PRIMARY IMMUNODEFICIENCIES: UPDATES ON THE OLD, PREVIEWS OF THE NEW
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OBJECTIVES

- DEFINE IMMUNODEFICIENCY
- UNDERSTAND THE GENETIC BASIS
- DESCRIBE TYPES OF IMMUNODEFICIENCIES
- LEARN HOW TO DIAGNOSE IMMUNODEFICIENCY
- CONSIDER TREATMENT OPTIONS FOR PATIENTS
A. Normal Immune System

Maintains balance between host defense and infection.

B. Immunodeficiency

Leads to chronic viral infection and cancer.

Taken with permission from Shearer WT. J Allergy Clin Immunol 2005;116:263-266.
DEFINITIONS

● IMMUNODEFICIENCY DISEASES
  ● RESULT FROM ABSENCE OR MALFUNCTION OF COMPONENTS OF IMMUNE SYSTEM
  ● CAUSED BY GENETIC MUTATIONS (PRIMARY IMMUNODEFICIENCIES)
  ● CAUSED BY EXTERNAL FACTORS (SECONDARY IMMUNODEFICIENCIES)
# THE IMMUNE SYSTEM

<table>
<thead>
<tr>
<th>INNATE</th>
<th>ADAPTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CELLULAR</strong></td>
<td><strong>HUMORAL</strong></td>
</tr>
<tr>
<td>PHAGOCYTIC CELLS</td>
<td>TOLL RECEPTORS COMPLEMENT</td>
</tr>
<tr>
<td>T CELLS</td>
<td>ANTIBODY (B CELLS)</td>
</tr>
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</table>
TYPES OF IMMUNODEFICIENCY

- >150 GENETICALLY DEFINED IMMUNODEFICIENCIES
- ESTIMATED GENERAL INCIDENCE 1:10,000 (EXCEPT FOR IGA DEFICIENCY 1:500)
- SERIOUS IMMUNODEFICIENCIES 1:100,000 LIVE BIRTHS
- X-LINKED, RECESSIVE, AND DOMINANT INHERITANCE
Lymphoid development and genetic lesions leading to immunodeficiency.

Courtesy Dr. Rebecca Buckley
CLINICAL FEATURES

- INCREASED SUSCEPTIBILITY TO INFECTION:
  - INCREASED FREQUENCY
  - INCREASED SEVERITY
  - PROLONGED DURATION
  - UNEXPECTED COMPLICATION

- ASSOCIATED AUTOIMMUNE DISEASES AND CANCER
ANTIBODY (B-CELL) DISORDERS

X-LINKED (BRUTON’S) AGAMMAGLOBULINEMIA (X-LA):

- NO SERUM IG’S, NO B CELLS
- INFECTIONS BEGIN AT 6-9 MONTHS OF AGE
- INFECTIONS WITH PNEUMOCOCCUS, STAPHYLOCOCCUS PROMINENT
- PNEUMONIA, SINUSITIS, OTITIS PREVALENT
- AVOID LIVE VIRAL VACCINES
PATIENT WITH X-LA
X-LINKED AGAMMAGLOBULINEMIA

- RFLP: PREFERENTIAL INACTIVATION OF AFFECTED X-CHROMOSOME IN FEMALE CARRIERS SUGGESTS INTRINSIC B-CELL DEFECT
- GENE DEFECT (Xq21.3-22): MUTANT BRUTON’S TYROSINE KINASE (CYTOPLASMIC SIGNAL TRANSDUCTION PROTEIN)
- PRE-B-CELL DEVELOPMENT ARREST
SELECTIVE IGA DEFICIENCY

- ABSENT SERUM + MUCOSAL ANTIBODY (DIMERIC FORM + SECRETORY PIECE)
- USUALLY ASYMPTOMATIC
- GASTROINTESTINAL, RESPIRATORY INFECTIONS
- FAMILIAL ASSOCIATIONS, CVID LINKAGES
- ALLERGY, AUTOIMMUNITY ASSOCIATIONS
COMMON VARIABLE IMMUNODEFICIENCY (CVID)

- ONSET 15-35 YEARS: LOW IGG, IGA, IGM
- PNEUMONIA, BRONCHIECTASIS, SINUSITIS, GASTROINTESTINAL INFECTIONS
- CELLULAR IMMUNITY WEAKENS
- ASSOCIATED AUTOIMMUNITY, MALIGNANCY
- SUSCEPTIBILITY GENE, CLASS II MHC REGION, 6TH CHROMOSOME
CHEST X-RAY IN CVID
CVID IMMUNE BASIS

