Clinical Basis of the Immune Response and the Complement Cascade

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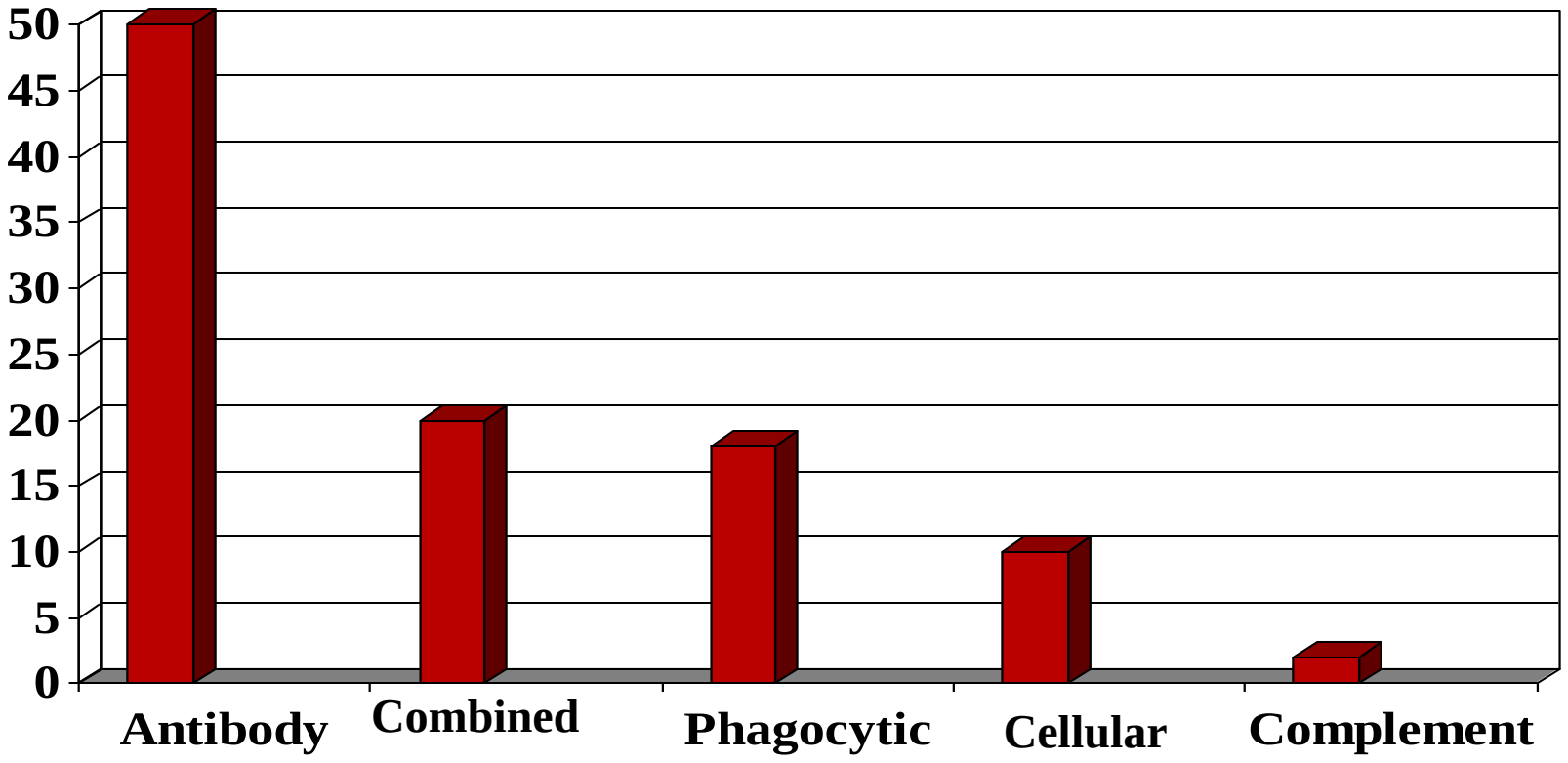
Disclosures

- None

Objectives

- Pass the boards!
- Provide a framework for the evaluation of primary immune deficiencies that may affect adults
- Review the Immune response using a case based approach

Primary Immunodeficiencies
Relative Distribution



I seem to get a lot of infections

- 35 year old female comes to see you with a chief complaint of “I’m sick a lot.” She wants to know if this is normal or if there is something wrong with her immune system.
- Where do we start with this patient?
  1. CBC, liver function tests, immunoglobulins, and CH50?
  2. Reassurance
  3. Titers for CMV, mono and hepatitis
  4. Careful complete history
  5. Chest x-ray, CBC and flow cytometry

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History

- All the other answers are wrong, because we need to start with the history
  - **History drives the testing we will do.**
- How often does she get sick?
  - Is there any sort of pattern as to when she gets sick?
  - Is there a seasonal component?
- What kinds of illnesses does she have?
  - Have organisms been identified?
- How severe are the illnesses?
- What did she need to do to recover?
- New exposures? New Job? i.e. new teacher?

The Patient

- 35 year old female
- “I always seem to be sick!” “Whenever someone in the family has something I get it too!”
  - **Recurrent upper respiratory infections, sinusitis, bronchitis and pneumonia**
  - **No organisms identified**
  - **No history of opportunistic fungal or mycobacterial infections**
- What test(s) do we order?
  1. CBC
  2. CBC and CH50
  3. CBC and immunoglobulins
  4. CBC and flow cytometry
  5. CBC and dihydrorhodamine test

The Patient with Hypogammaglobulinemia

- 35 year old female
- “I always seem to be sick!” “Whenever someone in the family has something I get it too!”
- Recurrent upper respiratory infections, sinusitis, bronchitis and pneumonia
- No history of opportunistic fungal or mycobacterial infections
- What test(s)do we order?
  1. CBC
  2. CBC and CH50
  3. **CBC and immunoglobulins**
  4. CBC and flow cytometry
  5. CBC and dihydrorhodamine test

Clues to help define Immunodeficiency

- Features associated with specific immunodeficiency disorders

1. Recurrent bacterial otitis media, sinusitis and pneumonia: **Hypogammaglobulinemia**
2. Fungal, protozoal and viral infections: **defective cell mediated immunity**
3. Uncommon bacteria, typically of low virulence: **chronic granulomatous disease**

