Primary Immunodeficiency: What is It and How to Manage It?

Robert G. Penn, MD, FACP, FSHEA, FIDSA
Healthcare Epidemiologist and ID Specialist
Medical Director of Healthcare Epidemiology and Infection Prevention
Nebraska Methodist Hospital
Infectious Diseases Associates, PC
RobertPenn@IDmidwest.com
March 16, 2018
There are no conflicts of interest relevant to this presentation to report.

Robert G. Penn, MD, FACP, FSHEA, FIDSA
Healthcare Epidemiologist and ID Specialist
Medical Director of Healthcare Epidemiology and Infection Prevention
Nebraska Methodist Hospital
Infectious Diseases Associates, PC
RobertPenn@IDmidwest.com
March 16, 2018
Outline

- Overview of the immune system
- Primary immunodeficiency
- Case Presentation
- CVID
- Management
Identifying the Problem

Early microscope
Fundamental ID Principle

Infectious Disease \( \propto \) \( \frac{Dose \times Time \times Virulence}{Host \ Resistance} \)
Fundamental ID Principle

Infectious Disease $\propto \frac{Dose \times Time \times Virulence}{Host \ Resistance}$
Fundamental ID Principle

↑ Infectious Disease ∞ \[ \frac{↑ Dose \times ↑ Time \times ↑ Virulence}{↓ Host Resistance} \]
What is this immune system thing?
Decreased Host Resistance

Recurrent Infections

- Anatomic lesions
  - Congenital or acquired

- Disorders affecting the function of specific organs

- Secondary immune disorders
  - Other medical conditions
  - Treatments

- Primary (Congenital) immunodeficiencies
  - Often require repeated hospitalizations for serious infections at an early age and may develop growth retardation from chronic and recurrent illnesses
  - Increasing reports of milder phenotypes of disorders or presentation in adulthood
What is Immunity?

- The immune system keeps most people healthy most of the time.
- It is composed of different types of cells, proteins and body organs that work together (or separately) to protect us from infection.
How does the immune system keep people alive?

Recognizes and responds to DANGER

Source: Agriculture Research Service, U.S. Department of Agriculture.
Immunity

Immune Response
- Pathogens (bacteria, virus, fungi, etc.)

First line of defense (nonspecific)
- Mechanical
- Chemical
- Reflexes

Second line of defense (nonspecific)
- Protective proteins-cytokines
- Fever

Third line of defense (specific) immunity
- NK cells
- Inflammation

Nonspecific Immunity
- Phagocytosis
- Cell-mediated

Specific (acquired) immunity
- Life

Innate Immunity
Adaptive Immunity
Immune System – Innate vs Adaptive

**Innate:**
- Nonspecific
- Responds quickly

**Adaptive:**
- Specific
- Responds slowly the 1st time
Adaptive Defenses

- **Specific** – recognizes and targets specific antigens
- **Systemic** – not restricted to initial site
- Have **memory** – stronger attacks to "known" antigens
- Two separate, overlapping arms
  - Humoral (antibody-mediated) immunity
  - Cellular (cell-mediated) immunity
Cells of the Immune System

- Stem Cell
  - Lymphoid Stem Cell
    - Lymphocytes
      - T Cell Progenitor
        - Natural Killer Cell
        - Tc Cell
          - Memory Cell
        - Th Cell
      - Plasma Cell
  - Myeloid Progenitor
    - Granulocytes
      - Neutrophil
      - Eosinophil
      - Basophil
      - Mast Cell
    - Monocyte
      - Dendritic Cell
      - Macrophage
CHARACTERS OF THE IMMUNE SYSTEM
The Enemy Invader

- Usually a bacteria or virus.
- Comes in many different forms and attacks the body.
- The "Danger" signal.
The Macrophage

- *Body's Radar*
- Type of cell normally present in the blood
- Detects the enemy
The Neutrophil

- **First Responder**
- Kills bacteria by producing toxic substances
- Important for abscess formation
The Killer T-Cell

- The Assassin

[Image of cartoon figure and a gun]
The T-Helper Cell

- Communication Link

- Between the body's macrophages and b-cells

- Produces chemokines or signal proteins
The B-Cell

- The War Factory
- Makes antibodies that defend against "Danger"
Antibodies

- **Antigen Busters**

- Designed to seek and destroy the specific enemy antigen

- Prevent viral infections

- Neutralize toxins

- Stick to bacteria

IgG

IgA

IgM
Classes of Antibodies

- **IgM**
  - Pentamer (snowflake, larger than others); first antibody release
  - Readily fixes and activates complement
- **IgA** (secretory IgA)
  - Monomer or dimer; in mucus and other secretions
  - Helps prevent entry of pathogens
- **IgD**
  - Monomer attached to surface of B cells
  - Functions as B cell receptor
- **IgG**
  - Monomer; 75–85% of antibodies in plasma (most abundant)
  - From secondary and late primary responses
- **IgE**
  - Monomer active in some allergies and parasitic infections
  - Causes mast cells and basophils to release histamine

- B cells can switch antibody classes but retain antigen specificity
  - IgM at first; then IgG
  - Almost all secondary responses are IgG
Complement

- **Support Troops**
- Assists the antibodies to neutralize the enemy antigen
Immune Complex

- When antibodies and complement attack the antigen, an immune complex is formed.
T-Suppressor Cell

- Braking System
- Signals to the b-cell to stop making antibodies once the "danger" is gone
Other Characters

- Skin
- Mucous membranes
- Innate immunity
- Natural proteins
- Many, many, many, other things!!!!
Organs of the Immune System

- Tonsils and adenoids
- Lymph nodes
- Lymphatic vessels
- Thymus
- Spleen
- Peyer’s patches
- Appendix
- Lymph nodes
- Lymphatic vessels
- Bone marrow
"Hello, B-cell. Stop production. All's clear!"
Antibodies work where we meet the outside world
The Immune Response
What is Immune Deficiency

- A term to describe what happens when the immune system is unable to protect against pathogens in the environment
Primary Immunodeficiency

