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# Primary Immune Deficiencies: Diagnosis

Or

Office Evaluation of Children with Recurrent Infection

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# Primary Immunodeficiency

- A disorder in one or more components of the immune system.

# Components of Immunity

- Skin and mucosal barriers
- Innate immune system (nonspecific)
  - Phagocytic cells, NK cells, complement
- Adaptive immune system (specific)
  - T and B lymphocytes, antibodies

# Classification of Immunodeficiency

1. Humoral (B-cell) – quantitative or qualitative defects in antibody production account for more than 50% of defects.
2. Cellular (T-cell) – usually combined with humoral; account for 20-30%.
3. Phagocytic – defects in migration, or killing; account for ~18%.
4. Complement – account for ~2%

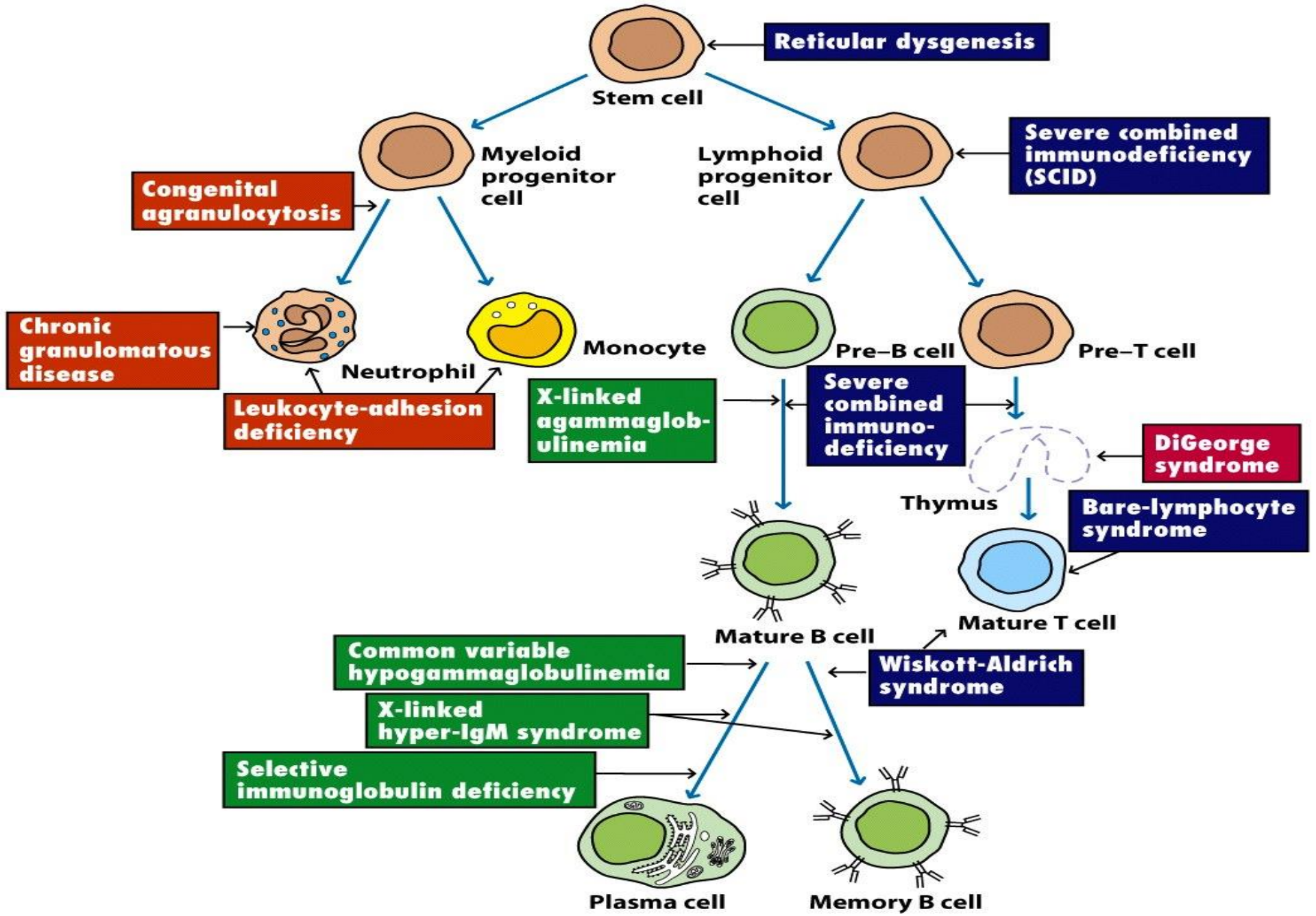


**Figure 20-1**
***Kuby IMMUNOLOGY, Sixth Edition***

- Overdiagnosis And Underdiagnosis

# PID

- Up to 1 in 2000 live births carry PIDs

- At infancy, there is a 5:1 predominance of males over females
    - Many of the PIDs are X-linked

