"Hey Doc I'm sick again "
or
Clinical Immunology review for Adults

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OBJECTIVE

To improve the recognition of, diagnosis and treatment of Primary Immunodeficiencies

OUTLINE

I. **The Immune System**
   a. **Function**
   b. **Components**
II. Primary Immunodeficiency
   a. Definition
   b. Symptoms and Signs
   c. Presentation – pattern of infections
III. Specific immunodeficiency diseases
   a. Antibody defects
   b. Cellular defects
   c. Phagocytic defects
   d. Complement defects

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
   - Increases affinity with experience
   - Two compartments:
     - Cellular- Mediated by cells
     - Humoral-Mediated by soluble factors

The Immune System

Components

	Cellular	Humoral
Innate	Monocytes, macrophages, NK cells	Complement
Adaptive	T cells	Antibody (B cells)

Lymphoid organs/tissues

- Primary or central lymphoid organs
  - Bone marrow – B cells
  - Thymus – T cells
- Secondary or peripheral lymphoid organs
  - Spleen
  - Lymph nodes
  - Organ-associated lymphoid tissue (gut, mucosa-associated lymphoid tissue [MALT], Peyer's patches), also skin

B Cells

- Develop in the Bone marrow
- Mediate humoral specific immunity by producing antibodies

Immunoglobulins = Antibodies

- NEUTRALIZE viruses, toxins by binding, forms IMMUNE COMPLEXES
- OPSONIZE microbes for phagocytosis, usually with complement
- Targets cells for cytotoxicity (antibody-dependent cellular cytotoxicity, ADCC)

T Cells

- Develop in the Thymus
- Mediate specific cellular immunity, kill infected cells
- Provide help to B cells for antibody production
- Regulate immune responses through cytokine secretion

Complement

- System of soluble proteins and cellular receptors
- Kills microbes alone or with antibodies
- Opsonizes microbes for phagocytosis alone or with antibodies
- Contributes to inflammation after tissue damage

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Primary Immunodeficiency Diseases

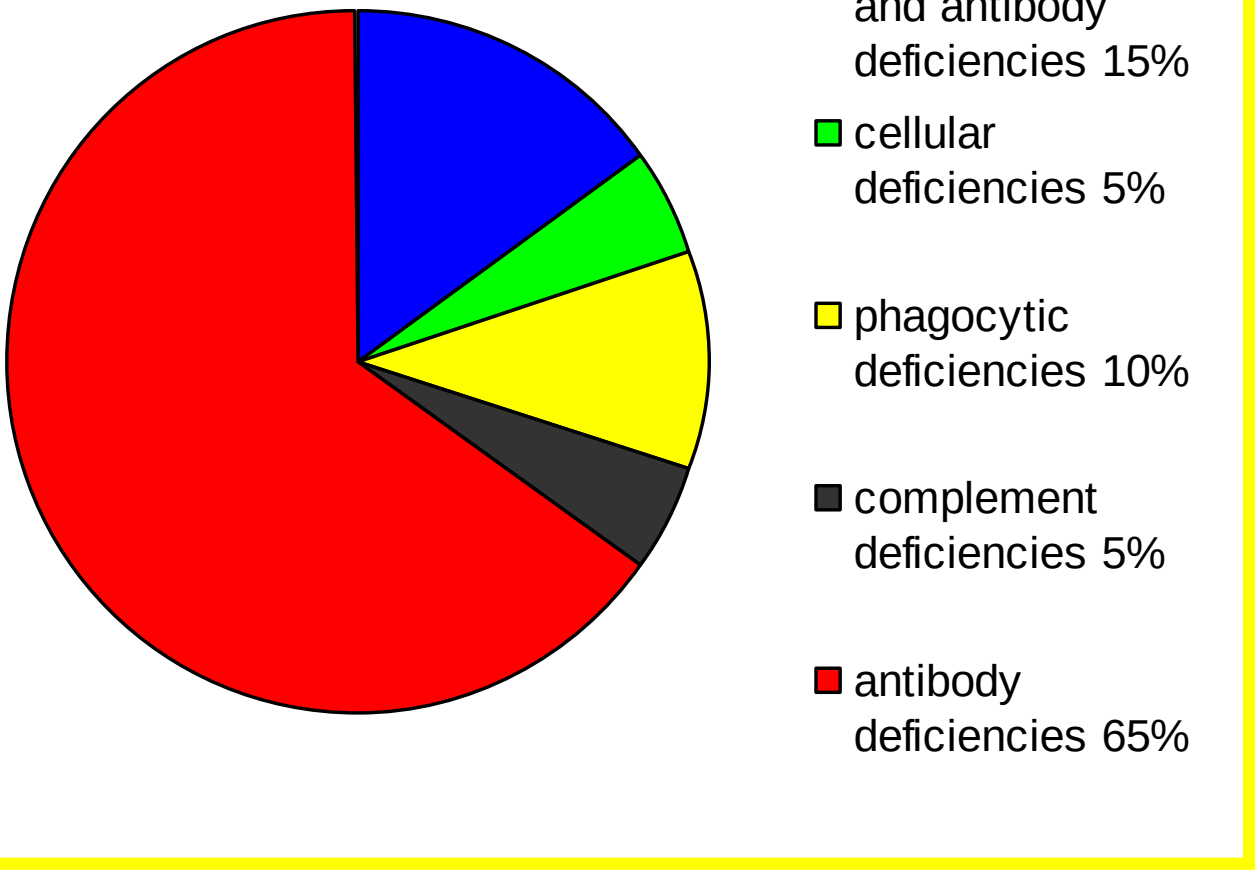
Definition:

Primary immunodeficiency diseases are conditions characterized by intrinsic deficits within the immune system and are caused by inherited or *de novo* genetic defects

Secondary Causes of Immunodeficiency

- Steroid use
- Viral – HIV, EBV, Hepatitis B
- Diabetes
- Splenectomy
- Inflammatory bowel diseases (protein loss)
- Chemotherapy
- Malignancy

Primary Immunodeficiency Diseases



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

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10 Warning Signs of Immunodeficiency*

*The Jeffrey Modell Foundation, Inc.

Diagnosis of Primary Immunodeficiency

- Medical history
  - Family history
  - Characteristic infectious susceptibilities and **patterns of infection**
- Physical examination
- Laboratory testing
- Referral to an immunologist
  - Specific diagnosis and treatment
  - Co-management with primary care

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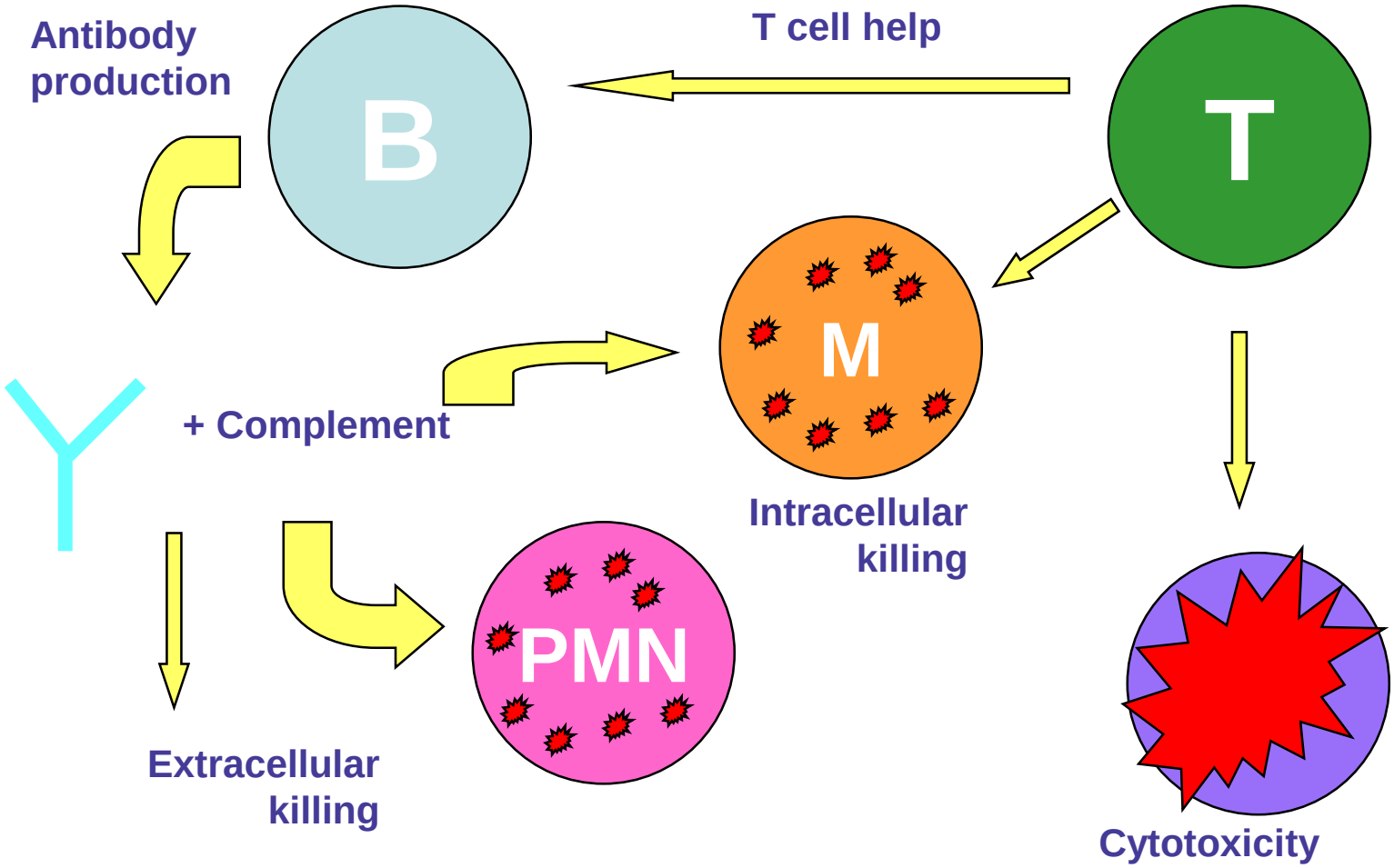
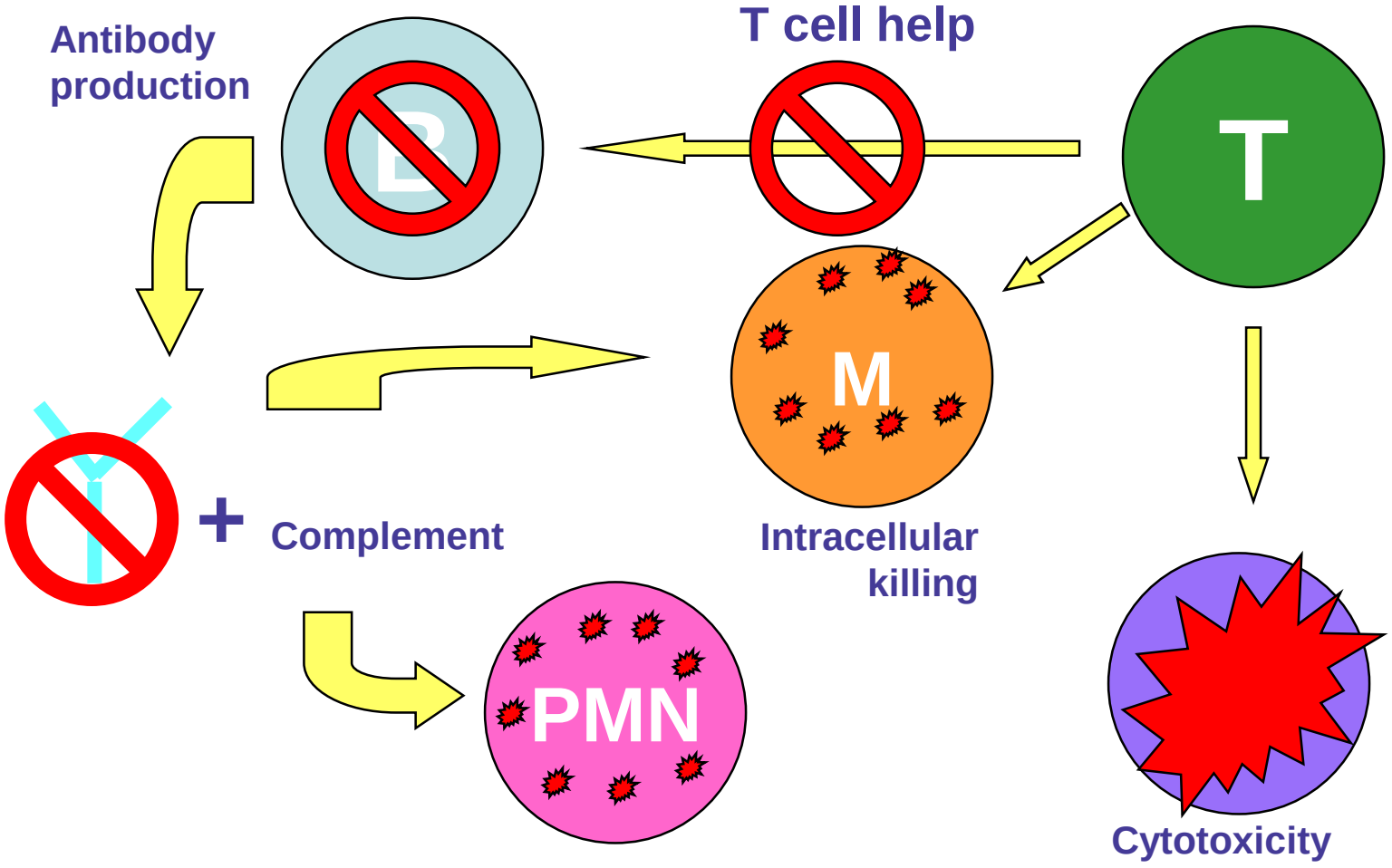
Immune effector mechanisms