- Inherited defects of the immune system
- Multiple isolated defects and combined disorders
- Over 300 individual diagnoses classified as PI
- Patients present with increased vulnerability to infections
- Vulnerability depends on the type of deficiency
Primary Immunodeficiency

- Antibody: 50%
- Combined: 20%
- Phagocytic: 18%
- Cellular: 10%
- Complement: 2%
Growth in the Numbers of PID(s)

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of recognized PID(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>60</td>
</tr>
<tr>
<td>1999</td>
<td>71</td>
</tr>
<tr>
<td>2017</td>
<td>&gt; 300</td>
</tr>
</tbody>
</table>
Chief Complaint

- 36-year-old male referred for an ID office consultation for chronic left eye swelling associated with chronic nasal congestion, nasal blockage, and facial pain/pressure
History of Present Illness

- Nasal and sinus problems “whole life”
- Sinus operation 10 years ago
- Multiple recurrent episodes of acute sinusitis and pneumonias
  - Three pneumonias in the past four months
- Six months of progressive left eye swelling and double vision
  - Prism glasses to correct
- Score of “48” on the SNOT-22
Quality of Life Measures

Sinonasal Outcome Test – 22 (SNOT-22)

A. Considering how severe the problem is when you experience it and how frequently it happens, please rate each item below on how ‘bad’ it is by circling the number that corresponds with how you feel using this scale:

No problem | Very mild | Mild | Moderate | Severe problem | Problem is bad | Most important

| 1. Need to blow nose | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 2. Sneezing | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 3. Runny nose | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 4. Nasal obstruction | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 5. Loss of smell or taste | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 6. Cough | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 7. Post-nasal discharge | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 8. Thick nasal discharge | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 9. Ear fullness | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 10. Dizziness | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 11. Ear pain | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 12. Facial pain/pressure | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 13. Difficulty falling asleep | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 14. Wake up at night | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 15. Lack of a good night’s sleep | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 16. Wake up tired | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 17. Tongue | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 18. Reduced productivity | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 19. Reduced concentration | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 20. Frustrated/restless/irritable | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 21. Sad | 0 | 1 | 2 | 3 | 4 | 5 | blank |
| 22. Frustrated | 0 | 1 | 2 | 3 | 4 | 5 | blank |

Morley 2005
Browne 2007
Gillet 2009
FINDINGS:

- The nasal septum is midline. Patient appears to have had previous maxillary sinus surgery.
- There is opacification of all paranasal sinuses. A large left intraorbital mass is present and appears to originate from the ethmoid air cells. This measures 3.6 cm. This mass displaces the medial rectus muscle and extends superiorly into the intraorbital region.
- This has the appearance of a large mucocele.

IMPRESSION:

- Pansinusitis with probable left intraorbital mucocele.
Lab Test Results

- WBC 12,600 per mm$^3$
- Hgb 14.7 mg/dL
- Platelets 323,000 per mm$^3$
- hsCRP 8.0
- Procalcitonin 0.05
Lab Test Results

- **WBC** 12,600 per mm³
- **Hgb** 14.7 mg/dL
- **Platelets** 323,000 per mm³
- **hsCRP** 8.0
- **Procalcitonin** 0.05

**Immune studies**

- **IgG** 109 [IgG1 79, IgG2 <20, IgG3 8, IgG4 <1], IgA <5, IgM <5,
  Pneumococcal antibodies [+] 19/23 (83%), **Mumps IgG < 5.0**, 
  **Rubeola IgG Ab negative**, **Rubella Ab negative**, VZV IgG >3999,
  Diphtheria Ab 0.1, Tetanus Ab 1.1
Diagnoses and Management

Diagnoses
- Recurrent acute superimposed on chronic rhinosinusitis
- Left frontal sinus mucocele with erosion into left superior orbit with displacement of globe and secondary diplopia
- Common variable immunodeficiency

Management
- High dose amoxicillin/clavulanate orally
- MRSA nasal screen → [+] → added minocycline orally
- Nasal irrigations
- Fluticasone nasal spray
- Operative procedure
Operative Procedure

PREOPERATIVE/POSTOPERATIVE DIAGNOSES:
- History of agammaglobulinemia, chronic sinusitis, left frontal sinus pyocele with erosion into left superior orbit with displacement of globe and secondary diplopia

OPERATION PERFORMED:
- Bilateral revision, total endoscopic ethmoidectomies with antrostomies, bilateral frontal sinusotomies and marsupialization and drainage of left frontal sinus pyocele with culture and sensitivity

SPECIMENS
- Culture and sensitivity of drainage of middle meatus, culture and sensitivity of left frontal sinus pyocele tissue, right and left ethmoid
Cultures

- Left frontal sinus:
  - Methicillin Resistant *Staphylococcus aureus*
  - Prevotella sp.

<table>
<thead>
<tr>
<th>Drug</th>
<th>MICInt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>R</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>R</td>
</tr>
<tr>
<td>Levofloxacin (3)</td>
<td>R</td>
</tr>
<tr>
<td>Nafcillin (2)</td>
<td>R</td>
</tr>
<tr>
<td>Penicillin</td>
<td>R</td>
</tr>
<tr>
<td>Tetracycline (1)</td>
<td>S</td>
</tr>
<tr>
<td>Trimethoprim/Sulfa</td>
<td>S</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>S</td>
</tr>
</tbody>
</table>
Cultures

- Left middle meatus drainage:
  - *Streptococcus pneumoniae*
  - *Staphylococcus* species coagulase-negative
  - Methicillin Resistant *Staphylococcus aureus*
  - Alpha hemolytic *Streptococcus*
  - *Neisseria* species
  - *Prevotella* sp.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Streptococcus pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin (meningitis) (3)</td>
<td>R</td>
</tr>
<tr>
<td>Benzylpenicillin (non-meningitis) (2)</td>
<td>I</td>
</tr>
<tr>
<td>Ceftriaxone (meningitis) (5)</td>
<td>I</td>
</tr>
<tr>
<td>Ceftriaxone (non-meningitis) (5)</td>
<td>S</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>R</td>
</tr>
<tr>
<td>Erythromycin (4)</td>
<td>R</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>S</td>
</tr>
<tr>
<td>Azithromycin (1)</td>
<td>R</td>
</tr>
<tr>
<td>Trimethoprim/Sulfa</td>
<td>I</td>
</tr>
</tbody>
</table>
Histopathology

