Managing Multiple Conditions

Immune Deficiency Foundation Meeting
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Disclosures

Consultant to Takeda, Horizon, Pharming and Grifols but I will not be discussing any specific products

The Immune Response

- Protects against invading pathogens
  - Clears extracellular pathogens and their toxins
  - Kills intracellular pathogens
  - Kills virally infected cells
- Surveillance for and killing of malignant cells
- Can result in allergic or autoimmune disease

Primary Immune Deficiencies

- Single gene defects (>485 different diseases/gene defects)
- Affect one or more components of the innate or adaptive immune response
- Susceptibility to
  - Recurrent infections
  - Autoimmunity
  - Inflammation
  - Malignancy
- Recent recognition of genetic causes of immune dysregulation and auto-inflammation has led to the name Inborn Errors of Immunity (IEI)

IEI Classification

The International Union of Immunological Societies classifies IEI in 10 subgroups:

1. Immunodeficiencies affecting cellular and humoral immunity
2. Combined immunodeficiencies with associated or syndromic features
3. Predominantly antibody deficiencies
4. Diseases of immune dysregulation
5. Congenital defects of phagocyte number or function
6. Defects in intrinsic and innate immunity
7. Autoinflammatory disorders
8. Complement deficiencies
9. Bone marrow failure
10. Phenocopies of inborn errors of immunity

Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. Journal of Clinical Immunology (2022) *42:1473–1507* (*https://doi.org/10.1007/s10875-022-01289-3*)

Agammaglobulinemia

X-linked agammaglobulinemia (XLA):

- First immunodeficiency to be described ~70 years ago by Dr. Ogden Bruton
- Patient had absent gammaglobulins and recurrent infections
- Plasma transfusions reduced the frequency of infections
- Characterized by defect in B cell development, (absent B cells, lymph nodes and tonsils)
- Gene defect in a tyrosine kinase named Bruton's tyrosine kinase

Autosomal recessive agammaglobulinemia:

- Also results from defects in B cell development
- Affected gene is necessary for B cell development
- Affects males and females equally

Common Variable Immune Deficiency

CVID, the most common symptomatic immune deficiency is not a single disease but a phenotype characterized by:

- Reduced serum levels of IgG, IgA and/or IgM
- Reduced or absent isohemagglutinins and/or poor response to vaccines
- Patient older than 2 years of age
- All other causes of immune deficiency ruled out

Common Variable Immune Deficiency

- Peak onset usually in 2nd or 3rd decade of life
- Low IgG with low IgA and/or low IgM
- Immunodeficiency evolves over time
- Recurrent sinopulmonary infections (usually bacterial in origin)
- Granuloma formation in lungs and liver
- Autoimmune, gastrointestinal, endocrine, and hematologic disorders can be associated
- 10% of patients have no history of infection

Complications in 473 CVID Patients

Associated Condition	Number	Percentage
Infections only (no complications)	151	31.9
Chronic Lung Disease	135	28.5
Bronchiectasis	53	11.2
Autoimmunity ITP Autoimmune Hemolytic Anemia	134 67 33	28.6 14.2 7
GI Disease Malabsorption IBD (Crohn's, UC, Proctitis)	73 28 20	15.4 5.9 4.2
Liver Disease / Hepatitis	43	9.1
Granulomatous Disease	46	9.7
Lymphoma	39	8.2
Cancer	33	7
Splenectomy	39	8.2

Resnick and Cunningham-Rundles, Curr Opin Allergy Clin Immunol 2012, 12:595-601

Journal of Clinical Immunology (2019) 39:440–447
https://doi.org/10.1007/s10875-019-00640-5

ORIGINAL ARTICLE

Factors Beyond Lack of Antibody Govern Pulmonary Complications in Primary Antibody Deficiency

