Immunodeficiency: Recognizing Subtle Signs, Diagnosis & Referral

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Disclosures

- Nothing relevant to this presentation
- Some of these slides were derived from information in the AAAAI teaching slide set

Topics for discussion

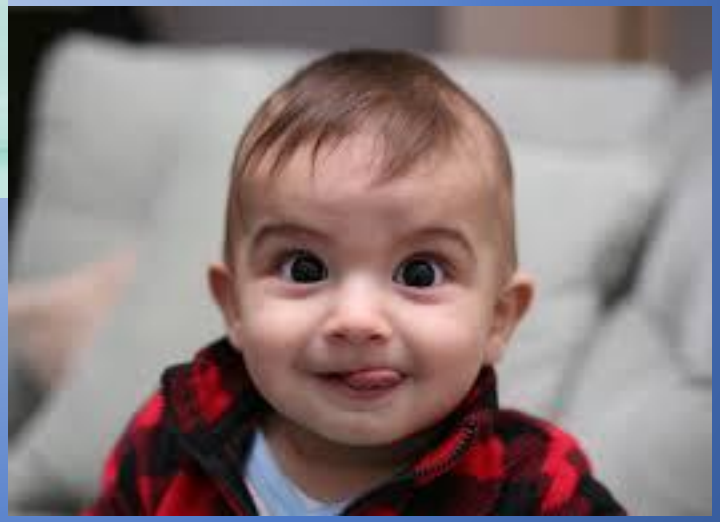
- What does immune deficiency look like?
- How does the immune system work?
- What happens when it doesn't?
- What are the warning signs of immune deficiency?
- How can you screen for immune problems?
- Who should you screen?
- Cases if we have time

Which one has immune deficiency?

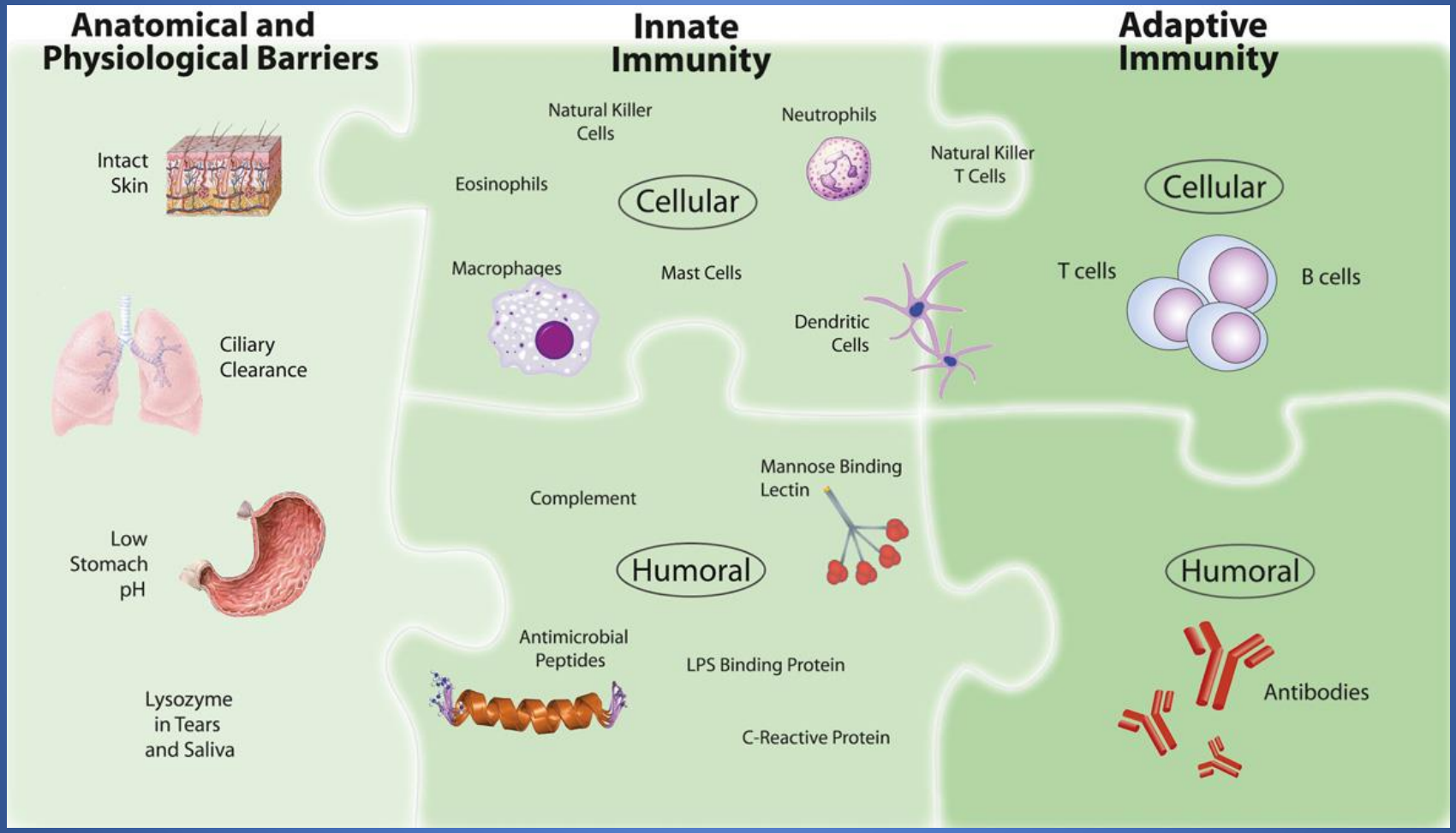
Which one has immune deficiency?

Which one has immune deficiency?

Which one has immune deficiency?

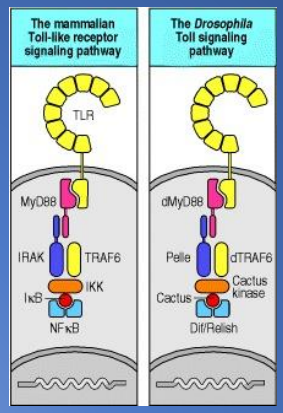


Immune System Components



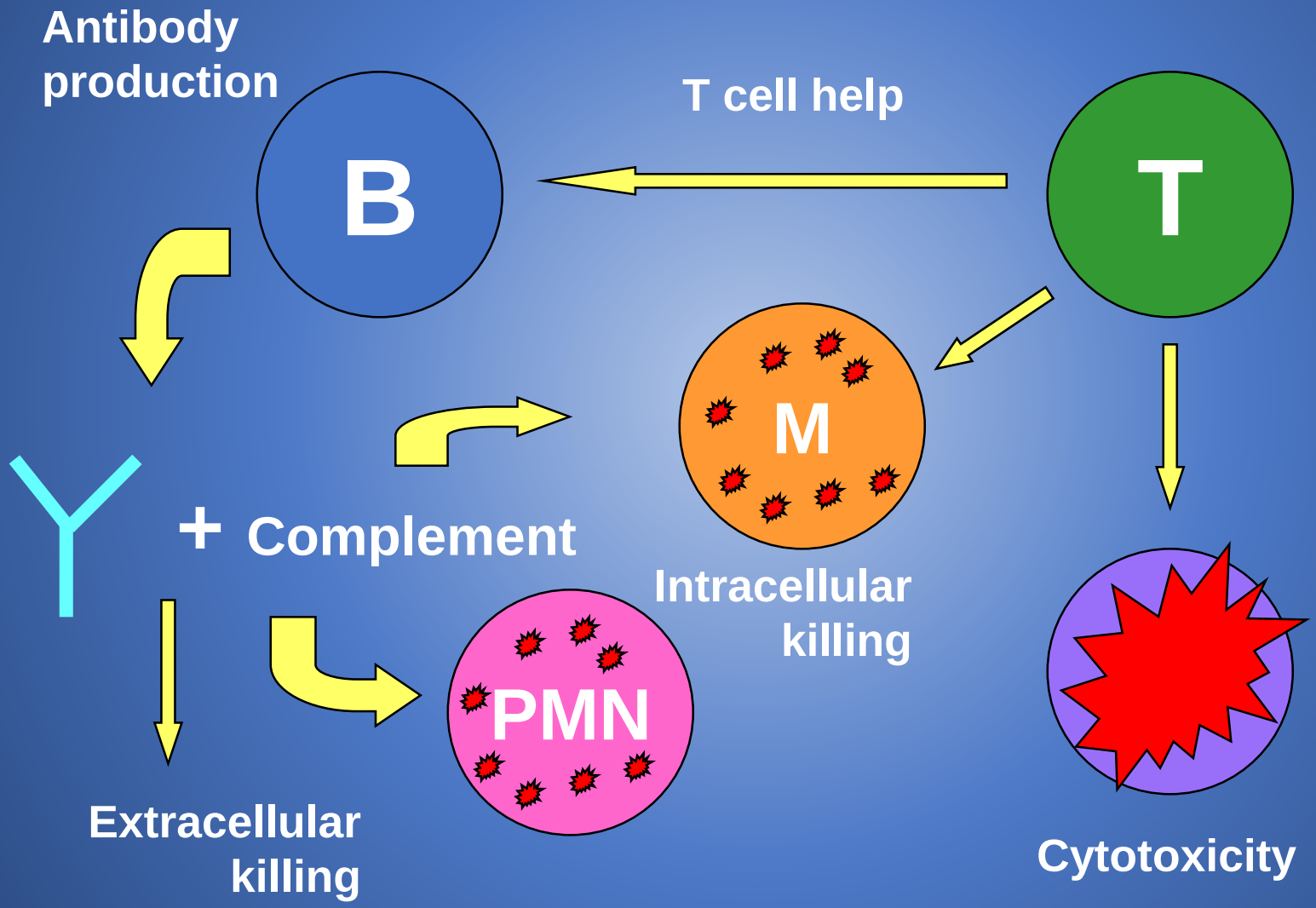
Turvey SE, Broide DH. J Allergy Clin Immunol 2010;125:S24-32.

The Immune System



1. Innate
   - Present from birth
   - Specificity is “pre-programmed”
   - Includes “non-immunological” cells (e.g. skin and cilia)
2. Adaptive
   - Develops during life with exposure to infection (memory)
   - Increases affinity with experience (specificity)
   - Two compartments:
     - Cellular- Mediated by cells
     - Humoral-Mediated by soluble factors
   - Memory and Specificity are key features

