Primary Immune Deficiency: Overview

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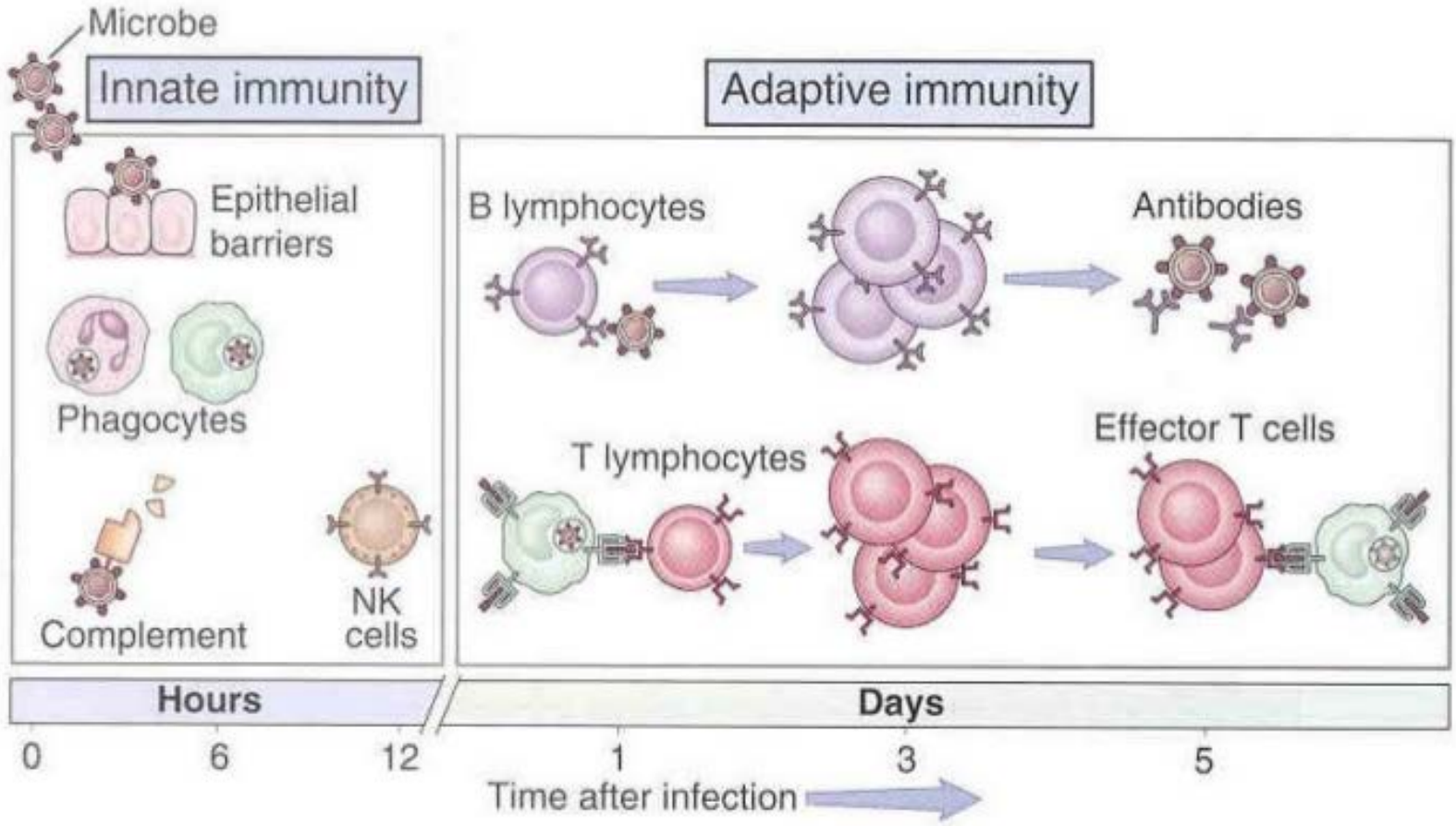
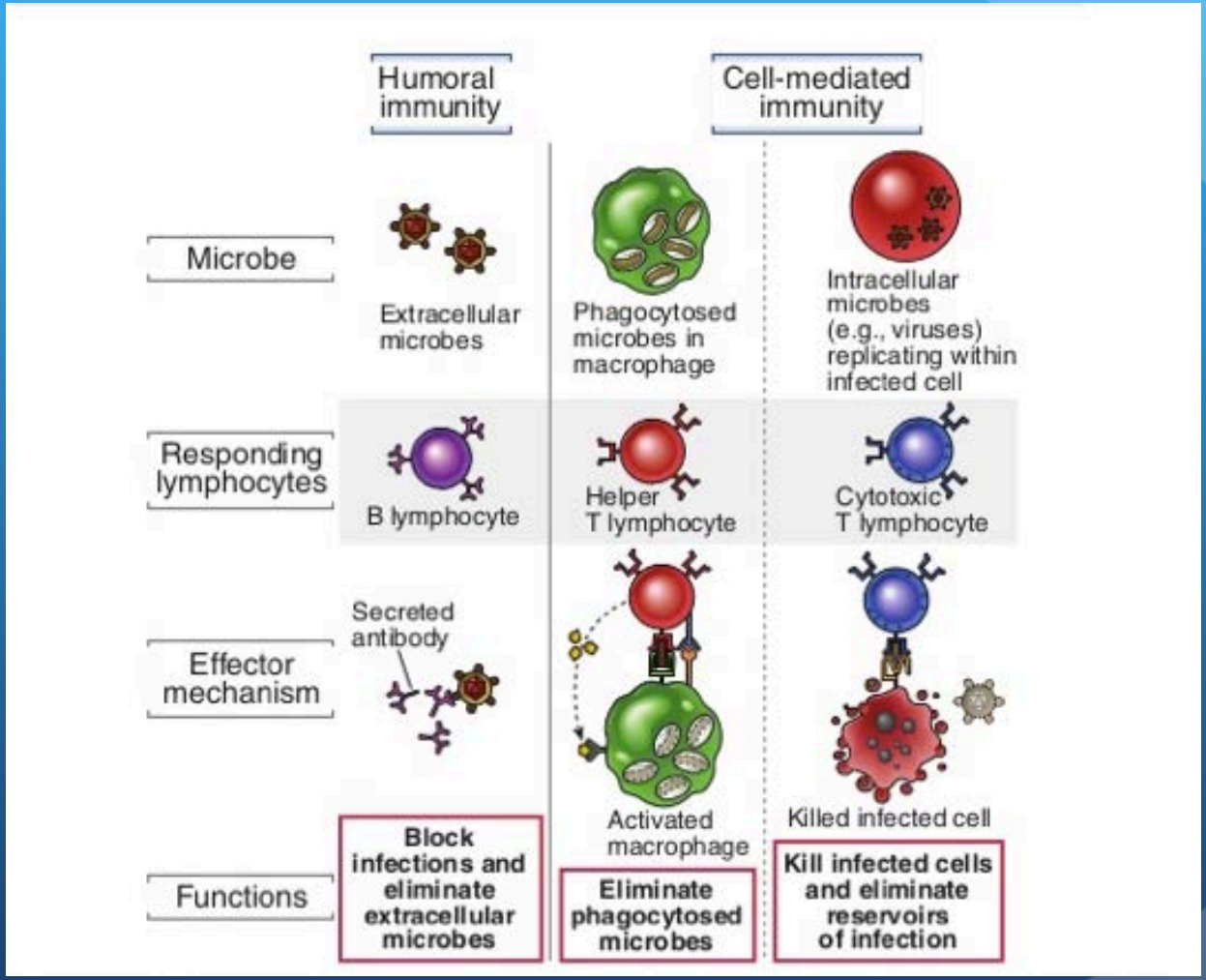
Immune System: Overview