Diagnosis

- Left ethmoid sinus contents:
  - Chronic sinusitis
  - Fragments of membranous bone and fibrous tissue

- Right ethmoid sinus contents:
  - Benign sinusoidal polyp
  - Chronic sinusitis
  - Fragments of bone and fibrous tissue
Clinical Management & Outcome

Diagnoses:
- Recurrent acute superimposed on chronic rhinosinusitis
- Left frontal sinus pyocele with erosion into left superior orbit with displacement of globe and secondary diplopia
- Common variable immunodeficiency

Treatment
- IV daptomycin and IV ertepenem via PICC
- IVIG
Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1 in 500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Two or more new ear infections within 1 year.
2. Two or more new sinus infections within 1 year, in the absence of allergy.
3. One pneumonia per year for more than 1 year.
4. Chronic diarrhea with weight loss.
5. Recurrent viral infections (colds, herpes, warts, condyloma).
6. Recurrent need for intravenous antibiotics to clear infections.
7. Recurrent, deep abscesses of the skin or internal organs.
8. Persistent thrush or fungal infection on skin or elsewhere.
10. A family history of PI.

Presented as a public service by:

Jeffrey Modell Foundation
Curing PI Worldwide
CDC
National Heart, Lung, and Blood Institute (NHLBI)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institute of Child Health and Human Development (NICHD)
Baxter Bioscience
CSL Behring
GRIFOLS
octapharma
Talecris

These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board. Consultation with Primary Immunodeficiency experts is strongly suggested. © 2009 Jeffrey Modell Foundation For information or referrals, contact the Jeffrey Modell Foundation: 866-INFO-4-PI | info4pi.org
Infections that warrant an evaluation of antibody-mediated immunity

<table>
<thead>
<tr>
<th>Indications</th>
<th>Number of episodes</th>
<th>Allergy/Immunology Clinic LSUHSC, New Orleans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 to 5 years of age</td>
<td>&gt;5 years of age</td>
</tr>
<tr>
<td><strong>Respiratory infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>URI treated with antibiotics in last 12 months</td>
<td>≥4</td>
<td>≥2</td>
</tr>
<tr>
<td>Otitis treated with antibiotics (per year)</td>
<td>≥3*</td>
<td>≥2</td>
</tr>
<tr>
<td>Sinusitis episodes (per year)</td>
<td>≥2</td>
<td>≥2</td>
</tr>
<tr>
<td>Chronic, treatment-resistant sinusitis (&gt;1 month)</td>
<td>≥1</td>
<td>≥1</td>
</tr>
<tr>
<td>Pneumonias (per year)</td>
<td>≥2</td>
<td>≥2</td>
</tr>
<tr>
<td>Invasive infections (sepsis, meningitis, osteomyelitis)</td>
<td>≥2</td>
<td>≥2</td>
</tr>
<tr>
<td>Severe invasive infections</td>
<td>≥1</td>
<td>≥1</td>
</tr>
<tr>
<td><strong>Gastrointestinal infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic diarrhea due to rotavirus, other</td>
<td>≥1</td>
<td>≥1</td>
</tr>
<tr>
<td>Chronic/recurrent <em>Giardia lamblia</em> infection</td>
<td>≥1</td>
<td>≥1</td>
</tr>
<tr>
<td><strong>Antibiotic use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need for preventive antibiotic use</td>
<td>≥1</td>
<td>≥1</td>
</tr>
</tbody>
</table>

LSUHSC: Louisiana State University Health Sciences Center; URI: upper respiratory tract infection.
* After placement of ventilation tubes.

When Do We Suspect a PI?

Types of Infections

- **Severe**, even if only one infection
- **Unusual**, caused by an infection agent that does not cause infections in most exposed individuals
- **Chronic** infection with pathogen that usually causes self-limited infection
- **Recurrent** infections, multiple pathogens, frequent antibiotic use
- **Inflammation**, low or excessive

WHY?
Question?

• Is it more difficult to think of CVID?
• Or
• Is it more difficult to diagnose CVID?
Diagnostic difficulties

• Age of onset - adult
• Rarity
• **Infections** >90% – chest, sinus, ear, skin, sepsis, meningitis, bone
• **Autoimmunity** approx. 25% – cytopenias, RA, B12, SLE, Vitiligo, alopecia, IBD, others
• **Granulomas**
• **Inflammation**

CVID
**Infections**

- Streptococcus pneumoniae
- Haemophilus influenzae
- Staphylococcus aureus
- Moraxella catarrhalis
- Pseudomonas in bronchiectasis

**Inflammatory and Autoimmune**

- Rhinovirus

- LIP
- GLILD
- Lymphadenopathy
- Nodules/Opacities

- Splenomegaly
- Nodular regenerative hyperplasia
- Granulomatous hepatitis

- Diarrhoea
- Malabsorption
- Inflammatory bowel disease
- Nodular lymphoid hyperplasia
- Idiopathic enteropathy

**Autoimmune**

- Immune thrombocytopenic purpura
- Autoimmune Haemolytic anaemia
- Evans syndrome
- Rheumatoid Arthritis
- Anti-IgA antibodies
- Alopecia & Other

*The variable in common variable immunodeficiency: a disease of complex phenotypes, Jolles S.*

Can we detect CVID earlier?
What is calculated globulin?

- Total Protein – Albumin = Calculated Globulin

“P.I.”
Pattern of Infections: Clinical Immunology

The type of infectious agent and the location of the infection may give valuable insight into the nature of the immunologic defect...

