**Therapeutic Approaches**  
(in Secondary? Immunodeficiencies)

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## Disclosures

I have the following real or perceived conflicts of interest that relate to this presentation:

<table>
<thead>
<tr>
<th>Type of Relationship</th>
<th>Disclosure</th>
<th>Name of Commercial Interest [Clinical Area/Topic]</th>
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<tr>
<td>Employment</td>
<td>none</td>
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<td>Equity Ownership</td>
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<tr>
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<td>Speaker’s Bureau</td>
<td>Takeda [Immunology]</td>
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<tr>
<td>Other financial interest</td>
<td>none</td>
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Primary or secondary immunodeficiency?

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<tr>
<th>Classical Onset</th>
<th>Diagnostic workup</th>
<th>Treatment</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Primary</td>
<td>Pediatric &gt; Adult</td>
<td>IgRT, &quot;targeted&quot; biologics, HSCT</td>
<td>1:2,000 in children, 1:1,200 in patients of any age</td>
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<tr>
<td>Secondary</td>
<td>Adult</td>
<td>trigger profiling &gt; immune treatment of triggers + ?</td>
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"Inborn error" Immune deficiency

"Acquired" Drugs, cancer, chronic illness

Secondary Hypogammaglobulinemia

- Excessive loss of immunoglobulins
- Protein-losing enteropathy
- Nephrotic syndrome
- Severe burns
- Malignancy
- Chronic lymphocytic leukemia
- Multiple myeloma
- Good's syndrome
- Non-Hodgkin B cell lymphomas
- Drug induced:
  - Anti B cells monoclonal antibodies
  - Immunosuppressants and chemotherapeutics
52 year-old business man: “Doc, what is wrong with me?”

**Medical history:**
- Triggers are viral infections
- 46 yo: admitted for platelet count of 0
  - splenomegaly (18 cm), bone marrow aspiration negative
  - steroid/high dose 1Vg/ rituximab (anti-CD20 therapy)
  - Excellent response with platelet count increase
  - “Bystander improvement” of lung nodules

First team of specialists (before Rituximab):
Primarily managed by pulmonary (pulmonary nodules) and hematology (ITP)

Second team of specialists (after Rituximab):
“new onset” hypogammaglobulinemia (Immunologist) – excellent response to IgRT
Chronic URIs/sinus disease (ENT and Infectious diseases): antibiotics

**Immune evaluation (after Rituximab):**
No detectable IgA and IgM (1 year after first RTX)
progressive B and T cell lymphopenia (including naive CD4 T cell count and fraction)
Genetic testing (WES): VUS in AIRE and NFAT genes
52 year-old business man: “Doc, what is wrong with me?”

Can we answer with full certainty?

1. Primary or secondary immunodeficiency?
   **Primary:** predisposition to infections / immune dysregulation
   **Secondary:** result of medical therapy (i.e. RTX) and/or chronic disease

2. Risk of infections and length and dose of IgRT?
   **Primary:** lifelong (dosing: replacement vs anti-inflammatory)
   **Secondary:** until full T and/or B cell immune reconstitution occurs

3. When and how to immunomodulate or correct?
   High dose IgRT, targeted biologicals, HSCT

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**Clinical case of an adolescent with cytopenias**

- **AIHA**, hemolysis → low platelet count → ITP → infections
- **Coombs+**, Lymphopenia
- **HD Ig, Steroid**, RTX → IgRT → mTOR inhibitor
- **No response**, Partial response → Sustained response, Remission

**Response to therapy**

- **16** → **17**
- **Age (years)**

**Diagnosis**

- **Evans Syndrome**
- **Dx: Autoimmune lymphoproliferative syndrome (ALPS)**
- **AIHA**
- **HD Ig**
- **Evans Syndrome**
- **MPS**
- **RTX**
- **mTOR inhibitor**
- **HD Ig**, Steroid
- **No response**, Partial response
- **Sustained response**, **Remission**

**Antibody deficiency syndrome**

**Secondary?**

**Primary!**

*Modified from Engel E, Walter, J. 2020 PMID: 33275746*
Autoimmune complications: New faces of IEI

- Often hard to treat
- May precede infections
- Multi-autoimmune diseases

Non-infectious complications in IEI

Example of ITP: Purpura and petechiae

Autoimmunity as initial presenting manifestation of IEI

>16K patients with PID of any kind (ESID)

AIC is the first symptoms 33% in CTLA4 deficient patients
Schwab et al JACI 2018, PMID: 29729943

Thalhammer J, Ehl S, ESID Registry Working party al, JACI 2021, PMID 33895260
Autoimmunity is very common in IEI

Take home messages:
- AIC is common across all IEIs
- Primary Immune Regulatory Disorder (PIRD) group is highly enriched in AI with overlapping phenotypes
- IEI patient has multi-autoimmune disorders (e.g., 77% in LRBA def)
- Large cohort studies in specific genetic defects are available