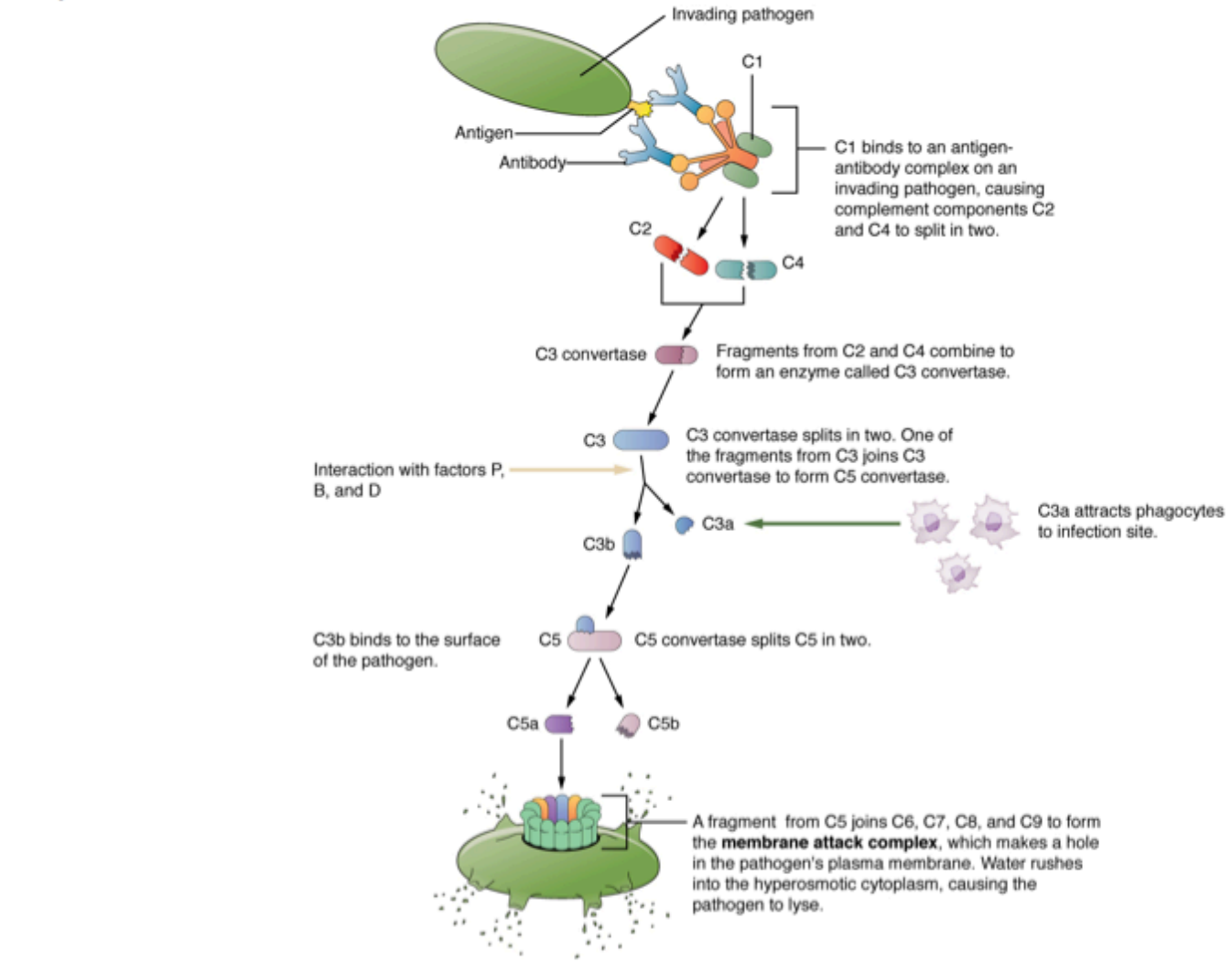


Courtesy: Abbas and Litchman; Basic Immunology

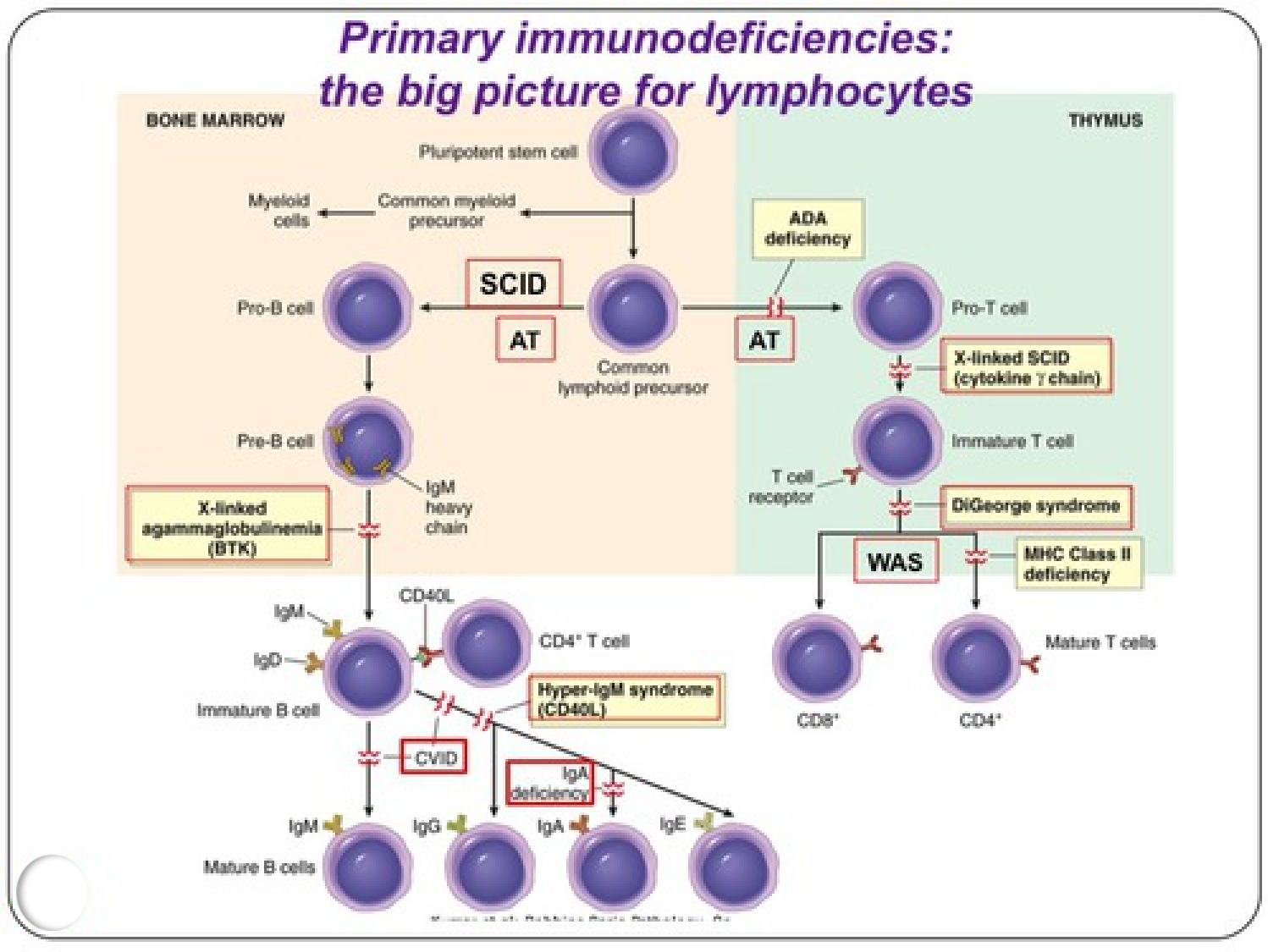
Adaptive Immunity



Complement


Complement Cascade and Function
Invading pathogen
C1
Antigen
Antibody
C1 binds to an antigen-antibody complex on an invading pathogen, causing complement components C2 and C4 to split in two.
C2
C4
C3 convertase
Fragments from C2 and C4 combine to form an enzyme called C3 convertase.
C3
C3 convertase splits in two. One of the fragments from C3 joins C3 convertase to form C5 convertase.
Interaction with factors P, B, and D
C3a
C3a attracts phagocytes to infection site.
C3b
C3b binds to the surface of the pathogen.
C5
C5 convertase splits C5 in two.
C5a
C5b
A fragment from C5 joins C6, C7, C8, and C9 to form the membrane attack complex, which makes a hole in the pathogen's plasma membrane. Water rushes into the hyperosmotic cytoplasm, causing the pathogen to lyse.

PID Overview



PID Overview

- Severe Combined Immune Deficiency (SCID)
- X-Linked Agammaglobulinemia (XLA)
- Wiskott-Aldrich Syndrome (WAS)
- Common Variable Immune Deficiency (CVID)
- Complement Deficiency
- Selective IgA deficiency

CASE 1

- 3 month old male hospitalized with pneumonia, failure to thrive
- No lymph nodes palpated
- CBC w/diff showed WBC 3.5, nl Hgb and plt counts
- Total lymphocyte 500/ microl

SCID