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

Cellular immunodeficiency: pattern of infections

- Herpes viruses (shingles)
- Mycobacteria, esp. atypical and including BCG
- Salmonella
- Candida
- Pneumocystis

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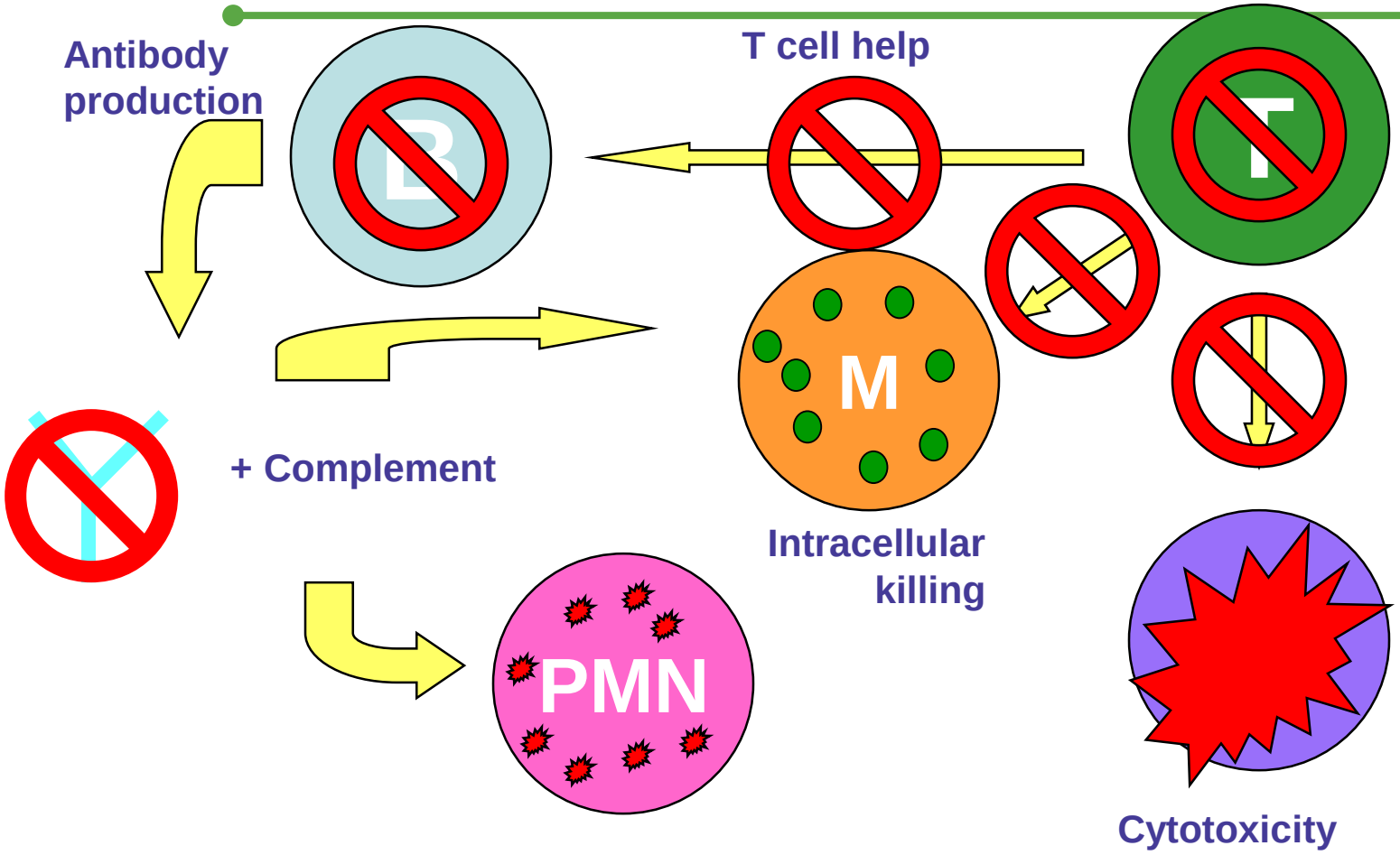
Combined immunodeficiency

