IMMUNODEFICIENCY: WORK UP AND WHEN TO REFER TO AN ACADEMIC CENTER

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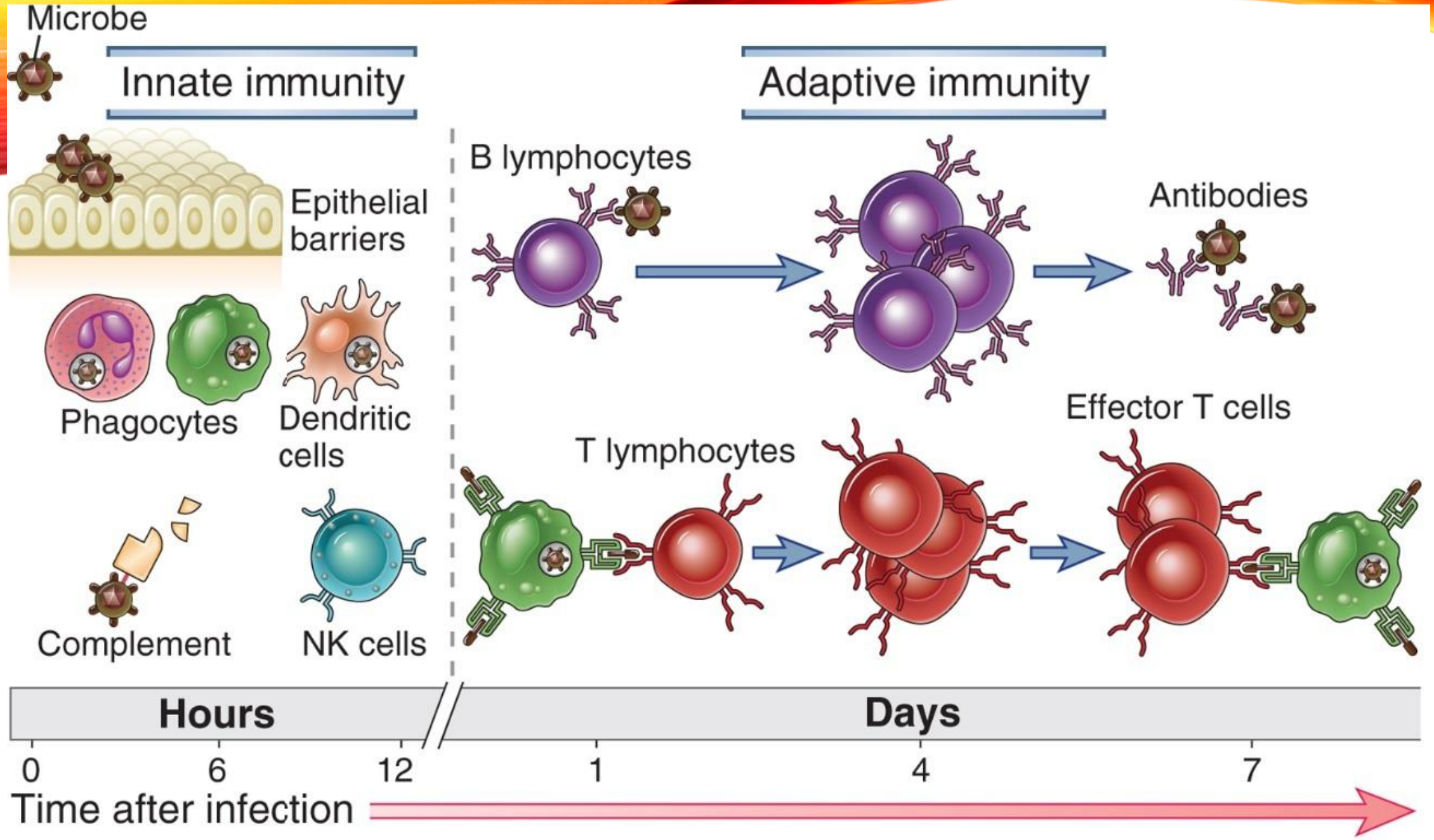
Sep 22, 2024

- I have no relevant disclosures

OVERVIEW

- Basic review of the immune system
- When to consider an immune deficiency
- Basic Evaluation
- Selected Conditions