Hypogammaglobulinemia

- Common adult form of immunodeficiency
  - Onset at any age (typically symptomatic at 15-35)
- Recurrent infections, typically with bacterial pathogens
- **Chronic sinopulmonary infections**
- Few problems with fungal or viral pathogens
- Increased allergy/autoimmune diseases
- Normal life span is possible

Question: Answers and Distractors

1. CBC alone will not give us enough data: this will likely be normal
2. CBC and CH50: CH50 is a test for the complement cascade; these will both likely be normal.
3. **CBC and immunoglobulins**
   - **B cell #'s normal, total Ig and IgG low**
4. CBC and flow cytometry: flow cytometry can provide a great deal of information via cell counting and cell sorting, but this is an antibody problem
5. CBC and dihydrorhodamine test: this is a flow cytometry based test of NADPH Oxidase activity to test for Chronic Granulomatous Disease (CGD)

The test results come in

- CBC is normal (as expected)
- Low total Ig, Low IgG, IgM normal or low
  - Most likely diagnosis is Common Variable Immunodeficiency (CVID)
  - Treatment would be immunoglobulin replacement with IVIG or subcutaneous IG
- ON THE OTHER HAND, IF:
  - Normal total Ig with Low IgA, normal IgG & IgM
    - Most likely diagnosis is **selective IgA deficiency**
    - **Not** treated with immunoglobulin replacement
    - Patients will have normal life span
    - Most common immunodeficiency in Caucasians

Antibody response to vaccination

- Measurement of specific antibody response to vaccination
  - Protein antigens: tetanus toxoid, diphtheria toxoid
  - Carbohydrate antigens: pneumovax, HiB vaccine
- Blood samples taken to measure specific antibodies prior to vaccination and four weeks post vaccination
- Evaluates patient's ability to produce specific antibodies

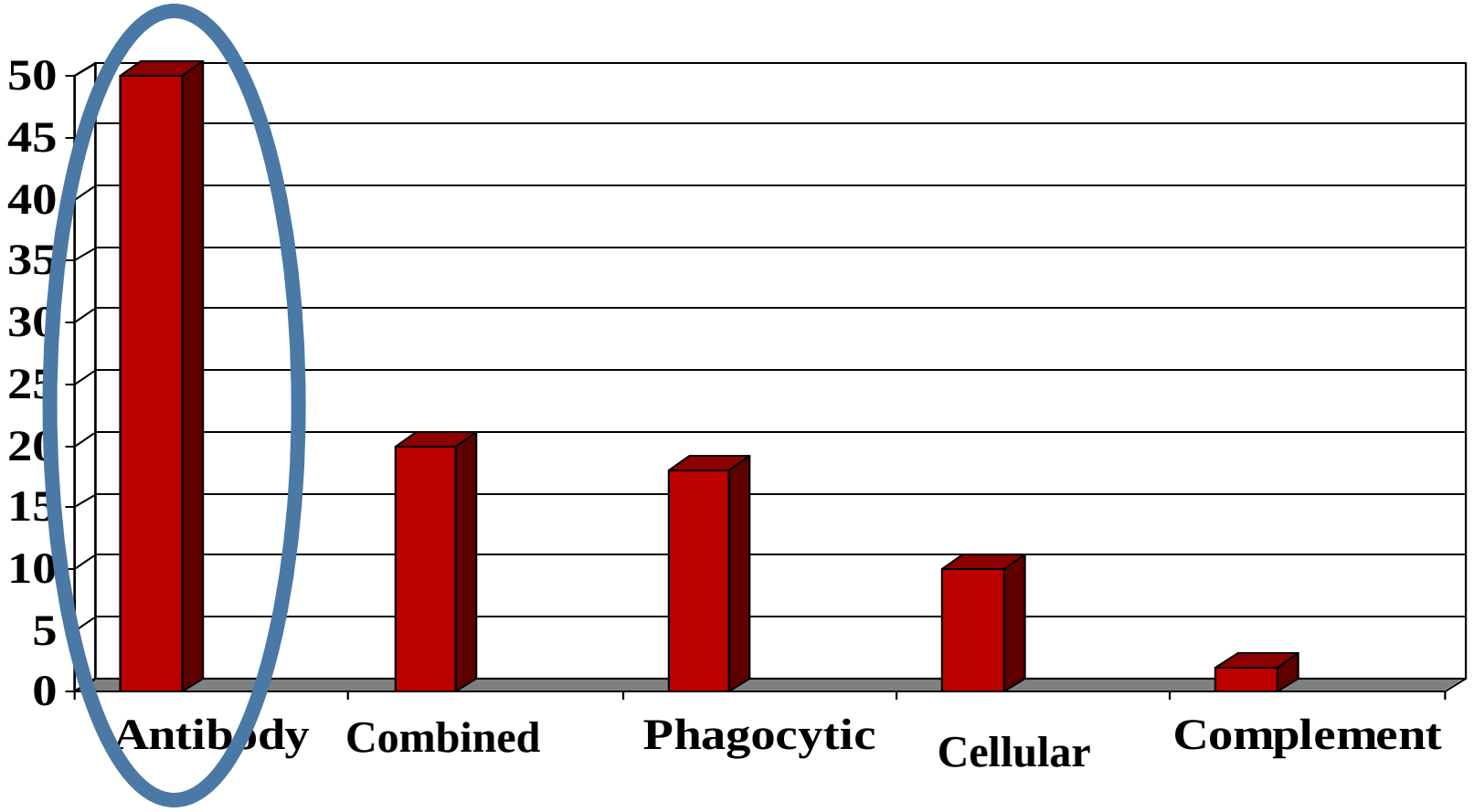
Common Variable Immunodeficiency

- Diagnostic: Failure to produce Ab following specific immunization
- Major complication: Chronic lung disease that may develop in spite of adequate therapy
  - Increased prevalence of malignant disease: leukemia, lymphoma and gastric carcinoma
- RX: IVIG 100-200mg/kg per month

Selective IgA deficiency

- Most common immunodeficiency
  - 1:600-1:800 prevalence
  - IgA < 5 mg/dl, other Ig levels normal
- Associated with allergies, recurrent sinopulmonary infections, GI tract disease and autoimmune disease
- In atopic population prevalence is 1:200-1:400

