Clinical Basis of the Immune Response and the Complement Cascade

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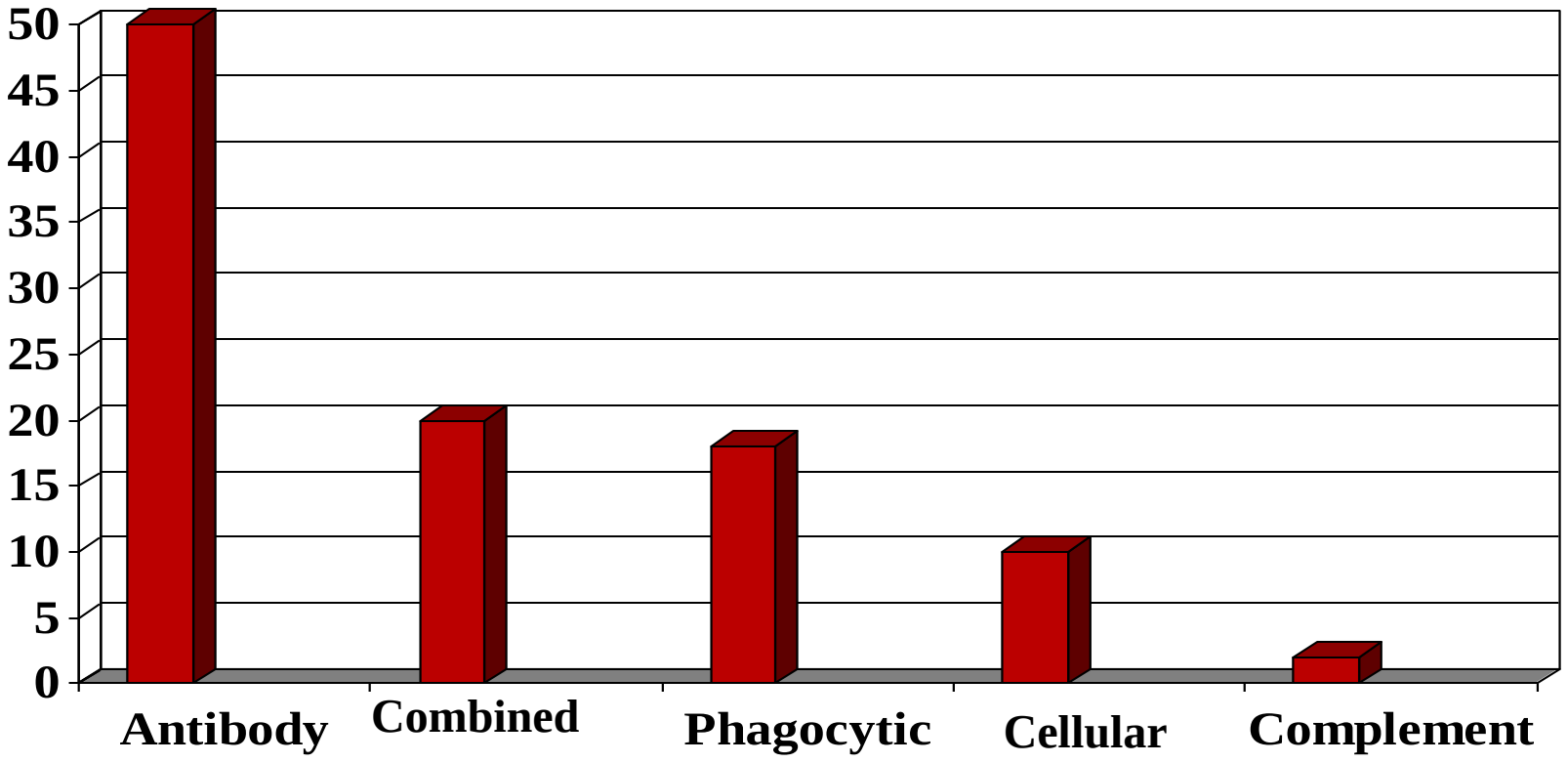
Disclosures

- None

Objectives

- Pass the boards!
- Review the Immune response using a case based approach
- Review primary immune deficiencies that may affect adult patients in our practices

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?
  - CBC, liver function tests, immunoglobulins, and CH50?
  - Reassurance
  - Titers for CMV, mono and hepatitis
  - Careful complete history
  - Chest x-ray, CBC and flow cytometry

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  - **Careful complete history**
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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 do we order?
  - CBC
  - CBC and CH50
  - CBC and immunoglobulins
  - CBC and flow cytometry
  - CBC and dihydrorhodamine test

The Patient with Hypogammaglobulinemia

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- Recurrent upper respiratory infections, sinusitis, bronchitis and pneumonia
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  - CBC
  - CBC and CH50
  - **CBC and immunoglobulins**
  - CBC and flow cytometry
  - CBC and dihydrorhodamine test