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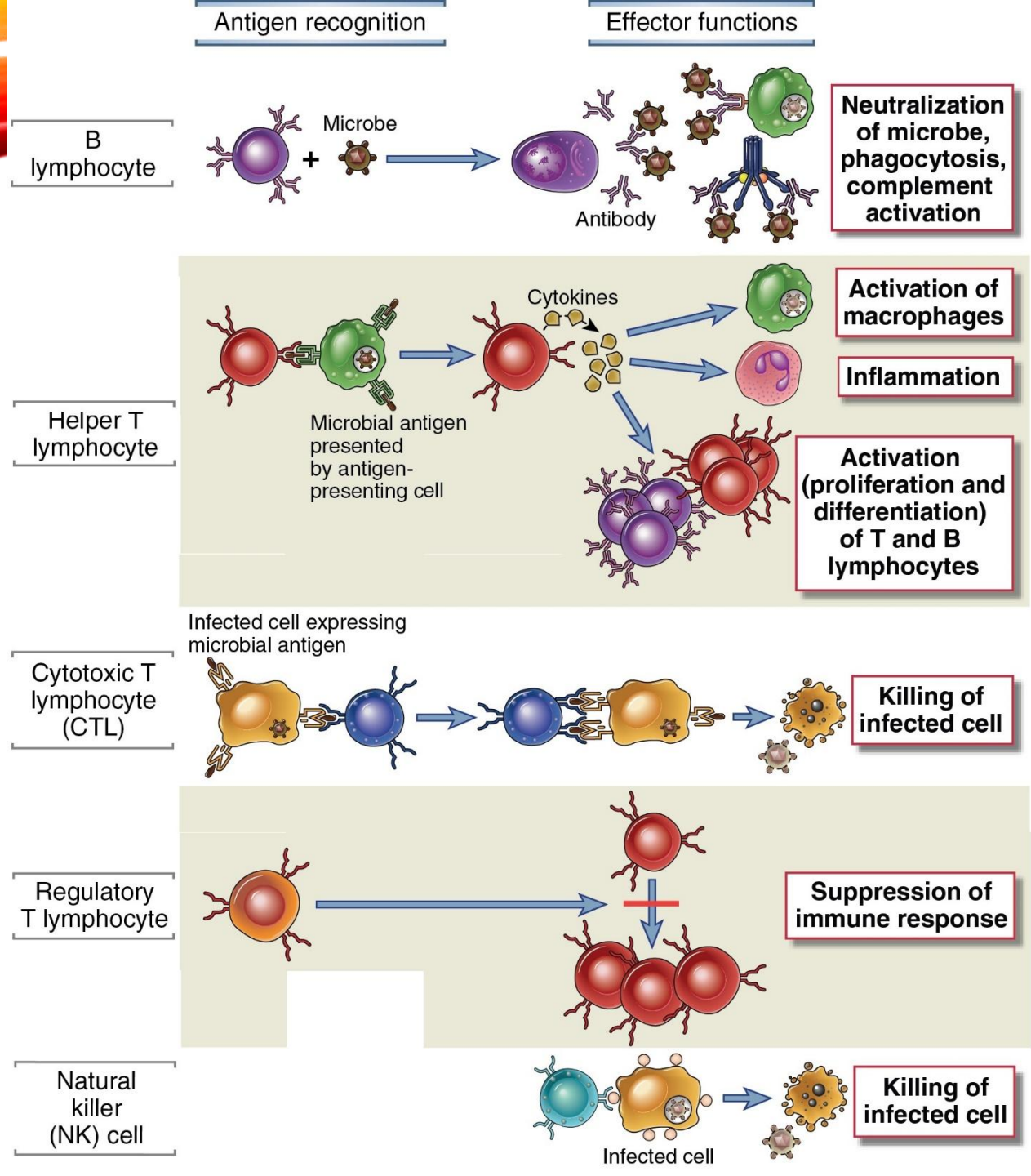

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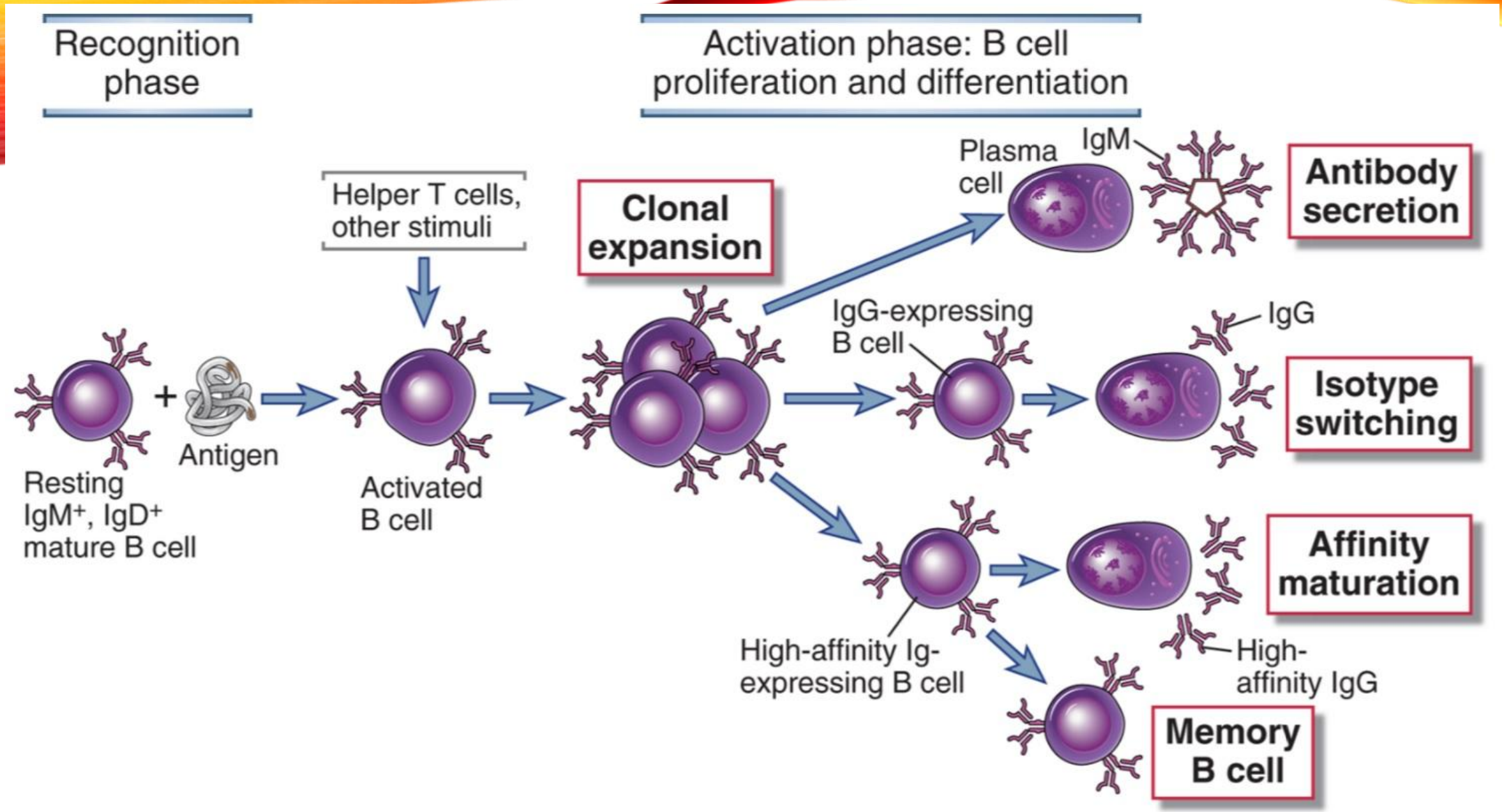