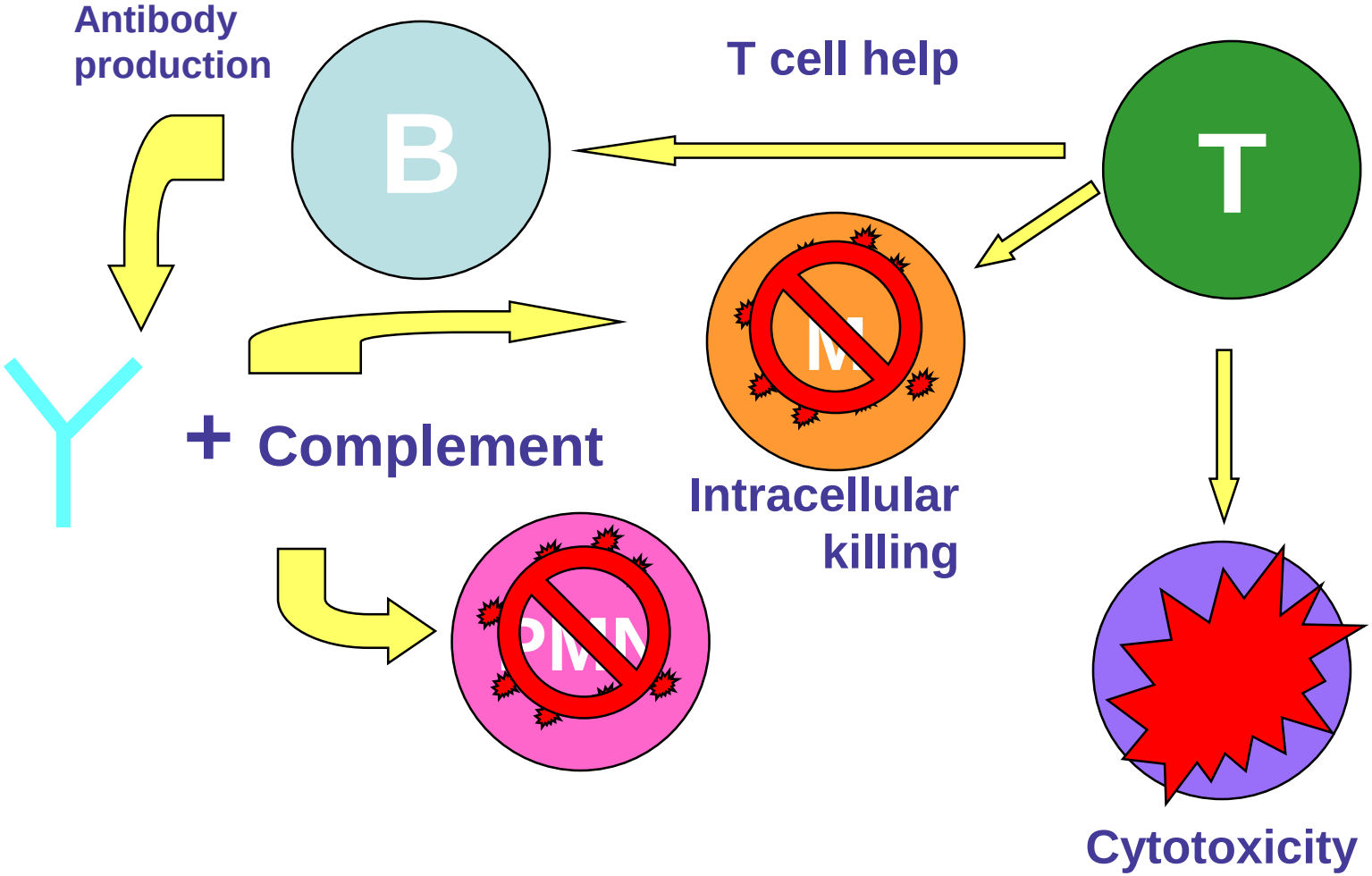


Combined immunodeficiency: pattern of infections

Same as for antibody and cellular deficiencies plus:

- Bacteria: Listeria, enteric flora
- Viruses: herpesviruses, RSV, influenza, parainfluenza, measles (also vaccine strains)
- Fungi: Pneumocystis, Candida, Cryptococcus, Histoplasma
- Protozoa: Toxoplasma, Cryptosporidium

Phagocyte defects



Phagocyte defects: pattern of infections

- Bacteria: catalase-positive S. aureus, enteric flora, Pseudomonas, Salmonella, Nocardia
- Mycobacteria including BCG
- Fungi: Candida, Aspergillus