Primary Immunodeficiencies
Relative Distribution



23 year old with Meningitis

- Your patient is a 23 year old male college student with an unremarkable past medical history admitted to the hospital for meningitis.
- Culture of lumbar puncture fluid reveals Neisseria Meningitis
- What immunodeficiency is most likely
  1. Hypogammaglobulonemia
  2. Selective IgA deficiency
  3. Terminal complement deficiency
  4. Ataxia telangiectasia
  5. Chronic Granulomatous Disease (CGD)

25 year old with Meningitis

- Your patient is a 25 year old male with an unremarkable past medical history admitted to the hospital for meningitis.
- Culture of lumbar puncture fluid reveals Neisseria Meningitis
- What immunodeficiency is most likely
  1. Hypogammaglobulinemia
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  3. **Terminal complement deficiency**
  4. Ataxia telangiectasia
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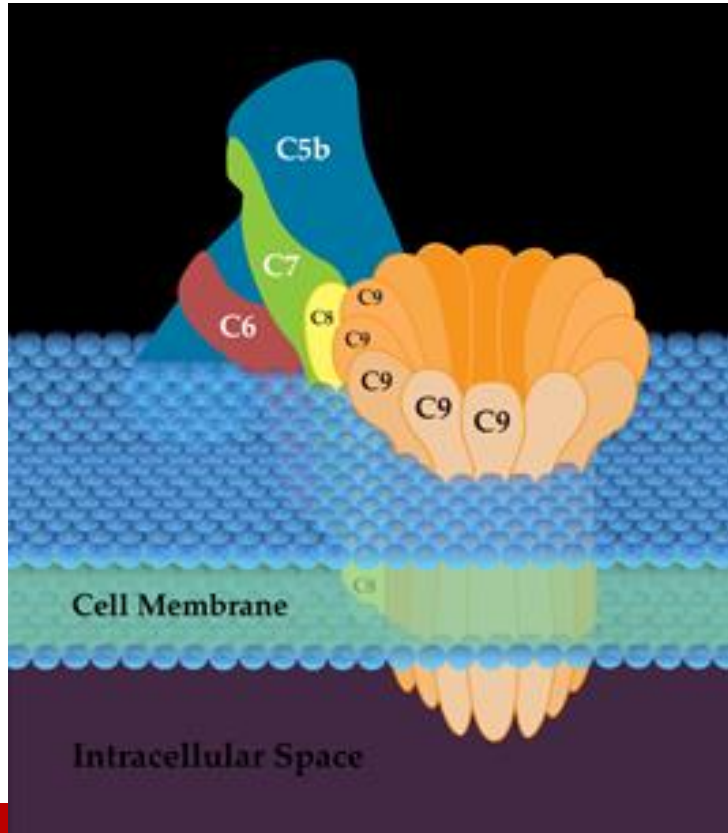
Terminal Complement Deficiency

- All complement pathways converge at C3
  - C3 Cleavage generates C5 convertase which results in C5b and C5a (a potent chemoattractant and anaphylatoxin)
- The terminal complement pathway forms the membrane attack complex
  - Formed by the sequential fusion of C6, C7, C8 & C9 to C5b
- Deficiencies of Terminal complement components lead to increased susceptibility to meningococcal organisms such as Neisseria

Terminal Complement Deficiency

- Seems to be a perennial board favorite
- If you see Neisseria as an infective agent, or disseminated gonococcal disease, look for evidence of Terminal Complement deficiency

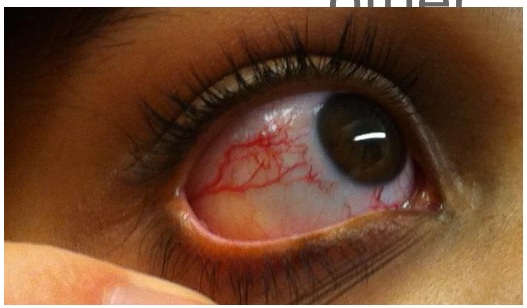


Distractors: Terminal Complement Deficiency

1. Hypogammaglobulinemia
    1. Typical history is of recurrent bacterial infections, typically sinopulmonary infections
2. Selective IgA deficiency
    1. Again, typical history is of recurrent, non life threatening infections
3. **Terminal complement deficiency**
4. Ataxia telangiectasia
5. Chronic Granulomatous Disease (CGD)

Distractor:
Ataxia telangiectasia

- Ataxia telangiectasia is a primary immunodeficiency that is typically identified by two non-immune factors
- Ataxia and neurologic problems
  - Often wheelchair bound
- Telangiectasia:
  - Often appear in eye, can appear in other sun exposed skin
  - Don’t bleed or itch and don’t change