Clues Immunodeficiency

- Features associated with specific immunodeficiency disorders
- Recurrent bacterial otitis media, sinusitis and pneumonia: **Hypogammaglobulinemia**
- Fungal, protozoal and viral infections: **defective cell mediated immunity**
- 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

Answers and Distractors

- B cell #'s normal, total Ig and IgG low
  - CBC alone will not give us enough data: this will likely be normal
  - CBC and CH50: CH50 is a test for the complement cascade; these will both likely be normal.
  - 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
  - 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 caucasions

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

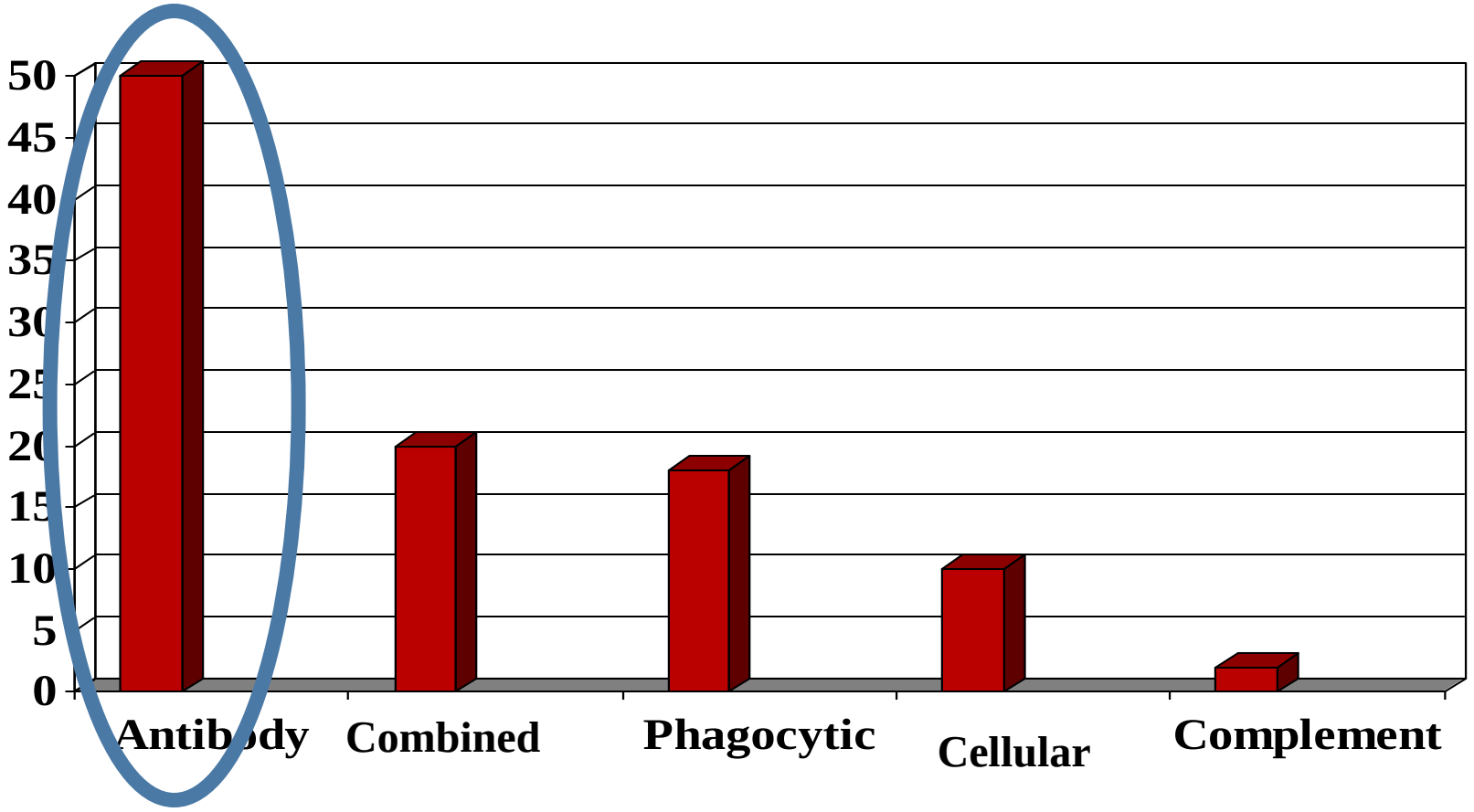
Common Variable Immunodeficiency

- 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



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
  - Hypogammaglobulonemia
  - Selective IgA deficiency
  - Terminal complement deficiency
  - Ataxia telangiectasia
  - Chronic Granulomatous Disease (CGD)