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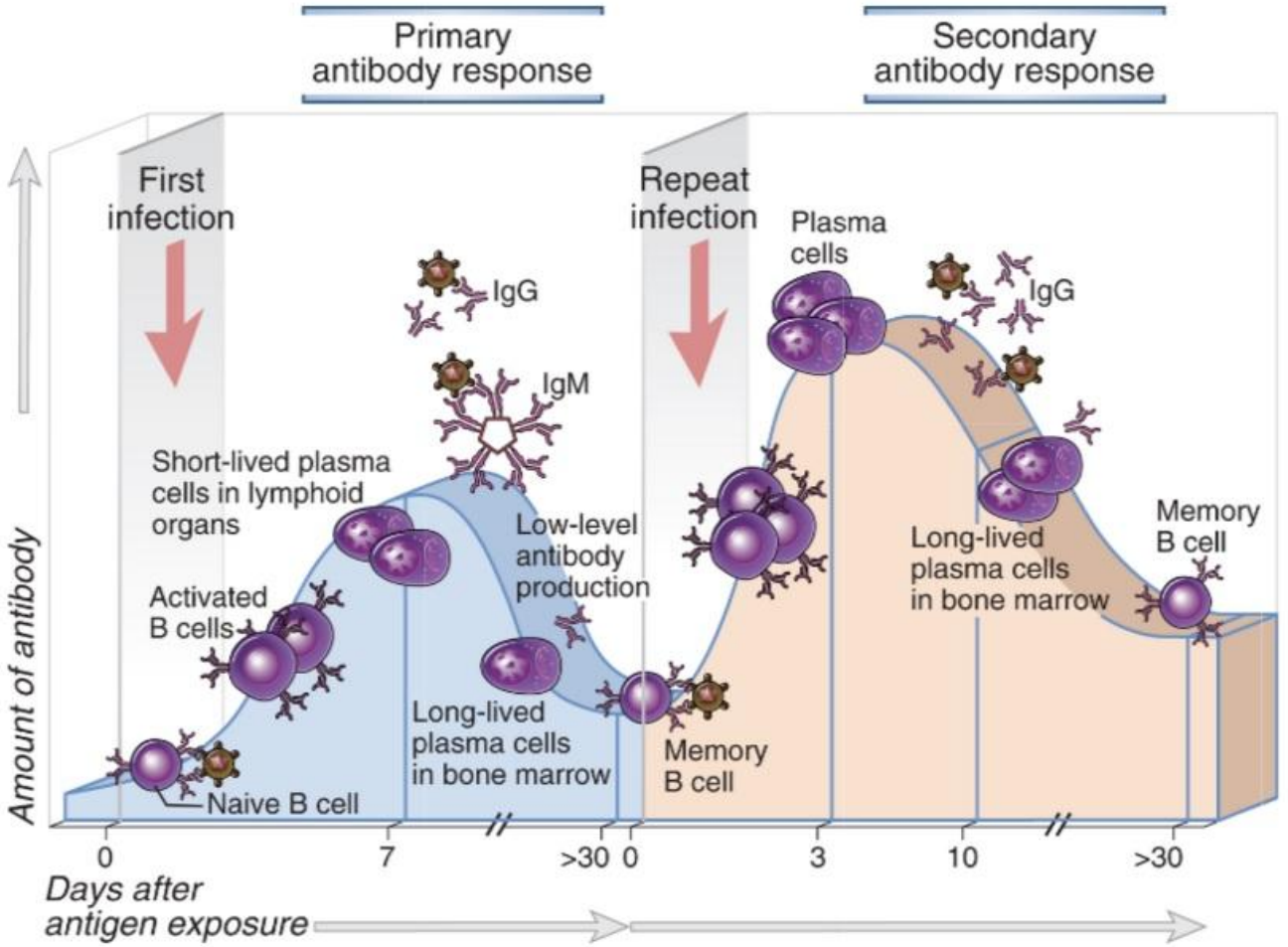

Feature	Primary response	Secondary response
Peak response	Smaller	Larger
Antibody isotype	Usually IgM > IgG	Relative increase in IgG and, under certain situations, in IgA or IgE
Antibody affinity	Lower average affinity, more variable	Higher average affinity (affinity maturation)
Induced by	All immunogens	Only protein antigens

Abbas AK, et al. Cellular and Molecular Immunology, 7th ed.