- 1% T-cells, 1% B-cells, 90% NK cells
- Gene testing shows mutation in *RAG1* gene
- SCID 1 in 58,000 births
- Numerous gene defects cause dysfunction in T cells with varying B and NK cells

SCID Gene Defects

T-B+NK- SCID	
X-linked SCID¶, common gamma chain (gamma-c)	*IL2RG*
Janus kinase 3	*JAK3*
T-B+NK+ SCID	
Interleukin-7 receptor alpha chain (CD127)	*IL7RA*
Actin-regulating protein coronin 1A (CORO1A)	*CORO1A*
CD3 chain components	
CD3 delta	*CD3D*
CD3 epsilon	*CD3E*
CD3 zeta	*CD3Z*
CD45	*PTPRC*
T-B-NK+ SCID	
Recombinase-activating genes 1 and 2	*RAG1, RAG2*
Artemis	*DCLRE1C*
DNA protein kinase catalytic subunit (DNA-PKcs)	*PRKDC*
DNA ligase IV	*LIG4*
Cernunnos/XRCC4-like factor (XLF)	*NHEJ1*
T-B-NK- SCID	
Adenosine deaminase	*ADA*
Reticular dysgenesis	*AK2*

SCID – Clinical

- Recurrent severe infections
- Chronic diarrhea
- Failure to thrive
- Thrush
- No discernable lymph nodes
- MMR/Varicella may be fatal

SCID - Diagnosos

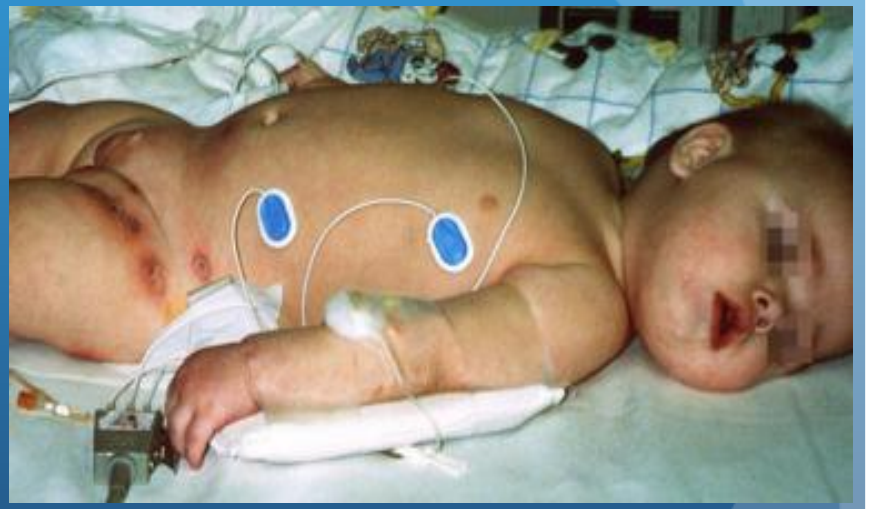
- Very low lymphocyte counts (<2000), especially T cells
- Hypogammaglobulinemia often found but not required
- Genetic testing

SCID - Treatment

- Hematopoietic stem cell transplant may be curative if given early enough
- HCT given in first 3.5 months increased survival compared to given after (94% vs 70%)
- 5 year survival if given in first 3.5 months 94%
- Gene therapy for X-linked and *ADA*, promising