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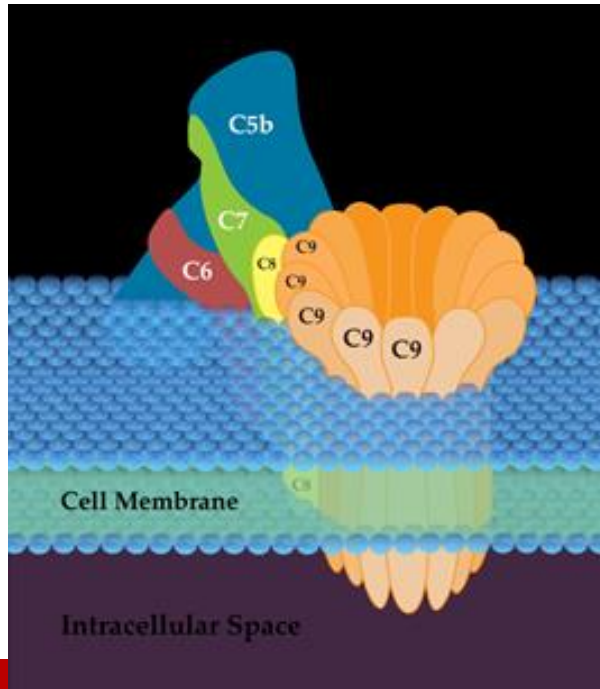
Terminal Complement Deficiency

- 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 ot Neisseria spp.

Terminal Complement Deficiency

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

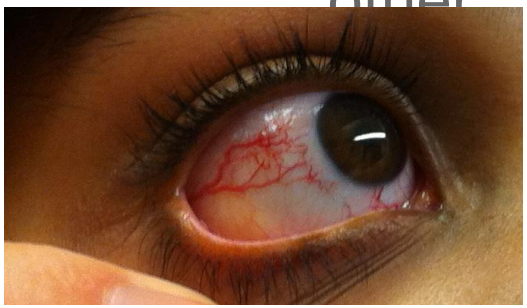


Distractors: Antibody Deficiency

- Hypogammaglobulinemia
  - Typical history is of recurrent bacterial infections, typically sinopulmonary infections
- Selective IgA deficiency
  - Again, typical history is of recurrent, non life threatening infections

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

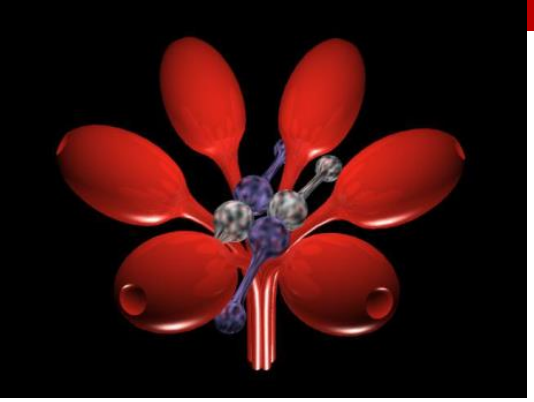


Distractor: Chronic Granulomatous Disease

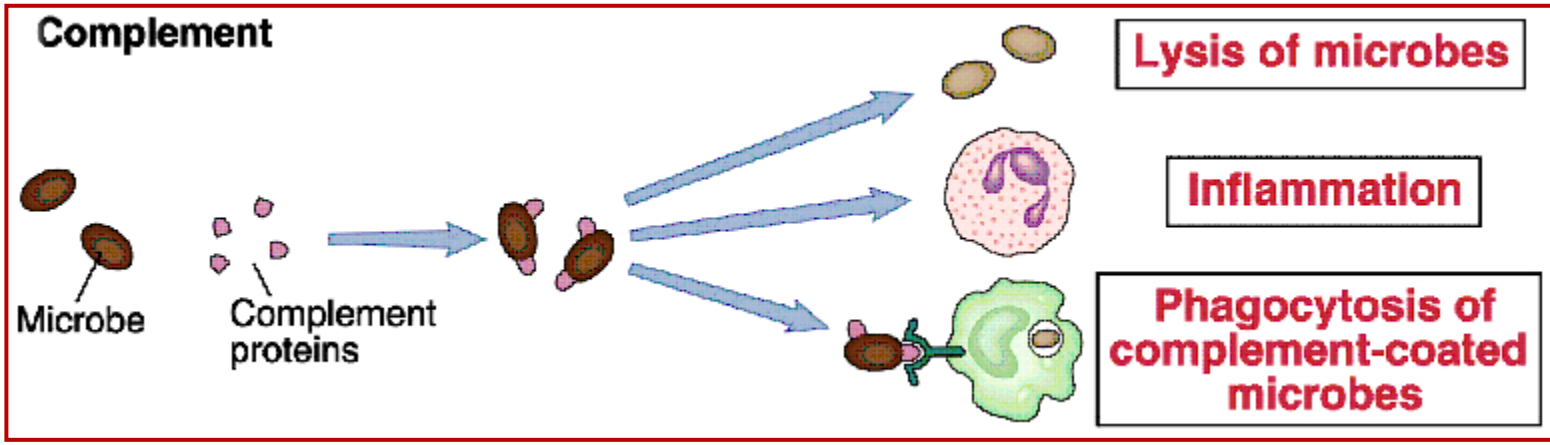
- Phagocytic disorder in which phagocytes are unable to undergo the respiratory burst.
- May be infected with bacteria that typically do not cause disease in humans
  - Particularly catalase-positive organisms
- Recurrent bouts of infections
  - Pneumonia
  - Abscesses of skin, tissues and organs
  - 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