- With the exception of selective IgA deficiency (1:333 to 1:700), PIDs are rare
    - Agammaglobulinemia 1:50,000
    - SCID 1:10,000 to 1:100,000

# Recurrent Infections Vs. Frequent Infections

- Immune system not fully developed until at least two years of age.
- Immuno-competent kids may have up to six URIs per year. Ten URIs per year if they attend daycare.

# Recurrent Infections Vs. Frequent Infections

- Common Risk Factors for Frequent Infections
  - Day-care, school-aged siblings
  - Second-hand smoke
  - Atopy
  - Anatomic abnormalities including ciliary defects
  - Retained foreign body
  - Gastroesophageal reflux

# Recurrent Infections Vs. Frequent Infections

- Frequent or recurrent sinopulmonary infections, malabsorption, nasal polyps…

•Cystic Fibrosis

  –1:2500

  –More common than most of the immunodeficiencies

# Secondary Immunodeficiencies

- Two most common
  - Malnutrition
    - Vit. A deficiency - Infections of GI and resp. tract
    - Zinc deficiency – Acrodermatitis enteropathica, SCID-like syndrome
    - B12 deficiency – impaired immunoglobulin production
    - Protein and caloric deficiency – impaired immune response

# Secondary Immunodeficiency

- Two most common
  - HIV infection – seventh leading cause of death in children 1-4 years in the US.
    - Third leading cause in black children 1-4 in the urban northeastern US.
    - Always think about it…

# Key clinical features when considering a PID are:

- Infection with atypical severity, atypical pathogens, or frequency higher than expected
- Unusual or very early onset autoimmunity
- Unusually severe atopy
- Auto inflammation
- Lymphoproliferation

# Key clinical features when considering a PID are:

- The most important clues are the atypical, unusual presentation.
- Since most PIDs have a genetic origin, PID in the family history alone can suggest a PID diagnosis.

# Index of Suspicion

- >10 episodes acute otitis media per year (infants and children).
- >2 episodes consolidated pneumonia per year.
- >2 life-threatening infections per lifetime.
- Two or more serious sinus infections within 1 year.
- Unusual organisms.
- Unusual response to organism.

# Index of Suspicion

- Recurrent deep skin or organ abscesses.
- Two or more deep-seated infections such as meningitis, osteomyelitis, cellulites or sepsis.
- Persistent oral thrush or candida infection elsewhere on the skin, after age 1 year.
- Recurrent autoimmune phenomena.
- Dysmorphic features associated with recurrent infection.
- Development of vaccine pathogen after vaccination (e.g., HiB infection despite previous HiB vaccine).
- Family history of immunodeficiency or recurrent infection.

# Eight common clinical presentations of primary immune deficiency

| Recurrent ENT and airway infections (including bronchiectasis) | Predominantly antibody deficiencies |
|---|---|
| Failure to thrive from early infancy (including intractable diarrhea, severe eczema) | Immunodeficiency's affecting cellular and humeral immunity |
| Recurrent pyogenic infections (including granulomatous inflammation, poor wound healing | Congenital defects of phagocyte number or function |
| Unusual infections or unusually severe course of infections | Immunodeficiency's affecting cellular and humeral immunity |
| Recurrent infections with the same type of pathogen | Defects in intrinsic and innate immunity |
| Autoimmune or chronic inflammatory disease: lymphoproliferation | Diseases of immune deregulation: auto inflammatory disorders |
| Characteristic combinations of clinical features | Combined immunodeficiency's with associated or syndrome features |
| | |

# Red flags for antibody deficiencies

- Sinopulmonary infections
- Recurrent bacterial Pneumonia
- *Bronchiectasis
- *Hearing loss secondary to infection
- *ENT infections more severe/frequent than expected