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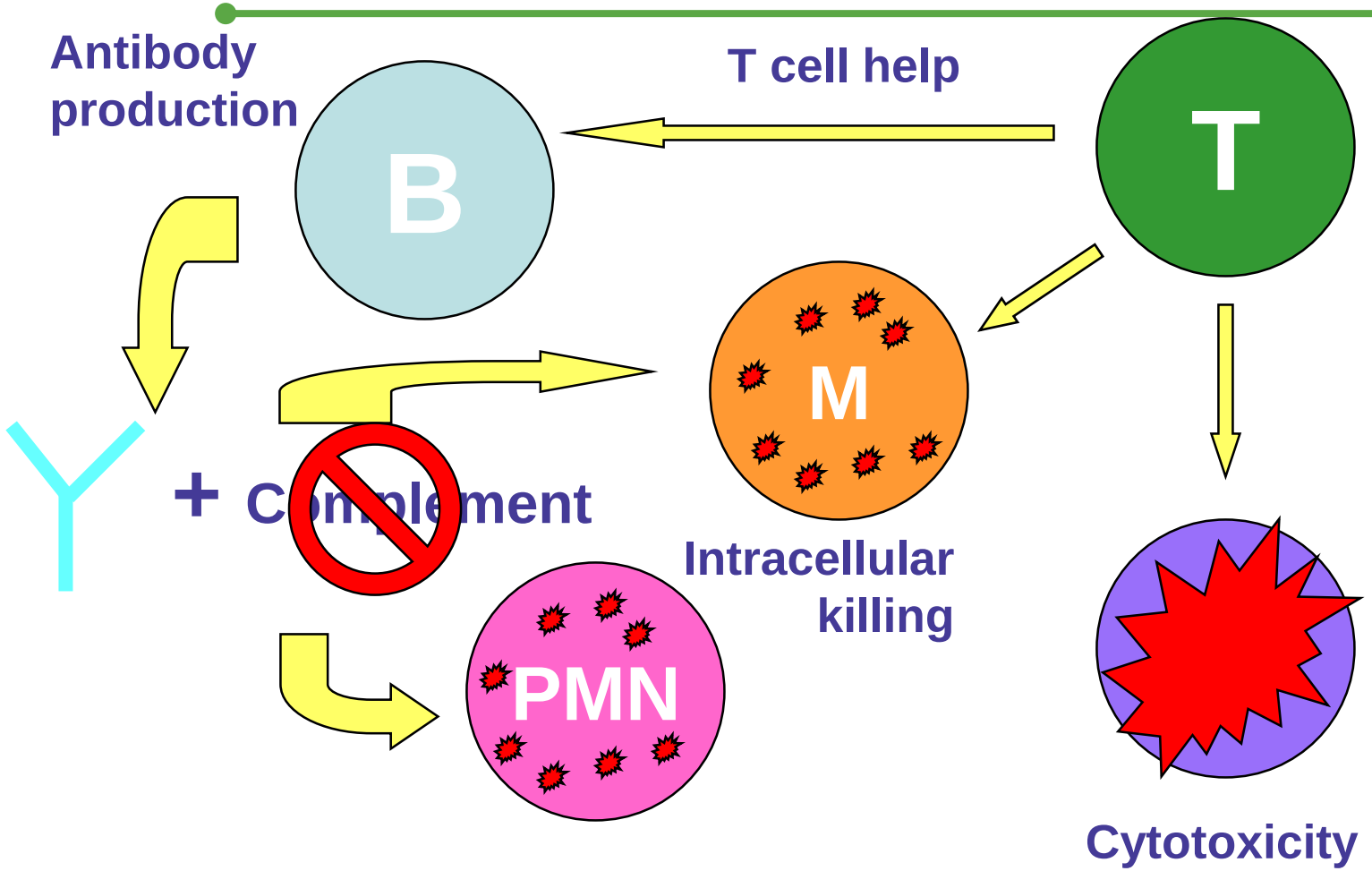
Complement deficiency



Complement deficiency: pattern of infections

- Encapsulated organisms:
  - Neisseria
  - Pyogenic infection
- Autoimmune disease frequent

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IgA deficiency: Diagnosis

- Serum IgA < 7 mg/dL is severe deficiency.
- Partial deficiency is > 7 but less than the lower limit of normal.
- Must have normal IgG and IgM levels.