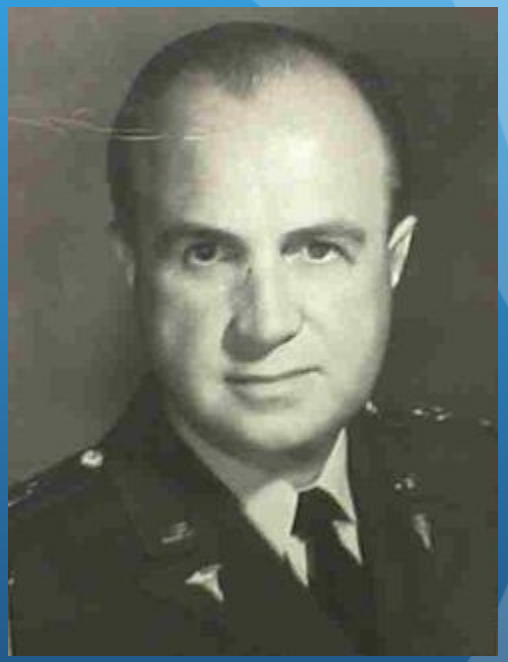
Case 2

- 12 month old male recurrent otitis
- Chronic high fevers
- Pseudomonas cellulitis
- CBC shows total lymphocytes 600/ microl



XLA

- Mutation in *BTK* gene, named after Colonel Ogden Bruton, described in 1952 as X-linked
- 1 in 190,000 male births
- Bruton Tyrosine Kinase is signal transduction molecule, promotes pre-B cell expansion



XLA - Clinical

- Recurrent bacterial infections, otitis, pneumonia, cellulitis
- Sepsis
- Recurrent enteroviral infections
- 50% develop symptoms by first year of age
- Maternal antibodies protect for the first few months of life
- Absence of tonsils (B-cell rich) is hallmark

XLA - Diagnosis

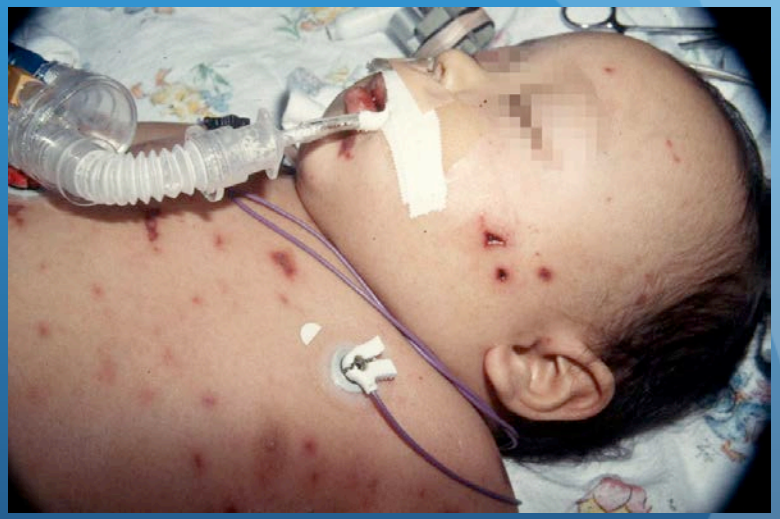
- Reduction in CD19+ B cells and all classes of antibodies (IgG/IgA/IgM)
- Deficient antibodies to all vaccines
- Gene defect in *BTK*

XLA - Treatment

- IV or SC replacement of IgG (IgM and IgA replacement not available)
- Substantial reduction in infections and hospitalizations
- Chronic antibiotics
- Very good life expectancy

Case 3

- 10 month old male with disseminated Neisseria infection
- 2 months prior had episode of Strep pneumonia
- Normal CBC w/diff
- Low CH50



Complement Deficiencies

Complement Deficiencies and Disease Alternative Pathway

Pathway/Component	Disease	Mechanism
Factors B or D	Susceptibility to pyogenic (pus-forming) bacterial infections	Lack of sufficient opsonization of bacteria
C3	Susceptibility to bacterial infections	Lack of opsonization and inability to utilize the membrane attack pathway
C5, C6, C7 C8, or C9	Susceptibility to Gram-negative infections	Inability to attack the outer membrane of Gram-negative bacteria

Complement - Clinical

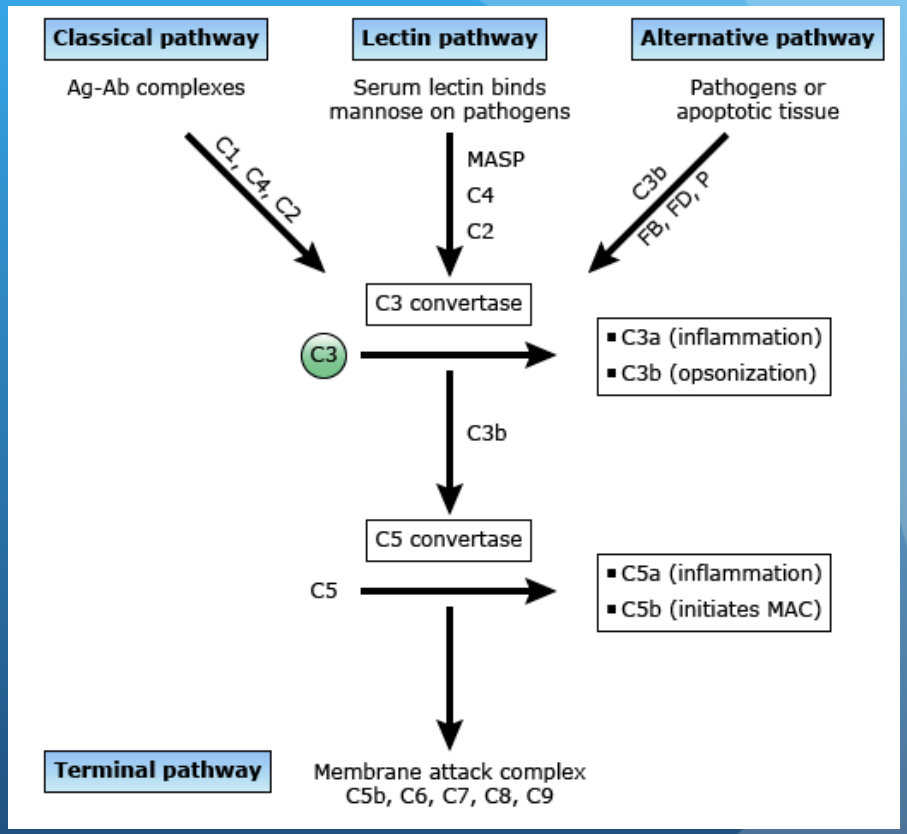
- C1 – SLE
- C4 – SLE
- C2 – pyogenic infections with encapsulated bacteria
- C3 – severe recurrent infections with encapsulated bacteria shortly after birth
- C5-C9 – recurrent Neisseria infections

