Clinical Basis of the Immune Response and the Complement Cascade

Bryan L. Martin, DO, MMAS, FACAAI, FAAAAI, FACOI, FACP
Emeritus Professor of Medicine and Pediatrics
President, American College of Allergy, Asthma & Immunology
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

Antibody
Combined
Phagocytic
Cellular
Complement
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
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
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?
- What kinds of illnesses does she have?
  - Have organisms been identified?
- How severe are the illnesses?
- What did she need to do to recover?
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 dihydorhodamine 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 do we order?
  - 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 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
Common Variable Immunodeficiency

- Onset at any age: Usually become symptomatic at age 15-35
- Recurrent pyogenic infections
- Autoimmune diseases
- Recurrent sinopulmonary infections
- Total Ig and IgG low, B cell #'s NORMAL
- Normal life span possible
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

- Antibody
- Combined
- Phagocytic
- Cellular
- Complement
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
  - Job’s syndrome
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
  - Hypogammaglobulinemia
  - Selective IgA deficiency
  - Terminal complement deficiency
  - Ataxia telangiectasia
  - Chronic Granulommatous Disease (CGD)
Terminal Complement Deficiency

- All complement pathways converge at C3
  - C3 Cleavage generates C5 convertase which results in C5b and C5a (a potent anaphylatoxin and chemoattractant)

- 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 of 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
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
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-tetrazolium (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

- Antibody
- Combined
- Phagocytic
- Cellular
- Complement
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
What is the diagnosis

- Leukocyte Adhesion Deficit (LAD) 1
- **Chronic Mucocutaneous Candidiasis (CMC)**
- Job’s syndrome
- Chediak-Higashi syndrome
- Wiskott Aldrich Syndrome
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
- May survive into 3rd decade
- 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/CD 18 complex
  - Autosomal recessive: Chromosome 21q22.3 (codes for CD 18)
- LAD II: Endothelial cells have the problem
  - NORMAL levels of CD18
  - Defective expression of sialyl-Lewis X on endothelial cells
Selectin-mediated adhesion to leukocyte sialyl-Lewis\textsuperscript{x} is weak, and allows leukocytes to roll along the vascular endothelial surface.

\textbf{Figure 2-44 part 2 of 3} Immunobiology, 6/e. (© Garland Science 2005)
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
    - CGD
Distractor 2: Job’s Syndrome

- Also known as Hyperimmunoglobulin E Syndrome
- STAT3 defect: Autosomal dominant
  - Mnemonic is FATED
    - Coarse of leonine Faces
    - Cold staph Abscesses
    - Retained primary Teeth
    - Increased IgE
    - Dermatologic 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 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.
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
Primary Immunodeficiencies
Relative Distribution
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

Innate immunity
- Epithelial barriers
- Phagocytes
- Complement
- NK cells

Adaptive immunity
- B lymphocytes
- T lymphocytes
- Antibodies
- Effector T cells

Time after infection:
- Hours: 0, 6, 12
- Days: 1, 3, 5
QUESTIONS?