Understanding Primary & Secondary Immunodeficiencies

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MISSION

Improving the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency through fostering a community empowered by advocacy, education, and research.
VISION

IDF seeks to ensure that everyone in the U.S. affected by PI has a fully informed understanding of

1. the PI diagnosis that affects them,
2. all available treatment options,
3. the expected standard of care,
4. all their opportunities for connection and support within the PI community.
Questions?
IDF is here to help.

PRIMARYIMMUNE.ORG/ASK-IDF
Get Connected Groups

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Upcoming Forums

• March 9: IDF Lunch & Learn – Hyper IgM Syndrome
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Understanding Primary and Secondary Immune Deficiencies

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Secondary Immune Deficiency (SID)

• Definition ---
  • Secondary hypogammaglobulinemia is characterized by reduced immunoglobulin levels due to a medication or a disease process, leading to decreased antibody production or increased antibody loss.
  • It can be challenging to distinguish between SID and Primary immunodeficiency
    • PI focuses on identifying monogenic causes that affect immune function; over 450 inherited inborn errors of immunity described thus far.
  • Most frequent causes of SID are immunosuppressive medications or loss of immunoglobulins (IgG) in the GI or urinary systems
    • The largest proportion of SID (hypogammaglobulinemia) is due to the increasing use of immunosuppressive drugs, most notably B-cell depleting therapies, and certain cancers
Medications that Cause Hypogammaglobulinemia

- Anti-rheumatic and anti-inflammatory drugs -
  - Gold, d-penicillamine, sulfasalazine

- Anticonvulsants –
  - Phenytoin, carbamazepine, levetiracetam, valproic acid, oxcarbazepine, chlorpromazine, lamotrigine, and zonisamide
  - Reduction in serum IgA most common
    - Increased incidence of IgA deficiency associated with phenytoin
  - The mechanism for drug-induced hypogammaglobulinemia is unknown
Secondary immunodeficiency (SID) associated with hematological malignancies

• B cell lymphoproliferative diseases (CLL, MM, lymphoma) – a double edge sword for SID
  • B-cells in these diseases are the initiator/origin of an immune deficiency
    • Clonal expansion
  • B-cells are a target for therapy with immunosuppressive or cell deleting drugs
    • Rituximab

• The onset of SID results in serious infections and consequences on quality of life

Often the clinician is faced with the dilemma of “which is the cart and which is the horse” –

• does the patients have an underlying primary immune deficiency that was unrecognized prior to using immunosuppressive medications
Prolonged hypogammaglobulinemia and severe B-cell deficiency that required IgG replacement in a patient treated with Rituximab

• Case history –
  • 55 year old female who was treated with 2 courses of Rituximab 7 years ago for idiopathic thrombocytopenia purpura (ITP)
    • Developed 2 episodes of pneumonia
    • Referred to clinical immunology for evaluation with low serum IgG and absent B-cells
  • Immune evaluation-
    • Serum IgG 260 mg/dl, IgA – 24 mg/dl and IgM 40 mg/dl
    • Poor response to vaccines
    • Flow cytometry showed only 1% B-cells
  • Consequences of Rituximab or does she have CVID?
    • Started on Ig replacement therapy
    • Genetic evaluation showed she had LRBA deficiency
Increased risk for Hematological Malignancies in PIDD patients

- 3844 patients (2003-2015)
- 1.42-fold excess relative risk of cancer in PIDD patients vs. general population
  - 10-fold increase in risk of lymphoma in men (p<0.001)
  - 8.34-fold increase in risk of lymphoma in women (p<0.001)

Rituximab - Anti-B-cell therapy - Recommendations

- Prolonged hypogammaglobulinemia and severe B-cell deficiency with infection requiring IgG replacement therapy
  - Concomitant other immunosuppressive therapy may contribute to the secondary immune deficiency
  - Rituximab therapy may impair vaccine responses to some degree, especially polysaccharide vaccines
    - Immunize prior to starting rituximab
  - Patients with autoimmunity treated with rituximab should have baseline serum immunoglobulin levels and enumeration of peripheral blood B-cells

Levy R et al Autoimmunity Rev, 2014
Makatsori M et al QJM, 2014
Pescovitz et al J Allergy Clin Immunol, 2011
**CAR-T-cell Therapy**

- **Chimeric antigen receptor**, or **CAR T-cell therapy**, is a novel treatment option for ALL and adult B cell lymphoma.
  - The patient's T cells (a type of immune system cell) are changed in the laboratory so they will attack cancer cells. T cells are taken from a patient’s blood. Then the gene for a special receptor that binds to a certain protein on the patient’s cancer cells is added to the T cells in the laboratory.
    - The special receptor is called a chimeric antigen receptor (CAR). Large numbers of the CAR T cells are grown in the laboratory and given to the patient by infusion.