- IMMUNIZATIONS RESULT IN LOW IGM ANTIBODIES, NO IGG SWITCHING
- ↓ B-CELL PRODUCTION OF ANTIBODY
- INDUCIBLE CO-STIMULATOR (ICOS) 5% GENE DEFECT (2q 33)
- TACI 15% GENE DEFECT (17 p11.2)
HYPER IGM (HIM) DISORDERS

- MOSTLY MALES, RARELY FEMALES
- SEVERE RESPIRATORY INFECTIONS, SINUSITIS
- SERUM IGG, IGA VERY LOW, IGM HIGH, 7S IGM OCCASIONALLY
- NO IGG SWITCHING, T-CELL IMMUNITY WEAKENS WITH TIME
- ABNORMAL GERMINAL CENTERS IN LYMPH NODES
- ASSOCIATED AUTOIMMUNITY, MALIGNANCY
FEATURES OF HYPER-IgM SYNDROMES - 1

(Ectodermal dysplasia with immunodeficiency)

(NEMO: Nuclear factor κB essential modulator)

(Class-switch recombination)

(Somatic hyper-mutation)

(Activation-induced deaminase)

(Uracil DNA glycosylase)

### FEATURES OF HYPER-IgM SYNDROMES - 2

<table>
<thead>
<tr>
<th>Protein affected</th>
<th>CD40L defect</th>
<th>CD40 defect</th>
<th>XL-EDA-ID</th>
<th>AR-AID</th>
<th>UNG defect</th>
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<tbody>
<tr>
<td>Inheritance</td>
<td>XL</td>
<td>AR</td>
<td>XL</td>
<td>AR</td>
<td>AR</td>
</tr>
</tbody>
</table>

**Clinical features**

- **Bacterial infections**
  - CD40L: +
  - CD40: +
  - XL-EDA-ID: +
  - AR-AID: +
  - UNG: +

- **Opportunistic infections**
  - CD40L: +
  - CD40: +
  - XL-EDA-ID: -
  - AR-AID: -
  - UNG: -

- **Lymphadenopathy**
  - CD40L: -
  - CD40: -
  - XL-EDA-ID: -
  - AR-AID: ++
  - UNG: +

- **Autoimmunity**
  - CD40L: ±
  - CD40: ±
  - XL-EDA-ID: +
  - AR-AID: +
  - UNG: -

- **Tumors**
  - CD40L: +
  - CD40: -(?)
  - XL-EDA-ID: -
  - AR-AID: -
  - UNG: -(?)

WISKOTT-ALDRICH SYNDROME (WAS)
## WISKOTT-ALDRICH SYNDROME (WAS) WASP GENE MUTATIONS

<table>
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<tr>
<th>PHENOTYPE</th>
<th>00</th>
<th>WAS</th>
<th>XLTI</th>
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<tbody>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>+</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
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<tr>
<td>Small Platelets</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Eczema</td>
<td></td>
<td>+/++/++++</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Immunodeficiency</td>
<td></td>
<td>+/++</td>
<td>-/(+)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td>+/++</td>
<td>-/(+)</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Autoimmunity and/or Malignancies</td>
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<td>Frequent</td>
<td>Possible</td>
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<td>Congenital Neutropenia</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Disease Scores</td>
<td></td>
<td>3, 4 or 5</td>
<td>1, 2 or (5)</td>
<td>&lt;1</td>
<td>0</td>
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Taken (modified) with permission from Ochs HD, Thrasher AJ. J Allergy Clin Immunol 2006;117:725-738.
T-CELL DEFICIENCY

DIGEORGE SYNDROME:

- DEFECT IN EMBRYOGENESIS: HEART, PARATHYROID, THYMUS
- HYPOCALCEMIC SEIZURES
- ABNORMAL FACIES
- CHEST X-RAY: ABSENT THYMUS
- OPPORTUNISTIC INFECTIONS
- FREQUENCY 1/4,000
DIGEORGE SYNDROME
DIGEORGE SYNDROME
FINDINGS

- CHROMOSOME DELETIONS: 22q11*, 10p13 IN 95%

- PART OF SPECTRUM OF VELOCARDIOFACIAL SYNDROME*

- FULL VS PARTIAL DIGEORGE SYNDROME (1/50 RATIO)

- T CELLS LOW: CD3+, CD4+, CD8+
  FEW HAVE OLIGOCLONAL T CELLS

- B CELLS PRESENT, SERUM IG’S NORMAL BUT ABSENT FUNCTION
X-LINKED SEVERE COMBINED (T/B CELL) IMMUNODEFICIENCY (SCID)