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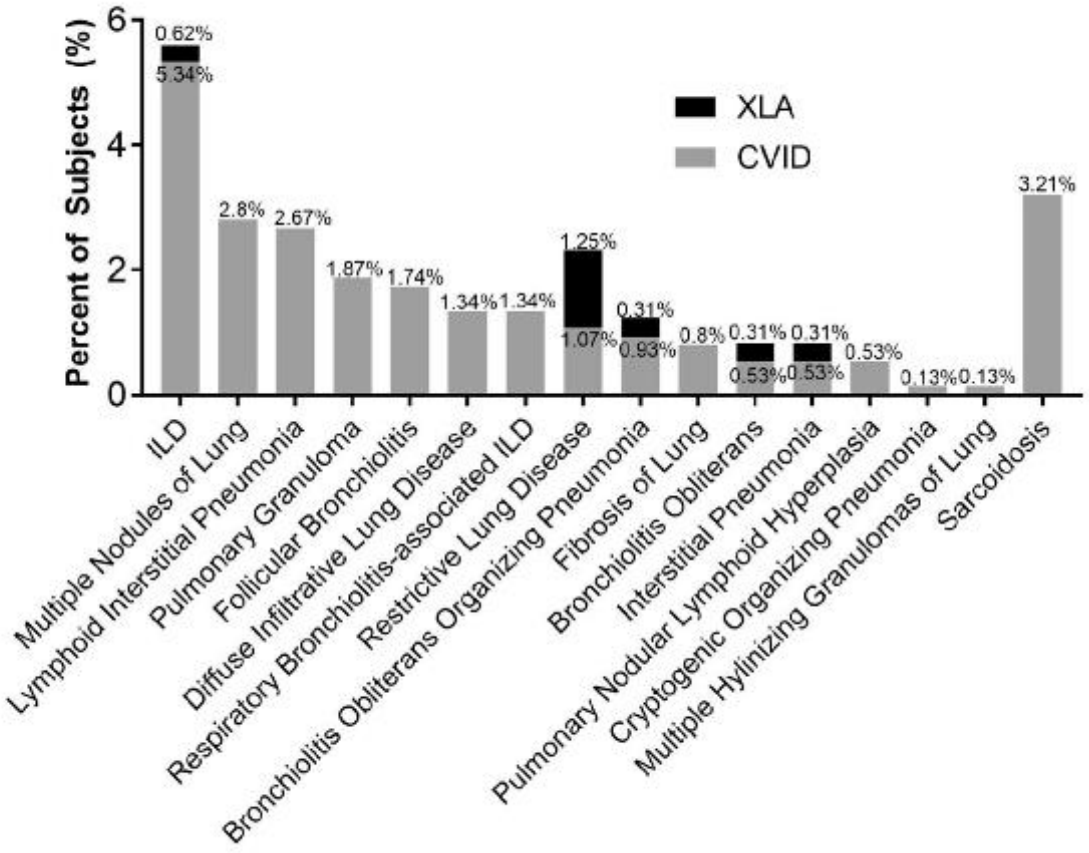

Treatment of Antibody Deficiency

- Antibody replacement: IV (500-600 mg/Kg every 3-4 weeks) or SC (150-200 mg/Kg every 1-4 weeks) in patients who cannot produce protective antibody levels from:
  - Agammaglobulinemia (no B cells)
  - Hyper IgM Syndrome
  - Common Variable Immunodeficiency
  - Hypogammagobulinemia
  - Antibody deficiency syndrome (especially if they fail antibiotic prophylaxis or are associated with severe infections)

- Trough levels are not as important as clinical response: In a UK study, different doses and trough levels were required to maintain patient infection free with the widest range seen in CVID

Lucas et al, J Allergy Clin Immunol 2010;125:1354-60

Managing Multiple Conditions

- First things first:
  - Keep up with management plan to prevent complications
  - Regular visit and maintenance of health program by PCP
  - Maintain healthy life-style to prevent other diseases such as Type II DM, Chronic Lung Disease, Heart Disease
    - No smoking
    - Limited alcohol use
    - No recreational drugs
    - Healthy diet
    - Regular exercise

Managing Multiple Conditions

- Autoimmunity:
  - Autoimmune cytopenias (ITP, AHA, AN):
    - Treatment:
      - Steroids (Immunosuppression)
      - High Dose IVIG (More of a good thing!)
      - Anti-B cell antibodies (wipe out B cells that make autoantibodies but also normal antibodies)
  - Rheumatologic Diseases (Arthritis, SLE, MCTD, Dermatomyositis)
    - Treatment:
      - Immunosuppression
      - Biologics (anti-cytokines)

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- Chronic Lung Disease including bronchiectasis:
  - Frequent/Chronic Antibiotics
- Granulomatous Lymphocytic Interstitial Lung Disease (GLILD)
  - Granulomas, T cell and B cells, nodules
  - T cell and B cell immunosuppression
- Rheumatologic Diseases: (Arthritis, SLE, MCTD, Dermatomyositis):
  - Treatment:
    - Immunosuppression
    - Biologics (anti-cytokines)

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- GI Disease:
  - Protein-losing enteropathy
    - IgG loss in the gut as well as T cells and B cells
    - Complicates Ig replacement therapy
    - Subcutaneous infusion better than IV infusion
  - Inflammatory Bowel Disease
    - Treatment:
      - Biologics
      - Immunosuppression
      - Hematopoietic Stem Cell Transplant depending on the underlying immunodeficiency

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- GI Disease (cont):
  - Liver Disease
    - Specific therapy for Hep C disease
    - If need for a liver transplant, consider hematopoietic stem cell transplant too

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- Cancer:
  - Lymphoma and other cancers
    - Needs specific therapy
    - Ig replacement provides a layer of immunity and prevention of infections
  - Hypersplenism
    - May require splenectomy
    - Ig replacement helps prevent hospital infections

Managing Multiple Conditions

- Bad News:
  - Many immunodeficiency diseases associated with immune dysregulation and/or predisposition to cancer
- Good News
  - Ig replacement therapy IV or SubQ will provide immunity throughout treatment of other diseases

Summary

- Primary Immune Deficiencies (PID) are rare inherited disorders that present in early childhood but may also present later in life
- A high index of suspicion is necessary to identify patients with PID
- Treatment depends on the immune deficiency and the underlying cause (primary vs. secondary)
- Many options for treatment of Primary Immune Diseases
- PID associated with Immune Dysregulation and other inflammatory diseases
- Management of multiple conditions necessary to manage all diseases and their complications
- Ig replacement provides antibody immunity while receiving immunosuppressive therapy.
- Healthy life-style helps prevent complications/associated diseases

Questions?