Immune effector mechanisms



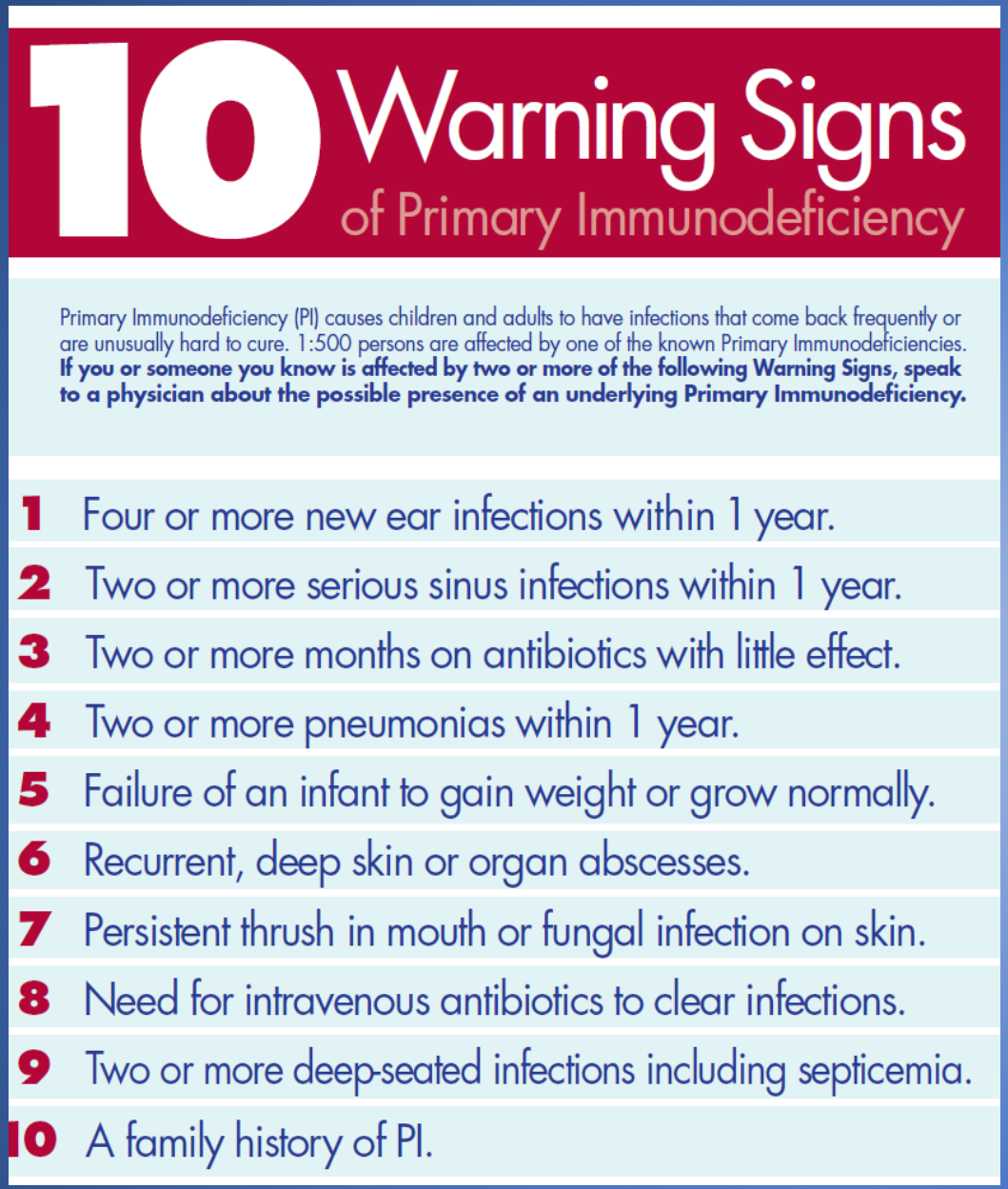
The rules

- 1. We should think about immune problems more often
- 2. We should check people for immune problems even though immune problems are uncommon
- 3. We should know (broadly) what to look for
- 4. We should know now how to look

Rule 1-Why should we think about immune issues more often?

- Many people with immune problems look completely normal-until they get a catastrophic infection that their immune system fails to respond to
- Delayed recognition means delayed treatment, and delaying treatment can lead to fatal infections, debilitating end-organ damage, and worse outcomes from available treatments
- Some of this is going to be easier if newborn screening starts (~~47 48 49~~50) states active or planned)

Warning Signs of Immune deficiency



The Jeffrey Modell Foundation Medical Advisory Board

Is it just an infection?

You should be suspicious if you have an infection that is…

Severe
requires hospitalization or intravenous antibiotics

Persistent
won't completely clear up or clears very slowly

Unusual
caused by an uncommon organism

Recurrent
keeps coming back

or if it

Runs in the Family
others in your family have had a similar susceptibility to infection

THINK ZEBRA!

and help promote awareness of primary immunodeficiency diseases.

If any of these words describe your infection, the Immune Deficiency Foundation (IDF) recommends that you ask your physician to check for the possibility of a primary immunodeficiency disease. These diseases are caused by genetic defects and can affect anyone, regardless of age or sex. People with primary immunodeficiencies are more susceptible to infections and health problems that lead to serious and debilitating diseases. It is critical to get an early diagnosis and proper medical care.

IMMUNE DEFICIENCY FOUNDATION

Questions? Contact IDF to learn more.
www.primaryimmune.org • 800.296.4433

www.primaryimmune.org

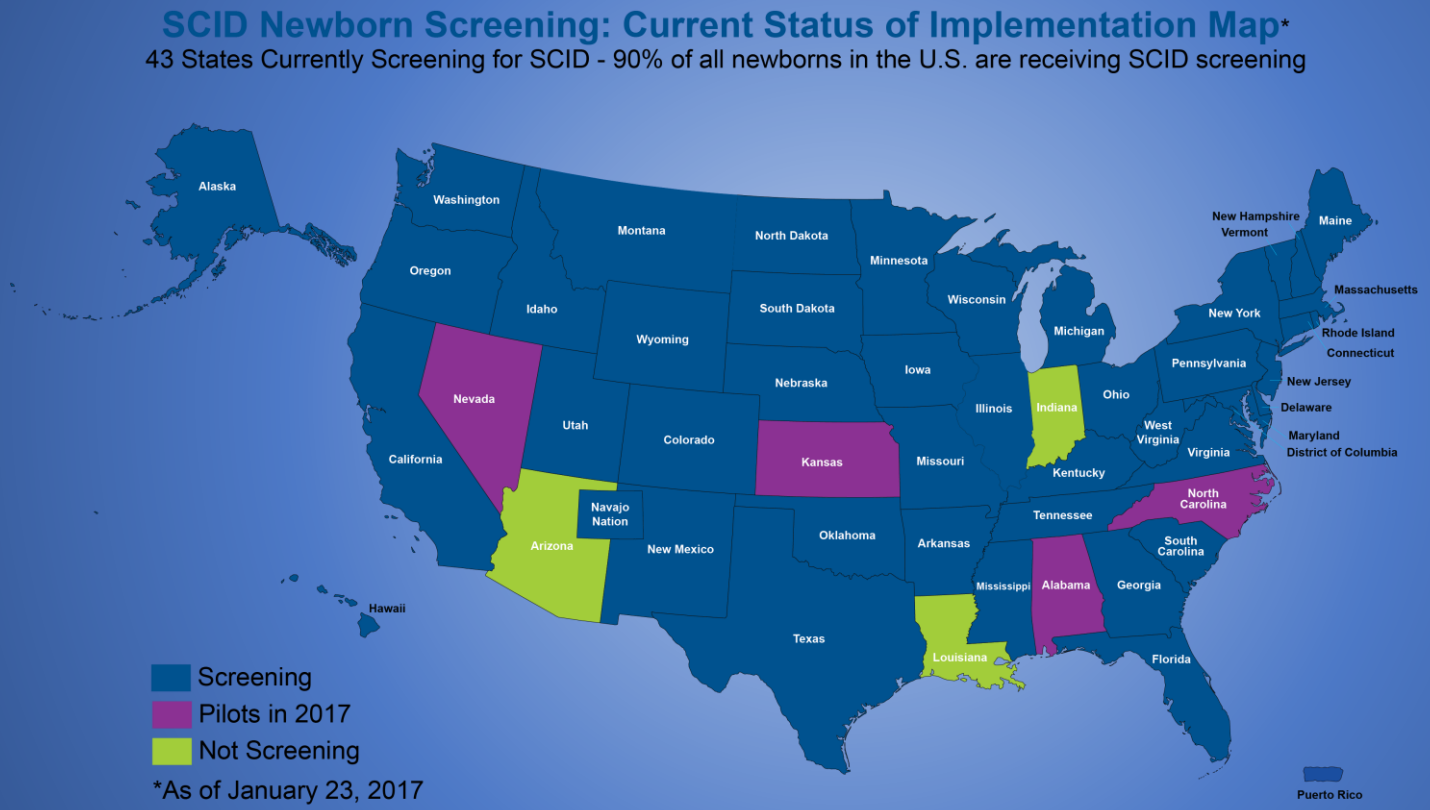
Rule 2-Why should we check for immune problems (even though they are uncommon)

- Difficult to sort out normal variants of sick kids from those with immune deficiency-not all kids are nice enough to look like the answer to a boards question
- While immune deficiencies are uncommon, they're significantly less uncommon than we thought they were a decade ago

Symptoms of immunodeficiency

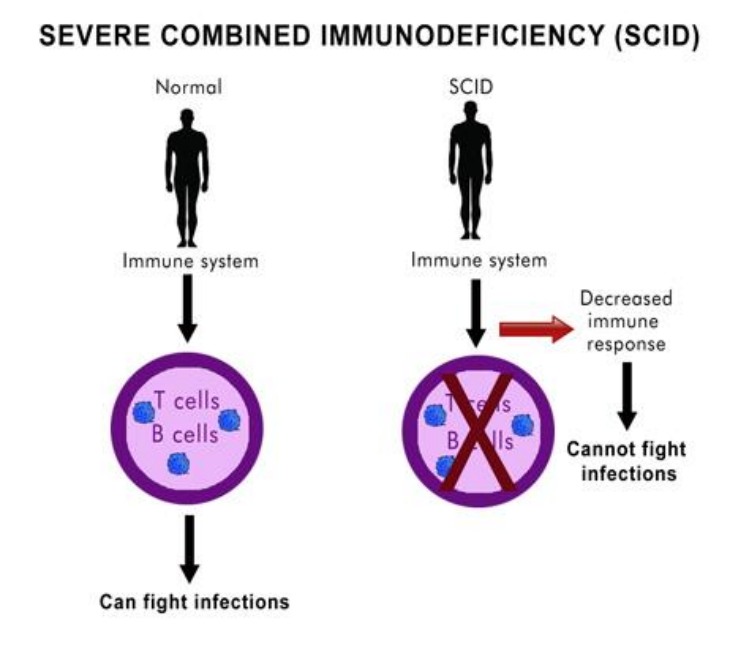
1. Infections
   - Frequent, severe, unusual organisms, difficult to treat
   - Failure to thrive
2. Autoimmune disease
   - Immune system no longer able to properly distinguish self from non-self
3. Immune dysregulation
   - Impaired tumor surveillance
   - Hematopoietic malignancy

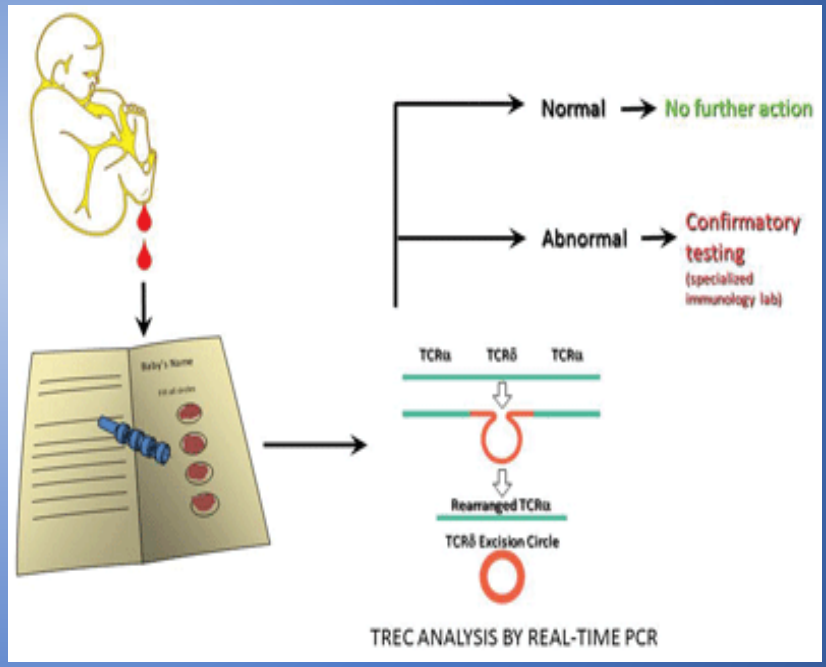
Why are immune deficiencies more common now?