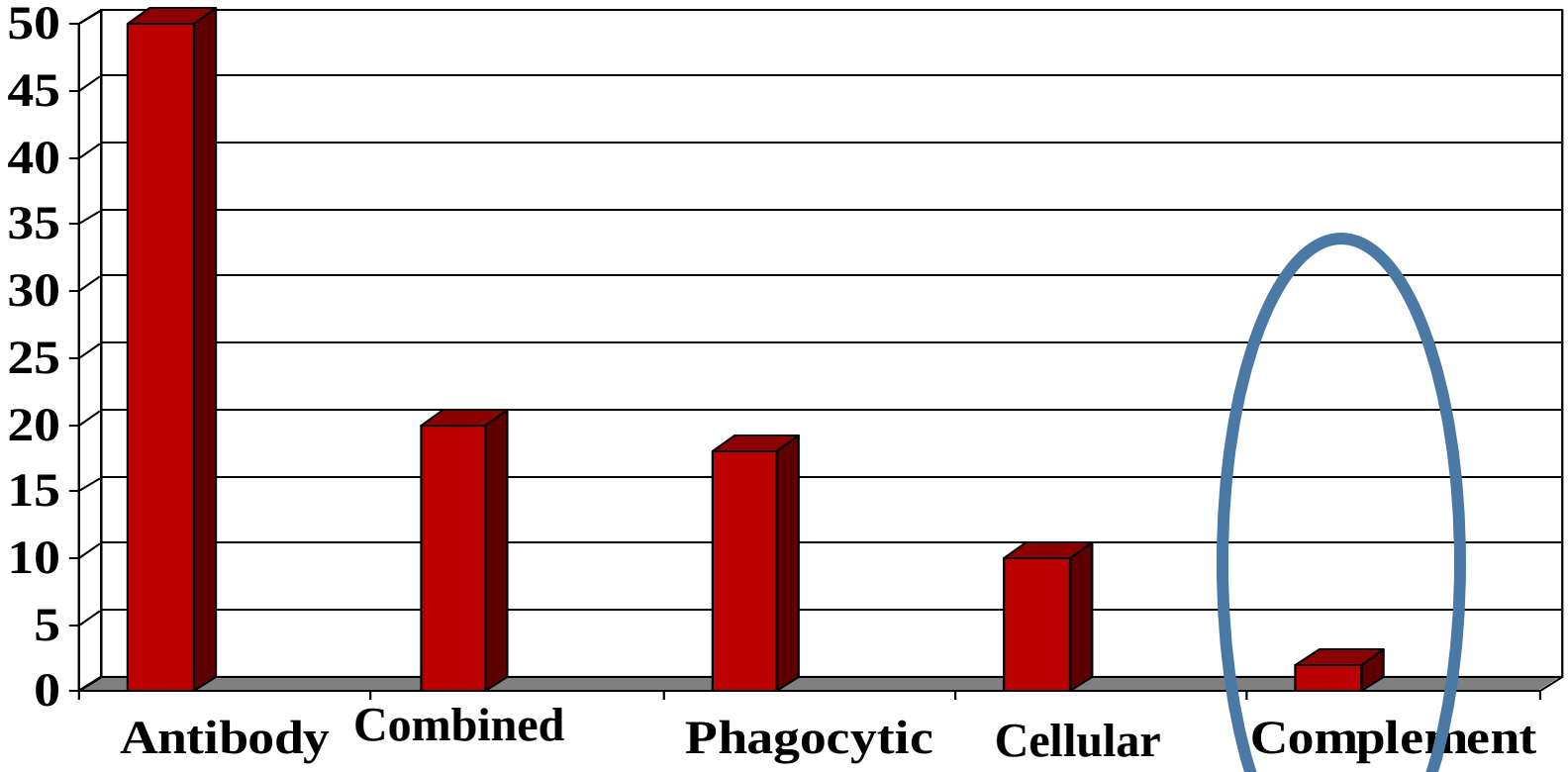
- C3 deficiency
  - C3b is opsonic ligand when bound to bacteria
  - increased susceptibility to bacteria for which opsonization is primary defense mechanism
    - Streptococcus pneumoniae
    - Haemophilus influenzae
- C1,C4 or C2 deficiencies
  - Similar to C3 deficiency, as these components are necessary 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