IgA deficiency: Management

- Treatment is not needed unless associated with another condition (e.g. IgG subclass deficiency) or progresses to common variable immunodeficiency.
- Note that risk of malignancy is moderately increased.
- Risk of severe anaphylaxis to blood transfusions
  - Blood products should be from IgA deficient donor, or at least saline-washed red blood cells.

Antibody Deficiencies: Specific Diagnoses

Common Variable Immunodeficiency (CVID)

IgG Subclass Deficiency

Specific Antibody Deficiency

Transient Hypogammaglobulinemia of Infancy

Agammaglobulinemia

- X-linked
- Autosomal Recessive

Hyper IgM Syndrome (HIGM)

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

Common Variable Immune Deficiency

Infection Susceptibility: Bacteria, common respiratory and enteroviruses (including vaccine strains), rotavirus, giardia, cryptosporidium

Clinical Features: Recurrent sinopulmonary infections, bronchiectasis, diarrhea, arthritis, giardiasis, autoimmunity (20%), asthma (10%), lymphoproliferative disease, gastric CA and lymphoma

Inheritance: sporadic, autosomal recessive

Diagnosis: Hypogammaglobulinemia (IgG, IgA, IgM), B cells present. Impaired antibody response

Lab Tests

- Serum concentrations of IgM, IgG, IgA are reduced
- Usually a normal number of B cells
- A variable degree of T-cell dysfunction
- Isohemagglutinins are absent
- Responses to protein and polysaccharide vaccines are poor

- Malignancies are increased in patients with CVID. A 100-fold increased risk for malignant lymphoma and a 50-fold increased risk for gastric cancer with CVID

Clinical Features

Autoimmune disorders:

- Idiopathic thrombocytopenia (**ITP**), autoimmune hemolytic anemia, pernicious anemia, rheumatoid arthritis, systemic lupus erythematosus in patients with CVID.

- Sarcoid-like gramulomata of the lungs, liver, spleen and conjunctivae also may affect patients with CVID.

Lab tests in immunodeficiency

Persistent **lymphopenia** can be a sign of cellular **immunodeficiency**. Lymphopenia is defined as less than 3000 cells/mm3 in infants, whereas in older children or adults, a total lymphocyte count of less than 1500 cells/mm3 is abnormal.

Lab tests in immunodeficiency

- Thrombocytopenia and small platelet size are characteristic of patients with Wiskott-Aldrich syndrome
- Autoantibodies causing autoimmune hemolytic anemia, thrombocytopenia or neutropenia can occur in some of the B-cell immunodeficiencies

Lab tests in immunodeficiency

- Quantitation of serum immunoglobulins (IgG, IgM, IgA) is the first step in evaluating humoral or B-cell immunity
- Low IgA level – IgA deficiency or other immunoglobulin deficiency diseases
- High IgM level – hyper-IgM syndrome

Lab Diagnosis

- CBC, ESR
- B cell defects
- Screening tests
- IgA, IgM, IgG measurement
- Isohemagglutinins
- Antibody titers to tetanus, diphtheria, S. Pneumoniae, H. influenzae

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Advanced Tests

- B cell enumeration (CD19 or CD20)
- IgG subclass estimation
- In vitro stimulation of B cells to produce immunoglobulins

CVID: Diagnosis

- Serum IgG below 500 + low IgA or IgM + poor vaccine response + no other immunodeficiency (i.e. HIV).
- Repeat Ig levels in 3 months if they had nephrotic syndrome or protein-losing enteropathy.
- Acute illness or short-term steroids will not affect levels, but chronic glucocorticoids may reduce IgG levels.

CVID: Management

- IgG replacement either IV or SC, by immunologist about once a month.
- Should consult an immunologist before giving any live vaccines, which include:
  - MMR
  - Varicella
  - Zostavax
  - Yellow fever
  - Rotavirus
  - Oral typhoid
- Vigilant medical follow-up