Immune Deficiency Foundation
www.primaryimmune.org

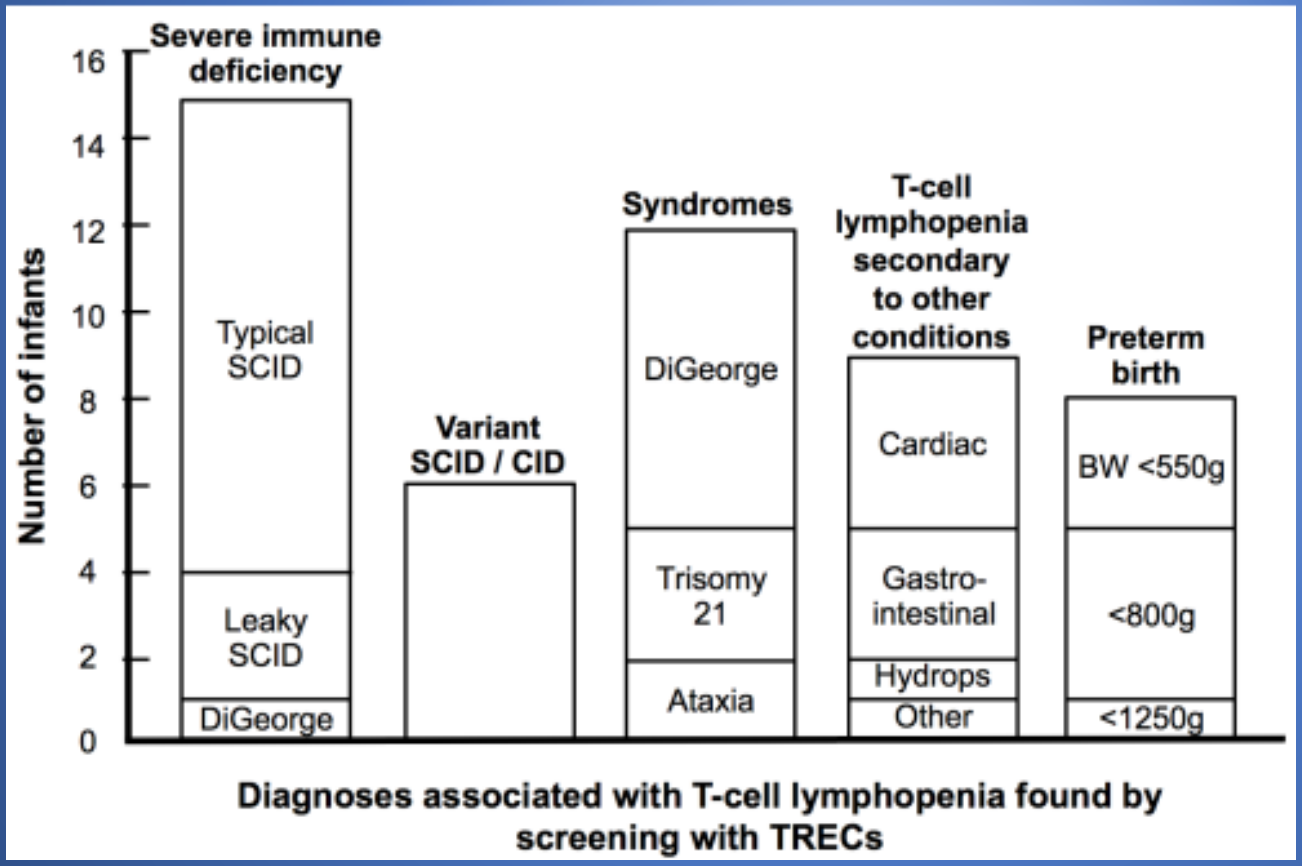
How do you screen newborns for immune problems?





California data from newborn screening

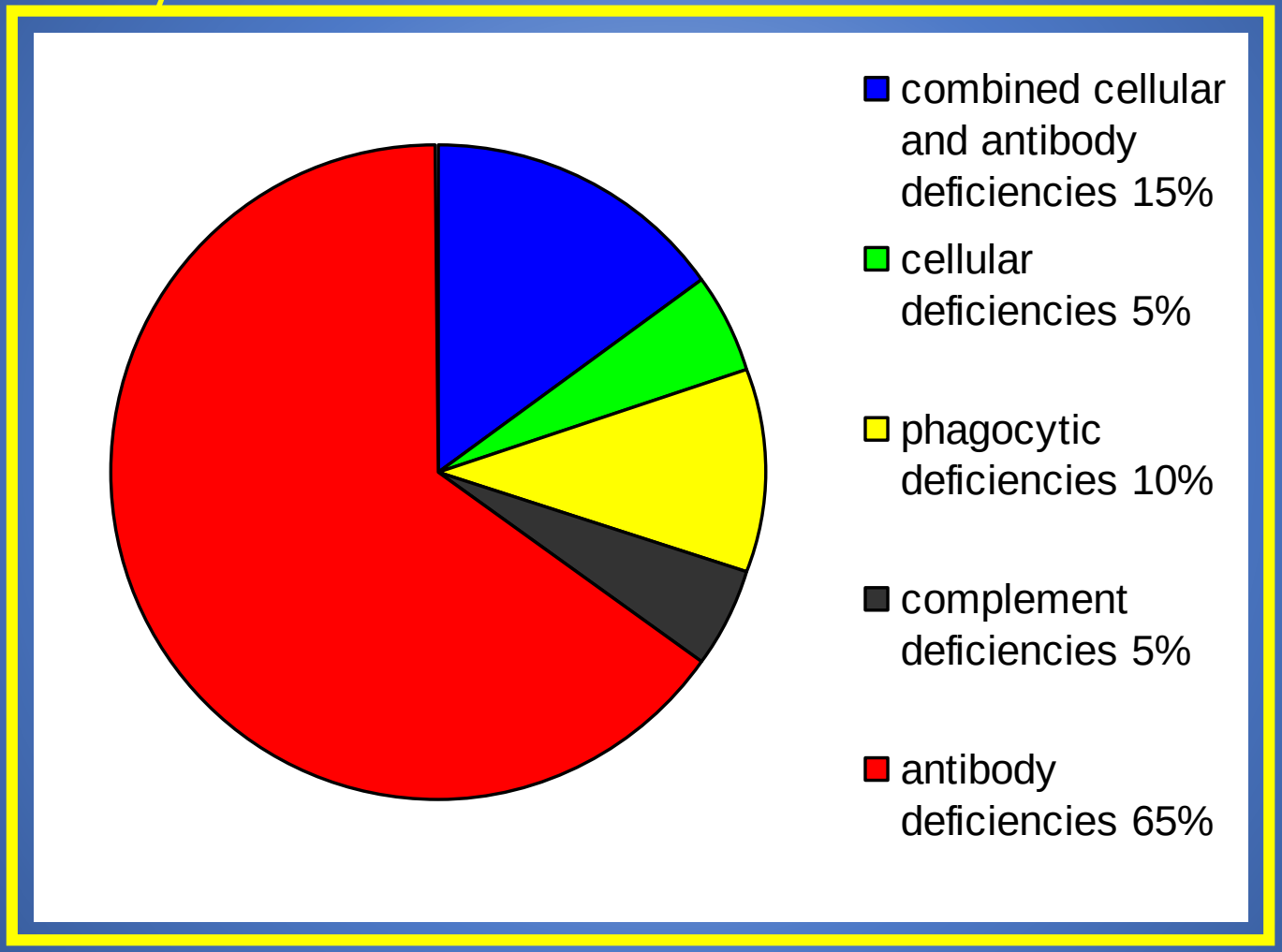
96% needing immune reconstitution surviving



Rule 3-what should we be looking for?

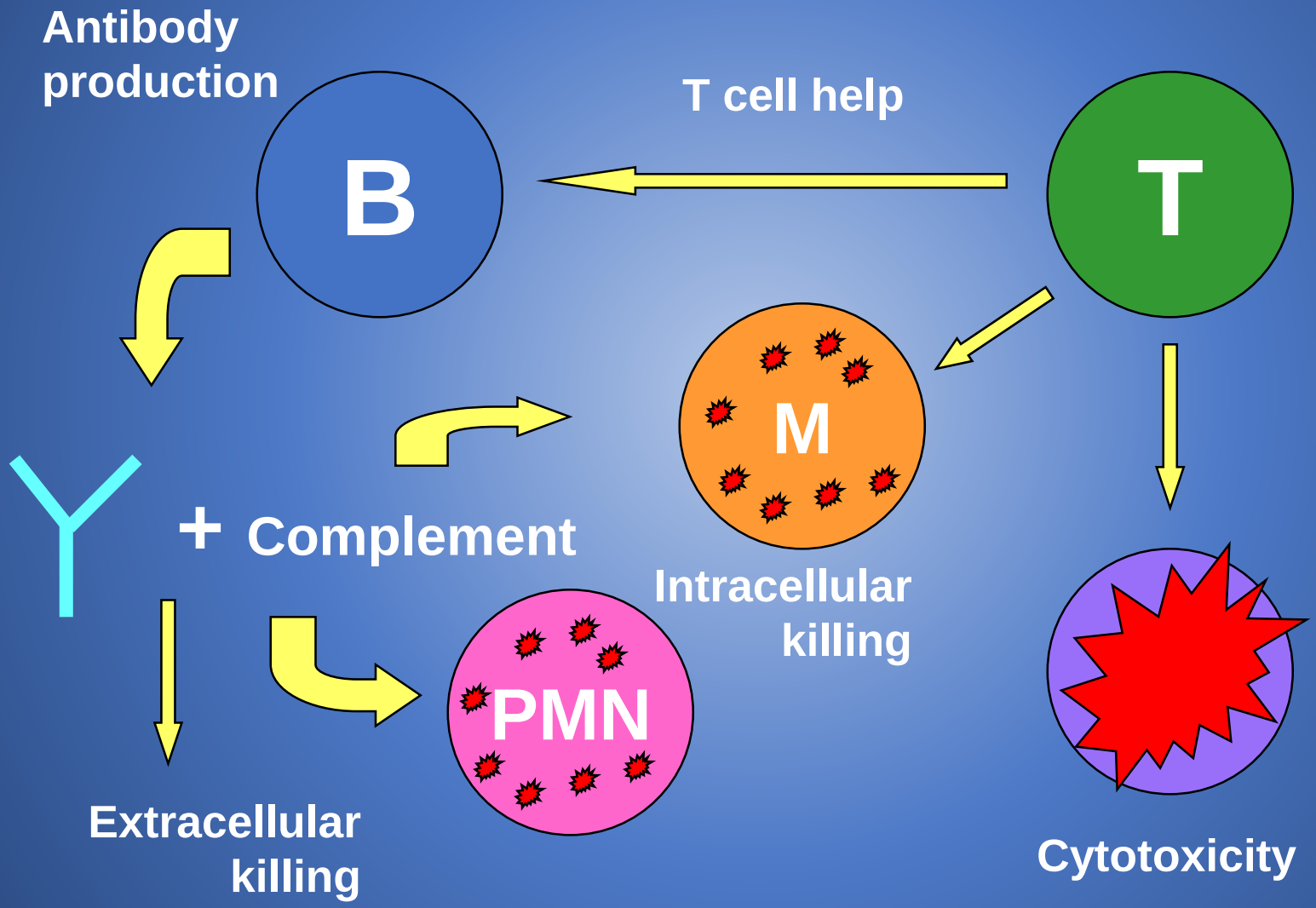
- Some immune problems are very common, but fortunately less severe
- Others are severe, but less common
- Everyone wants an exceptionally good immune system, but we have limited ways to intervene so there aren't a lot of ways to assess people whose immune systems are only adequate