Complement - Diagnosis

- CH50 – Total hemolytic component (represent C1-C9)
- If low, measure specific components
- Recurrent pneumococcus, measure C3
- Recurrent Neisseria, measure C5-C9
  - C6 African American
  - C9 Asian
  - Autosomal recessive

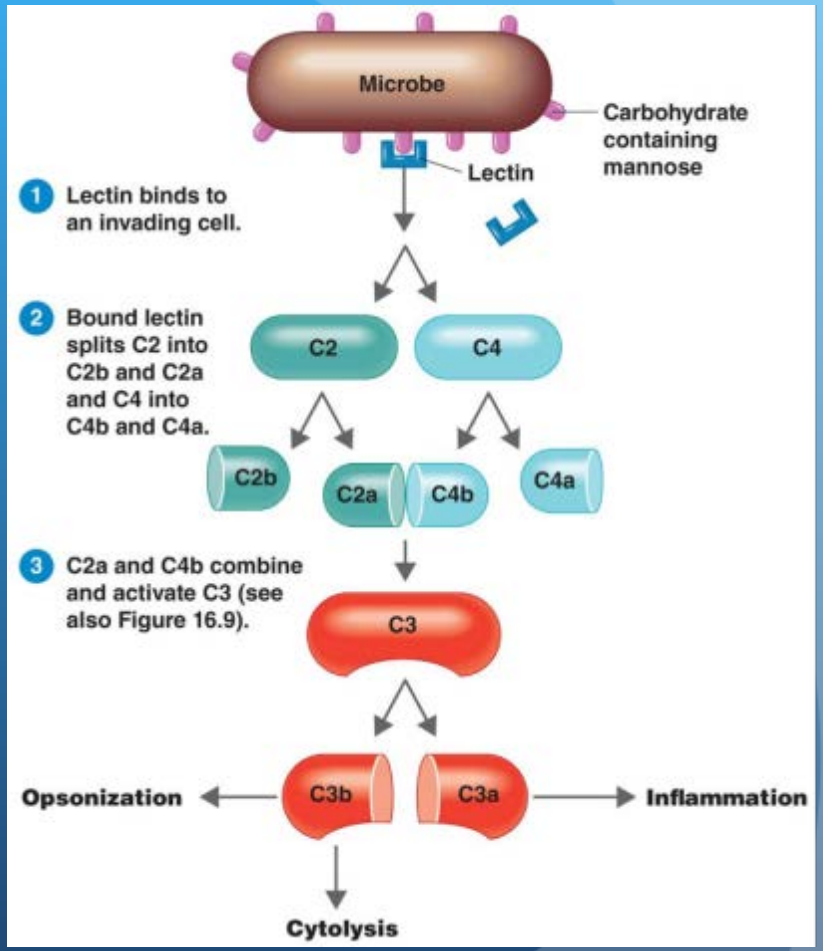
Complement - Alternative

- Very rare
- Properdin
  - Neisseria Meningitis
  - High mortality
- Factor D
  - <5 cases
  - Meningococcal sepsis
- Factor B
  - 1 case, severe pneumococcus



Mannose Binding Lectin (MBL)

- MBL < 500 ng/ml
- Does not correlate with disorder
- Low levels in healthy individuals
- Pneumococcal disease
- Treat infections

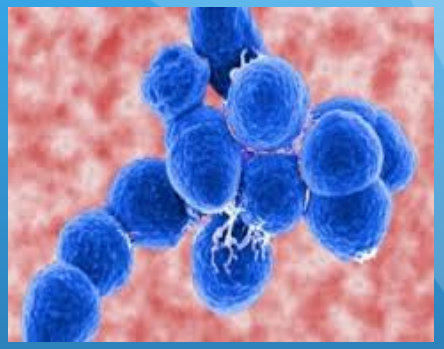


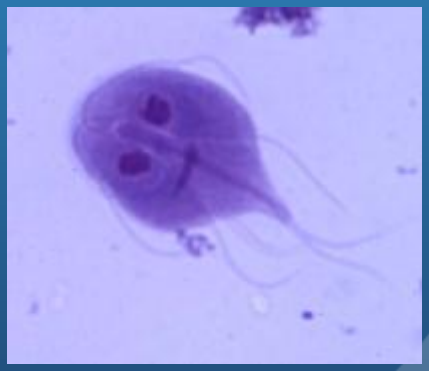
Complement - Treatment

- Pneumococcus and Meningococcus vaccines
- In theory, plasma infusions
  - Rarely done
  - Risk of antibody formation to missing component
  - Risk of bloodborne illness
  - Need for frequent infusions