- **T cell deficiencies**
  - Fungi
  - Viruses
  - *Pneumocystis jirovecii*

- **B-cell deficiencies**
  - *S. pneumococcus*
  - *H. influenzae*
  - Enteroviruses

- **Complement deficiencies**
  - Bacteremia
  - Meningitis
  - C5-9: *Neisseria*
  - C1/2/4: SLE

- **Phagocytic disorders**
  - Staph skin infections
  - *Burkholderia cepacia*
  - Infections of the reticuloendothelial system
  - Abscesses
Clinical Scenario: Recurrent infections

- 32 y/o previously healthy female who has a 3 year history of sinus drainage and recurrent sinus infections.

- Differential:
  - Allergies
  - Chronic sinusitis
  - Allergic fungal sinusitis
  - Antibiotic resistance
  - Mechanical derangement
Clinical Scenario: Recurrent infections

- 32 y/o previously healthy female who has a 3 year history of sinus drainage, recurrent sinus infections, who developed bilateral otitis media requiring tympanostomy and IV antibiotics.

Differential
- Allergies
- Chronic sinusitis
- Allergic fungal sinusitis
- Antibiotic resistance
- Mechanical derangement
- Humoral immune deficiency
- Cystic fibrosis
- Primary Ciliary Dyskinesia
Clinical Scenario: Recurrent infections

- Now it’s the same 32 y/o female . . . who develops fevers, increased sputum, and an infiltrate seen on CXR

- Differential
  - [ ] Humoral immune deficiency
  - [ ] CF
  - [ ] Primary Ciliary Dyskinesia
## Differential for Humoral Immune Deficiency in Adults

### Drugs
- Antimalarials, captopril, carbamazepine, steroids, gold, penicillamine, phenytoin, sulfasalazine

### Systemic disorders
- Chronic medical conditions
  - CF
  - Sickle Cell
  - Malnutrition
- Hypercatabolism of Ig
- Excessive loss of Ig
  - Nephrosis, burns, diarrhea, lymphangiectasia

### ID
- HIV, EBV
- Malignancy
  - CLL
  - Immunodeficiency with thymoma (Good’s syndrome)
- NHL
- CVID
- IgA deficiency
- IgG Subclass deficiency
Common Variable Immunodeficiency

*CVID*—What is it?

Common variable immunodeficiency: the immune system in chaos

Jagadeesh Bayry\(^1,2\), Olivier Hermine\(^3\), David A. Webster\(^4\), Yves Lévy\(^5\) and Srinivasa Kaveri\(^1\)

\(^1\)INSERM Unité 681 and Université Pierre et Marie Curie, Institut des Cordeliers, 15, rue de l’Ecole de Médecine, Paris, 75006, France
\(^2\)The Edward Jenner Institute for Vaccine Research, Compton, Newbury, Berkshire, RG20 7NN, UK
\(^3\)Department of Hematology and CNRS-UMR 8603, Hôpital Necker, Paris, 75015, France
\(^4\)Department of Immunology, UCL Medical School, Royal Free Medical School, London, NW3 2QG, UK
\(^5\)Service d’Immunologie Clinique, Hôpital Henri Mondor, Créteil Cedex, 94010, France
Common Variable Immunodeficiency

**CVID**

- **Definition:** a disease characterized by low levels of immunoglobulins and recurrent sinopulmonary infections
- It is a relatively **common** immunodeficiency with **variable** levels of immunoglobulins and clinical course between patients
Heterogeneous group of disorders of humoral immunodeficiency with associated bacterial infections, autoimmune disease, and malignancy

Bimodal distribution
- Major peak 25-45 y/o
- Second peak 5-15 y/o

M=F

Prevalence estimated at 1:10,000-50,000¹ ²

CVID: Pathogenesis

- Some molecular defects identified
  - TACI mutation (~20% of CVID)
- Most cases are sporadic
- Familial inheritance has been demonstrated
  - X-linked
  - Autosomal recessive
  - Autosomal dominant
CVID: Pathogenesis

- Environmental triggers
  - Viral infection
  - Drugs
    - Antimalarials, captopril, carbamazepine, steroids, gold, penicillamine, phenytoin, sulfasalazine
CVID: Clinical Manifestations

- **Infectious Disease**
  - Recurrent pyogenic sinopulmonary infections
  - Chronic enteroviral infections
  - Meningoencephalitis
  - Chronic *Giardia lamblia*
  - Recurrent HSV and/or VZV
Remember
Infection - the upper airway - Sinuses

- 16 CVID and 1 XLA
- MRI and sinus micro
- 53% radiological sinusitis
- 87% bacteria
- 47% viruses

Virus shedding after human rhinovirus infection in children, adults and patients with hypogammaglobulinaemia

RT-PCR, real-time polymerase chain reaction
CVID: Clinical Manifestations

- Pulmonary manifestations
  - Pneumonia
  - Asthma
  - Bronchiectasis
  - Lymphoid interstitial pneumonia (LIP)
  - Pulmonary Fibrosis

Best predictor of improved pulmonary outcome is early diagnosis and aggressive treatment.

Tree-in-bud

Chest CT with arrow A pointing to extensive tree-in-bud and arrow B of dilated and thickened airways.

CT: computed tomography.
Lymphoid interstitial pneumonia on chest x-ray and CT scan

A chest x-ray (A) shows bilateral non-specific diffuse interstitial coarsening and a cyst in the right lower lobe (arrow). A coronal reconstruction of a CT scan (B) confirms the presence of cysts in the right lower lobe and left upper lobe (arrows). An axial CT scan (C) shows extensive bibasilar cystic changes (dashed arrow) and interstitial thickening (arrow) with changes in the left pleural space (arrowhead) following wedge biopsy. A diagnosis of LIP was confirmed by biopsy.