# Key alternative considerations

*Cystic fibrosis, ciliary dyskinesia

*Allergies/asthma

*Anatomical issues

*Periodic fever syndromes wrongly ascribed to sinopulmonary infections

# Recurrent sepsis or meningitis with encapsulated organisms

*Asplenia

*Complement deficiencies

*Antibody deficiency states

# History Our Guide

- Important historical points
  - Frequency, duration, severity, complications, response to treatment
  - Risk factors
  - Family history
  - Infection with low-virulence or unusual organisms
  - Age of onset

# History Our Guide

- Predominant B-Cell defects
  - Onset after maternal antibodies diminish, usually after 5-7 mos, later childhood to adulthood.
  - Recurrent sinopulmonary infections, chronic GI symptoms, malabsorption, arthritis, viral meningoencephalitis
  - Bacteria: strep, staph, H.flu; Campylobacter, enteroviruses, giardia, cryptosporidia
  - Autoimmunity, lymphoreticular malignancy; thymoma, lymphoma

# History Our Guide

- Predominant T-Cell Defects
  - Early onset, usually 2-6 mos
  - Bacteria, mycobacteria, viruses: CMV, EBV, varicella; fungi, parasites, PCP, mycobacterium avium-intracellulare
  - FTT, protracted diarrhea, extensive mucocutaneous candidiasis
  - GVHD caused by maternal engrafment, nonirradiated blood
  - Hypocalcemic tetany in infancy

# History Our Guide

- Granulocyte Defects
  - Early onset, delayed separation of cord (>8 weeks), poor wound healing
  - Bacteria: staph, Pseudomonas, Serratia, Klebsiella; Fungi: Candida, Nocardia, Aspergillus
  - Dermatitis, impetigo, cellulitis, abscesses, supparative lymphadenitis, periodontitis, osteomyelits

# History Our Guide

- Complement Defects
  - Late (C5-C9) – Neisserial infections: *meningitidis*, septic arthritis from *gonorrhoeae*.
  - Early (C1, C4, and C2) – autoimmune disease
  - C3 deficiency – overwhelming sepsis, especially with gram negative organisms

# Predominant T-Cell Defects

- Initial laboratory evaluation of individuals suspected to have a T-cell disorder should include a white blood cell count and differential focusing on the absolute lymphocyte count compared with age-matched control ranges for proper interpretation .

# Predominant T-Cell Defects

- Because 50% to 75% of circulating lymphocytes areCD3+Tcells, any process that interferes with T-cell development or increases T-cell loss will result in absolute lymphopenia. It is important to recognize that the total lymphocyte count associated with lymphopenia.

# Predominant T-Cell Defects

- Profound lymphopenia, particularly in an infant, should prompt immediate immunologic evaluation because int suggests (SCID) or complete DiGeorge syndrome, both life-threatening conditions.
- However, a low number of T cells during infancy is not always found in SCID, because infants with spontaneous engraftment of maternal cells or with leaky SCID (including Omen syndrome) may have normal or elevated total lymphocytes due to oligoclonal expansion.

# Predominant T-Cell Defects

- In either of these circumstances, the T cells will consist primarily or memory (CD45ROT Cells) as compared with the T cells found normally in infants, which are primarily naïve (CD45RA+T cells) .

# Predominant T-Cell Defects

- However, the heel-stick blood spotted onto filters to screen infants for rare metabolic disorders can be used to isolate DNA for detection of T-cell receptor excision circles (TRECs), formed as byproducts of normal T-cell receptor (TCR) gene rearrangement as T cells mature in the thymus .

# Physical Exam

- A benign physical exam does not rule out immunodeficiency.
- Look for:
  - General appearance, weight, overall health
  - Hair, connective tissue
  - Dysmorphic features
  - Gingivitis, dental erosions, signs of sinusitis
  - Tonsillar tissue, adenopathy, splenomegaly
  - Arthritis, ataxia, neuro deficits

# Disease Specific Skin Findings

- Eczema and petechiae – Wiskott-Aldrich Syndrome
- Telangiectasia – Ataxia-Telangiectasia
- Oculocutaneous albinism – Chediak-Higashi
- Dermatomyositis-like rash – XLA
- Chronic dermatitis – Hyper-IgE
- Generalized molluscum, extensive warts, candidiasis – T-Cell defects

# Physical Exam

- One of the most telling findings can be whether tonsils are visible. Although a healthy child with recurrent sinusitis of otitis would be expected to have large tonsils, the absence of tonsils, a tissue containing primarily B cells, in this clinical setting strongly suggests a humeral immune defect involving an abnormality in B-cell development(XLA).