Case 4

- 8 year old girl 3 years of sinusitis, 3 times a year
  - Pneumococcus cultured on several occasions
- Episode of Giardia when she was younger
- Type 1 Diabetes





IgA Deficiency

- 1 in 600 people, low IgA or deficient
- Most people asymptomatic and no workup is needed
- Primary found in respiratory and gastrointestinal mucosa
- Patients that are symptomatic, recurrent sinopulmonary infections
- Precise defect and inheritance pattern unknown

IgA Deficiency

- Not a lot of GI infections because IgM, but Giardia more common
- 20-30% have autoimmune disorders
  - Graves
  - Type 1 Diabetes
  - Rheumatoid Arthritis
  - ITP
  - Thought to be from compromise of negative selection

IgA Deficiency - Diagnosis

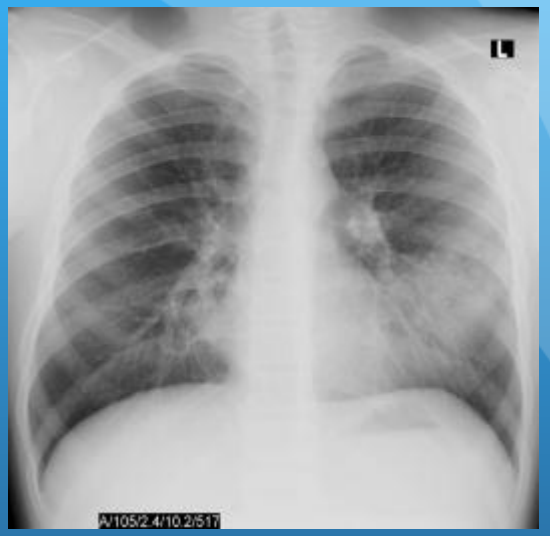
- Low or absent serum IgA, with normal IgG
- Recurrent sinopulmonary infections
- Impaired antibody response: pneumococcus, measles, Hib, diphtheria, etc.

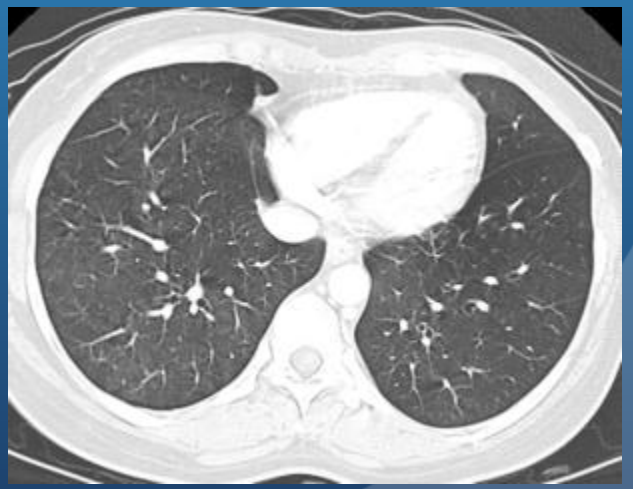
IgA Deficiency - Management

- Treat infections – if frequent, prophylactic antibiotics
- IVIG
  - Only if evidence of lack of antibody response
  - Does not replete IgA, but provides passive specific IgG antibodies
- Rule out meds
  - Cyclosporine, anticonvulsants, captopril, gold, thyroxine, sulfasalazine

Case 5

- 33 year old female presents with fever, chills, productive cough
- Found to have pneumonia
- Further history shows sinusitis 3-4 times a year
- CT for chronic cough shows bronchiectasis





Case 5

- Labs showed CBC with normal WBC, HgB, Plt, but decreased lymphocyte count
- IgG/IgA/IgM checked
  - All lower than detectable limits
- Antibody studies show lack of titers to most vaccines (measles, varicella, tetanus, diphtheria, pneumococcus)
- Low CD 19+ B-cells, normal T cells

CVID

- Common variable immune deficiency
- Primary immune disorder where impaired B cell differentiation leads to impaired antibody production
- Heterogeneous clinical disorders
- Adults and children, 1:25,000-1:50,000
- Recurrent sinupulmonary infections

CVID - Diagnosis

- Low IgG AND low IgA and/or IgM
- Absent antibody response to most or all vaccines (pneumococcus, measle, varicella, tetanus, Hib, diphtheria, etc)
- T & B lymphocytes may be low or normal
- No specific genetic defect has been identified
  - Several gene defects associated, but none diagnostic of disease