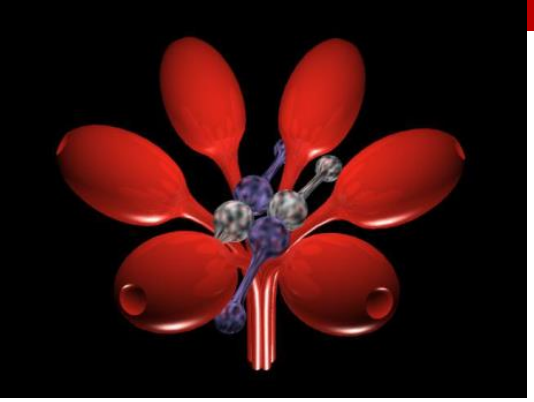


Distractor: Chronic Granulomatous Disease

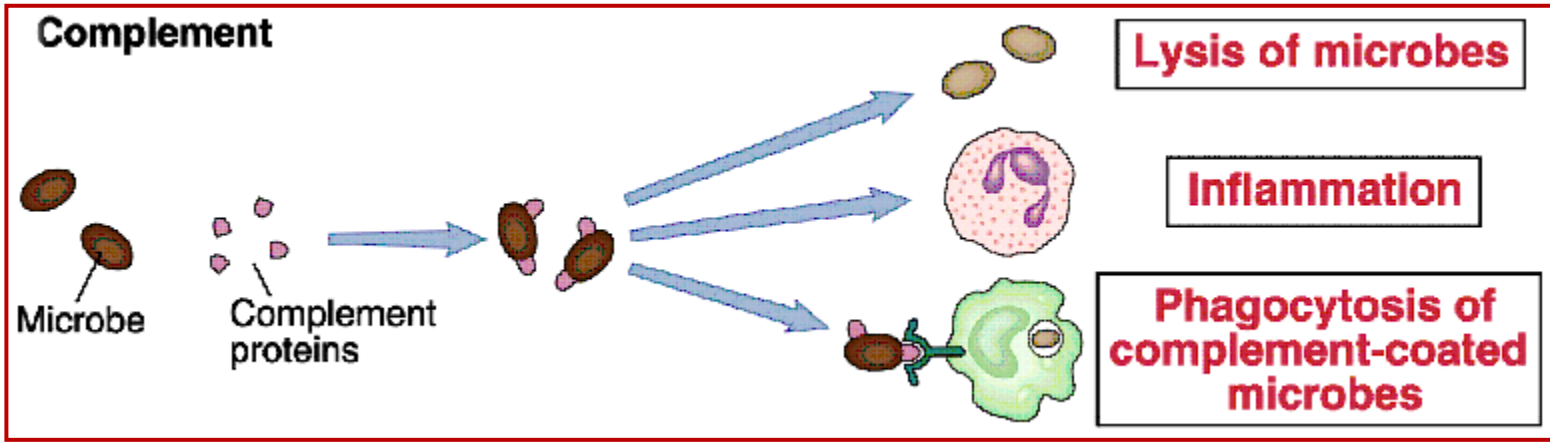
- Phagocytic disorder in which phagocytes are unable to undergo the respiratory burst.
- May be infected with bacteria that typically do not cause disease in humans
  - Particularly catalase-positive organisms
- Recurrent bouts of infections
  - Pneumonia
  - Abscesses of skin, tissues and organs
  - Suppurative arthritis
  - Osteomyelitis
  - Bacteremia
- Diagnosis based on inability to undergo respiratory burst
  - Nitroblue-tetazolium (NBT) test: reduction of NBT to the insoluble blue compound formazan by NADPH oxidase (blue is good)
  - Dihydrorhodamine (DHR) test: Normal phagocytic cells oxidize DHR to rhodamin.

Complement Deficiency
Role of Complement

- Critical role in defense against bacteria, fungi and virus
- Most important in early stage of infection
- Critical in limiting infection to original site and preventing dissemination
- Helps clear microorganism from blood stream



Complement Proteins



- Membrane Attack Complex: can cause lysis of microbes
- Allows more efficient phagocytosis

Three Complement Pathways

- **Classical Pathway**
  - C1, C4, C2, C3
  - Antigen-antibody complexes
  - IgM (most effective) and IgG bind complement
- **Mannan-binding Lectin Pathway**
  - Mannan-binding lectin binds mannose on pathogen surfaces
  - MBL, MASP, C4, C2, C3
    - MASP (mannan-binding lectin-associated serum protease)
- **Alternative pathway**
  - Binds to pathogen surface
  - Amplifies effects of the Classical Pathway
  - C3b, B, D, C3
- Although they initiate differently ALL pathways converge at C3 convertase

ABC's of complement

- A is for anaphylatoxin (smaller cleavage fragment)
  - C3a, C4a and C5a are peptide mediators of local inflammation
  - C5a is the most active
  - C4a is relatively weak
- B is for binding (larger cleavage fragment)
  - C3b binds to complement receptors on phagocytes and allows for effective opsonization of pathogens
  - C5b associates with the bacterial membrane and forms membrane attack Complex
  - C4b is a weak opsonin

Deficiency of early components

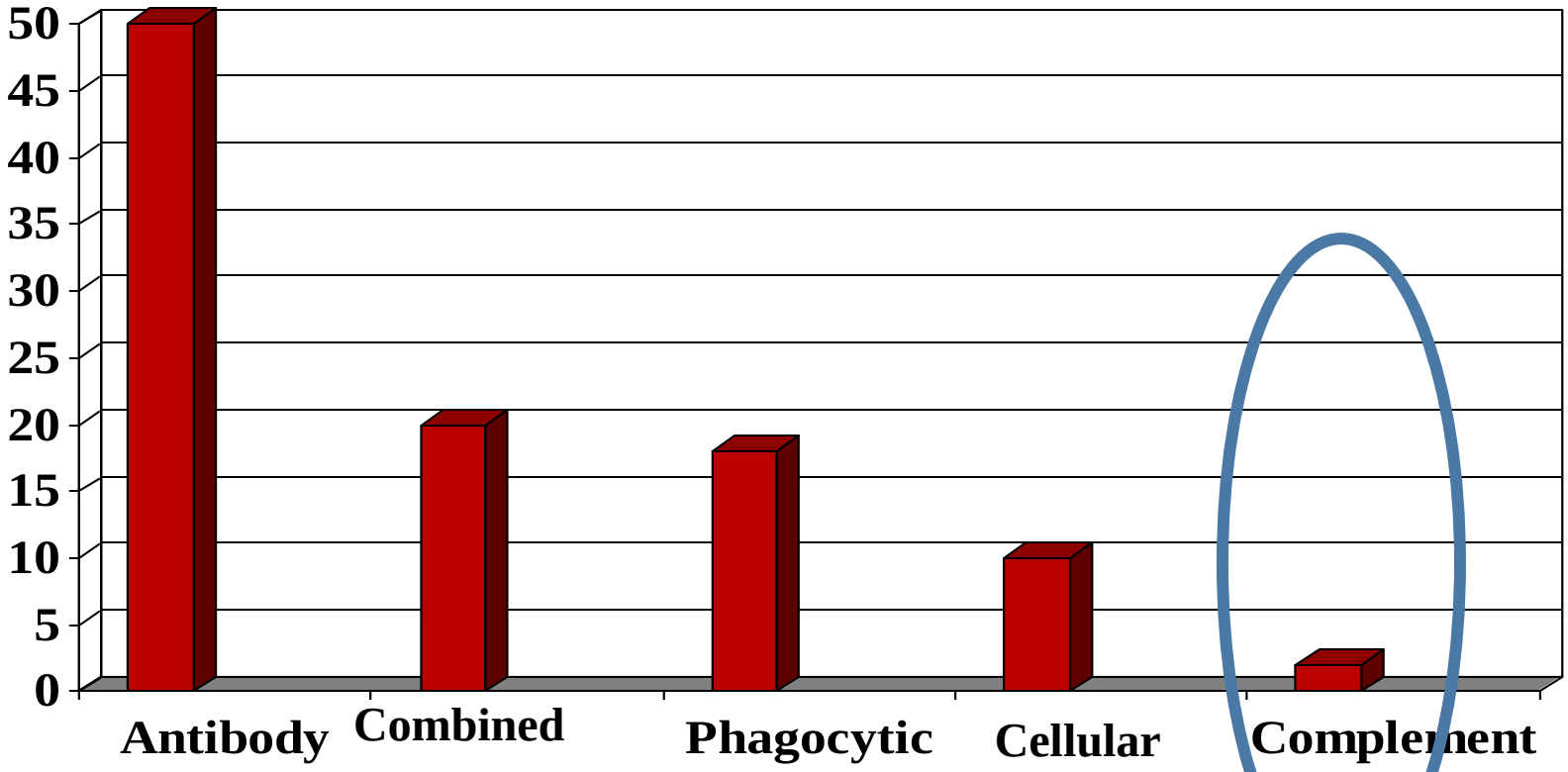
- C3 deficiency
  - C3b is opsonic ligand when bound to bacteria
  - increased susceptibility to bacteria for which opsonization is primary defense mechanism
    - Streptococcus pneumoniae
    - Haemophilus influenzae
- C1,C4 or C2 deficiencies
  - Similar to C3 deficiency, as these components are necessary for activation of C3 via classical pathway
  - Not as susceptible as those with C3 deficiency
- Most common inherited complement deficiency is C2
  - Approximately 1 in 10,000