- LIFE THREATENING INFECTIONS SOON AFTER BIRTH
- WASTING, FAILURE-TO-THRIVE
- LACK OF THYMIC SHADOW
- LACK OF CD3\(^+\), CD4\(^+\), CD8\(^+\) T CELLS AND L’CYTE RESPONSE TO ANTIGENS
- MUTANT IL-2R\(\gamma\) CHAIN
CHILD WITH SCID
SEQUENCING OF IL2RG: T to C SUBSTITUTIONS #16 EXON 1

Taken with permission from Fleisher TA, Oliviera JB. J Allergy Clin Immunol 2006;117:227-234.
CLASSIFICATION OF SCID BY LYMPHOCYTE PHENOTYPE - 1

- **T(-)B(+)NK(-)**
  - MUTATION IN COMMON $\gamma$ CHAIN ($\gamma_c$), IL2RG GENE, X-LINKED
  - MUTATION IN JAK3 ENZYME, JAK3 GENE, AR

- **T(-)B(+)**NK(+)**
  - MUTATION IN $\alpha$ CHAIN OF IL-7 RECEPTOR, IL7RA GENE, AR
  - CD3δ DEFICIENCY, AR
SEVERE CONGENITAL NEUTROPENIAS

- ABSOLUTE NEUTROPHIL COUNT < 500 CELLS/μL
- KOSTMAN SYNDROME: INFECTIONS
- SCHWACHMAN DIAMOND: DEFECTS IN EXOCRINE & PANCREAS, MYELOPOIESIS, BONE FORMATION
- CYCLIC NEUTROPENIA: 21 DAY CYCLE
OTHER CELL-DERIVED COMBINED IMMUNODEFICIENCIES

- MONOCYTES/MACROPHAGES
  - IFN-\(\gamma\)R DEFICIENCY (MONOCYTE)
  - IL-12R DEFICIENCY (T CELL)
  - ATYPICAL MYCOBACTERIAL INFECTION

- NK CELL DEFICIENCY
  - T/B CELL DEFENSES OVERWHELMED
  - CHRONIC VIRAL INFECTION
PHAGOCYTE DEFICIENCY: CHRONIC GRANULOMATOUS DISEASE

- SKIN, LYMPH NODE, LUNG INFECTIONS
- X-LINKED, AUTOSOMAL RECESSIVE
- HIGH WBC, NO INTRACELLULAR KILLING/H$_2$O$_2$
- MEMBRANE/CYTOSOLIC PARTS OF CYTOCHROME B
- DIAGNOSIS: NBT, DHR ASSAYS
NADPH OXIDASE SYSTEM

Taken with permission from Bonilla FA, Geha RS. J Allergy Clin Immunol 2003;111:S571-S581.
PHAGOCYTE DEFICIENCY: LEUKOCYTE ADHESION DEFICIENCY

- GINGIVOSTOMATITIS, SKIN INFECTIONS
- VERY HIGH WBC
- AUTOSOMAL RECESSIVE INHERITANCE (21q22.3)
- BETA INTEGRIN (CD18) NOT EXPRESSED
- COMPLEX OF CD11_{A,B,C} NOT CO-EXPRESSED
- SEVERE AND MODERATE FORMS
Leukocyte Adhesion Defect
TOLL RECEPTORS + COMPLEMENT DEFICIENCIES - 1

- PATHOGEN RECOGNITION RECEPTORS TLR-2,3,4,5,9
- 31 PROTEINS: 20 PLASMA, 5 MEMBRANE, 7 RECEPTORS COMPROMISE CLASSICAL ALTERNATE, LECTIN PATHWAYS
- AUTOSOMAL CO-DOMINANT, DOMINANT, X-LINKED INHERITANCE
IRAK-4 DEFICIENCY TLR/IL-1

C1, C2, C4 DEFICIENCIES: PYOGENIC INFECTIONS, AUTOIMMUNE DISEASES

C5-C9 DEFICIENCIES: MENINGOCOCCAL, GONOCOCCAL INFECTIONS
COMPONENT PATHWAYS

RX ANTIBODY (B CELL) DISORDERS

- REPLACE IGG DEFICIENCIES WITH IVIG
- GENERAL SUPPORTIVE CARE (FREQUENT ANTIBIOTICS)
- AVOID LIVE VIRAL VACCINES
- RX COMPLICATIONS -- AUTOIMMUNE DISEASES MALIGNANCIES
Treatment of Immunodeficiency: Improved Outcome and Quality of Life
RX CELLULAR (T/B, Mφ) DISORDERS