10 Warning Signs of Primary Immunodeficiency

Jeffrey Modell Foundation

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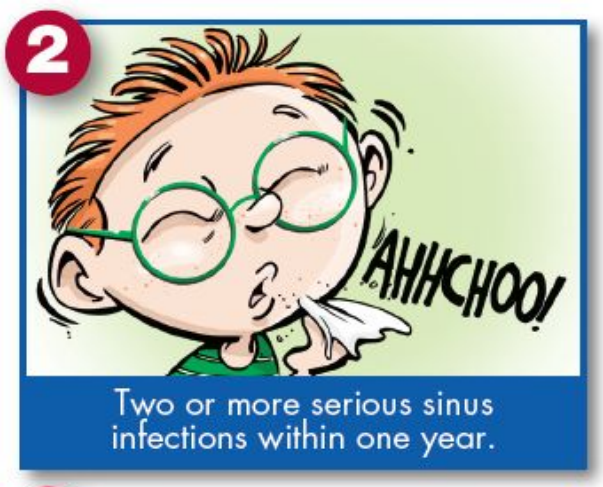
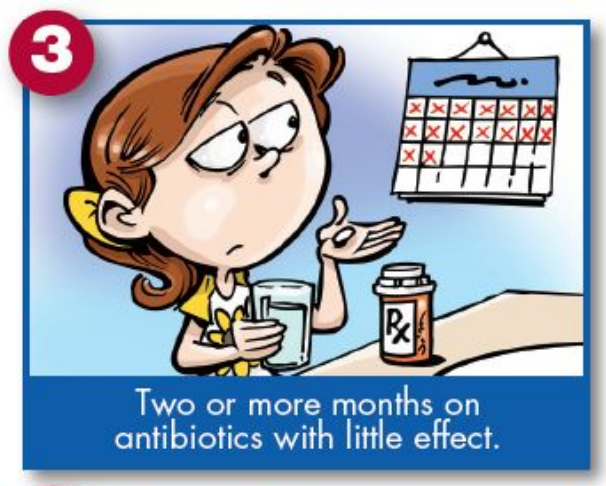
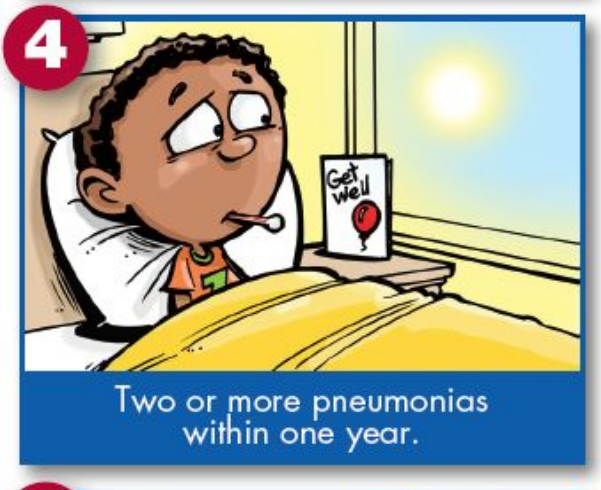
Four or more new ear infections within one year.



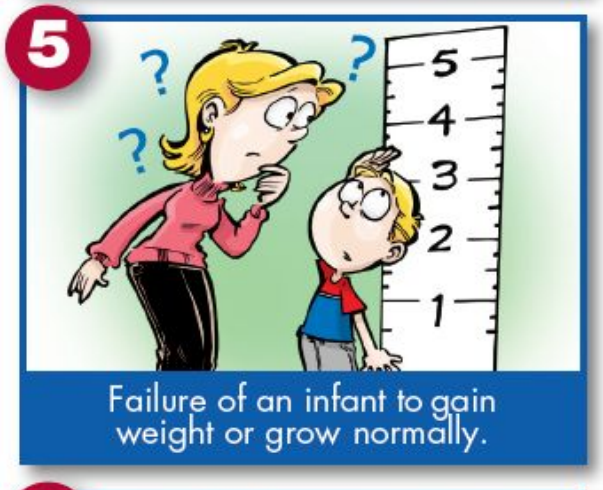
Two or more serious sinus infections within one year.



Two or more months on antibiotics with little effect.



Two or more pneumonias within one year.

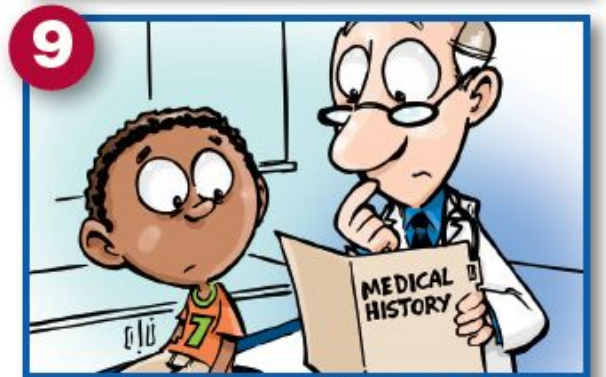


Failure of an infant to gain weight or grow normally.

Recurrent, deep skin or organ abscesses.

Persistent thrush in mouth or fungal infection on skin.

Need for intravenous antibiotics to clear infections.



Two or more deep-seated infections including septicemia.

A family history of PI.

10 FOR ADULTS Warning Signs of Primary Immunodeficiency

1. Two or more new ear infections within 1 year.
2. Two or more new sinus infections within 1 year, in the absence of allergy.
3. One pneumonia per year for more than 1 year.
4. Chronic diarrhea with weight loss.
5. Recurrent viral infections (colds, herpes, warts, condyloma).
6. Recurrent need for intravenous antibiotics to clear infections.
7. Recurrent, deep abscesses of the skin or internal organs.
8. Persistent thrush or fungal infection on skin or elsewhere.
9. Infection with normally harmless tuberculosis-like bacteria.
10. A family history of PI.

Immune defect	Infections
Immunoglobulins and/or complement	Sinopulmonary infections, gastrointestinal infections, bacteremia, meningitis -*S. pneumoniae*, *H. influenzae*, and *N. meningitidis* -*Giardia*, *Cryptosporidia*, and *Campylobacter*.
Neutrophil	Invasive skin and soft tissue infections, especially abscesses. -*S. aureus*, gram-negative bacilli, *Aspergillus*, *Nocardia*
T-cells	Viruses, fungi, opportunistic infections. -CMV, EBV, HSV, myobacteria, fungi
Dysregulation	Autoimmune manifestations Combined/mixed defects

LABORATORY EVALUATION OF IMMUNE SYSTEM

The following are labs that are generally readily available at commercial lab centers

This is not a comprehensive list of all available laboratory tests

BASIC EVALUATION OF INNATE IMMUNE SYSTEM

CBC with differential	Neutrophils, Eosinophils, Monocytes, Basophils	May need to check more than once
CH50	Tests C1 to C9	Homozygous deficiency will cause undetectable CH50. Heat labile. Can be falsely low if left at room temperature Elevated CH50 has no specific clinical meaning.