# Laboratory Evaluation

- CBC with differential
  - Total WBC, ANC, ALC, AEC (age-appropriate values)
  - Lymphopenia = < 3,000 in infants, < 1500 in children and adults
  - Persistently high ANC occurs in LAD
  - Hemolytic anemia, thrombocytopenia, leukopenia occurs in some B-Cell deficiencies.

# Laboratory Evaluation

- Quantification of serum immunoglobulins
  - IgG, IgA, IgM is the first-step in evaluation for humoral immunity.
  - Quickie – subtract albumin from total protein. $\geq 2$ indicates adequate antibody. (But we don't know what types)
  - IgG subclasses do not need to be ordered as screening.
  - IgE only if severe atopy, or chronic dermatitis

# Laboratory Evaluation

- Qualitative Evaluation of Antibodies
  - Isohemagglutins – Antibodies to ABO blood-group determinants
  - Antibodies to tetanus and diptheria glycoproteins and pneumococcal polysaccharides.
    - If low titers, give booster, then repeat titers 4 weeks later.
    - Children younger than 2 can not be tested for polysaccharide antigen antibody.

# Laboratory Evaluation

- T-Cell Immunity
  - Delayed-hypersensitivity skin tests
    - Intradermal injection of antigens; Candida, tetanus, trichophyton.
    - Should produce redness and induration of > 5mm by 48-72 hours.
    - Severe illness, or steroids can cause diminished responses. (anergy)
  - Mitogen testing
    - In vitro proliferative responses to concanvalin A, phytohemagglutinin

# Laboratory Evaluation

- Phagocytic Cell Function
  - Adhesion antigens by flow cytometry (CD11/CD18) – checks for adhesion defects
  - Chemiluminescence – phagocytic killing power

# Laboratory Evaluation

- Complement function
  - Total hemolytic complement ($CH_{50}$) – tests functional integrity of classic complement pathway.
  - $AH_{50}$ – tests the functional integrity of alternate pathway.
  - The most common reason for an abnormal $CH_{50}$ is improper handling of specimen.

# EVALUATING SUSPECTED Natural KILLER DEFECTS

- Testing of natural killer (NK) cell function is indicated in patients experiencing recurrent viral infections. Particularly infections involving the herpes virus family and papilloma virus, as well as patients with hemophagocytic syndromes known as hemophagocytic lympho histiocytosis (HLH).

# Natural KILLER DEFECTS

- Evaluation includes enumerating NK cerlls by flow cytometry (CD3CD16+/CD56+ cells) and assaying cytotoxicity using specific in vitro assays .

| Affected Immunity | Typical Site of infection | Common Pathogens | Screening Tests |
|---|---|---|---|
| B cells/antibody | Sinopulmonary tract, Gi tract, joints, CNS | Pyogenic bacteria: Streptococcus, Streptococcous, Haemophilus influenza<br>Enteroviurses: ECHO, polio<br>Mycoplasma, Ureaplasma | IgG<br>IgA<br>IgM<br>IgE<br>Vaccine responses (titers) |
| T cells | Sepsis, lung, GI tract, skin | Viruses: CMV, adenovirus, measles, Mollscum contagiousum, Fungi: Candida, Aspergillums<br>Pneumocystis Jirovecii<br>Pyogenic bacteria<br>Protozoa: Cryptosporidium | CBC with differential<br>Flow cytometry for T cells and T-cell proliferation to mutagens and antigens (typically Candida, tetanus) |
| NK cells | Skin, lung, GI tract, disseminated infections | Viruses: EBV, CMV, VZV, HSV, HPV | Flow cytometry for NK cells<br>CD107a surface expression<br>NK cytotoxicity assays |

| Affected Immunity | Typical Site of infection | Common Pathogens | Screening Tests |
|---|---|---|---|
| Phagocytes | Skin infections, lymphadenitis, liver, lung, bone, Gl tract, gingivitis/periodontitis | Bacteria: Staphylococcus, Serration marcescens, Burkholderia cepacia, Klebsiella, Escherichia coli, Salmonella, Proteus Fungi: Candida, Aspergillus,Nocardia | Absolute neutrophil count<br>Flow cytometry for expression of CD11/CD18<br>Dihydrorodamine 123 flow cytometry (DHR) test |
| Complement | Systemic infections, meningitis | Pyogenic bacteria: Streptococcus, Hemophiles influenza, | CH50<br>AH50 |

# WITH THANKS

WORLD ALLERGY ORGANIZATION

A World Federation of Allergy, Asthma & Clinical Immunology Societies