

# Guidelines for the Diagnosis and Treatment of Primary Immune Deficiency

Bruce Mazer MD

McGill University Health Center – Montreal  
Children's Hospital

Meakins Christie Laboratories



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# National Consensus

- Canadian Blood Services and Canada's National Advisory Committee on Blood and Blood Products.
- The Use of Immunoglobulin Therapy for Patients With Primary Immune Deficiency: An Evidence-Based Practice Guideline
- N. Shehata, V. Palda, T. Bowen, E. Haddad, T.B. Issekutz, B. Mazer, R. Schellenberg, R. Warrington, D. Easton, D. Anderson, and H. Hume, Transfusion Medicine, January 2010

# Primary Immune Deficiency

- Focus: Treatment with Immunoglobulin replacement
- Largest group: Humoral (antibody) deficiencies
  - X-Linked Agamaglobulinemia
  - Hyper-IgM syndrome (X-linked and Autosomal Recessive)
  - ICOS Deficiency
  - Common Variable immune deficiency
  - Specific Antibody Deficiency

# Primary Immune Deficiency

- Combined Immune Defects
  - Wiskott Aldrich Syndrome
  - Ataxia Telangectasia
  - Severe Combined Immune Deficiency (pre and post transplant)
- Secondary and Acquired Immune Defects
  - HIV
  - Post chemotherapy
  - Autoimmune
  - Drug induced

# Diagnosis

- Complete blood count (lymphopenia)
- IgG, A, M, E
- B and T cell enumeration
- Responses to vaccines
  - Protein (e.g. diphtheria, tetanus)
  - Polysaccharide (e.g. pneumococcus, hemophilus)
- Assessment of end organ damage

# Diagnosis

- Ancillary testing includes
- Urine analysis and other protein loss studies if applicable
- B and T cell functional studies
  - In vitro proliferation
  - Cytokine production
- Genetic Diagnosis if available

# Diagnosis

- Humoral Immune deficiency should not be diagnosed on the basis of low antibody levels alone!!
  - Low IgG??
  - Low IgA??
  - Low IgM??

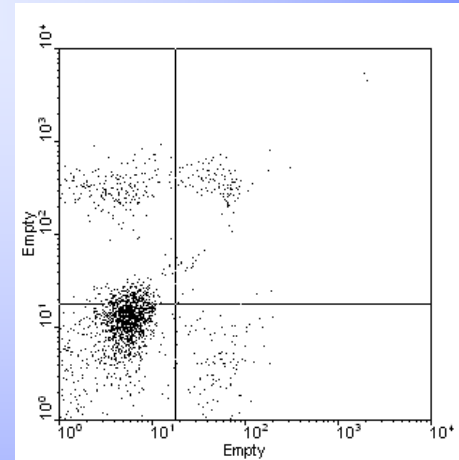
# Screening for genetic causes of immune deficiency

- Referral of the those patients who are more ill or resistant to treatment
- We have a large number of immune deficiencies (>100) which have the genes identified, allowing for screening and ultimately, diagnosis
  - Hospital for Sick Children, BC Children's
  - NIH, Saint Jude's, Seattle Children's, GENE-DX
  - Hopital Nekker, Brompton's

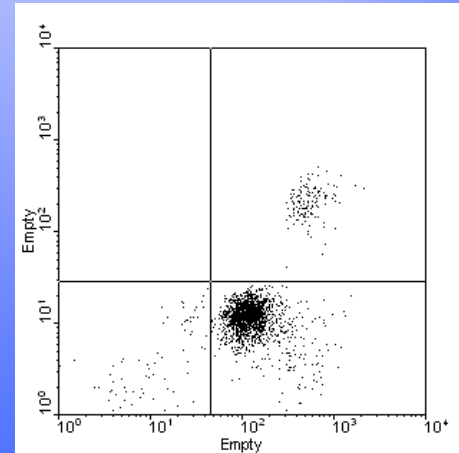
# B cell phenotyping

- CD19 and sIgM
- CD5
- CD27
- Use to follow patients, better characterize, and understand evolution of disease

FL-3 CD27



sIgM Cy-5



FL1 CD19

# Evaluation

- 1. Patients with confirmed immunodeficiency should have their care coordinated by a comprehensive care clinic/expert in the care of immune deficiencies.
- 2. An immunologist should be consulted for all pediatric and adult patients with suspected immunodeficiency syndromes (including primary immune deficiency) before the administration of immunoglobulin
- 3. Consider the diagnosis of primary immune deficiency among pediatric and adult patients who have recurrent infections as listed in Table 1.