ADDITIONAL TESTS OF INNATE IMMUNE SYSTEM

Dihydrorhodamine 123 test	NADPH oxidase	Chronic granulomatous disease
AH50	Factor B, Factor D, Properdin	Rare

BASIC EVALUATION OF THE ADAPTIVE IMMUNE SYSTEM

Immunoglobulins	IgG, IgA, IgM, IgE	
Flow Cytometry	CD 3/4/8/19/56	T cells, B cells, NK cells
Tetanus and Diphtheria antibody levels	Protein-based vaccine	Also called anti-toxoid antibodies
Pneumococcal Antibody levels	Protein and polysaccharide-based vaccines available	Can be complicated to interpret
HIV		Rule out acquired immune deficiency

ADDITIONAL TESTS OF ADAPTIVE IMMUNE SYSTEM

Lymphocyte proliferation	Mitogen and antigen panels	Mitogens nonspecifically stimulate lymphocyte proliferation. Antigens (candida, etc) can evaluate memory in cell-mediated immunity
IgG subclasses	IgG 1, 2, 3, 4	Isolated deficiencies may not be clinical meaningful
Genetic tests	Multiple small and large panels available	Can test genes involved in innate and adaptive immunity +/- insurance coverage

- For most low suspicion evaluations I obtain:

- CBC with differential
- IgG, IgA, and IgM
- Often with IgE as part of a respiratory allergy panel for allergy contribution to sinusitis or asthma exacerbations

SELECTED CONDITIONS

SEVERE COMBINED IMMUNODEFICIENCY (SCID)

- About 1 in 60,000 births
- Caused by gene defects impairing T cell development or function
  - May also directly impair B cells or NK cells
  - Any severe T cell defect precludes effective B cell activity
- Previously classified as T-B+NK+, T-B+NK-, T-B-NK+, or T-B-NK-
- Now preferentially classified by the specific gene defect

SCID PRESENTATION

- Appear healthy in their first months, partly protected by maternal antibodies.
- Symptoms of infections, diarrhea, failure to thrive
- Without treatment, most will die by 2 years of age

- If treated BEFORE any serious infections, long term survival is 90%
- Stem cell transplant is the most common definitive treatment
- Newborn screening is now available in all 50 states, although some uncommon cases can be missed
- Most infants identified by newborn screening are well appearing