CT: computed tomography. LIP: Lymphoid interstitial pneumonia
CVID: Clinical Manifestations

- GI manifestations
  - Sprue-like syndrome
    - Weight loss, diarrhea, vitamin deficiency, hypoalbuminemia
  - Nodular follicular hyperplasia of the intestines
  - Gastric atrophy, achlorydria
  - Colitis
  - MALT lymphoma
  - Giardiasis
Nodular Lymphoid Hyperplasia of the Duodenum

Nodules develop through lymphocyte proliferation in the lamina propria and submucosa, but are not directly linked to increased malignant potential.
Infections most commonly seen in patients with common variable immunodeficiency (CVID)

<table>
<thead>
<tr>
<th>Lungs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pneumonia (bacterial, especially encapsulated bacteria/mycoplasma)</td>
<td></td>
</tr>
<tr>
<td>• Bronchiectasis resulting from recurrent infections</td>
<td></td>
</tr>
<tr>
<td>• Acute or chronic bronchitis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Head and neck</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rhinosinusitis (bacterial, especially encapsulated bacteria, and viral)</td>
<td></td>
</tr>
<tr>
<td>• Otitis media</td>
<td></td>
</tr>
<tr>
<td>• Conjunctivitis (especially nonencapsulated H. influenzae)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal tract</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute infectious diarrhea (Norovirus, Campylobacter jejuni, Salmonella)</td>
<td></td>
</tr>
<tr>
<td>• Acute or chronic infections with Giardia lamblia (causing diarrhea, malabsorption, weight loss)</td>
<td></td>
</tr>
<tr>
<td>• Helicobacter pylori</td>
<td></td>
</tr>
<tr>
<td>• Cytomegalovirus</td>
<td></td>
</tr>
<tr>
<td>• Bacterial overgrowth</td>
<td></td>
</tr>
<tr>
<td>• Cryptosporidium</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urinary tract</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mycoplasma/ureaplasma species</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Joints</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Septic arthritis (acute monoarthritis or chronic degenerative polyarthritis)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Herpes zoster</td>
<td></td>
</tr>
<tr>
<td>• Molluscum</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Central nervous system</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Meningitis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bacterial sepsis, especially encapsulated bacteria</td>
<td></td>
</tr>
</tbody>
</table>
Autoimmunity in CVID
CVID: Clinical Manifestations

- Autoimmune manifestations (22-50%)
  - Pernicious anemia
  - Vitiligo
  - Autoimmune thrombocytopenia
  - Autoimmune hemolytic anemia
  - Autoimmune thyroiditis
  - Alopecia areata
  - Keratoconjunctivitis sicca
  - Inflammatory arthritis
### Autoimmune disorders in common variable immunodeficiency

<table>
<thead>
<tr>
<th>Dermatologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia totalis</td>
</tr>
<tr>
<td>Vitiligo</td>
</tr>
<tr>
<td>Psoriasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune thrombocytopenia</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
</tr>
<tr>
<td>Autoimmune neutropenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endocrinologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rheumatologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascitis</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
</tr>
<tr>
<td>Sicca syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Primary biliary cholangitis</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
</tr>
</tbody>
</table>

CVID: Clinical Manifestations

- Hematologic manifestations
  - Granulomatous disease
    - Noncaseating epithelioid granulomas of liver, lung, spleen, skin, gut
  - Amyloidosis
  - Tonsillar tissue normal or enlarged
  - Lymphadenopathy
  - 25% splenomegaly
CVID: Clinical Manifestations

- Malignancy
  - 300+ fold increase in lymphomas in women between 50-60 y/o
  - 50 fold increase in gastric carcinoma
  - Thymoma
  - MALT lymphoma
  - Lymphoreticular malignancy
Laboratory evaluation of Humoral Immune Deficiency

- Targeted H&P for recurrent infections and autoimmunity
- Quantitative serum Ig G, A, M (age and sex matched controls)
- Measurement of Ab production
  - Pneumococcal polysaccharide
  - Tetanus & diphtheria toxoid
- Measurement of quantitative Ag-specific Ig titer pre- and post-immunization
  - 4 week post-immunization level within protective range and >4 fold rise from baseline
- Peripheral blood lymphocyte subset analysis
Algorithm for Dx of Humoral Immunodeficiency

2-1. Suspected antibody deficiency. Screening of humoral immune function.

2-2. Is there profound hypogammaglobulinemia?
   - Yes
   - No

2-3. Is cellular immunity abnormal?
   - Yes
   - No

2-4. Is specific antibody production impaired?
   - Yes
   - No

2-5. Pursue diagnosis of combined defect

2-6. Are Immunoglobulins normal?
   - Yes
   - No

2-8. Consider complement or phagocyte defect, other conditions

2-9. Consider SIGAD, IGGSD, THI

2-10. Consider CVID, SIGAD, IGGSD, HIM, SAD

2-11. Consider XLA, ARA, CVID

Algorithm 2. Diagnosis of humoral immunodeficiency. ARA indicates autosomal recessive agammaglobulinemia; CVID, common variable immunodeficiency; HIM, hyper-IgM syndrome; IGGSD, IgG subclass deficiency; SAD, specific antibody deficiency; SIGAD, selective IgA deficiency; THI, transient hypogammaglobulinemia of infancy; and XLA, X-linked agammaglobulinemia.

Quality *not* Quantity

- Measurement of Antigen-specific
  - Tetanus, diphtheria, pneumococcal
    - IgG titer pre- and post-immunization
- 4 week post-immunization level within protective range and/or >4 fold rise from baseline
Immunoglobulin Defects

*Hypogammaglobulinemia + S.A.D.*

- <2 SD below the mean in IgG and another Ig class or <5\textsuperscript{th} percentile of total IgG for a given age
- Poor or absent response to immunization
  - <Two-fold increase in Ag-specific titer
CVID: Clinical Surveillance

- PFT’s
- High resolution CT of the chest to evaluate for bronchiectasis (or MRI?)
- Stool O&P, bacterial cx, *C. difficile* for changes in GI sx (FilmArray™ GI Panel)
- CBC q6 mo for autoimmune cytopenias
- Low threshold for lymphoma
Case Presentation

  - Obtunded, headache, febrile, nuchal rigidity
  - History of agammaglobulinemia
  - Weekly IM gammaglobulin
Case Presentation

  - Obtunded, headache, febrile, nuchal rigidity
  - History of agammaglobulinemia
  - Weekly IM gamma globulin

- Positive CSF for Echovirus 25
  - Treatment options?
Case Presentation

  - Obtunded, headache, febrile, nuchal rigidity
  - History of agammaglobulinemia
  - Weekly IM gamma globulin