Primary Immunodeficiencies



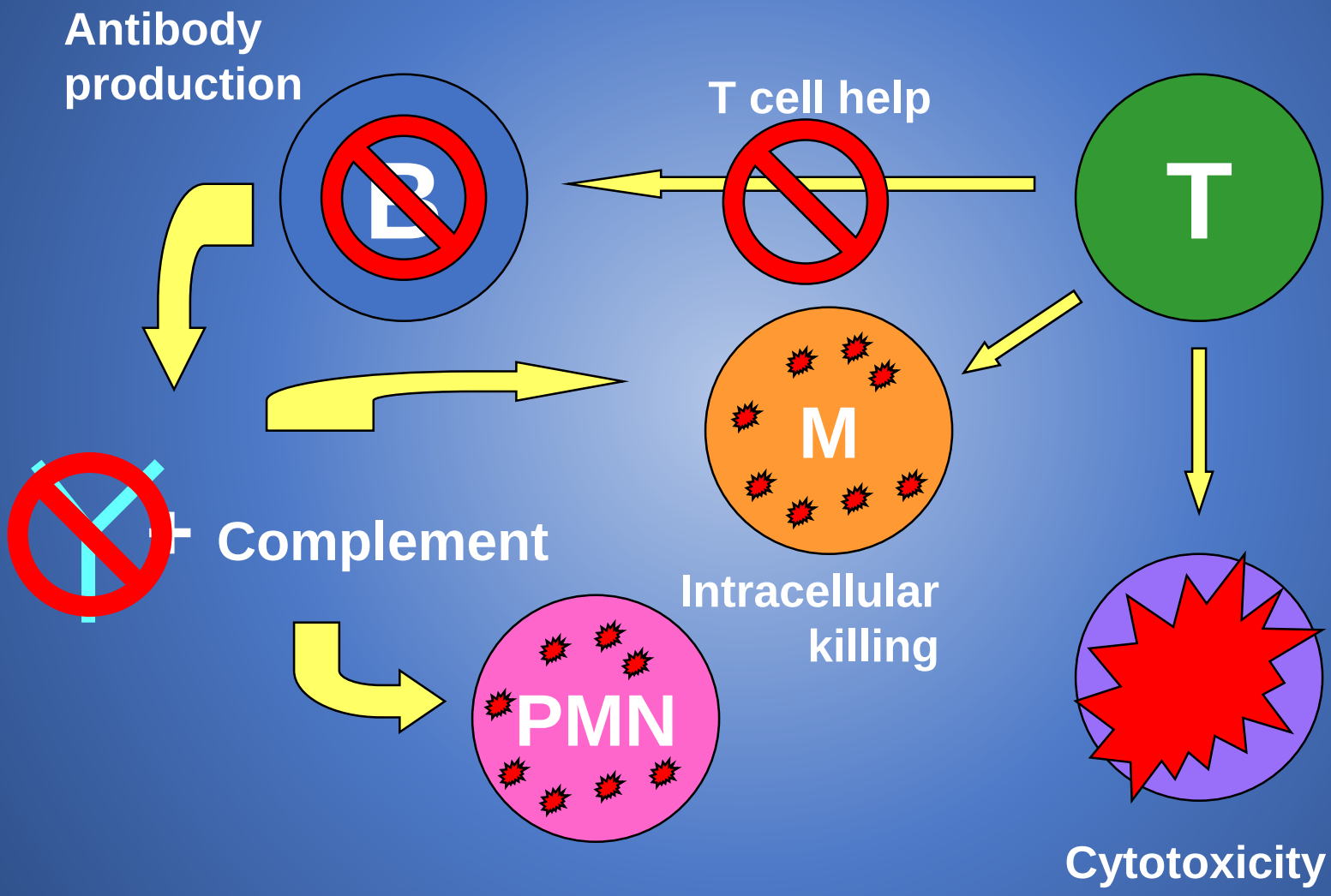
Modified from Stiehm: Immunologic Disorders of Infants and Children – Fifth Edition, Chapter 12, pg 293

Immune effector mechanisms



Antibody Deficiencies

B cell / humoral / antibody deficiencies



Antibody deficiency: pattern of infections

- Bacteria: pneumococcus, H. flu, Moraxella, Staph aureus, meningococcus, Pseudomonas, Campylobacter

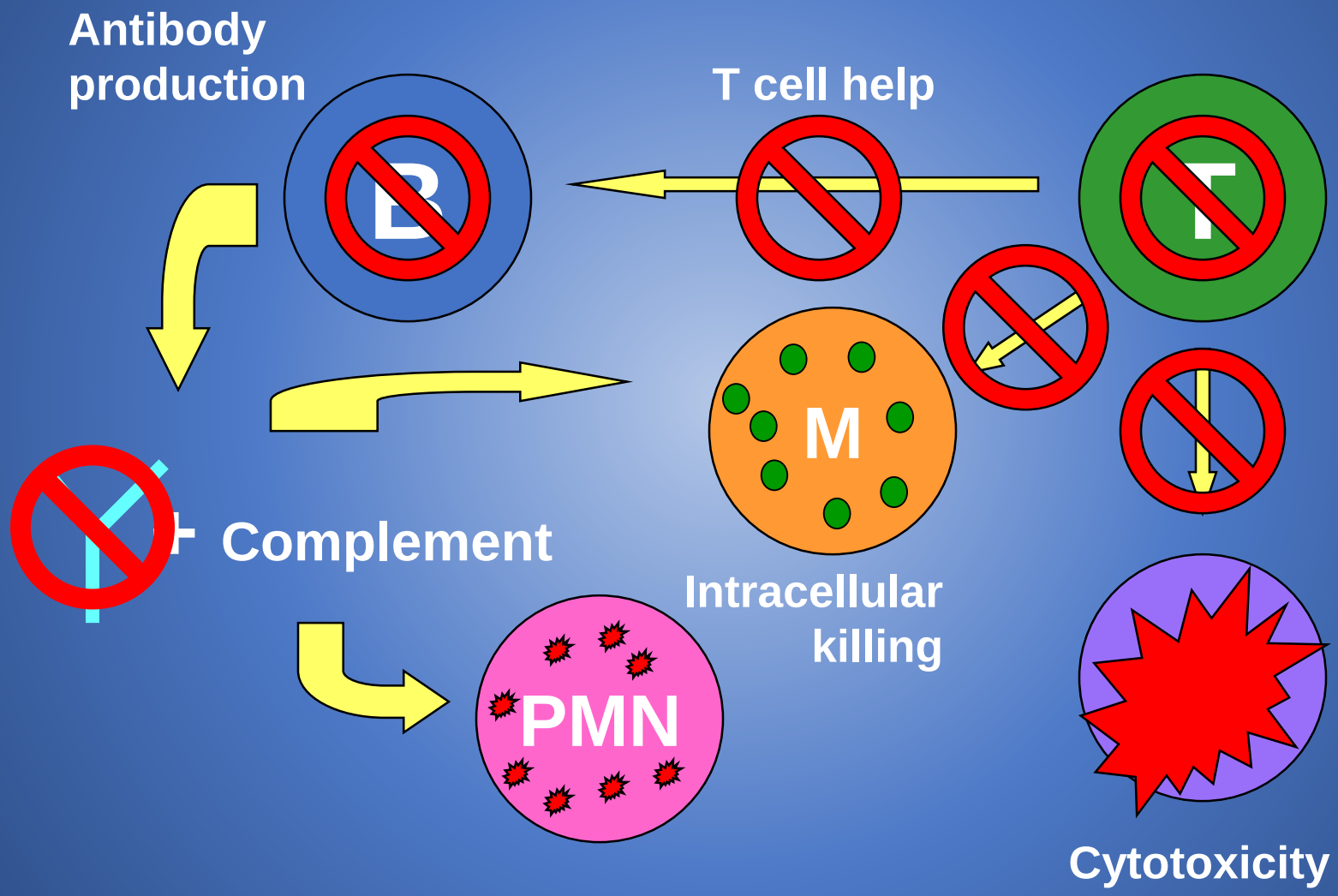
  Mycoplasma, Ureaplasma

- Viruses: common respiratory and esp. enteroviruses (including vaccine strains), rotavirus

- Protozoa: Giardia, Cryptosporidium

Combined Immune Deficiencies (SCID, CID, DiGeorge)

Combined immunodeficiency

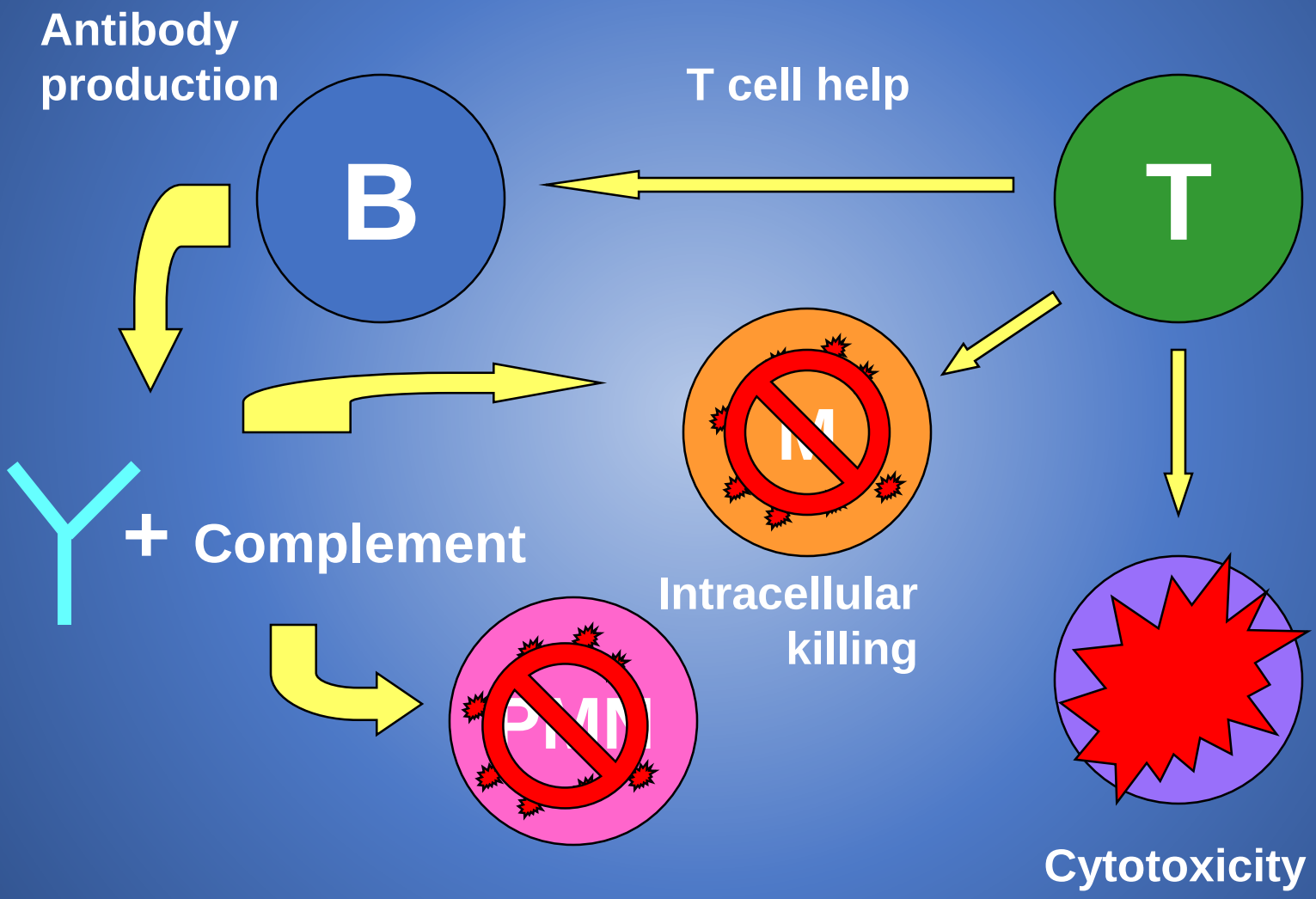


Combined immunodeficiency: pattern of infections

- Mycobacteria, esp. atypical and including BCG
- Salmonella
- Candida
- Herpes viruses
- Pneumocystis
- Bacteria: Listeria, enteric flora
- Viruses: herpesviruses, RSV, influenza, parainfluenza, measles (also vaccine strains)
- Fungi: Pneumocystis, Candida, Cryptococcus, Histoplasma
- Protozoa: Toxoplasma, Cryptosporidium

Phagocytic Immune Deficiencies

Phagocyte defects



Phagocyte defects: pattern of infections

- Bacteria: catalase-positive
  - Most commonly: *Staphylococcus aureus, Burkholderia (Pseudomonas) cepacia, Serratia marcescens, Nocardia,*
  - Also: *Klebsiella,* enteric flora
- Mycobacteria including BCG
- Fungi: Candida, Aspergillus, Paecilomyces