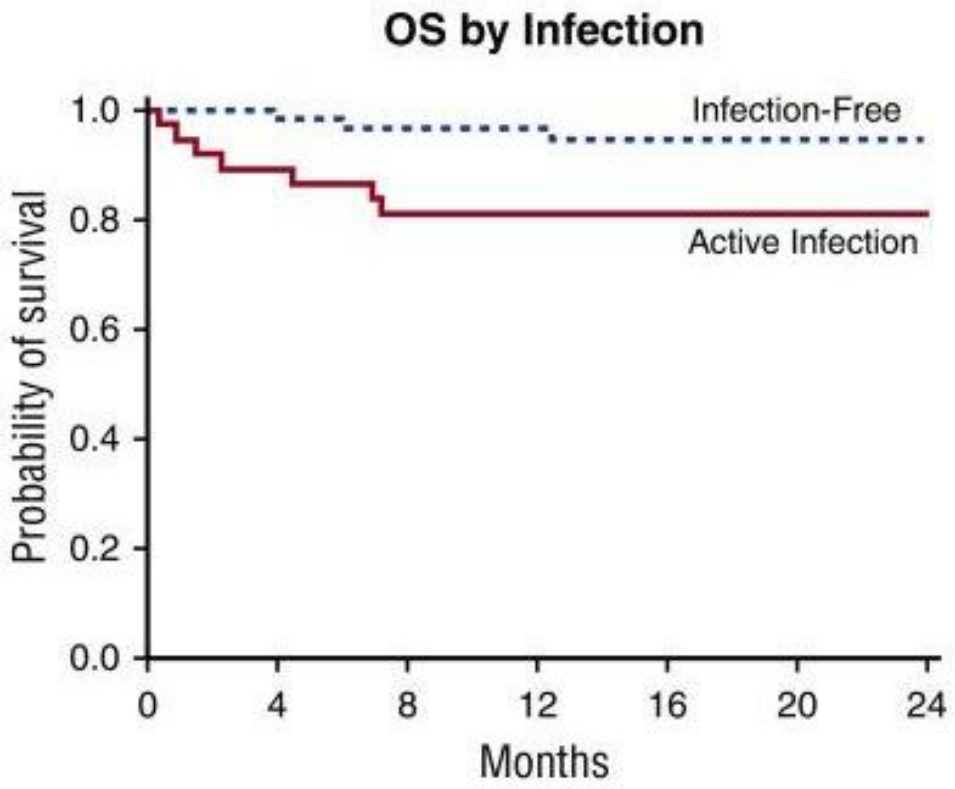
SCID NEWBORN SCREENING

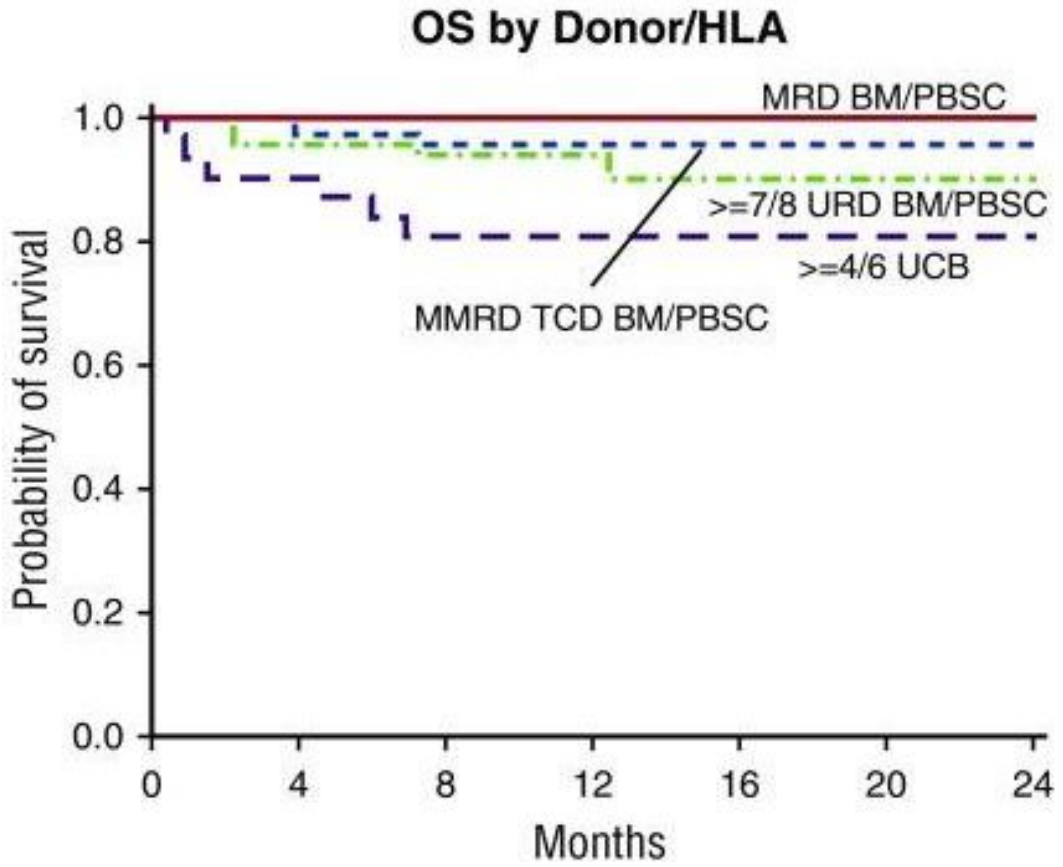
2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Wisconsin	Massachusetts	California	Delaware	Colorado	Minnesota	Guam	Arkansas	Alaska	Arizona	Nevada
		New York	Michigan	Connecticut	Ohio	Illinois	Hawaii	Georgia	Kansas	Alabama
				Florida	Pennsylvania	Iowa	Montana	Idaho	Missouri	Indiana
				Mississippi	Utah	Maine	New Hampshire	Kentucky	North Carolina	Louisiana
				Navajo Nation		Nebraska	Oklahoma	Maryland		
				Texas		New Jersey	Puerto Rico	North Dakota		
				Wyoming		New Mexico	South Carolina	Tennessee		
						Oregon	South Dakota	Vermont		
						Rhode Island	Virginia			
						Washington				
						Washington, D.C.				
						West Virginia				

Immune Deficiency Foundation

ABNORMAL NEWBORN SCID SCREEN

- Blood from a heel-stick is used to screen for multiple conditions
- TRECs reflect the number of T-cells in the blood
- Roughly half of low TRECs on initial screen are confirmed to have T-cell deficiency
- Most other cases have an alternate identifiable cause (prematurity, 22q11.2 deletion syndrome, ataxia-telangiectasia, trisomy 21, etc)
- **ALL patients** with abnormal screen, or other suspicion for SCID, should be referred to a center capable of further evaluation and stem cell transplant





Blood. 2017 Dec 21; 130(25): 2718–2727. doi: 10.1182/blood-2017-05-781849

SELECTIVE IGA DEFICIENCY

- 30 yo woman referred for undetectable IgA on a panel testing for celiac disease.
- Has frequent abdominal pain/bloating. Normal colonoscopy.
- 1 or 2 sinus infections per year, most resolve without antibiotics
- Normal IgG, IgM, IgE, CBC w/diff, Flow cytometry. IgA undetectable.

IMMUNOGLOBULINS			
IMMUNOGLOBULIN A		**<5 L**	47-310 mg/dL
IMMUNOGLOBULIN G	1145		600-1640 mg/dL
IMMUNOGLOBULIN M	135		50-300 mg/dL

SELECTIVE IGA DEFICIENCY

- Absent IgA with normal IgG and IgM, without identifiable cause
- Is the most common primary immune deficiency (about 1 in 400)
- Majority of patients are ASYMPTOMATIC
- Some have sinus or GI infections, autoimmune conditions, allergic conditions

SELECTIVE IGA DEFICIENCY

- In general, no specific treatment is needed
- Receive all routine vaccinations, except caution with live vaccines
- Treat concurrent conditions (rhinosinusitis, allergies, etc.)
- For those with continued infections, prophylactic antibiotics can be considered
- Immunoglobulin replacement is NOT indicated in most patients.
  - IVIG or SCIG does not replete IgA

NEW CASE:

- A man in his 60s with frequent sinusitis over the past year.
- Multiple courses of oral steroids and antibiotics
- Sinus CT showed prior surgery and multiple areas of mucosal thickening.
  - Frothy secretions and air-fluid level during acute episode
- Allergy skin and blood testing with slight positives to a few pollens

- CBC with differential is normal. Total IgE 72.