- Positive CSF for Echovirus 25
  - Treatment options?
CONFIDENCE

is the feeling you have before you fully understand the Situation.
March 30, 1984 Volume 76, Issue 3, Part 1, Pages 46–52

Thirty years of supplying the missing link

History of gamma globulin therapy for immunodeficient states

John M. Dwyer, M.D., Ph.D
New Haven, Connecticut USA

Abstract
Man has been injecting himself with gamma globulin for almost 100 years. As a result, both the benefits and the hazards of such therapy have been convincingly demonstrated. For 30 years physicians have realized that one group of patients must receive regular injections of this material to avoid death from overwhelming bacterial infections. The health of subjects with congenital or acquired hypogammaglobulinemia is directly related to the successful administration of adequate amounts of immunoglobulin G (IgG). Three phases are easily recognizable when examining the history of how physicians have accomplished such replacement therapy. Initially, therapy was limited to frequent and painful intramuscular injections of concentrated immune serum globulin. In some patients, the administration of monthly infusions of fresh plasma from "buddies" supplied a better approach. Now, the elusive goal of having a concentrated form of gamma globulin suitable for intravenous administration has been reached. Such preparations are revolutionizing the treatment of human immune deficiencies and expanding the therapeutic potential of gamma globulin itself.
Case Presentation

  - Obtunded, febrile, nuchal rigidity
  - History of agammaglobulinemia
  - Weekly IM gamma globulin

- Positive CSF for Echovirus 25
  - Treatment options?

- Intraventricular IG and IVIG

- Awoke, IVIG every 4 weeks since, now 46 y/o
Successful Reversal of ECHOvirus Encephalitis in X-Linked Hypogammaglobulinemia by Intraventricular Administration of Immunoglobulin

Kristian Eirlandsson, M.D., Timothy Swartz, M.D., and John M. Dwyer, M.D., Ph.D.

BECAUSE of the central role of immunoglobulins in protection from bacterial infections, hypogammaglobulinemic states frequently result in serious infections with these organisms. However, patients who do not produce normal amounts of immunoglobulin also have an increased incidence of certain viral infections. This is particularly true of infections with enteroviruses. Vaccine-induced poliomyelitis and echovirus encephalitis have been particularly troublesome infections for patients with hypogammaglobulinemia. Neurologic dysfunction progressing to death has been common in these patients. Since there is some evidence that cell-to-cell spread of enteroviruses may be minimized by specific antibody, therapy with high-titer specific immunoglobulin has been suggested and attempted.

Author Affiliations

From the Departments of Medicine and Pediatrics, Section of Clinical Immunology, Yale University School of Medicine. Address reprint requests to Dr. Dwyer at the Department of Medicine, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06510.
What is Immune Globulin?

- **Donor plasma pool**
  - Derived from 2000 to 10,000 donors
  - May be as much as 60,000 donors (FDA)

- **Composition**
  - Monomeric IgG (>95%) with small amounts of dimeric and polymeric IgG
  - Small amounts of IgM and IgA present

- **Antibody content**
  - One gram of IVIG contains $4 \times 10^{18}$ molecules of Ab
  - $>10^7$ specificities to a broad range of bacterial and viral pathogens
Historical Perspective on the Therapeutic Use of Gamma Globulin

- 1944 - Cohn’s cold ethanol fractionation of plasma
- 1952 - Treatment of agammaglobulinemia with intramuscular (IM) gamma globulin
- 1966 - Plasma therapy using a “buddy” system
- 1969 - Pepsin digested globulin for IV use
- 1975 - Initial studies with IVIG
- 1981 - Approval for use of IVIG in primary immune deficiencies
Is IVIG Safe?

- FDA Regulations¹
  - Must be prepared from at least 1,000 human donors
  - Must contain all four IgG subclasses
  - IgG must maintain biologic activity and lifetime at least 21 days
  - Does not contain samples from donors who are HIV, HBV, or HCV positive
  - Must be screened and treated in a manner which destroys viruses
  - Plasma for Ig given in the U.S. must be collected in the U.S.

¹www.fda.gov
Side Effects of IVIG

- IVIG infusion related adverse reactions (fever, HA, myalgia, chills, nausea, and vomiting)
  - Thought to be 2/2 formation of immunoglobulin aggregates during manufacture or storage

- Carbohydrates or proteins added to reduce aggregate formation
  - Stabilized with
    - Glucose, maltose, glycine, sucrose, sorbitol, or albumin

- In 1981, Gamimune became the first IGIV licensed in the United States.
  - It was formulated with 10% maltose as a stabilizer to eliminate the severe adverse events
Side Effects of IVIG cont.

- Mild side effects occur in approximately 10% of infusions
- Side effects often preventable with ASA (15 mg/kg/dose) or acetaminophen (15 mg/kg/dose) with diphenhydramine (1 mg/kg/dose).
- Occasionally, hydrocortisone (0.3 mg/kg/dose, max=50 mg) 1hr prior

<table>
<thead>
<tr>
<th>Common</th>
<th>Rare (Multiple Reports)</th>
<th>Very Rare (Isolated Reports)</th>
<th>Potential (No Reports)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills*</td>
<td>Chest pain or tightness*</td>
<td>Anaphylaxis*</td>
<td>Creutzfeldt-Jakob disease</td>
</tr>
<tr>
<td>Headache*</td>
<td>Dyspnea*</td>
<td>Acrodynia</td>
<td>HIV infection</td>
</tr>
<tr>
<td>Backache</td>
<td>Migraine headaches*</td>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td>Malaise*</td>
<td>Aseptic meningitis</td>
<td>Thrombosis</td>
<td></td>
</tr>
<tr>
<td>Fever*</td>
<td>Renal failure*</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Pruritis*</td>
<td>Hepatitis C</td>
<td>Direct Coombs’ test</td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td></td>
<td>Fulminant infection</td>
<td></td>
</tr>
<tr>
<td>Nausea*</td>
<td></td>
<td>Cryoglobulinemia</td>
<td></td>
</tr>
<tr>
<td>Tingling*</td>
<td></td>
<td>Neutropenia</td>
<td></td>
</tr>
<tr>
<td>Hypo- or hypertension*</td>
<td></td>
<td>Alopecia</td>
<td></td>
</tr>
<tr>
<td>Fluid overload*</td>
<td></td>
<td>Uveitis + retinal vasculitis and ANCA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Noninfectious hepatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypothermia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary insufficiency*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desquamation*</td>
<td></td>
</tr>
</tbody>
</table>

* Personally observed.
ANCA, anti-neutrophil cytoplasmic antibody.