Terminal Component Deficiency

- C5, C6, C7, C8 or C9
- Terminal components assembled into membrane attack complex (MAC)
- Only gram-negative bacteria are susceptible to its bactericidal effects
- Patients susceptible to gram-negative bacteria such as Neisseria meningitidis

- This is a long standing favorite question

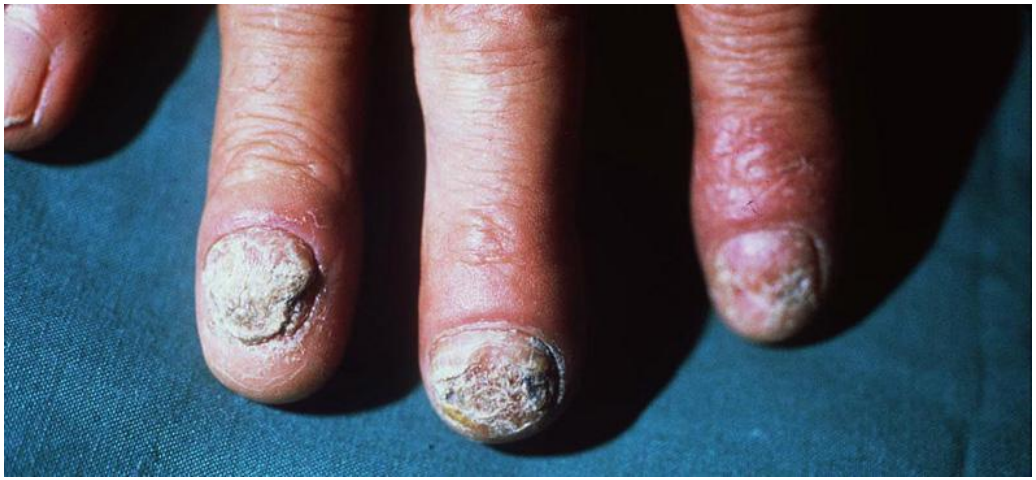
Primary Immunodeficiencies
Relative Distribution

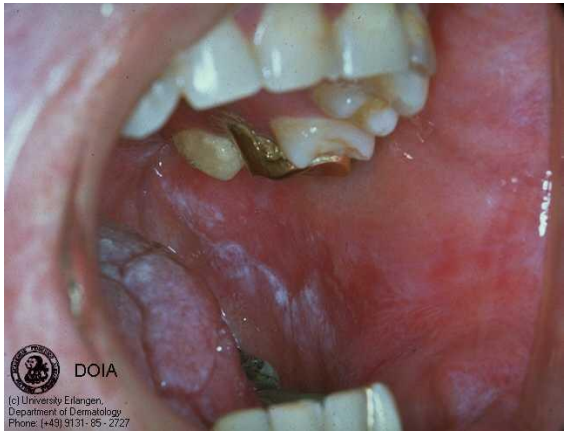


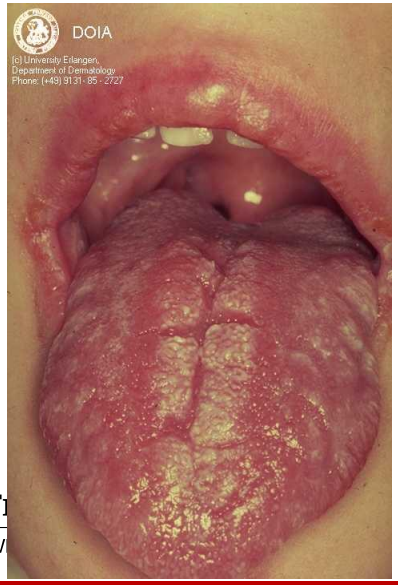
20 year old Male with Chronic Fungal Infection of nails

- Gone to the Doctor about a few times, but nobody ever fixed it
- His fingernails keep getting worse, but he doesn't feel sick or anything like that.

Physical examination







What is the diagnosis?