IMMUNOGLOBULINS			
IMMUNOGLOBULIN A	247		70-320 mg/dL
IMMUNOGLOBULIN G		**492 L**	600-1540 mg/dL
IMMUNOGLOBULIN M		**44 L**	50-300 mg/dL

- Repeat IgG/A/M similar. (Low IgG, low IgM)
- SPEP normal except hypogammaglobulinemia. UPEP normal.
- IgG subclasses 1, 2, and 3 all low.
- Flow cytometry with normal T/B cells
- Tetanus and Diphtheria antibody levels protective

Serotype	Titer
1	<0.3
2	<0.3
3	<0.3
4	<0.3
5	0.7
8	<0.3
9 (9N)	<0.3
12 (12F)	<0.3
14	**1.5**
17 (17F)	<0.3
19 (19F)	0.3
20 (20A)	0.9
22 (22F)	<0.3
23 (23F)	<0.3
26 (6B)	<0.3
34 (10A)	<0.3
43 (11A)	<0.3
51 (7F)	**1.7**
54 (15B)	<0.3
56 (18C)	**2.5**
57 (19A)	<0.3
68 (9V)	<0.3
70 (33F)	0.4

S. PNEUMONIAE TITERS

S. Pneumoniae titers only 3 of 23 >=1.3

Patient receives PPSV23 to check response to a polysaccharide antigen.

Serotype	Pre	Post	Double?
1	<0.3	<0.3	
2	<0.3	0.6	Y
3	<0.3	0.3	
4	<0.3	<0.3	
5	0.7	**14.8**	Y
8	<0.3	**5.9**	Y
9 (9N)	<0.3	<0.3	
12 (12F)	<0.3	0.5	
14	**1.5**	**2.4**	
17 (17F)	<0.3	<0.3	
19 (19F)	0.3	**1.9**	Y
20 (20A)	0.9	**3.4**	Y
22 (22F)	<0.3	<0.3	
23 (23F)	<0.3	<0.3	
26 (6B)	<0.3	**10.2**	Y
34 (10A)	<0.3	<0.3	
43 (11A)	<0.3	0.8	
51 (7F)	**1.7**	**11.3**	Y
54 (15B)	<0.3	<0.3	
56 (18C)	**2.5**	**15.8**	Y
57 (19A)	<0.3	**1.4**	Y
68 (9V)	<0.3	0.4	
70 (33F)	0.4	0.7	

Post vaccine only 9 of 23 >=1.3 (39%)

Post vaccine only 9 doubled (39%)

CASE SUMMARY

- Adult male with recurrent acute on chronic sinusitis
- Low IgG and low IgM
- Poor response to Pneumococcal polysaccharide vaccine

- Diagnosis?
- Common Variable Immunodeficiency

COMMON VARIABLE IMMUNODEFICIENCY

- CVID is the most common SYMPTOMATIC primary immunodeficiency disorder, affecting approximately 1 in 25,000 people.
- Most commonly diagnosed in adults ages 20 to 40 years
- Diagnosis commonly delayed 4 to 8 years.
- Affects men and women roughly equally.

CVID DEFINITION

- **Low IgG** on two occasions >3 weeks apart.
- **Low IgA or IgM**
- **Impaired antibody response** to T-dependent (protein) or T-independent (polysaccharide) antigens.
- **Other causes of hypogammaglobulinemia excluded**

- Clinical manifestation (Infection, autoimmunity, lymphoproliferation)
- Flow cytometry is not required, but may be helpful. Often show low levels of memory B cells (CD27+ B cells) and low isotype switched memory B cells (CD27+, IgD – IgM -).
- Genetic studies are generally not required, but may be helpful in certain cases

DDX HYPOGAMMAGLOBULINEMIA

- **Drug Induced**
  - **Anti-CD20 antibodies** (rituximab, ocrelizumab, ofatumumab, etc)
  - Anti-seizure medications (phenytoin, lamotrigine, carbamazepine, etc)
  - Long term (especially high dose) glucocorticoids
- **Malignancy**
  - Chronic Lymphocytic Leukemia, Lymphoma, Myeloma

- Infections (HIV, congenital Rubella, CMV)
- Protein loss (Nephrotic syndrome, Severe burns, Enteropathies)
- Other specified immune or genetic disorders (SCID, Hyper IgM, Trisomy 21, ataxia telangiectasia,)
- Thymoma with hypogammaglobulinemia (Good Syndrome)

VACCINE RESPONSES

- Ideally test both protein and polysaccharide responses
- Protein vaccines require intact B and T cell function
- Polysaccharide responses require B cell function only.

- Ideally do a pre-vaccine check and again 4 to 8 weeks after vaccination.

- 2 patterns:
  - Fail to respond to polysaccharide vaccine only
  - Fail to respond to both types of vaccines

PROTEIN VACCINE

- Use Tetanus and Diptheria (Td, Tdap, DT, DTap)
- Protective level for diptheria is 0.01 to 0.1 units/mL and tetanus is >0.1 units/mL
- Levels well above these are normal.
- If levels are low or borderline, vaccination should be given and titers re-checked.

PNEUMOCOCCAL POLYSACCHARIDE RESPONSES

- Should not be used in children under 2 years of age
- Pneumococcal polysaccharide vaccine (PPSV23) is the primary vaccine used
- Testing should include a panel of 14 or 23 (preferred) serotypes
- Levels ≥1.3 mcg/mL are considered a normal response