Modified from Walter IE et al. Current Opinion in Pediatrics 2019 PMID: 11981286

Primary immune regulatory diseases (PIRD): clinical phenotypes

Chandrakasan 2019 Pediatric Blood & Cancer PMID: 30697957
**HOW TO DIAGNOSE AND TRACK PIRD PATIENTS?**

Extensive immune phenotyping:
- Immunoglobulin levels (can be normal)
- Vaccine titers
- Lymphocyte subsets (T, B, NK)
- Unique developmental stages of immune cells:
  - Transitional B cell increased (APDS)
  - CD21 low cells (age-associated B cells), Tfh cells (monitoring)
  - Low switched memory B cells (CID, CVID-like presentation)
  - Increased double negative (TCR αβ+ CD4- CD8- (DN)) (ALPS-like group)
  - Regulatory T cell abnormalities (IPEX-like group)

**Too complicated**
**Too hard to access immune testing**

Genetic evaluation for genes of IEI (PID)

May need confirmatory functional assays

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**Genetic defects associated with PIRD**

- **BACH2**
- **FOXP3**
- **IKZF1**
- **NFKB1**
- **NFKB2**
- **NFKBIA**
- **REL**
- **TNFAIP3**
- **CRT4**
- **LRBA**
- **ICOS**
- **IL10**
- **IL10RA**
- **IL10RB**
- **IL2RA**
- **IL21R**
- **PIK3CD**
- **PIK3R1**
- **PTEN**
- **ERBIN**
- **ITCH**
- **PRKCD**
- **PSTPIP1**
- **ADAM17**
- **MVK**
- **RAG1**
- **RAG2**
- **CD3G**
- **DOCK8**
- **WAS**
- **WIP**
- **XIAP**

**www.rarediseasesnetwork.org**

*Chandrakasan 2019 Pediatric Blood & Cancer PMID: 30697957*
Flipping the coin: Is IEI common in AIC cohorts?

As high as 40% of multilineal cytopenia (Evans syndrome (ES)) can have IEI

_Hadjadj et al, Blood, 2019, PMID 30940614_

>10% of AIC patients can have IEI in a retrospective study (n=154)

- USF/Johns Hopkins All Children's, Tampa/St Pete, FL 2013-2016
- 17 (11%) of AIC patients had underlying PID
- 10 of 17 (58%) of AIC-IEI had confirmed monogenic IEI
- IEI was diagnosed 3 years later than AIC except in patients with pDGS

Risk factors for AIC-IEI:
- greater frequency of splenomegaly and short stature
- recurrent/chronic infections (p<0.001 or <0.0001)
- low T cells (CD3, CD8), immunoglobulins (IgG, IgA)
- higher prevalence of autoantibodies to erythrocytes, platelets, neutrophils

Treatment outcome:
AIC-IEI patients were more likely to fail first-line treatment

_Westermann E, Walter JE et al, Frontiers Imm, 2021, PMID 33968040_
Why should we care about underlying IEI in AIC? “Targeted therapy”

Furthermore: therapy (e.g. RTX) may unmask underlying IEI

Rituximab and immunodeficiency
Hypogammaglobulinemia post-RTX occurs in adults

At baseline:
- 85.4% did not have Ig levels checked
- 47.8% had ↓ IgG

Post-rituximab
- 87.5% did not have Ig levels checked
- 20% in each category worsened

Barmettler et al. JAMA 2018

Title: Primary and Secondary immunodeficiencies Associated with Rituximab Use in Children
Hypogammaglobulinemia is frequent post-rituximab. IgM > IgG > IgA in children.

According to isotype (IgG, IgA, IgM)

According to status pre-rituximab (normal vs low)

Labrosse & Barmettler et al. JACI 2021
Low IgG post-rituximab increases the risk of serious infections

49 (23.7%) patients had severe infections requiring ED visit (n=32 events) or hospitalisation (n=52 events) in the year following RTX

Prevalence of hypogammaglobulinemia, infections and IEI s/p RTX in non-hematological malignant disease (NHMD) patients