- BONE MARROW/PLACENTAL STEM CELL
- IVIG IF NECESSARY
- GENERAL SUPPORTIVE CARE
- GENE THERAPY, IF POSSIBLE
- AVOID LIVE VIRAL VACCINES
- CMV⁻/IRRADIATED/⇒ WBC BLOOD TRANSFUSION
STEM CELL TRANSPLANTS

- DONOR
  - HLA-MATCHED SIBLING
  - CD3 CELL + 1/2 MATCHED
  - MUD
  - PLACENTAL

- 95% SURVIVAL < 3 MONTHS
- NEWBORN SCREEN
Overall Survival of SCID Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage Surviving</th>
<th>Years after transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMRD, no conditioning</td>
<td>13/21 (62%)</td>
<td>0-20</td>
</tr>
<tr>
<td>MMRD, MUD, with conditioning</td>
<td>10/10 (100%)</td>
<td>0-26</td>
</tr>
<tr>
<td>MRD</td>
<td>10/10 (100%)</td>
<td>0-20</td>
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Texas Children’s Hospital
### STATUS OF IMMUNODEFICIENCY GENE THERAPY

#### PRESENT

- Carefully weigh risks and potential benefits for each patient.
- Chose patients most at risk from their disease process and least at risk from adverse effects of gene therapy.
- Recognize that therapeutic genes with growth-promoting properties might contribute to oncogenesis.
- Monitor insertion site profile, checking for clonal expansion of transduced cells.

#### FUTURE POSSIBILITIES

- Develop vectors that reduce targeting of transcriptional start sites (Lentivectors) or active genes.
- Use self-inactivating vectors, incorporate insulators, and include suicide genes.
- Improve methods to purify and expand undifferentiated HSCs in vitro so that vector insertion sites can be monitored before reinfusion.
- Develop safe and efficient methods for correction of genomic mutations rather than gene addition.

*Taken with permission from Puck JM, Malech HL. J Allergy Clin Immunol 2006;117:865-869.*
RX PHAGOCYTE DEFICIENCY

- IFN-γ FOR CGD
- GENERAL SUPPORTIVE CARE
- BONE MARROW STEM CELLS WHERE POSSIBLE

RX COMPLEMENT DEFICIENCIES

- GENERAL SUPPORTIVE CARE (FREQUENT ANTIBIOTICS)
Question 1
Which of the following individuals are heterozygous for Bruton’s tyrosine kinase deficiency diagnosed in the infant (lower right)?
CHOICES

A. Great grandmother of patient (upper left)

B. Grandfather of patient (upper right)
   holding mother of patient as an infant

C. Mother of patient (lower left)

D. Other
D is the correct answer

D. “Other” is correct since all of the individuals in the pictures carry one defective chromosome in an X-linked inheritance pattern.
Question 2
The image shows a phagocyte reaching out to engulf a bacterium. In which immune deficiency is this action impaired?
A. Chronic granulomatous disease of childhood

B. IFN-γ receptor deficiency

C. IL-12 receptor deficiency

D. Leukocyte adhesion deficiency
**ANSWER TO QUESTION 2**

D is the correct answer

D. “Leukocyte adhesion deficiency” lacks the CD18CD11A,B,C complex of glycoproteins that enable the leukocyte extend pseudopods to attach to and engulf bacteria.
Question 3

A lung biopsy of an infant with pneumonia showed these organisms present in the tissue. Flow cytometry showed this histogram of peripheral blood mononuclear cells. What diagnosis is applicable to this patient?
A. Complement component C3 deficiency
B. Hyper IgM disease
C. Severe combined immunodeficiency
D. Selective IgA deficiency
C is the correct answer

C. The infant has “severe combined immunodeficiency” and cannot kill the *Pneumocystic jerveci* fungus that causes severe pneumonia. A total lack of T cells in quadrant #1 of the histogram compared to the control subject is diagnostic.
Question 4

A 28-year old male has a wasted appearance with hyperexpanded lungs filled with granulomas and scarring. He was perfectly well until he was 20 when he developed recurrent pneumonias. Pneumococcal immunizations show no antibody responses. There are normal numbers of B cells in his blood. What is the most likely diagnosis?
CHOICES

A. Common variable immunodeficiency
B. Complement component C9 deficiency
C. DiGeorge syndrome
D. X-linked agammaglobulinemia
A. “Common variable immunodeficiency”. This patient was well until his third decade of life when his severe immunoglobulins became very low and T cells decreased as well. The other choices would cause illness from the beginning of life.
QUESTION 5

In 2009, 7 cases of severe, life-threatening diarrhea and dehydration in infants given the FDA-approved live attenuated rotavirus vaccine were reported to the Centers for Disease Control. All of these infants had a profound absence of T cells in the blood requiring bone marrow transplantation. A Public Health Officer is dispatched to investigate these cases. What were his findings likely to reveal?
A. Given the rare nature of these side effects, the diarrhea and rotavirus vaccination are probably not related.