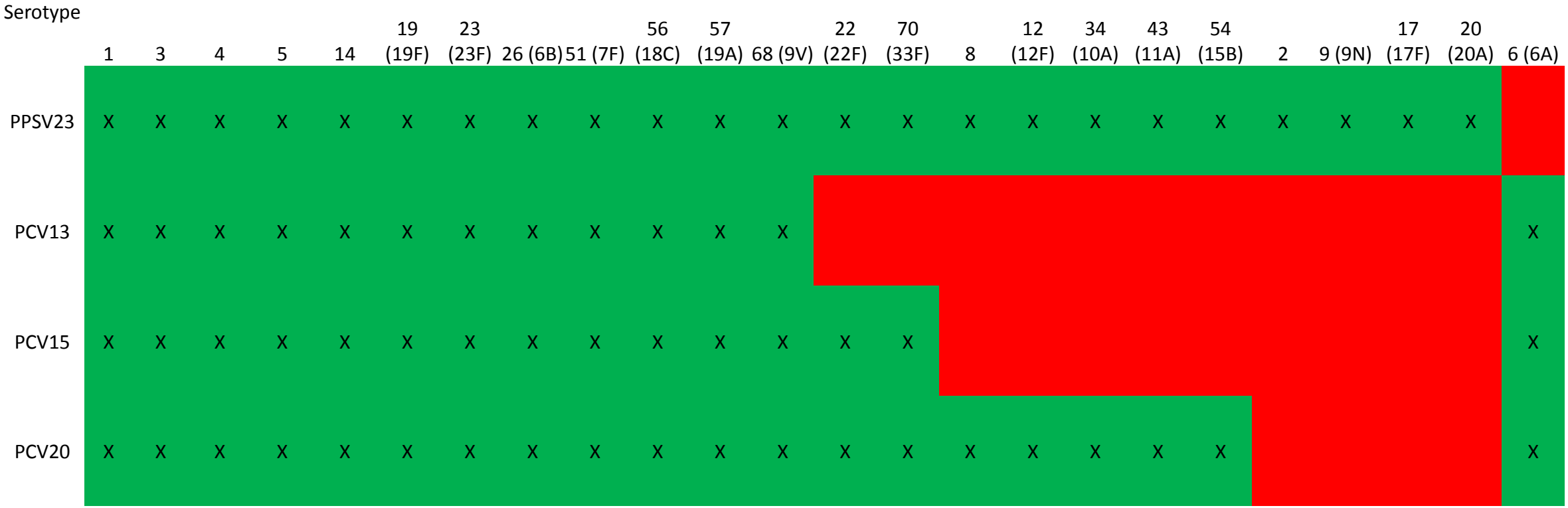
PNEUMOCOCCAL POLYSACCHARIDE RESPONSES

Phenotype	Age 2-6yo	Age >6yo
Mild	>1.3µg/mL >50% of types with 2-fold increase for <50%	>1.3µg/mL >70% of types with 2-fold increase for <70%
Moderate	>1.3µg/mL for <50% of types	>1.3µg/mL for <70% of types*
Severe	>1.3µg/mL for ≤ 2 serotypes	
Memory	Loss of response within 6 months	

J Allergy Clin Immunol. 2015 Nov;136(5):1186-1205

- The increasing use of protein-conjugate pneumococcal vaccines complicates interpretation
- Patients who have previously received a conjugated pneumococcal vaccine should generally have those titers excluded when assessing the polysaccharide antigen response

PNEUMOCOCCAL SEROTYPES IN VACCINES



CVID TREATMENT

- Immunoglobulin replacement: IV or SC
- 400 to 600mg/kg every 4 weeks
- Reduces number of infections, antibiotics, and hospitalizations
- Check trough IgG every 3 to 6 months and monitor clinically

- Some patients may need prophylactic antibiotics
- Should still get most non-live vaccines

- Multi-specialty care for comorbidities: bronchiectasis, cytopenia, etc.
  - Consider chest CT at time of diagnosis

SPECIFIC ANTIBODY DEFICIENCY

- Inadequate response to polysaccharide based vaccine.
- Normal response to protein vaccine.
- Normal immunoglobulins
- No other confirmed immune system abnormality
  - If IgG 2 subclass deficiency, some prefer to use that diagnosis

- Patients typically have recurrent/severe sinopulmonary infections

SPECIFIC ANTIBODY DEFICIENCY TREATMENT

Most patients

- Immunize with protein/conjugate vaccines (PCV20)
- Treat any concurrent disorders (asthma, allergic rhinitis, etc)
- Increased vigilance to treat infections

Some patients:

- Prophylactic antibiotics
- Immunoglobulin infusions (IVIG, SCIG)

IGG SUBCLASS DEFICIENCY

- Is a somewhat controversial diagnosis
- Have low levels of an IgG subclass with normal total IgG
- Most individuals missing an IgG subclass are asymptomatic
- If symptomatic, usually sinopulmonary infections
- IgG2 deficiency often clusters with IgA and IgG4 deficiency.

- Generally requires failure to respond to a polysaccharide vaccine (ie, PPSV23) to be clinically significant.
- Treatment is similar to Specific Antibody Deficiency

CASES THAT MAY NOT NEED REFERRAL TO ACADEMIC CENTER

- Selective IgA deficiency

- Specific Antibody Deficiency / IgG subclass deficiency
  - If you can do pre/post vaccine testing
- Common Variable Immunodeficiency
  - If you can do pre/post vaccine testing
  - Order SCIG or IVIG (home administration or at infusion center)
  - Subspecialty consultation for pertinent conditions

WHEN TO REFER TO ACADEMIC CENTER

- All cases of SCID or suspected SCID
  - Early treatment saves lives
- Most young children with confirmed or suspected immune deficiency
  - May need frequent blood draws or specialized tests
- Any condition you don't feel comfortable managing
  - Even if you are doing everything right, a second opinion can be valuable
  - If you have never seen the condition before, it's probably worth a referral.
  - Referring a patient out does not mean you have to stop treating them.

GREAT RESOURCES

- Immune Deficiency Foundation - https://primaryimmune.org/
  - Resources for providers and patients
- Jeffrey Modell Foundation - https://info4pi.org/
  - Educational materials and posters in multiple languages
- Joint Task Force Allergy Immunology Practice Parameters
  - https://www.allergyparameters.org/