1. Leukocyte Adhesion Deficit (LAD) 1
2. Chronic Mucocutaneous Candidiasis (CMC)
3. Job's syndrome
4. Chediak-Higashi Syndrome
5. Wiskott Aldrich Syndrome

What is the diagnosis

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2. **Chronic Mucocutaneous Candidiasis (CMC)**
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Chronic Mucocutaneous Candidiasis

- Selective T cell defect: B cell immunity intact
- Associated with idiopathic endocrinopathies; hypoparathyroidism is most common
- May appear as late as second decade
- Candidal infections of mucous membranes, skin, nails, vagina: usually NOT systemic candidiasis
- Multiple phenotypes/genotypes

Distractor 1:
Leukocyte Adhesion Deficit (LAD)

- Leukocyte Adhesion Deficit is a problem with the interaction between phagocytes and the endothelial cells
- LAD I: Leukocyte has the problem: lacks leukocyte integrin CD11/CD18 complex
  - Autosomal recessive: Chromosome 21q22.3 (codes for CD 18)
- LAD II: Endothelial cells have the problem
  - NORMAL levels of CD18
  - Defective expression of selectins on endothelial cells

How phagocytes get to the job site

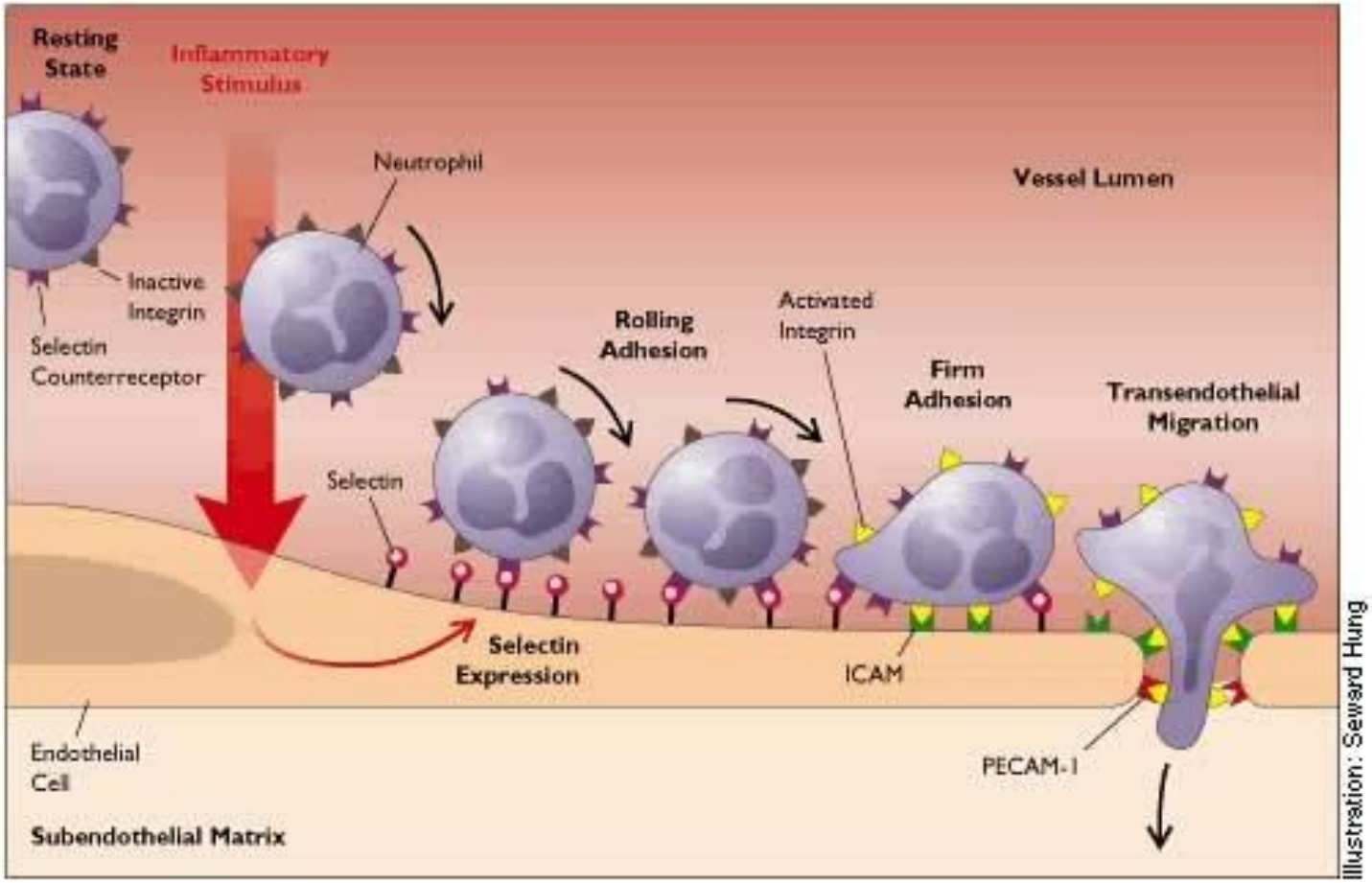


Figure 1. Cell-to-cell adhesions that enable a neutrophil to leave the circulation begin with both the neutrophil and the vascular endothelium in a resting, noninteractive state. Activated by an inflammatory stimulus, the endothelium expresses selectins, whose binding to their receptors on neutrophils initiates a rolling adhesion of neutrophils to the vessel's luminal wall. The neutrophils activate their integrins, which bind to endothelial ICAMs, permitting a firmer, stationary adhesion. Transepithelial migration may be guided by further adhesive interactions, perhaps involving molecules such as PECAM-1, which endothelial cells express at intercellular junctions.

Leukocyte Adhesion Deficiency (LAD)

- Disorder of migration and/or adhesion
- Extreme leukocytosis
  - 15,000-70,000 consistently
  - >100,000 in face of infection
- Abnormal inflammatory response: no pus
- Recurrent bacterial infections
- delayed separation of the umbilical cord

Phagocytic Disorders:

- Neutropenia
  - Not enough
- Leukocyte Adhesion Deficiency (LAD)
  - Lots, but can’t get where needed
- Disorder of microbicidal activity
  - Enough, but they don’t work
    - Chronic Granulomatous Disease

Distractor 2:
Job's Syndrome

- Also known as Hyperimmunoglobulin E Syndrome
- STAT3 defect: Autosomal dominant
  - Mnemonic is FATED
    - Coarse or leonine **F**acies
    - Cold staph **A**bscesses
    - Retained primary **T**eeth
    - Increased Ig**E**
    - **D**ermatologic Problems (eczema)
- Dock 8 immunodeficiency is an autosomal recessive form of Hyperimmunoglobulin E syndrome