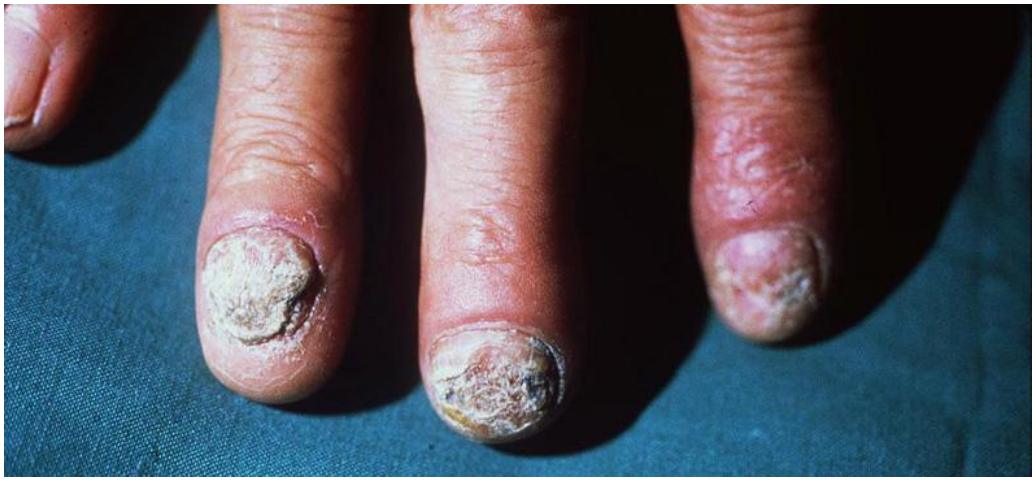
Primary Immunodeficiencies
Relative Distribution

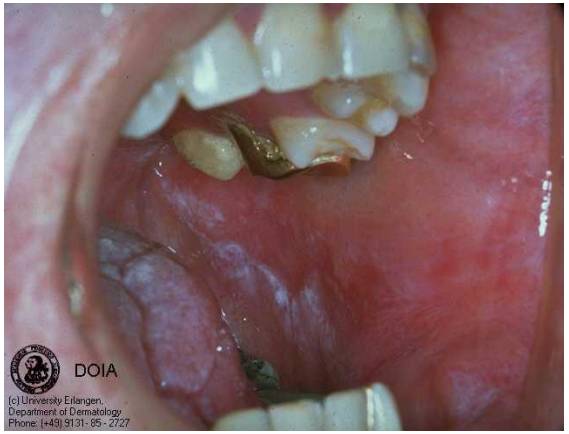


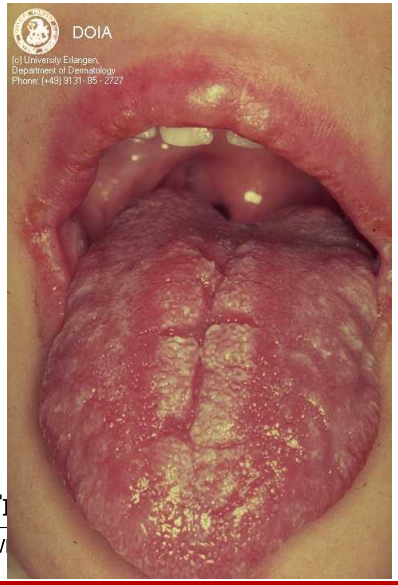
20 year old Male with Chronic Fungal Infection of nails

- 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

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

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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