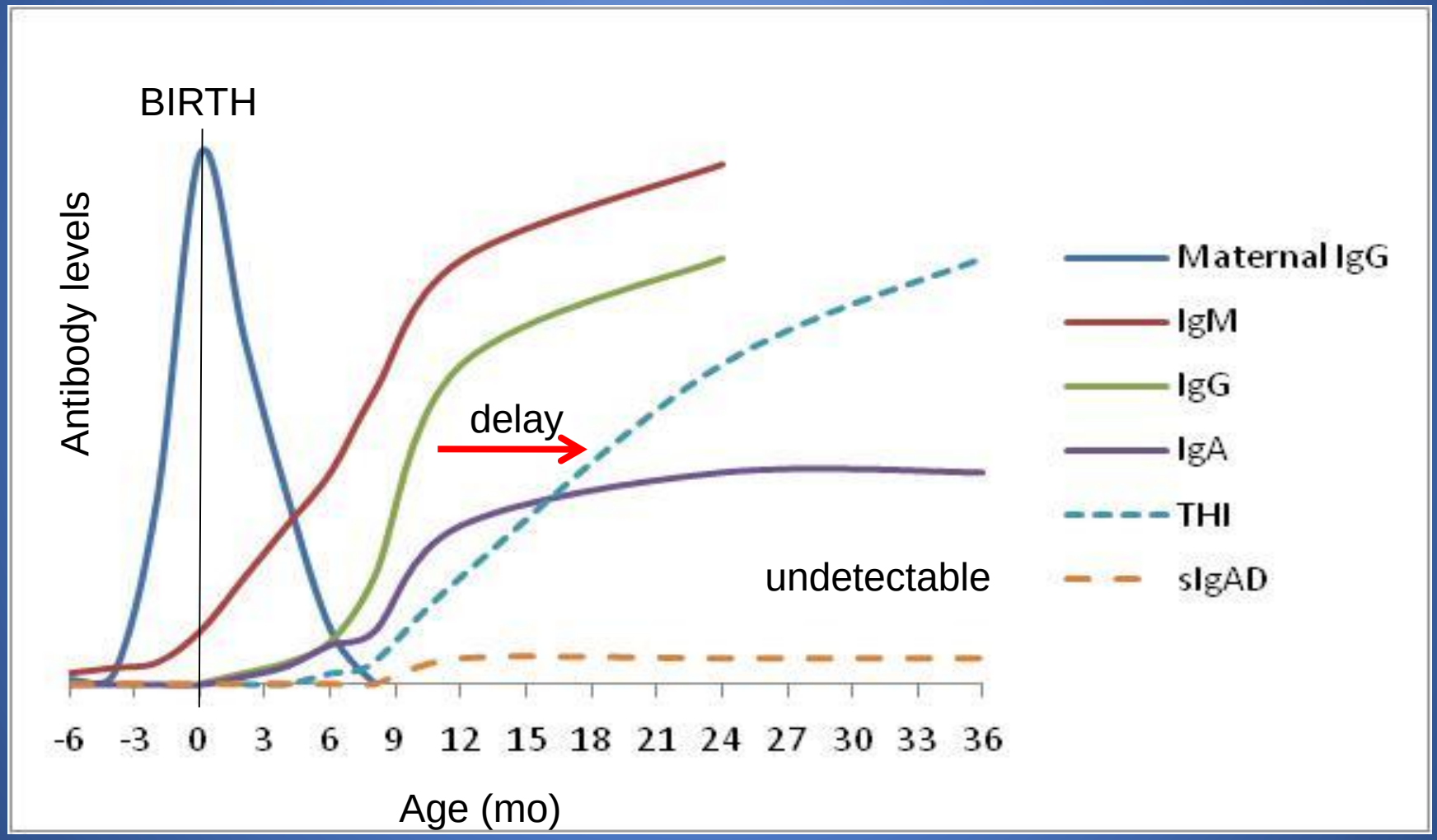
Rule 4-How should we look

- It depends

Looking

- You can’t look at everything, you have to follow your history and physical
- Family history, types of infections, locations of infections all can help direct where you look
- Age, acute illness, vaccination status can limit what you look at
- You should critically look at all the labs you already have
  - Newborn screen
  - CBC with dif (ALC), platelet count

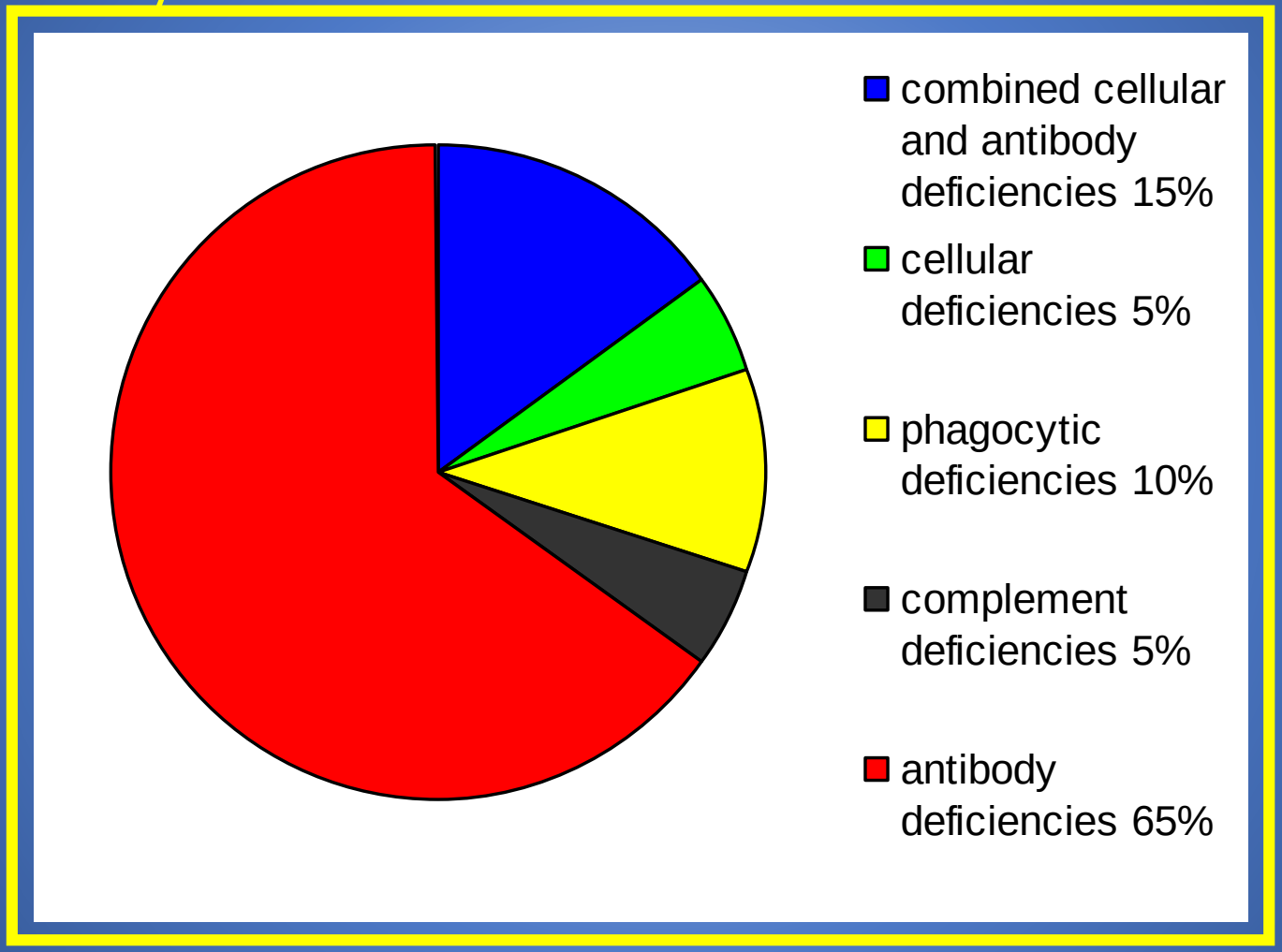
Impact of age on immune evaluation



Still looking

- Parts of the evaluation needs to be individualized, but general screening is important
  - Newborn screen results if available
  - CBC with dif (ALC) when healthy
  - IgG, A, and a titer to something you know the patient has been exposed to

Primary Immunodeficiencies



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Diagnostic Tools for Antibody Deficiency

Deficiency	Screening Tests	"Advanced Tests"
Antibody	Quantitative serum immunoglobulins (IgG, A, M, E)	IgG subclasses (only helpful in some cases)
	Antibody response to vaccinations (tetanus, diphtheria, pneumococcus)	Antibody response to vaccinations post boosting
	Isohemagglutinin titer (IgM)	B cell enumeration CD19, CD20
		Bacteriophage (neoantigen)

Antibody deficiencies comprise about 65% of primary immunodeficiency diseases

Diagnostic Tools for T cell deficiency

Deficiency	Screening Tests	"Advanced Tests"
Cellular (T cell or combined)	Absolute lymphocyte count	T cell enumeration CD3, CD4, CD8 NK cell enumeration CD16/56
	Delayed Type Hypersensitivity Skin Testing	Lymphocyte proliferation to mitogens: PHA, PWM, ConA Lymphocyte proliferation to antigens: Tetanus, Candida
	HIV Antibody or PCR	

- T cell deficiencies generally characterized by FTT, diarrhea, rash, recurrent viral, fungal, and opportunistic infections.
- SCID is an absence of T cell number and function, also associated abnormalities of B cells, NK cells or both.

Diagnostic tools for Complement Deficiency

Deficiency	Screening Tests	"Advanced Tests"
Complement	CH50 AH50 C3, C4 MBL level	Individual component testing MBL genotype

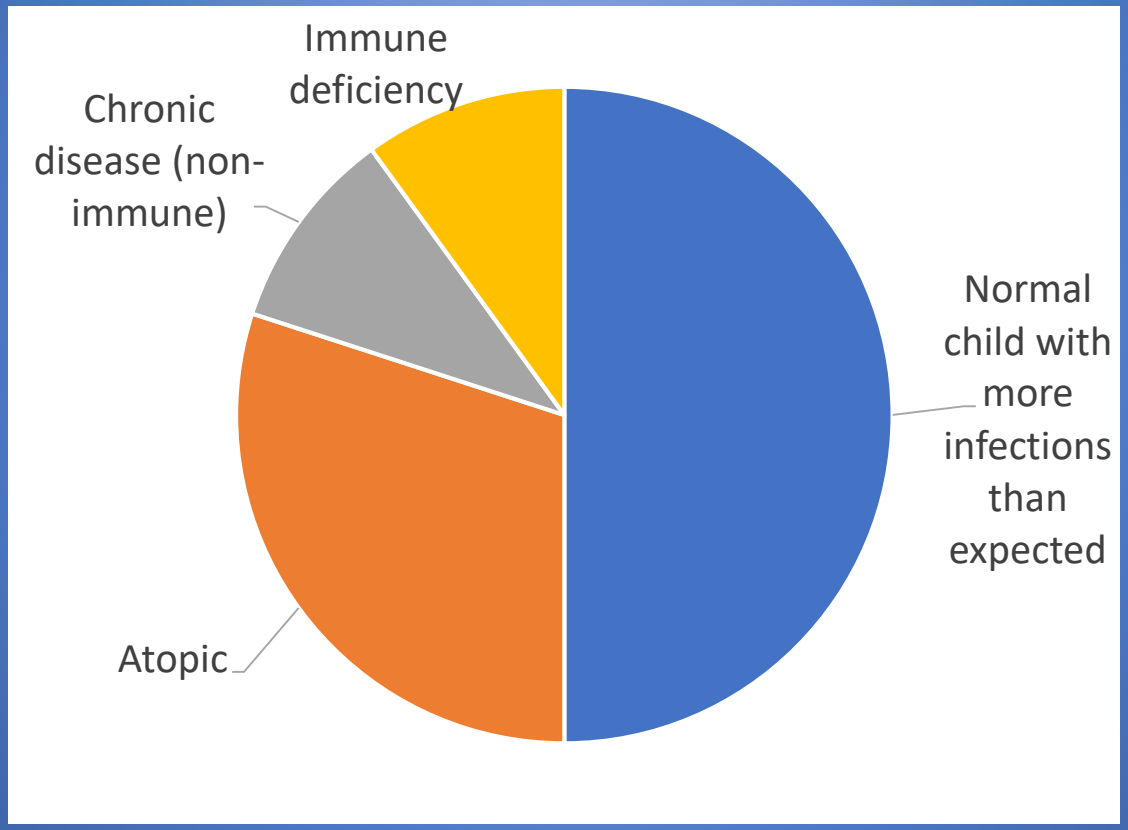
- Complement pathway defects
- Early components: C1q, C2, C4, C3 = recurrent encapsulated bacterial infections
- Terminal components, C5-C9: recurrent meningococcal infections

Diagnostic tools for Neutrophil defects

Deficiency	Screening Tests	"Advanced Tests"
Neutrophil/Phagocyte	Absolute neutrophil count Cell morphology	Evaluation of oxidative burst: DHR (flow cytometry) NBT (microscopy)
		Evaluation of adhesion molecules (CD18, CD11) IFNg R on monocytes
		Phagocytic, chemotaxis, bacterial killing assays (research labs)

- CGD = defect in oxidative burst. Recurrent infxn with catalase + organisms, abscesses of liver, lung, brain, osteo, granuloma, aspergillus.
- LAD = defect in leukocyte migration, leukocytosis (marked), delayed umbilical cord separation, gingivits. (RARE!)
- IFNGR deficiency = recurrent mycobacterial infections

What do we end up finding in patients sent for immune eval?