B. Screening of all infants at birth for severe immunodeficiency would have avoided these accidents.

C. The benefit/cost ratio of childhood immunization is so great that unqualified immunizations are necessary.

D. Infants are prone to frequent bouts of diarrhea as part of normal childhood illnesses.
ANSWER TO QUESTION 5

B IS THE BEST ANSWER

B. Infants with severe combined immunodeficiency should be screened for SCID at birth as part of the rare diseases screening of all children currently in operation. Having this information would prevent such infants the to avoid the complications of receiving live viral vaccines.
QUESTION 6

A one-month-old boy develops severe respiratory syncytial virus infection and requires ventilator support. His father is healthy, but his 21-year-old mother has never enjoyed good health since being 15 years of age. His T and B cell phenotyping and function are normal. His phagocyte function and complement function are normal. His serum IgM and IgA levels are normal, but his serum IgG level is almost zero. How would you explain this child’s illness?
CHOICES

A. The child has selective IgG deficiency.
B. The child has hyper IgM syndrome.
C. CVID is being expressed at an early age.
D. The mother has an immuno-deficiency.
D. Although this child is very sick, all of his laboratory tests except for IgG prove to be normal. His illness is the result of the lack of maternal antibody transfer due to the mother’s immunodeficiency (Common Variable Immunodeficiency).
QUESTION 7

4-YEAR OLD GIRL
PECTUS CARINATUM, LOW FAT SOLUBLE VITAMINS, AND NEUTROPENIA.

WHAT IS HER DISORDER?

A. CYCLIC NEUTROPENIA
B. CHRONIC GRANULOMATOUS DISEASE
C. SEVERE CONGENITAL NEUTROPENIA
D. LEUKOCYTE ADHESION DEFICIENCY
ANSWER TO QUESTION 7

C is the correct answer

THE MOST STRIKING FEATURE OF THIS CASE IS BONE ABNORMALITY OF THE CHEST; HER PANCREAS DOES NOT WORK SO SHE CANNOT ABSORB FAT; SHE HAS SEVERE CHRONIC NEUTROPENIA (<500 CELLS/µl): SCHWACHMAN-DIAMOND SYNDROME.
A 2-year boy was found to have repeated infections, easy bruisability, and mucosal bleeding. His platelet count was \(10,000/\mu L\) (low) and his antibody isotype failed to switch from IgM to IgG upon boosting with a de novo polysaccharide antigen (\(\phi X-174\) bacteriophage). What test would lead to a definitive diagnosis?
ANSWERS

A. Lymphoproliferation to φ X-174.

B. Flow cytometry test for intracellular WASP.

C. Delayed hypersensitivity test for TB.

D. Superoxide generation by neutrophils.
B. Recurrent bleeding episodes, low platelets, and recurrent infections is a sign of Wiscott-Aldrich syndrome. The correct and definitive test is to look for the WASP protein inside of T cells by flow cytometry.
A one-year-old girl is brought to the pediatrician because of a deep and painful perirectal abscess. Her white blood cell count (WBC) (mostly neutrophils) is greater than 50,000 (normal less than 10,000), and her spleen is greatly enlarged. Mother, father, and two siblings are healthy. Lymphocyte function, antibody formation, DHR test, and complement function are normal. What would you tell the anxious parents?
ANSWERS

A. The child has an intercurrent illness that requires antibiotics.
B. The WBC is too high and needs reduction by splenectomy.
C. Another white blood cell test is necessary.
D. IFN-\( \gamma \) therapy will eliminate the infection.
ANSWER TO QUESTION 9

C is the correct answer

C. The nature of deep infections and extremely high white blood cell counts would indicate that the child has leukocyte adhesion deficiency and needs another blood cell test (CD18) in view of a normal test for chronic granulomatosis disclose (DHR).
QUESTION 10

An 18-year-old student who has been well all of his life develops three bouts of gonococcal infections in his first year at college. How would you respond?
A. There might be a defect in the C5-C9 complement pathways.

B. The patient needs intravenous IgG to remain infection free.

C. The IFN-γR on his antigen-presenting cells is defective.

D. The exuberance of youth explains this problem.
A is the correct answer

A. Neisserial (gonococcal) infection in young adults can be the result of a deficiency of late acting complement components that form the membrane attack complex pore in bacteria causing its contents to be extruded with bacterial cell death. Meningitis is another form of neisserial disease that affects teenagers.