How Does IVIG Work?

- Provides IgG antibodies to a wide range of bacteria and viruses so that their ability to cause infection is neutralized
- Increases opsonization
  - Process of identifying bacteria to white blood cells so WBC’s can gobble up and destroy the bacteria
- Increases serum levels of IgG, but NOT IgM or IgA
- Regulates immune function
Treatment of CVID with IVIG

- Dose to keep trough IgG levels >500 mg/dl
  - 400-500 mg/kg/q2-4 weeks IV
  - Decreases infections, hospitalizations, need for ABX therapy and improves pulmonary function

- Pre-existing chronic lung disease is not improved by IVIG

<table>
<thead>
<tr>
<th>Author and City</th>
<th>Year</th>
<th>Type of Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham-Rundles et al.,* New York</td>
<td>1984</td>
<td>21 patients, 2-dose, 2-yr sequential observational study</td>
<td>300 mg/kg IVIG compared with 100 mg/kg im: reduced sick days, need for decreased antibiotic use and decreased hospitalized days</td>
</tr>
<tr>
<td>Roifman et al.,† Montreal</td>
<td>1985</td>
<td>7 patients with sinopulmonary disease, 2-dose sequential, 7–18 mo observational study</td>
<td>600 mg/kg IVIG compared with 100 mg/kg im: decreased acute infections, improved weight gain, improved pulmonary function and clearance of sinus infection</td>
</tr>
<tr>
<td>Roifman et al.,†† Montreal</td>
<td>1987</td>
<td>12 patients with decreased pulmonary function, 2-dose, 2-yr, crossover study</td>
<td>600 mg/kg IVIG compared with 200 mg/kg IVIG: decreased minor and major infections and greatly improved pulmonary function</td>
</tr>
<tr>
<td>Bernatowska et al.,# Warsaw</td>
<td>1987</td>
<td>12 patients, 3-dose, 2-yr crossover study</td>
<td>500 mg/kg IVIG compared with 150 mg/kg IVIG or 20 ml/kg of plasma: decreased infections, decreased days of fever, decreased days of antibiotics and improved pulmonary function</td>
</tr>
<tr>
<td>Liese et al.,* Munich</td>
<td>1992</td>
<td>29 patients, 3-dose, 2-yr sequential observational study</td>
<td>350–360 mg/kg IVIG compared with 200 mg/kg IVIG or 100 mg/kg im: decreased serious infections, decreased hospitalized days and improved pulmonary function</td>
</tr>
</tbody>
</table>

'It’s CVID Therapy Jim – but not as we know it...'

- Immunoglobulin
- Antibiotics
- Vaccination
Lots of Choices

- IVIg
- SCIg
  - Weekly SCIg
  - Bi-weekly SCIg
  - Rapid push
  - Facilitated SCIg

Jolles, S. Subcutaneous and intramuscular immunoglobulin therapy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on June 2017.)
Christian Louboutin meets IgG Pharmacokinetics

- Rapid Push
- Weekly SC Ig
- Bi-weekly SC Ig
- Facilitated SC Ig
- IV Ig

![Graph showing IgG levels over time](image)
Practical Considerations

- What would you choose and why?

- IVIg in hospital
- IVIg at home
- SCIg in hospital (wk/2wk)
- SCiG at home (wk/2wk)
- Rapid push at home
- fSCIg in hospital
- fSCIg at home
Practical Considerations

From daily up to every 2 weeks (biweekly)

Weekly

SCl

SCl with hyaluronidase
Real Life Factors

- Relationship with significant others
- Personal appearance
- Fears/phobias
- Spectrum of responsibility
- Prior experience of hospital/home treatment
- Work-life balance
- Flexibility to travel
- Availability of caregiver to assist with the infusion at home
- Home environment
- Ability to learn and administer infusions
- Compliance
Options are not fixed

Assess changes, problems & new options

Inform, explain, agree, consent, train

Review of independent and ongoing therapy
Patient Profiles - IVIg

- High dose needed – indication eg immunomodulation neurology, Weight
- Higher Trough needed – XLA, bronchiectasis
- Difficult to maintain trough on maximal SCIg
- Cytopenias
- Less needles
- Less frequent infusions
- Less involvement
- Unable to undertake home therapy
- Responsibility
- Shorter infusion times
- Need to load quickly
Patient Profile - SCtG

- Greater independence
- Responsibility
- Side effects on IVIg
- Poor venous access
- Children
- Flexibility
- Travel, logistics and work considerations
- Persisting ‘wear off’ effects on IVIg
- Need for stable levels
Limits of current therapy

Percentage of patients experiencing infections

<table>
<thead>
<tr>
<th>Year</th>
<th>Recurrent resp. tract infections</th>
<th>Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>2011</td>
<td>100</td>
<td>40</td>
</tr>
</tbody>
</table>

n=248 (1999), n=473 (2011)
Mount Sinai PID patient cohort (USA)
Efficacy of IVIG Therapy
Mean Number of Episodes of Infection Per Year Pre- and Post-IVIG Rx

IVIG Therapy: Decreases Hospitalization

Percent of Patients Hospitalized: Pre/Post-IVIg

- Year Prior to Diagnosis: 57%
- First Year IVIg: 36%
- Last Year IVIg: 25%

IVIG Therapy: Decreases Doctor Visits and Sick Days

Median Number of Doctor Visits and Sick Days Per Year: Pre- and Post-IVIG

“Uh-oh, your coverage doesn’t seem to include illness.”
CVID and Antibiotics

- **Prophylactic antimicrobials** — The efficacy of prophylactic antibiotics for preventing infections in patients with CVID has not been adequately studied
  - Do not routinely administer prophylactic antibiotics to all patients with CVID
  - Helpful in CVID patients with ongoing lung disease