# The 10 Warning Signs to investigate PID

- Eight or more new ear infections within 1 year.
- Two or more serious sinus infections within 1 year.
- Two or more months on antibiotics with little effect.
- Two or more pneumonias within 1 year.
- Failure of an infant to gain weight or grow normally.
- Recurrent, deep skin or organ abscesses.
- Persistent thrush in mouth or elsewhere on skin, after age 1.
- Need for intravenous antibiotics to clear infections.
- Two or more deep-seated infections.
- A family history of primary immunodeficiency.



These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board and are reprinted with permission.

# Other Diagnostic Parameters

- 5a. Consider the diagnosis of primary immune deficiency in adult and pediatric patients with autoimmune hematologic disease.
- 5b. In patients with autoimmune hematologic disease, draw quantitative IgA, IgG, and IgM levels before initiating IVIG therapy.

# Efficacy

- 6. Give IG to patients with primary immune deficiency to reduce infections.
- 7a. Give IG to reduce hospitalization and organ damage.
- 7b. Give immunoglobulin to improve survival and quality of life.

# Efficacy and Administration

- 8. With respect to clinical efficacy and adverse events, there is insufficient evidence to recommend one formulation of IG over another for currently available products.
- 9. With respect to clinical efficacy for reducing infections IVIG and SCIG preparations should be considered equivalent.
- 10. When deciding on route of administration, patient preference should be taken into account.

# Treatment Guidelines

- 11. Do not give IMIG for replacement therapy for primary immune deficiency.
- 12. Start IVIG at a dose of 400-600 mg/kg per 4 wk or SCIG at a dose of 100-150 mg kg<sup>-1</sup> wk<sup>-1</sup> in most patients.
- 13. Patients and practitioners should be aware that patients with primary immune deficiency will require immunoglobulin replacement therapy indefinitely.

# Vaccination Guidelines

- 14. Killed or recombinant vaccines are neither contraindicated nor specifically recommended as patients receiving IG have protective levels of antibodies to these agents through passive immunization.
- 15. The influenza vaccine **should** be offered to patients.



# Vaccination

- 16. Immunoglobulin therapy should not be stopped or the schedule modified to administer vaccination.
- 17. Live vaccinations, both oral and injectable (eg, MMR, varicella vaccine, LAIV, yellow fever vaccine, oral typhoid, BCG, OPV, smallpox and rotavirus) should not be given to patients with primary immune deficiency.



# Monitoring

- 18. Patients with primary immune deficiency should be monitored by a comprehensive care clinic at least annually.
- 19. Aim to achieve a minimum trough level of 7 g/L in most patients
- 20. Monitor trough levels every 3-6 mo in growing patients and every 6-12 mo in adult patients.

# Monitoring

- 21. The following conditions should prompt reevaluation of the immunoglobulin dosage regimen before the annual visit:
  - A. Any severe infection
  - B. Lack of expected reduction in infection
  - C. Continued failure to thrive in pediatric patients
  - D. Development of autoimmune complications

# Adverse Reactions

- 22. To minimize rate-related reactions, follow product specifications.
- 23. Because immunoglobulin is a human-derived blood product, with a possibility of home administration, it is recommended that the agency that dispenses the IG product ensures ongoing traceability of the immunoglobulin source and that the prescribing practitioner ensures a record of administration is kept.

# Early Investigation is Key

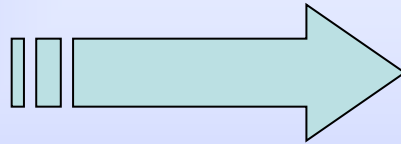
- Why is my child ill?
  - Antibody Defects
  - Cell mediated or T-cell defects
  - Innate Immune Defects
  - Other cellular dysfunction



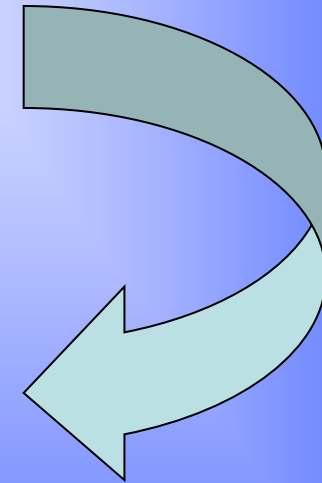
# Paradigm Shift

- Our immune investigations will go beyond cells
- **Even beyond antibodies!!**
- Much more functional and covering both innate and adaptive pathways!

**Screening**



**Diagnosis**



**Treatment**

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