>
</tbody>
</table>

GvHD, Graft versus host disease; MMF, mycophenolate mofetil; MTX, methotrexate.
Transplant Improvements Over Time

SCID

Practice pattern changes and improvements in hematopoietic cell transplantation for primary immunodeficiencies

Rebecca A. Marsh, MD*
Kyle M. Hebert, MD*
Daniel Kesdon, BS*
Josip J. Boelens, MD, PhD
Christopher C. Dorak, MD*
Michael J. Eckrich, MD, MPH*
Neena Kapoor, MD*
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Mary Eagen, MD*

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Transplant Changes Over Time

Non-SCID

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH
Transplant Improvements Over Time

Non-SCID
Transplant Differences by Disease Type

Non-SCID

Practice pattern changes and improvements in hematopoietic cell transplantation for primary immunodeficiencies
Transplant Non-Improvements Over Time

Infants (<2 years old)
Transplant Outcomes by Donor
Infants (<2 years old)
HCT Outcomes: Survival Can Be Poor

PIRD
Transplant Outcomes: Survival = Cure?

PIRD

Only 55% of survivors had complete phenotype reversal!
HCT: Who Needs it and When to Do It?
All about weighing risks and benefits

- SCID: Almost everyone, usually right away
- WAS: The vast majority, <5 yo of age
- CGD: An increasing percentage, <12 yo of age
- HLH: Almost everyone (if genetically proven), usually fairly promptly
- PIRD: Depends on the severity of the disease
Conclusions

- PIDs are incredibly complex, with each of >450 genotypes behaving somewhat differently.
- Some broad lumping can be done, but even there things get messy quickly (e.g. SCID has >20 genotypes, which have different transplant requirements and outcomes).
- Outcomes have generally improved with time, but certain groups (infants, PIRDs) still need a LOT more work.
- As we get better with HCT, the risk vs. benefit equation changes for less severe forms of PID.
CGD as an Example
Quality of Life

• Most CGD patients can survive for decades with their disease
• Historically, few were transplanted due to the inherent risks of HCT
• Then we began to appreciate that their quality of life was terrible as they got older and that HCT could change that
CGD as an Example

Quality of Life

Table 4 Performance score and disability in post-HSCT and non-HSCT subjects ≥15 years old at the last visit

|                      | Post-HSCT (n = 18) | Non-HSCT (n = 50) | p value*
|----------------------|--------------------|-------------------|---------
| Median age at assessment in years (range) | 24.0 (15.0–34.0)   | 27.0 (15.0–33.0)  | 0.080   
| Mean performance score ± SD (range)       | 93.16 ± 6.71 (70–100) | 85.88 ± 9.50 (50–100) | 0.0039* 
| Frequency of disability (%)                | 2 (11)             | 26 (52)           | 0.014*  

- Partial, 2 (11)
- Depression, 1
- Unspecified, 1
- Pulmonary insufficiency, 8
- CoHo's complications, 5
- Cognitive deficits, 2
- Vision impairment, 2
- Gait abnormality, 1
- End-stage renal disease, 1
- Depression, 1
- Anxiety, 1
- Unspecified, 3

|                      | Post-HSCT (n = 18) | Non-HSCT (n = 50) | p value*
|----------------------|--------------------|-------------------|---------
| Full, 0 (0)          |                    |                   | 0.42    
| Full, 2 (4)          |                    |                   |         
- Pulmonary insufficiency and malabsorption, 1 each
- Unspecified, 1

Role of Allogeneic Hematopoietic Stem Cell Transplant for Chronic Granulomatous Disease (CGD): a Report of the United States Immunodeficiency Network

Jennifer R. Yonen1, Aishah Gupta1, Yingfu Fu2, Elizabeth Garabedian3, Jignesh Dalal1, and the United States Immunodeficiency Network Consortium

Data Collection Forms

Some PIDs are common enough to warrant their own specific forms

- 2031: ID Pre-HSCT
- 2131: ID Post-HSCT
- 2033: WAS Pre-HSCT
- 2034: XLP Pre-HSCT
- 2039: HLH Pre-HSCT
- 2055: CGD Pre-HSCT
- 2056: Pigmentary Dilution Disorder Pre-HSCT (e.g. Chediak-Higashi)
  - These can predispose to HLH
- Not enough time to review all of these!
Data Collection: Form 2031 (ID Pre-HSCT)

Disease Assessment at Diagnosis (Q1-8)

• Is the mutated protein or enzyme expressed?
  – In the era of improved genetic testing, this test is not done very often (and it’s not super important if the genetic report is clear)!

• What is the pattern of inheritance?
  – Options: Sporadic / X-Linked / Autosomal Recessive / Unknown
  – Some “new” PIDs are Autosomal Dominant (e.g. STAT3 Deficiency, aka Job Syndrome) – I would call these “Sporadic”
Data Collection: Form 2031 (ID Pre-HSCT)

Disease Assessment at Diagnosis (Q1-8)

• Are there other blood relatives in the patient’s family with immunodeficiency disease?
  – Options: Yes / No / Unknown
  – “Mother of child reports that one of her siblings died as an infant 20 years ago in another country” – I would call this “Unknown”
Did the recipient receive supplemental intravenous immunoglobulins (IVIG) since the date of last report?
- This question did not account for the increased adoption of subcutaneous immunoglobulin (SCIG), and this counts!