- **Prevention of recurrent sinusitis** — Do not routinely recommend daily antibiotics to prevent recurrent sinusitis in patients with CVID who are receiving immune globulin replacement therapy, although there are no published studies examining this issue
  - Instead, encourage patients to maintain good nasal hygiene with saline irrigations, and we treat infections as they arise
  - We also try to avoid surgical treatment of chronic rhinosinusitis, as disease invariably returns

- **Chronic bronchiectasis** — Prophylactic antibiotic therapy may be helpful for patients with bronchiectasis, frequent exacerbations, and declining lung function and should target *Haemophilus influenzae* and mycoplasma
CVID and Antibiotics

- **Gastrointestinal infections** — There is no antibiotic prophylaxis that prevents gastrointestinal infections in patients with CVID, and the impact of immune globulin replacement therapy on the gastrointestinal tract appears to be minimal.

- **Patients with low CD4 counts** — Prophylactic antibiotics to prevent infection with *Pneumocystis carinii* (*P. jirovecii*) may be given to patients with CVID and CD4 counts <200 cells/μL.
  - However, it is not as standard as it is in patients with human immunodeficiency virus (HIV) infection.
  - Patients with CVID are generally not susceptible to *P. carinii* pneumonia unless given glucocorticoids or other immune suppressants.
  - eg, methotrexate or azathioprine for prolonged periods.
CVID & Detection of Malignancy

- **Must be monitored** for lymphoma, gastric cancer, and other malignancies
- **Early detection** — Patients with CVID should receive all age-appropriate cancer screening procedures that are recommended for the general population
- Many patients have lymphadenopathy and splenomegaly, although the development of constitutional symptoms, solitary nodules, expanding lymph nodes, or other masses should prompt consideration of lymphoma
  - Peripheral blood studies or lymph node or bone marrow biopsy may be indicated to assess clonality
- Bronchoscopy with biopsy may be indicated for focal pulmonary findings that fail to resolve with treatment.
- In older studies, gastric cancer was found more commonly in CVID patients, although it has not been seen with the same higher incidence in subsequent studies
  - Suggested surveillance protocol: screen all patients (at diagnosis) for *Helicobacter pylori* infection with urea breath testing, eradication therapy if infection is detected, and repeat breath testing to demonstrate clearance
  - In addition, serum B12 and iron concentration are measured annually for all patients
  - Patients who develop dyspepsia or unexplained weight loss during their follow-up period, those with positive urea-breath testing, and those with low serum B12 level should undergo upper gastrointestinal endoscopy, including biopsies of the antrum and fundus
  - A more conservative approach would be to perform endoscopy and biopsy for *H. pylori* in patients only if they develop symptoms of gastritis or gastroesophageal reflux disease
## Screening for Cancer in Adults

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Concerning family history</th>
<th>Hereditary breast and ovarian syndrome</th>
<th>Women ≥40</th>
<th>Refer for genetic counseling/testing</th>
<th>Screen per recommendations</th>
<th>Discuss screening, individual decision; if screening desired, screen with mammography every two years</th>
<th>Pap smear every three years</th>
<th>Pap smear every three years</th>
<th>Pap smear + HPV testing every five years</th>
<th>Consider screening with low-dose helical CT scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Women 21 to 29 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women ≥30 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Patients with risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients ≥50 years without risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Patients 55 to 74 years, ≥30 pack-year smoking history and either currently smoking or quit in the past 15 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>High-risk men 40 to 45 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Men ≥50 years without risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>High-risk patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average-risk patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© 2018 UpToDate, Inc. and/or its affiliates.
Advice for travel — Once on immune globulin replacement therapy, many patients are able to travel and participate in other activities that might not have been possible in the past for people with immunodeficiencies.

In general, we do not advocate restricting foreign travel, unless the travel is to a remote area with no access to health care.

Patients should bring antibiotics that they might need and consume bottled water from a clean source.

Patients should receive the killed vaccines applicable to that geographic area.
CVID and Vaccines

- **Vaccinations** — Certain live vaccines should not be given to patients with CVID (ie, oral polio, smallpox, live-attenuated influenza vaccine, yellow fever, or live oral typhoid vaccines), particularly those with significantly impaired T cell function
  - Family members and household contacts of patients with CVID may receive live vaccines

- The utility of killed or inactivated vaccines in patients with CVID has not been studied extensively. By definition, patients with CVID have impaired responses to vaccination, although vaccination might reinforce T cell immunity to viral agents, in addition to inducing the formation of specific antibodies. The former mechanism may be preserved in some patients with CVID, as there is a range of immunologic capacity in this disorder.

- We routinely administer [inactivated influenza vaccine](#) to patients with CVID, although at least one study showed that some CVID patients respond only partially
  - Vaccination guidelines support this practice
  - Patients receiving [immune globulin](#) replacement therapy may be partially protected from influenza due to the presence of anti-influenza antibodies in immune globulin preparations
Take home messages...

- Common variable immunodeficiency (CVID) is an immune disorder characterized by impaired B cell differentiation with impaired antibody production.
- The disorder is associated with a broad spectrum of clinical manifestations, including recurrent infections, chronic lung disease, gastrointestinal disease, autoimmune disorders, and malignancy.
- The cornerstone of therapy is immune globulin replacement, which has dramatically altered the clinical course of CVID by reducing the burden of recurrent infections and subsequent complications.
- Management also involves vigilant monitoring for associated problems, such as pulmonary damage, gastrointestinal, autoimmune, and granulomatous diseases, and malignancy.
Key References

Additional References

Additional References

- Farrington, M et al. CD40 ligand expression is defective in a subset of patients with common variable immunodeficiency. PNAS 1994. 91: 1099-1103.
Thank you for your attention.

Questions or Comments?