CVID - Clinical

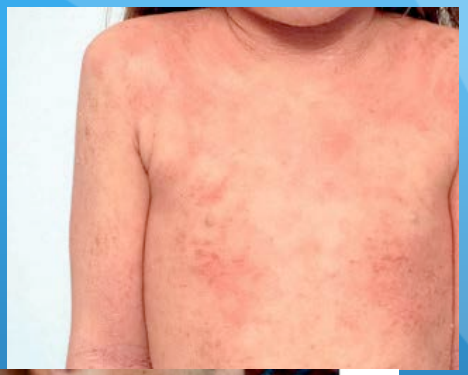
- Whole host of comorbidities
  - Autoimmune
    - ITP, AIHA, RA-like, biliary cirrhosis
  - Chronic lung disease (20%)
    - Chronic bronchiectasis
    - Granulomatous lung disease
  - Increased risk of malignancy
    - NHL (8%)
  - Gastrointestinal
    - Malabsorption

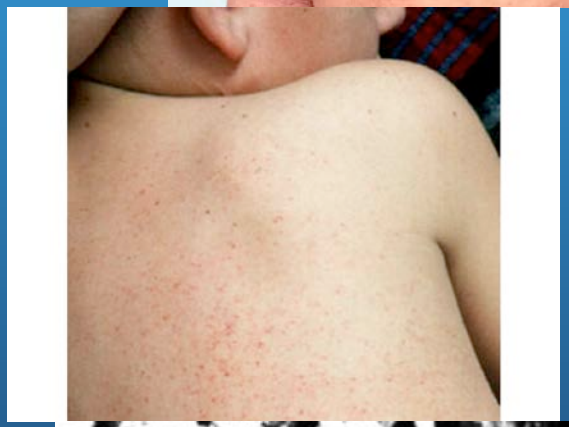
CVID - Treatment

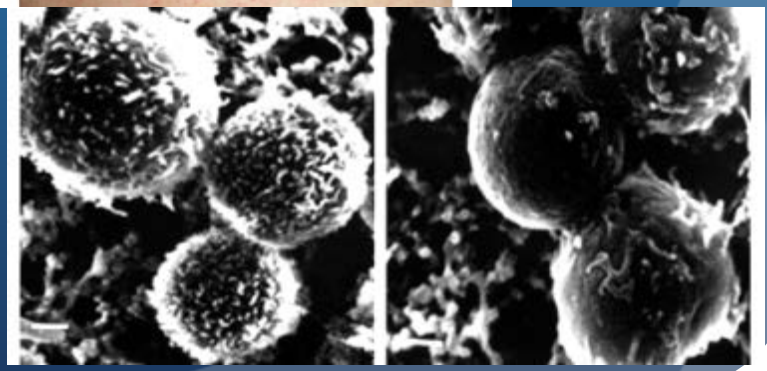
- IV – Q4weeks, IV
  - More side effects
  - Nursing required
- SC – Q1week, SC
  - Less side effects
  - More frequent
- SC – Q3-4weeks, SC
  - Hyqvia
  - More volume
  - Single site

Case 6

- 6 year-old boy, long standing eczema
- Further history reveals ITP at age 2
- Has had a few episodes of otitis
- Normal CBC
- Elevated IgA, normal IgG and IgM







Wiskott-Aldrich Syndrome (WAS)

- Rare X-linked disorder, 1:100,000
- Defect in the *WASp* gene
  - Crucial role in actin cytoskeleton remodeling
  - Impacts site of interaction between T cells and APCs
- Eczema
- Thrombocytopenia
- Sinopulmonary infections (Bacterial and viral)
- Autoimmune – AIHA, neutropenia, vasculitis

WAS - Diagnosis

- Mutation in *WASp* gene
- High IgA and IgE, normal IgG and IgM
- Decreased T cell number and function
- Lymphocytes devoid of microvillus projections
- Platelet count 20,000-50,000

WAS - Treatment

- Prophylactic Bactrim, Acyclovir for very low T cell counts
- IVIG if evidence of antibody deficiency
- Stem cell transplant can be curative
- Gene therapy promising

Question #1

18 yo college sophomore is following up with you after hospitalization 2 weeks ago for meningococcal meningitis. HIV antibody was negative. He had an episode of meningococcal meningitis last year after starting school when an outbreak went through his dorm. He received the meningococcal vaccination when he was 15. He is otherwise healthy, and takes no medications. Physical exam today is unremarkable.

Which of the following is most likely to establish a diagnosis?

A: CH50 (total hemolytic complement level)

B: Meningococcal titers

C: Lymphocyte panel

D: IgG, IgM, IgA

Question #2

24 yo following up with you after an episode of pneumonia 6 weeks ago. She received the pneumococcal vaccine 5 years ago. She tells you that she gets 3-4 sinus infections every year. She also has a chronic productive cough that has never been worked up. Physical exam reveals bibasilar crackles. Review of her hospital chart indicates that HIV antibody is negative.

Which of the following is the most likely diagnosis?

A: Complement deficiency

B: Selective IgA deficiency

C: CVID

D: XLA

Question #3

30 yo male comes to you after gastroenterologist found absent serum IgA for workup of celiac disease. Patient denies any severe or recurrent infections. IgG, IgM and IgG subclasses are normal. Antibody studies to all vaccines are normal.

What is the next step in treatment?

A: Initiate IVIG therapy

B: Prophylactic antibiotics

C: Revaccinate with pneumococcus and meningococcus

D: Careful observation

Thank You and Good Luck