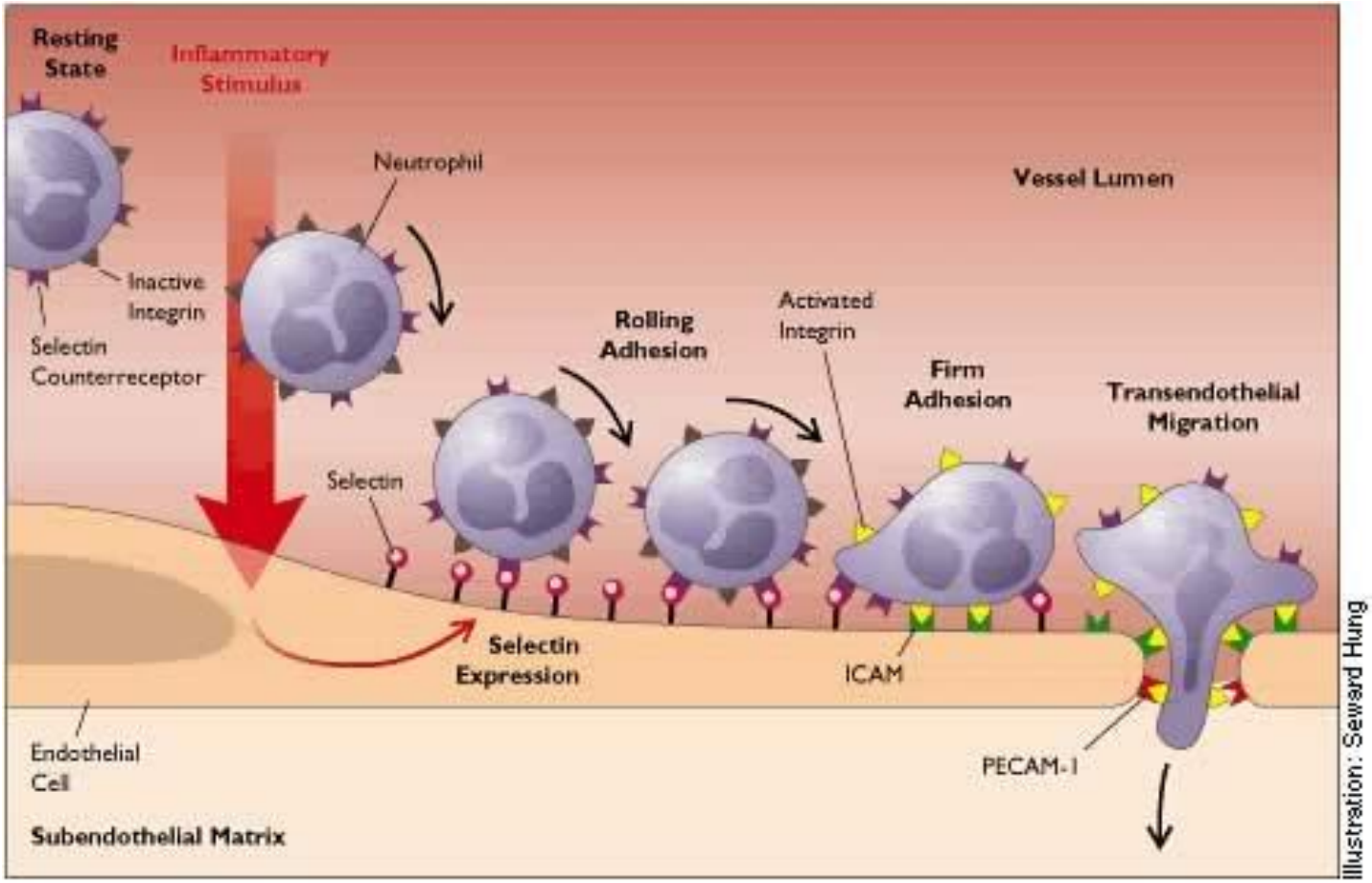


Figure 1. Cell-to-cell adhesions that enable a neutrophil to leave the circulation begin with both the neutrophil and the vascular endothelium in a resting, noninteractive state. Activated by an inflammatory stimulus, the endothelium expresses selectins, whose binding to their receptors on neutrophils 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