Conclusions

- Newborn screening for immune deficiency is going to dramatically change our approach to primary immune deficiency
- Secondary immune deficiencies won't get caught by newborn screening
- Screening isn't perfect, so we need to be vigilant and remember the signs of PID and how to screen
- Early diagnosis allows better treatment outcomes

Case #1: Antibody deficiencies

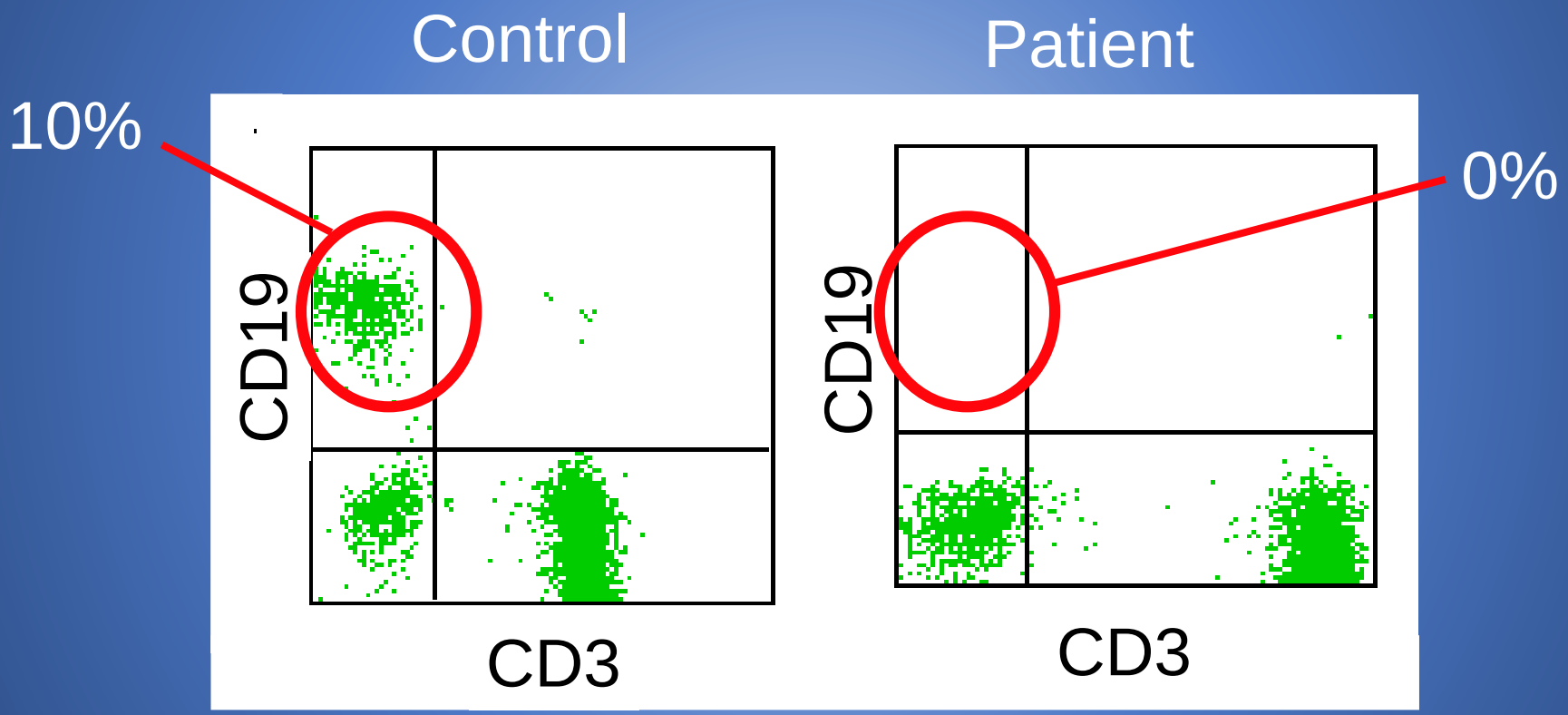
History

- 2 yr old boy
- Frequent ear infections
- 3 episodes of pneumonia
- One bacterial meningitis
- One pneumococcal sepsis

Laboratory

- IgG < 100 mg/dL
  (650-1,500)
- IgA 0-10
  (70-400)
- IgM 0-20
  (50-300)
- No specific antibody responses to vaccines
- Cellular immunity normal

Flow Cytometry: T cells vs B cells



Diagnosis: X-linked Agammaglobulinemia

Infection Susceptibility: pyogenic infections, viral meningo-encephalitis, vaccine strain poliomyelitis, mycoplasma arthritis

Clinical Features: infancy/childhood with recurrent sinopulmonary pyogenic infections, 25% with neutropenia

Inheritance: X-linked

Diagnosis: Absent B cells

Approximately 50% positive family history

IgG usually <100 mg/dL

B cells < 2% of lymphocytes (~ 0.05-0.3%)

Normal T cell number and function

Antibody Deficiencies: Specific Diagnoses

Agammaglobulinemia

- X-linked
- Autosomal Recessive

Hyper IgM Syndrome (HIGM)

- X-linked (lack of T cell help)
- Autosomal Recessive

Common Variable Immunodeficiency (CVID)

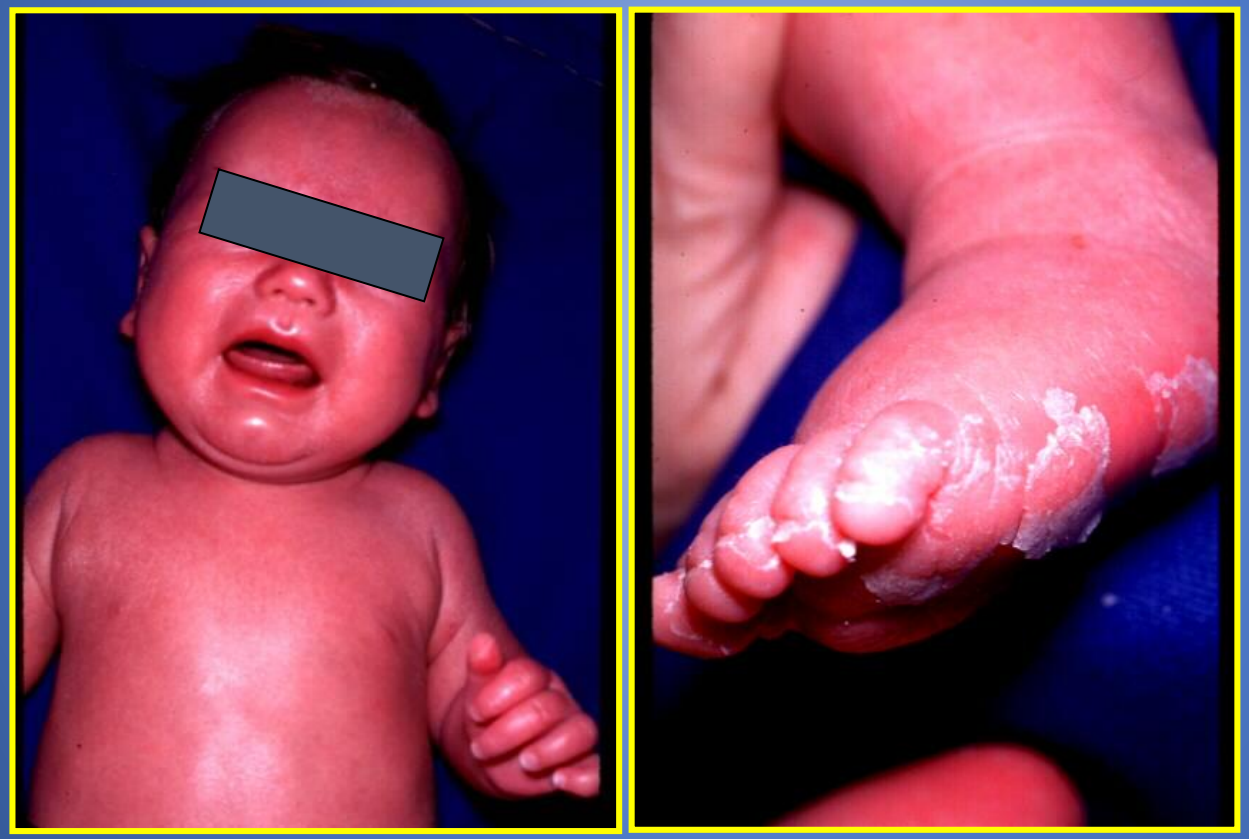
IgG Subclass Deficiency

Specific Antibody Deficiency

Transient Hypogammaglobulinemia of Infancy

TREATMENT: Immunoglobulins, antibiotic prophylaxis

Case #2: Cellular and Combined Immune Deficiencies



Case #2: Combined immunity deficiencies

History

- Born term
- Uneventful neonatal course
- At 4 weeks, progressive generalized dermatitis.
- Intermittent colic, emesis, and diarrhea.
- Failure to thrive.
- Skin findings as above
- Diffuse lymphadenopathy

Laboratory

IgG 155 mg/dL
IgA <7 mg/dL
IgM <5 mg/dL
Low IgE
Lymphocytes 9,000/mm3
Eos 3,500/mm3

CD3CD4 61%
CD3CD8 20%
CD19 1%
PHA 10% of control
T cells of host origin & oligoclonal