Job's Syndrome

Characteristic Faces

- Develops through childhood & adolescence

- Facial asymmetry
- Broad nose
- Deep-set eyes
- Prominent forehead

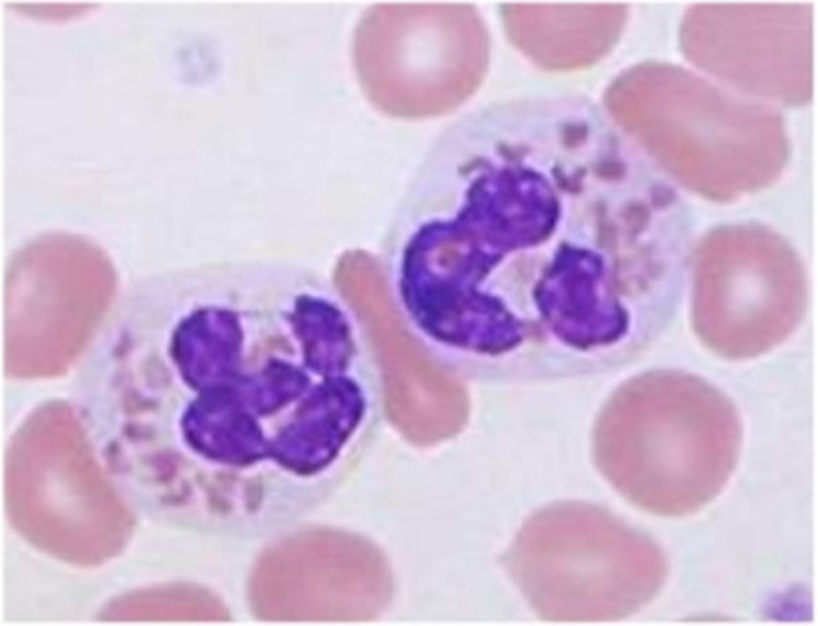
- Rough appearance with exaggerated pore size of facial skin

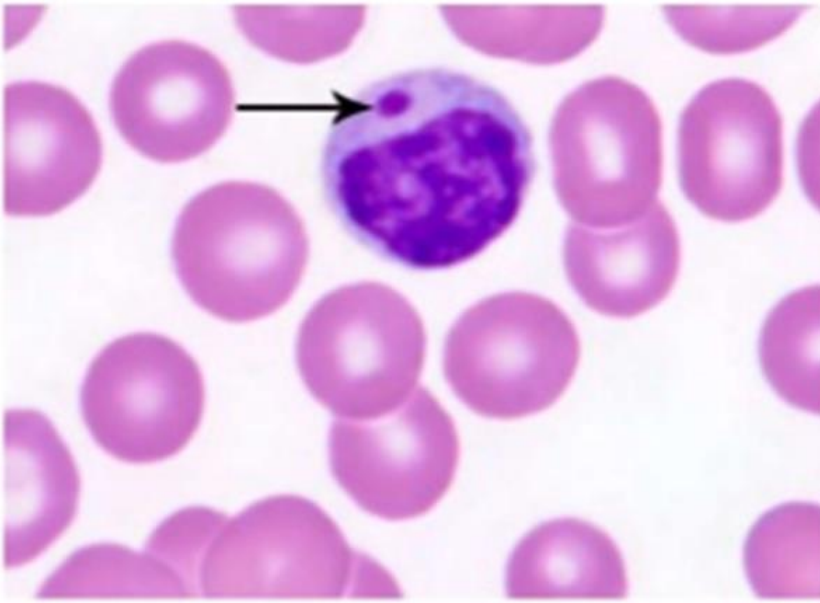
Grimbacher B. NEJM 1999;340:692-702.
Freeman AF, Holland SM. Immunol Allergy Clin N Am 2008;28:277-91.

Distractor 3:
Chediak-Higashi Syndrome

- Phagocytic Dysfunction
- Recurrent pyogenic infections and peripheral neuropathy
- Characteristic abnormality: **Giant cytoplasmic granular inclusions in leukocytes and platelets on routine peripheral blood smears**
- Autosomal recessive

Chédiak-Higashi





Chédiak-Higashi granules are very large red or blue granules that appear in the cytoplasm of granulocytes, lymphocytes, or monocytes in patients with the Chédiak-Steinbrinck-Higashi syndrome. It is a rare autosomal recessive disorder

Distractor 4: Wiskott Aldrich Syndrome

- Immunodeficiency with Thrombocytopenia, eczema and recurrent infection
- Thrombocytopenia characterized by small platelets
- X-linked inheritance
  - WASp gene
- Increased incidence of lymphoid malignancies
- IgM is usually low with elevated IgA & IgE