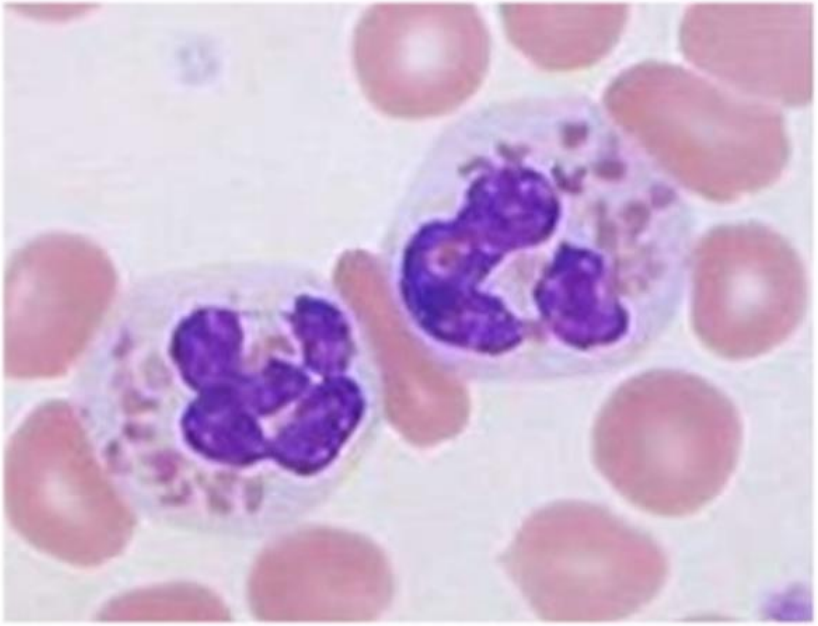
Distractor 2:
Job's Syndrome

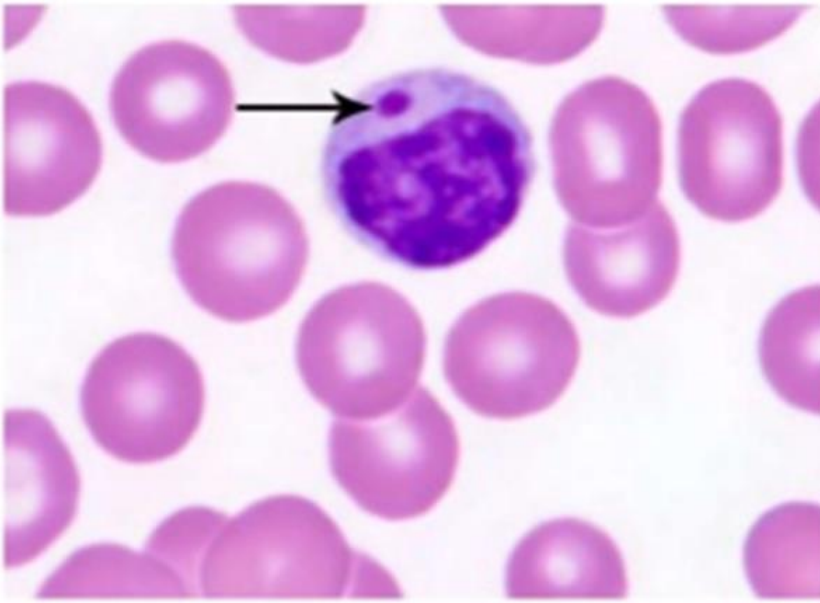
- Also known as Hyperimmunoglobulin E Syndrome
- STAT3 defect: Autosomal dominant
  - Mnemonic is FATED
    - Coarse of leonine **F**acies
    - Cold staph **A**bscesses
    - Retained primary **T**eeth
    - Increased Ig**E**
    - **D**ermatologic Problems (eczema)
- Dock 8 immunodeficiency is an autosomal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