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<tr>
<td>Reis et al (2000) (EAN)</td>
<td>77 – Mixed among patients with APS, adult or peds</td>
<td>128</td>
<td>&lt; 50 mg/dL, severe = &lt; 100 mg/dL</td>
<td>15/128 (12%)</td>
<td>9 years</td>
<td>12/32 (38%)</td>
<td>All treated with IVIG. 1 additional pt had total absence of antibody response to poliomyelitis vaccine for dys 3/122 patients were &lt; 18 yrs old</td>
</tr>
<tr>
<td>Levy et al. (2016) (EAN)</td>
<td>77 – Adult + Peds</td>
<td>128</td>
<td>500 mg/dL</td>
<td>28/128 (21.9%)</td>
<td>12 years</td>
<td>23/32 severe infections</td>
<td>23 of cases later diagnosed with CVID</td>
</tr>
<tr>
<td>Biddle et al. (2016) (EAN)</td>
<td>77 – Mostly adults (pts &lt; 18y)</td>
<td>31</td>
<td>&lt; 500 mg/dL, severe = &lt; 100 mg/dL</td>
<td>6/31 (19.4%)</td>
<td>43 months</td>
<td>None among patients known to have hypog</td>
<td>2/35 PNH, 1 pt recurrent herpetic</td>
</tr>
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<td>Barretti et al. (2018) (EAN)</td>
<td>Hematological disorder – Adults</td>
<td>66</td>
<td>&lt; 500 mg/dL, mild 400–500 mg/dL, moderate 200–400 mg/dL, severe &lt; 200 mg/dL</td>
<td>16/66 (24.2%)</td>
<td>12 months</td>
<td>50% of patients &lt; 1 year treated with RTX and remained hypog after, however did not become severe</td>
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<tr>
<td>Deshayes et al. (2019) (EAN)</td>
<td>77 – Adult</td>
<td>128</td>
<td>&lt; 500 mg/dL</td>
<td>28/128 (21.9%)</td>
<td>1 year</td>
<td>16/128 patients (21.6%) – 21 severe infection (6.5%)</td>
<td>1/128 had IgG levels &lt; 100 mg/dL, one pt with known hypog developed infections</td>
</tr>
<tr>
<td>Ottaviani et al. (2020) (EAN)</td>
<td>77 – Mixed, EL patients only, exclusion criteria is pre-existing CVID</td>
<td>53</td>
<td>IgG &lt; 1.10 for age</td>
<td>17/53 (32%)</td>
<td>Mean 30 months</td>
<td>17/53 (32%) infections requiring hospitalization, 6/53 (12%) recurrent respiratory infections</td>
<td>17/53 (32%) later diagnosed with PD</td>
</tr>
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Modified from Engel E, Walter, J. 2020 PMID: 33275746
Title: Primary and Secondary Immunodeficiencies Associated with Rituximab Use in Children (Abstract #197)
Session: 0050 - Oral Presentation Session - B/Plasma Cell Depleting Therapies No.1
Date & Time: 09/28/2021, 11:15-12:45

**Hypoimmune B cell lymphopenia**

- Hypogammaglobulinemia
- Normal B cell counts
- Normal IgG levels

**Hyperimmune**

- Hyperimmune phenotype
- Autoimmune disease
- Increased risk
- B cell lymphopenia
- Hypogammaglobulinemia

**Clinical state**

- Clinical and family history
- Immunizations
- Basic immune evaluation

**Risk assessment**

- Patients at risk for PH, infections, and refractory AI
- Pediatric age
- AIA/ Evans syndrome
- Underlying PID

**Clinical improvement**

- IgRT, antibiotic therapy
- Genetic evaluation for PID
- Mechanism-based tx
How to distinguish and treat primary among those presumed to have secondary immunodeficiency?

1. Clinical history
   multiple autoimmune manifestations
   progression with age
   complicated treatment refractory course (RTX)

2. Family history
   variable penetrance of disease (infectious and non-infectious)

3. Basic immune phenotyping (Ig) can be falsely reassuring:
   CVID/CID < ALPS < IPEX-like PIRDs

4. Genetic screen is of high importance

5. Biomarkers are needed for diagnosis and treatment response

6. Bridge therapy to control immune dysregulation

7. Hematopoietic stem cell transplant in selected cases

Multi-center multidisciplinary approach for pediatric and adult patients

Hematology team
BMT team
Pulmonary team
Rheumatology team
GI team

Pediatric and Adult Hematology team
Adult Pulmonary team

Pediatric Hematology group
Pediatric Pulmonary group

Adult BMT group
Adult Malignant Heme group
Rituximab and primary and secondary immunodeficiencies talks

**Title:** Primary and Secondary immunodeficiencies Associated with Rituximab Use in Children (Abstract #197)

**Session:** 0050 - Oral Presentation Session - B/Plasma Cell Depleting Therapies No.1

**Date & Time:** 28/09/2021 | 11:15-12:45

**Title:** Rituximab and Immunodeficiency: Chicken or Egg?

**Session:** Keynote Closing Lectures: When Secondary Immunodeficiency might be Primary Immunodeficiency

**Date & Time:** 29/09/2021 | 17:30-18:30

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CHU Sainte-Justine, Montreal, Canada
- Elie Haddad
- Guilhem Cros
- Jonathan Lacombe-Barrios
- Julie Barsalou

IWK Health Center, Halifax, Canada
- Beata Derfalvi
- Nora Alrumayyan

Massachusetts General Hospital/Harvard University, Boston, USA
- Sara Barmettler
- Nancy Yang
- Mei-Sing Ong
- Carlos A. Camargo
- Jolan Walter

Starship Children's Hospital, Auckland, New Zealand
- Annaliesse Blin
- Jan Sinclair
Why should we care about AI and IEI?

Survival is decreased in IEI with AI

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Fischer JACI 2017, PMID: 28192146