- CAR T-cell therapy is a cause of SID due to its CD19+ B cell depleting effect.
  - has significant immune adverse effects including B cell depletion and hypogammaglobulinemia.
  - It has been recommended that screening quantitative immunoglobulins and specific antibody titers in response to vaccines be sent prior to and 3 months after initiation of CAR-T cell therapy to risk stratify the need for prophylactic IgG-RT
Common causes of secondary antibody deficiency

Primary or secondary antibody deficiency?

Primary

“Acquired”
Drugs, cancer, chronic illness

“Inborn error”
Immune deficiency

Secondary

Primary (PID, PAD)
Pediatric > Adult
immune profiling + genetics
IgRT, “targeted” biologics, HSCT
1:2,000 in children
1:1,200 in patients of any age

Secondary (SAD)
Adult > Pediatric
trigger profiling > immune
treatment of triggers + ?
<30x higher (iatrogenic)

Incidence
1:2,000 in children
<30x higher
1:1,200 in patients of any age

Classical Onset
Diagnostic workup
Treatment
Incidence
Warning signs for PID

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

Example of ITP: Purpura and petechiae
Autoimmunity is very common in PID, especially in (PIRD)

Take home messages:
- AIC is common across all PIDs
- IEI patient has multi-autoimmune disorders
- Primary Immune Regulatory Disorder (PIRD) group: highly enriched in AI with overlapping phenotypes
- Large cohort studies in specific genetic defects are available

Modified from Walter JE et al. Current Opinion in Pediatrics 2019
PMID: 11981286
Primary immune regulatory diseases (PIRD): clinical phenotypes

ALPS-like
- ITP
- AIHA
- AIN
- LAP

IPEX-like
- Enteropathy
- Type 1DM
- Thyroiditis
- Arthritis
- Eczema
- Vasculitis

CVID-like
- Hypogammaglobinemia
- Recurrent infections

ALPS/ IPEX-Like
- Abnormal B cell number/function
- Normal IgG
- Immune cytopenia & Autoimmunity
- Lymphoproliferation

CVID-like
- Worsening B cell function
- Low IgG
- Sinopulmonary infections
- +/- Immune cytopenia & Autoimmunity
- +/- Lymphoproliferation

Late onset CID
- Worsening T and B cell function
- Low T cell number/function
- Low IgG
- Viral/ fungal infection
- Sinopulmonary infections
- +/- Immune cytopenia & Autoimmunity
- +/- Lymphoproliferation

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-ab+ CD4-CD8-) (ALPS-like group)
  - Regulatory T cell abnormalities (IPEX-like group)

Too complicated
Too hard to access immune testing

Genetic evaluation for PIRD
Genetic defects associated with PIRD


Chandrakasan 2019 Pediatric Blood & Cancer PMID: 30697957
Who is at risk and need of IgRT?

If you discover...

**“Inborn error”**
Immune deficiency

**“Acquired”**
Drugs, cancer, chronic illness

..PID:
High likelihood for need for IgRT

How about SID?
... not everyone needs IgRT:
We lack consensus between specialties
When to start IgRT, how long to treat, when to stop?

**Workup:**
- Infectious history
- IgG
- IgA, IgM
- Vaccine titers
- Immune subsets
- PAD Genetics?

**IgRT: START**

**Iatrogenic Tx Linked to SAD**

**Dx SAD**

**Anti-CD20 CAR-T**

**Monitor on IgRT**

**IgA, IgM**

Neoantigen challenge (salmonella, SARS-CoV2)

B cell immune reconstitution (counts, subsets [switched memory])

**Jolles, S. AJH 2021 Treating Secondary Antibody Deficiency in Patients with Haematological Malignancy:** European Expert Consensus. PMID: 33453130

**Barmettler JAMA 2018 Association of Immunoglobulin Levels, Infectious Risk, and Mortality With Rituximab and Hypogammaglobulinemia** PMID: 30646343
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
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
THANK YOU!

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YOUR QUESTIONS ANSWERED
THANK YOU!

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From all of us at IDF

Thank You!

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