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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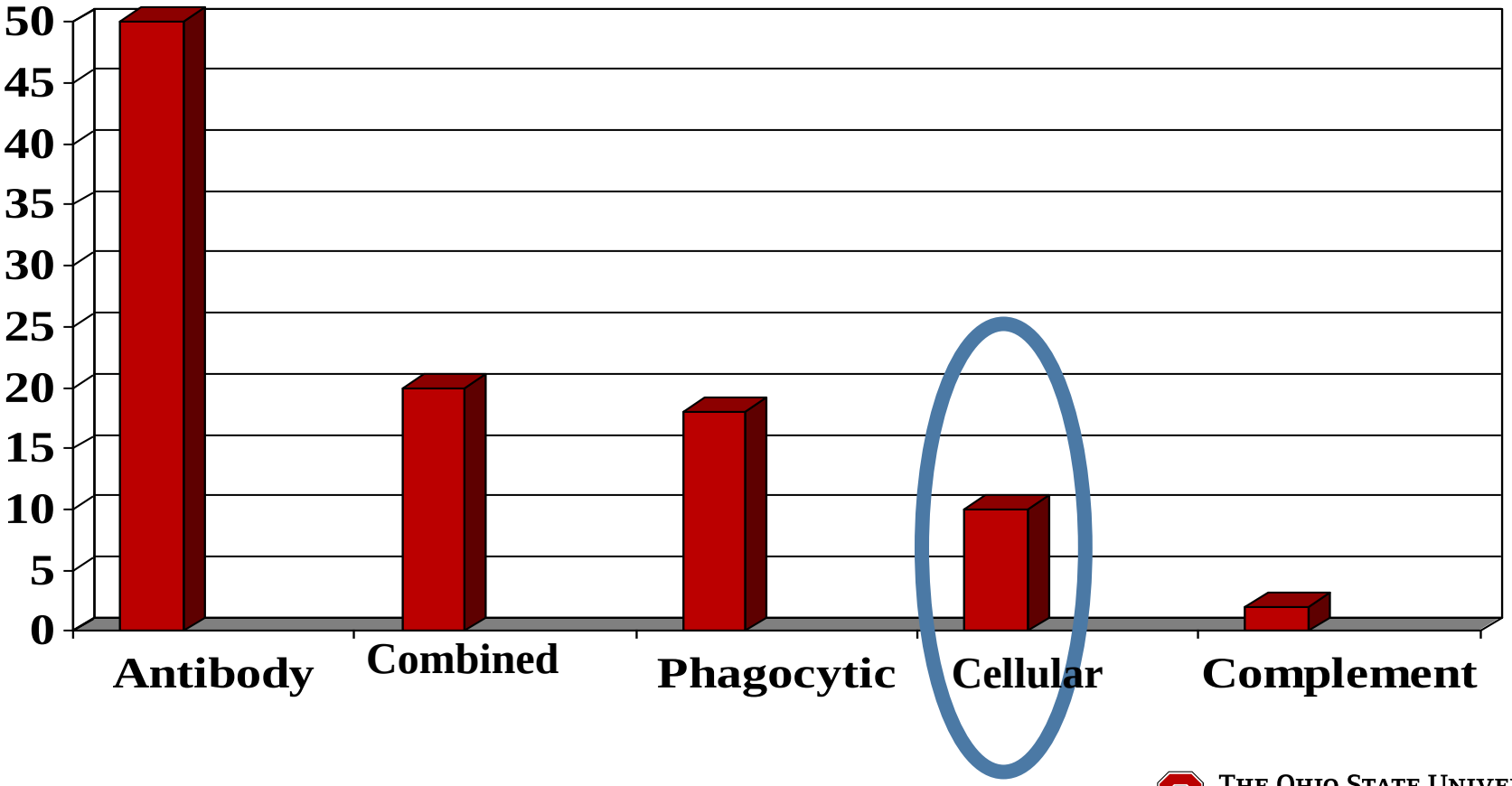
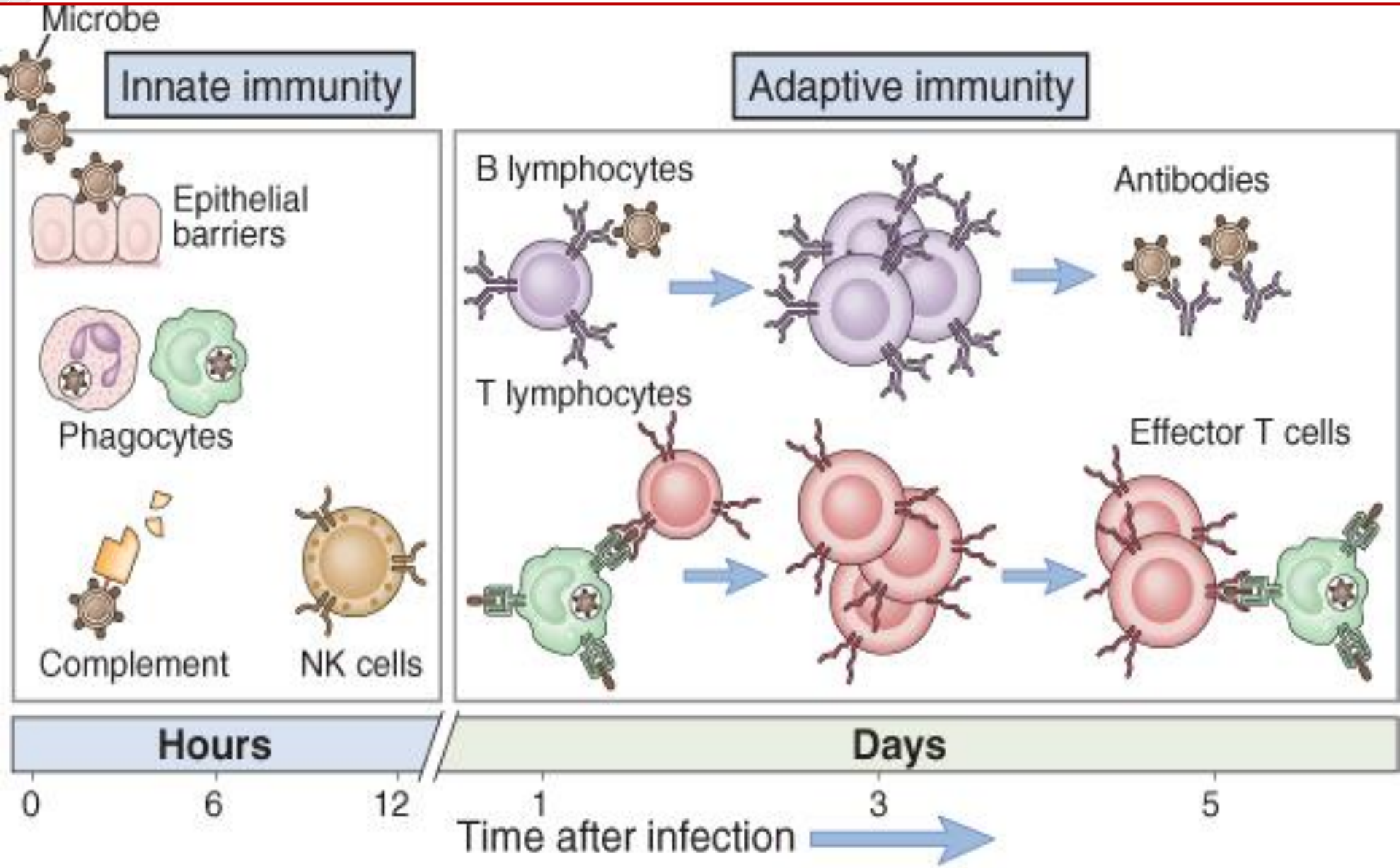


Graft vs host disease

- 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!