Was therapy ongoing within one month of immunoglobulin testing?
- IVIG tends to be administered monthly, and if given, will increase the reported IgG level
Data Collection: Forms 2031 and 2131

Lymphocytes

• B cells (CD20): May be measured by CD19
• NK cells (CD56): May be measured by CD16/CD56
• Memory T cells (CD4+/CD45RA+): These may be reported by the lab as only a % of total CD3+ cells. You cannot calculate the value CIBMTR is asking for from that number and should just report “not tested.”
Data Collection: Forms 2031 and 2131

Antibody Responses

- Bacteriophage phi X-174: This is a research test, that is only done at a few places in the world!
- Isohemagglutinins: Antibodies to blood type A or B that are made spontaneously to those blood types the patient is lacking.
  - E.g. Everyone who is blood type B and a normal immune system naturally has anti-A isos
  - Patients who will not make any isos include:
    - Patient and/or Donor blood type AB
    - Patient blood type A and Donor blood type B (or vice versa)
Data Collection: Forms 2031 and 2131

Antibody Responses

• Tetanus and Diphtheria and HIB:
  – Only expected to be positive in response to a vaccine
  – Are often tested twice (once prior to vaccination and once after the vaccination course is complete)

• Pneumococcal: 2 vaccines in the US
  – Polysaccharide (Unconjugated, 23 serotypes): Aka Pneumovax
  – Conjugated (13 serotypes): Aka Prevnar
Data Collection: Forms 2031 and 2131

Pneumococcal vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Serotypes included</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPSV23</td>
<td>1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F</td>
</tr>
<tr>
<td>PCV7</td>
<td>4, 6B, 9V, 14, 18C, 19F, and 23F</td>
</tr>
<tr>
<td>PCV10</td>
<td>1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F</td>
</tr>
<tr>
<td>PCV13</td>
<td>1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F</td>
</tr>
</tbody>
</table>
Data Collection: Forms 2031 and 2131
Lymphocyte Function (e.g. PHA)

• Lymphocyte function is determined by their ability to proliferate in response to a strong stimulus
• These tests are best done when compared to a normal control of the day
• Some labs report both a response in CD3+ cells and CD45+ cells – CD45+ is preferred
• The actual value to be used is NOT listed on most reports, it requires you to hand calculate it!
Data Collection: Forms 2031 and 2131
Lymphocyte Function (e.g. PHA)

- Max proliferation of PHA as % of CD45 (reference value ≥49.9%)
  - Example 1: 0.4% -> 0.4/49.9 = 0.8% (Absent)
  - Example 2: 8.3% -> 8.3/49.9 = 16.6% (Low)
  - Example 3: 24.5% -> 24.5/49.9 = 49.9% (Normal)
  - Example 4: 52.3% -> >100%! (Normal)
Data Collection: Forms 2031 and 2131
Infections Identified Post-HSCT

• If X (pneumonia, diarrhea, etc.) was present, was it a prominent feature of ID?
  – I.e. was this infection due to the transplant itself or due to the transplant not fully correcting the underlying PID?

• This is a judgement call! I would strongly encourage you to not answer this question without first asking your medical director or the patient’s primary attending!
Data Collection: Forms 2031 and 2131

Clinical Status Post-HSCT

- Is X (autoimmune hemolytic anemia, failure to thrive, etc) prominent?
- *I would define “prominent” to mean anything requiring systemic treatment*
- *This is a judgement call! I would strongly encourage you to not answer this question without first asking your medical director or the patient’s primary attending!*
Data Collection: Form 2131

Was Treatment Given (since the date of the last report)

• The point of these questions is to try to determine if the HCT has successful resolved the underlying immunodeficiency.
  – New term: Phenotype (i.e. the manifestations of that patient’s PID) Reversal
• For malignant diseases, it is easy to know that transplant has not worked when the patient relapses, and relapses typically occur within a set number of years.
• For non-malignant diseases like PID, a patient may temporarily improve post-transplant, and then have waning of immunity and recurrence of PID manifestations (e.g. return of opportunistic infections or autoimmunity)
Data Collection: Form 2131

Was Treatment Given?

• These questions are all about immunosuppressive medications and look similar to the GVHD questions.

• It can be very difficult to tell when a drug (e.g. corticosteroids) is given for treatment of GVHD vs. transplant-related autoimmunity vs. residual autoimmunity from incomplete treatment of underlying PID!

• Chimerism can be a clue (but is NOT perfect):
  – Full-donor = more likely to be GVHD
  – Mixed-chimerism = more likely to be autoimmunity

• *Ultimately, ask your Medical Director if unclear!*
• Chimerism is critically important to helping understand whether a patient with PID is cured after HCT
• T-cell: CD3
• B-cell: CD19 or CD20
• Myeloid: CD14/15 or CD33
  – This is the best marker for bone marrow stem cell engraftment (most PID patients won’t have routine bone marrow aspirations done post-HCT)
Data Collection Forms

• The Disease-Specific Forms are becoming outdated
• A new set of forms, harmonized with forms created by PIDTC experts, are anticipated soon!
Why Do We Need to Still Study PID?
We should be able to get to near 100% survival in these patients

• But there are still many things we don’t understand about how best to transplant these patients
  – What is the optimal donor when a matched sib doesn’t exist?
  – Can you use carrier donors?
  – How much conditioning do patients require?
  – What degree of myeloid chimerism is required for permanent phenotype reversal (aka ‘cure’)?
  – Does this vary from genotype to genotype?
CIBMTR Matters!

PIDS are very rare!

• No single center sees enough PID patients to be able to gather enough data to make definitive conclusions about these unresolved questions.

• We need cooperative registries to make this happen.
Thank You!

Questions?