Case #2: Cellular and Combined Immune Deficiencies

Diagnosis: Omenn's syndrome

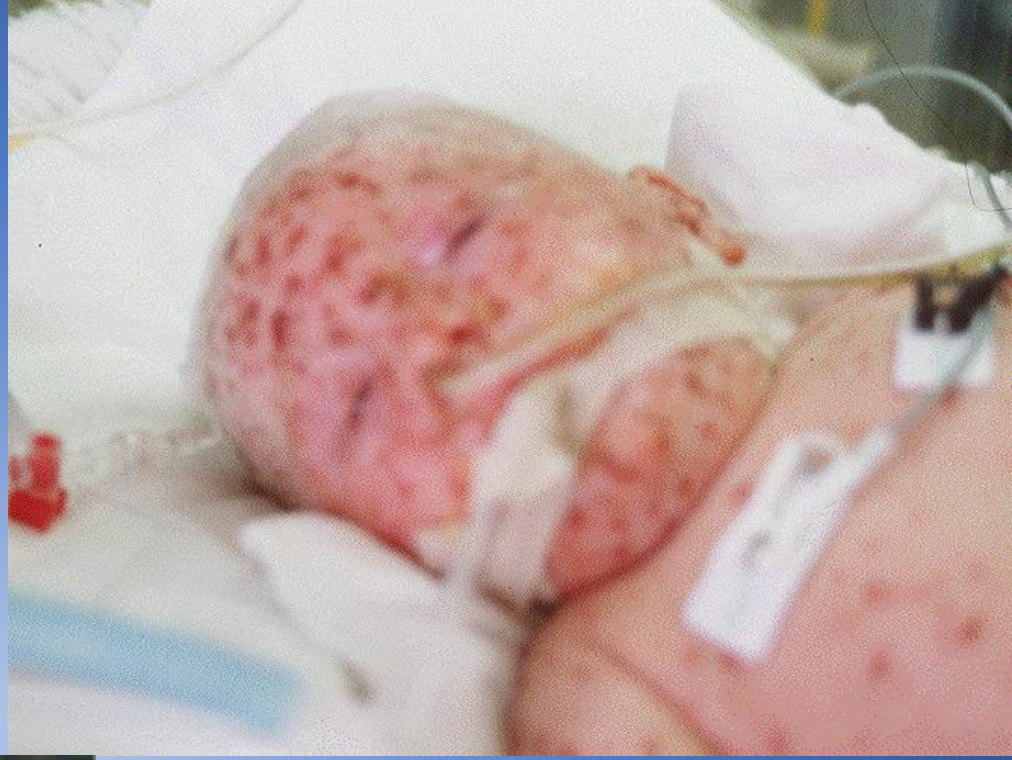
Treatment at age 3 months –

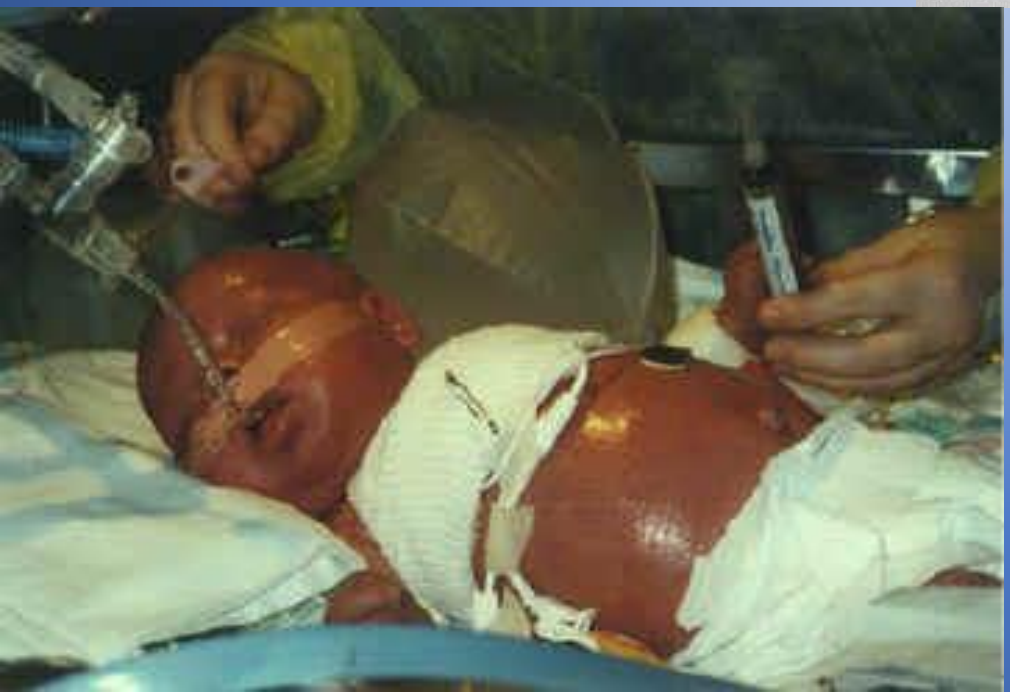
- Cyclosporine therapy
- haploidentical BMT from father
- 4 month hospital stay

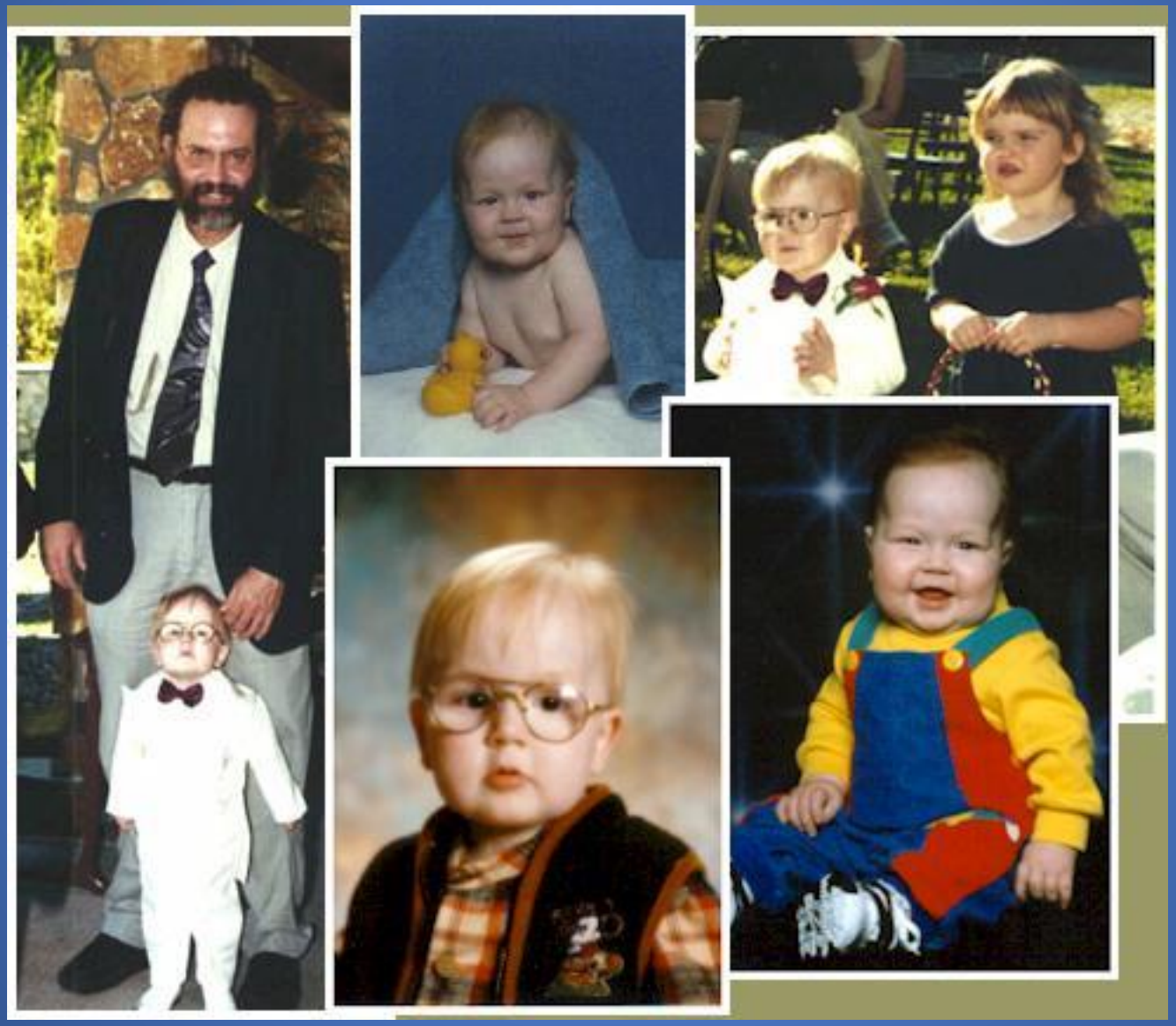
Post-transplant complications: Autoimmune hemolytic anemia, thrombocytopenia, Pneumatosis intestinalis, Chronic GVHD,

- Eventual bone marrow boost from father

Now doing well, normal immune function, mild chronic colitis

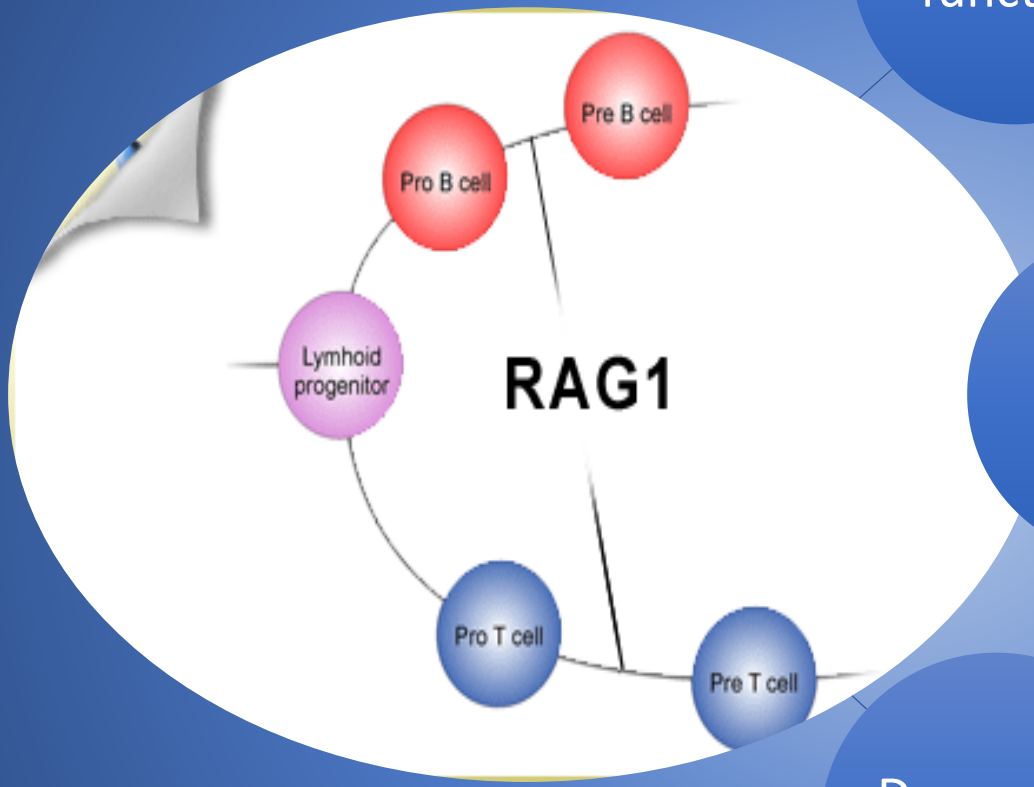






Genetics figured out in 1998

- Omenn's syndrome associated with a mutation in RAG genes
- Functional analysis of mutant RAG in Omenn's syndrome demonstrate partial function



Normal function

- Normal T/B cell development
- Normal immunity

Absent function

- No T/B cells
- SCID

Decreased Function

- Limited T cell development
- Omenn's syndrome

Severe Combined Immunodeficiency (SCID)

Infection Susceptibility: All infectious organisms including live vaccine strains and opportunistic infections.

Clinical Features: Failure to thrive, chronic diarrhea, erythroderma or other skin eruption. Specific gene defects may have associated features.

Inheritance: X-linked (most common) or autosomal recessive

Diagnosis: Lymphopenia in most, diminished or absent T cells in most (maternal T cell engraftment or aberrant oligoclonal T cells in Omenn, may confuse the picture), poor/absent *in vitro* mitogen-induced T cell proliferation in all.