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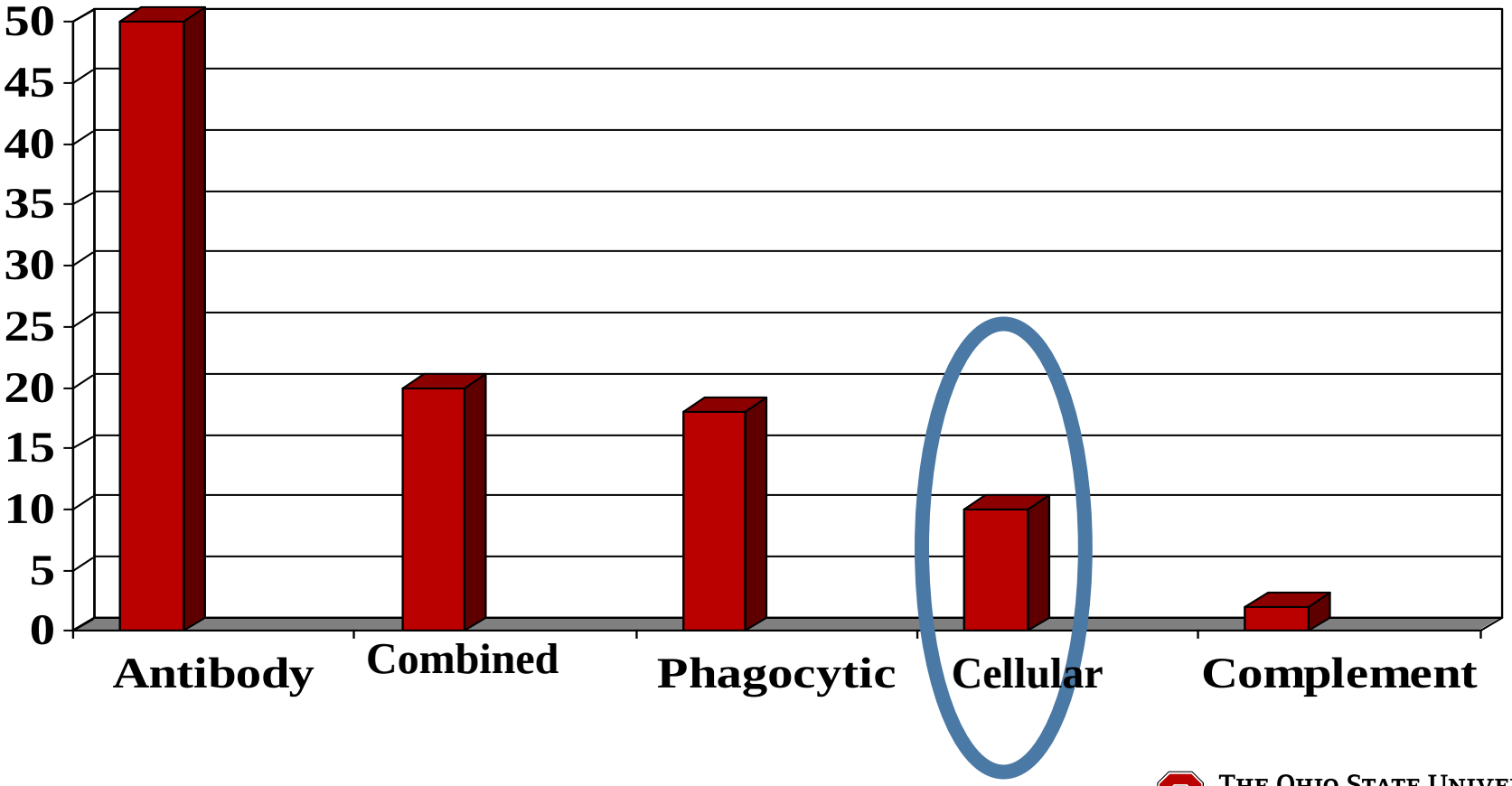
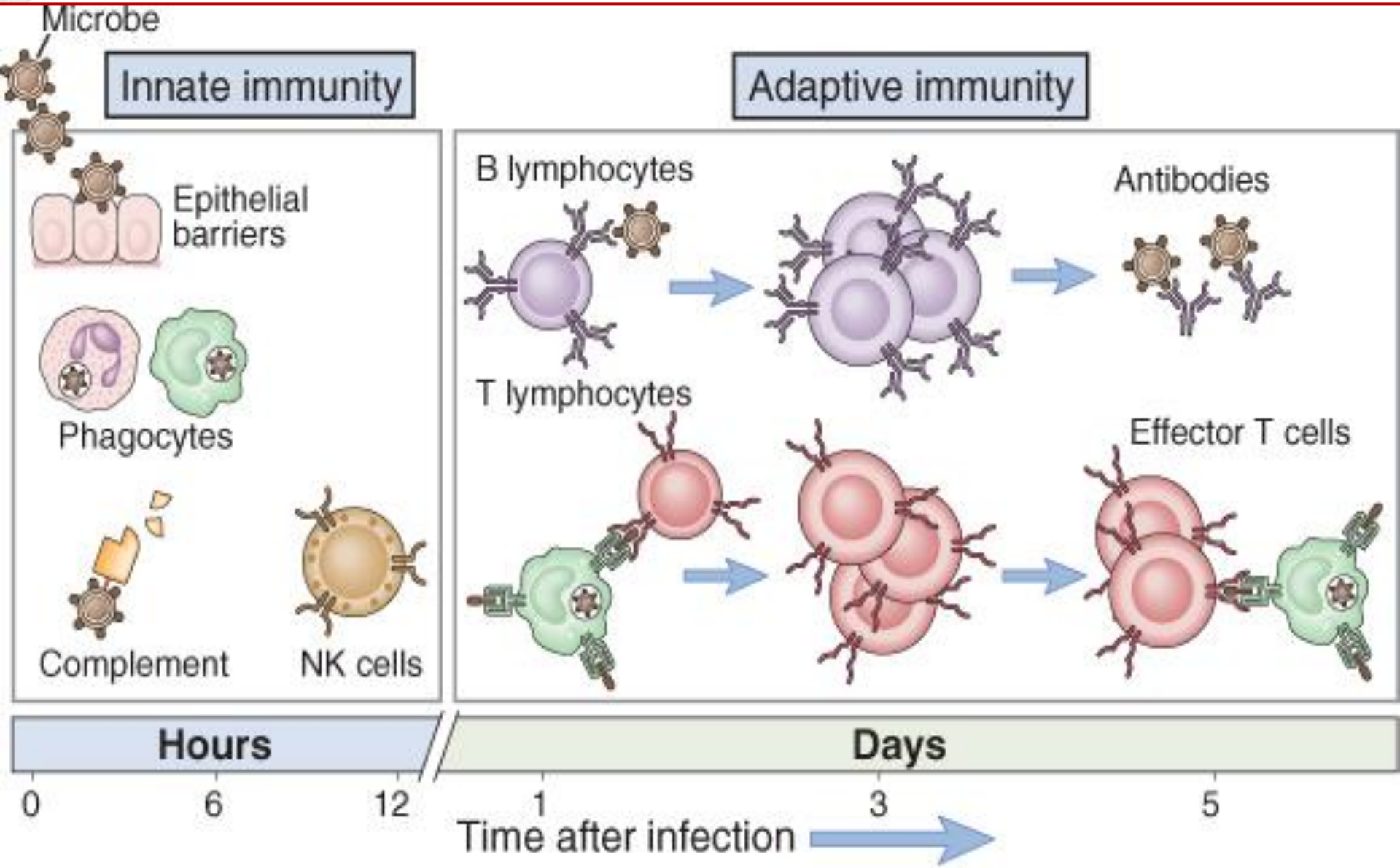


Graft vs host disease

- If presented with a patient who has had a transplant, you must consider graft vs host disease.
- **Hyperacute (7-14 days)**
  - maculopapular rash with rapid progression to that resembling toxic epidermal necrolysis, associated with severe diarrhea: Death shortly after reaction
- **Acute (5-47 days; median 19 days post transplant)**
  - Initial maculopapular rash
  - Diarrhea, hepatosplenomegaly, jaundice, cardiac irregularity, CNS irritability, pulmonary infiltrates
- **Chronic**
  - Chronic desquamation of skin, dysplastic nail growth, hepatosplenomegaly, chronic diarrhea

Immune Response



Good Luck!