Cellular and Combined Immune Deficiencies: Specific Diagnoses

SCID

Wiskott Aldrich

Ataxia Telangiectasia

DiGeorge Syndrome

Chronic Mucocutaneous Candidiasis

IL-12/IFN gamma axis

X-linked lymphoproliferative disorder

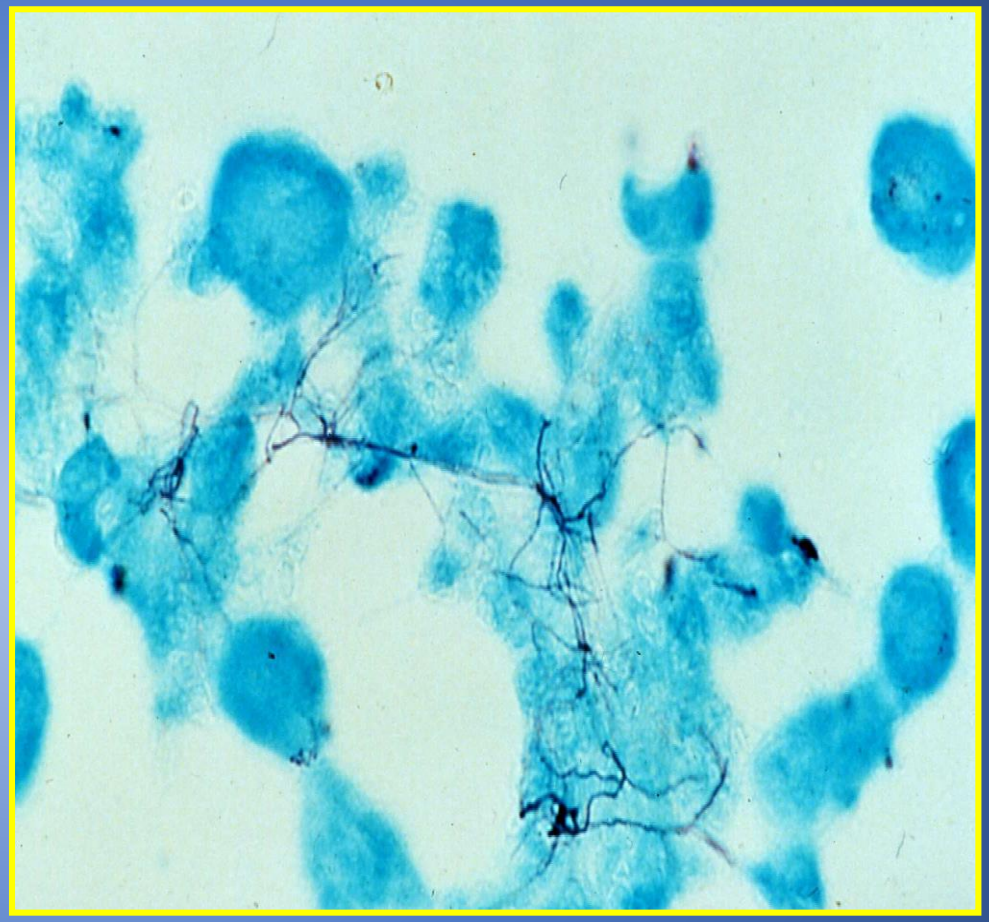
Ectodermal dysplasia with immune deficiency

WHIM syndrome

Case #3: Disorders of Phagocytes

History

- 15mo male with respiratory distress
- Chest x-ray with “white out” on right side
- Unresponsive to antibiotics
- CT scan with abscess
- Broncheoaveolar lavage: Hyphae

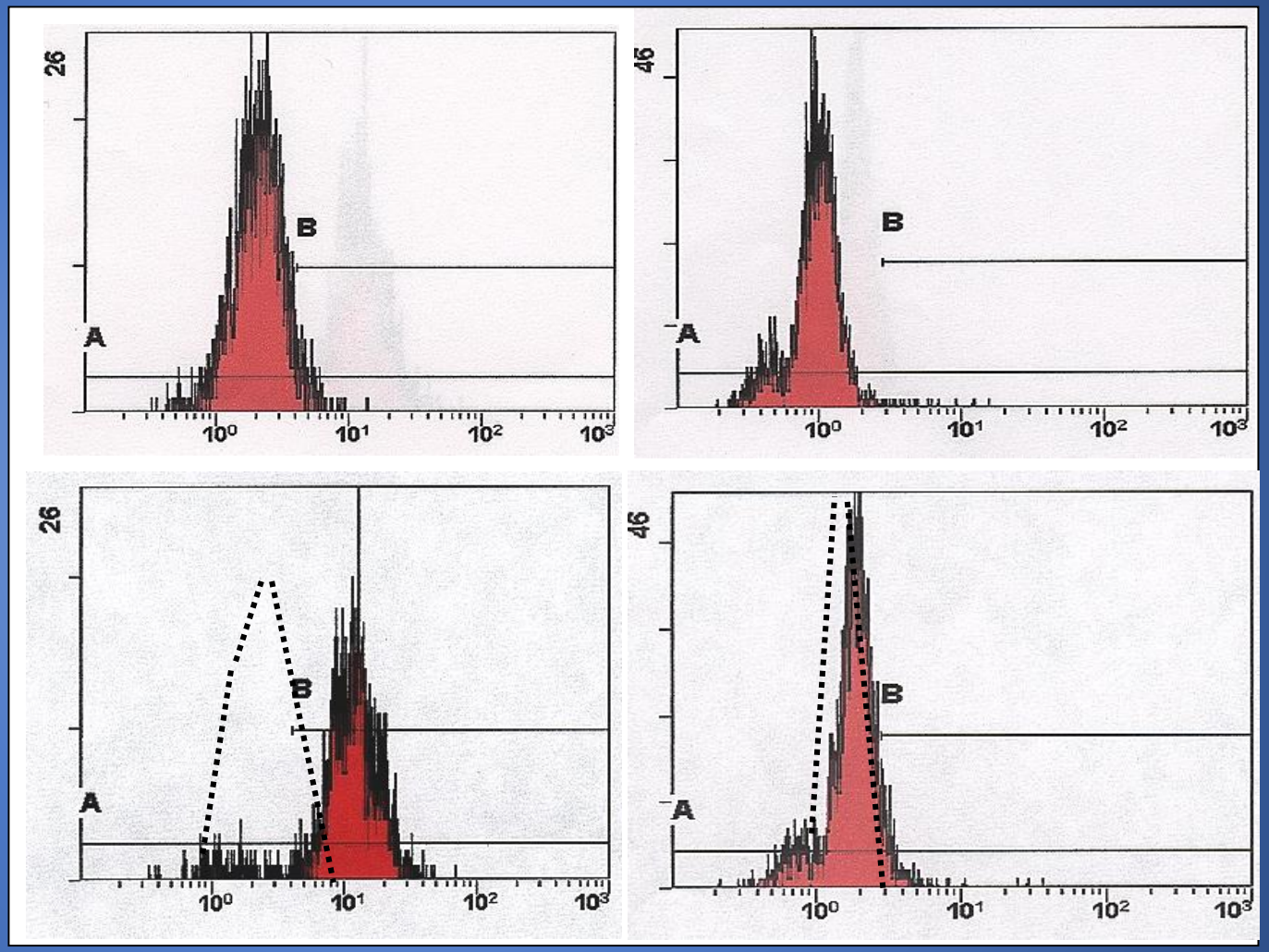


Case #3: DHR test for neutrophil oxidative burst

Control **Patient**

Pre-stimulation

Post-stimulation



Diagnosis: Chronic Granulomatous Disease

Infection Susceptibility: catalase positive organisms, and indolent fungal infections.

Clinical Features: Recurrent infections. Granulomas of skin, liver, lungs, lymph nodes, viscera, bones, joints. GI/GU obstruction secondary to granulomas

Diagnosis: Neutrophil oxidative burst assay by flow cytometry using dihydrorhodamine 123 (replacing NBT test)

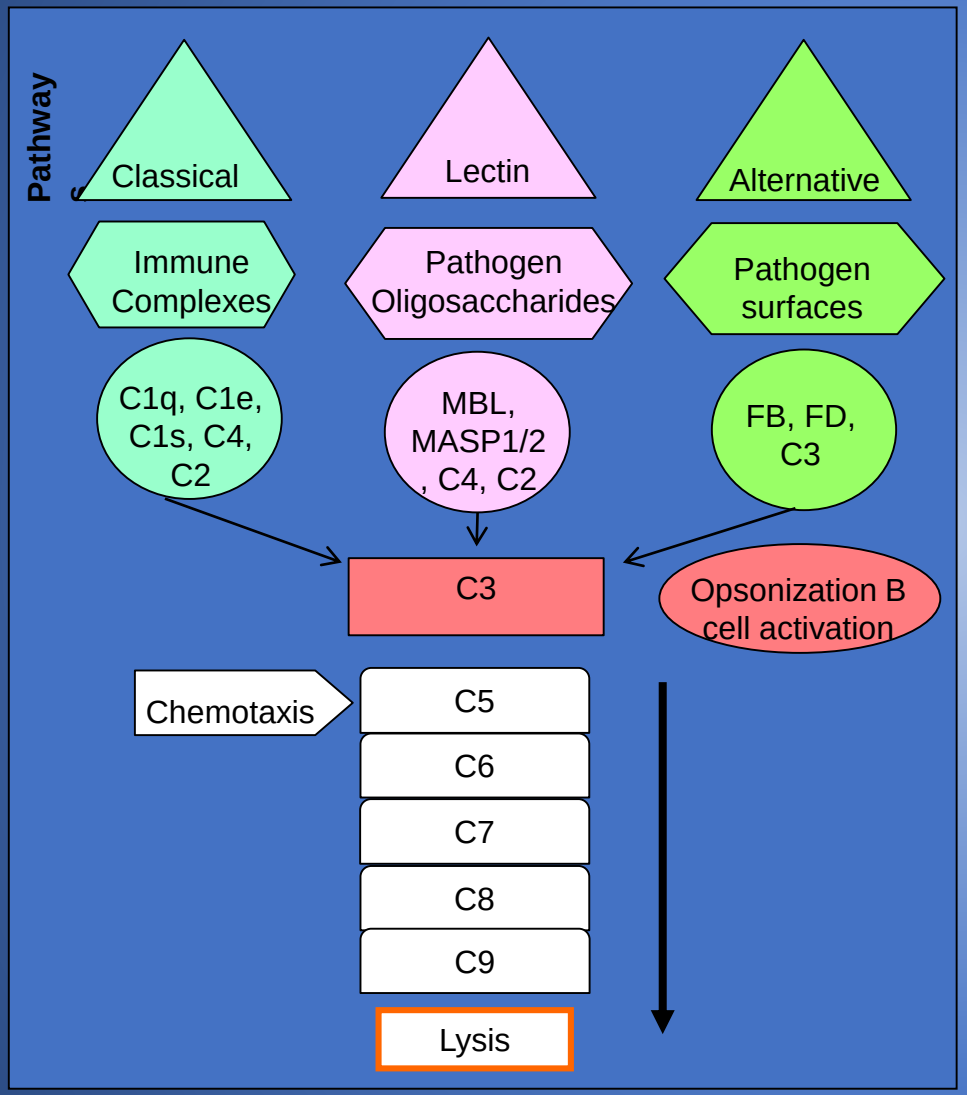
Treatment:

- Prophylactic antibiotics
- Gamma interferon
- Bone marrow transplantation

Phagocyte defects: Specific Diagnoses

- Chronic granulomatous disease
  - X-linked
  - Autosomal recessive
- Chediak-Higashi syndrome
- Leukocyte adhesion deficiency
- Neutrophil specific granule deficiency
- Congenital agranulocytosis

Case #4: Complement deficiency



History:

- 15 yo male with fever
- altered mental status
- petechial rash

Laboratory:

- Culture and gram stain of CSF = *N. meningitidis*
- CH50 = zero
- Terminal complement components analysis: Deficiency of C6.

Complement Component Deficiency

Infection Susceptibility and Clinical Features: Recurrent pyogenic infection and also connective tissue disease (especially C2 and C4)

Late component deficiency (C5 – 9) recurrent Neisseria species infection

- Deficiency of regulatory protein C1 esterase inhibitor is associated with angioedema

Diagnosis: CH50 for classical pathway, AH50 for alternative pathway, and/or individual complement component levels

Treatment:

- Prophylactic antibiotics
- Immunizations with bacterial polysaccharide vaccines (e.g. Pneumococcal vaccines)

Complement Disorders : Specific Diagnoses

Classical component deficiency: Early (C1-C4); Late (C5-C9)
Alternative component deficiency: Properidin, Factor D
Regulatory Components: C1 inhibitor – HAE, factor I, factor H
Lectin pathway deficiency: Mannose Binding Lectin
C2 deficiency most commonly reported

Component(s)	SLE-like auto-immune disease	Bacterial infections
C1, C2, C4	Yes	Multiple
C3	No	Multiple, severe
C5, C6, C7	Yes	Neisseria
C8, C9	No	Neisseria
Properdin	Yes	Multiple
Factor D	No	Multiple

Summary

- In less than 40 years, we progressed remarkably from the description of newly discovered Primary Immunodeficiency Diseases to the development of cellular and molecular cures.
- Molecular immunology is uncovering precise defects in many immunodeficiencies
- Prompt diagnosis and appropriate therapy are life saving