Systemic Allergic & Immunoglobulin Disorders

Bryan L. Martin, DO, MMAS
Associate Dean, Graduate Medical Education/DIO
Associate Medical Director, University Hospital
Professor of Clinical Medicine and Pediatrics

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Disclosures

- None

Objectives

- Pass the boards!

- Categorize primary immunodeficiencies by presenting symptoms and results of testing
- Recognize oral allergy syndrome
- Recognize and advise patients with food allergies
- Understand the current evaluation and treatment of patients with allergic reactions to medication

Primary Immunodeficiencies

- First recognized in 1952
- Over 200 genetically determined immunodeficiency diseases recognized
  - Molecular basis known for 80%
- Patient usually looks overtly normal
  - So when there is a visible abnormality, it is a great test question.

Immune System
Self Defense and Surveillance

- Innate
  - Non specific
- Specific
  - Use recognition and receptors
  - Can clonally expand

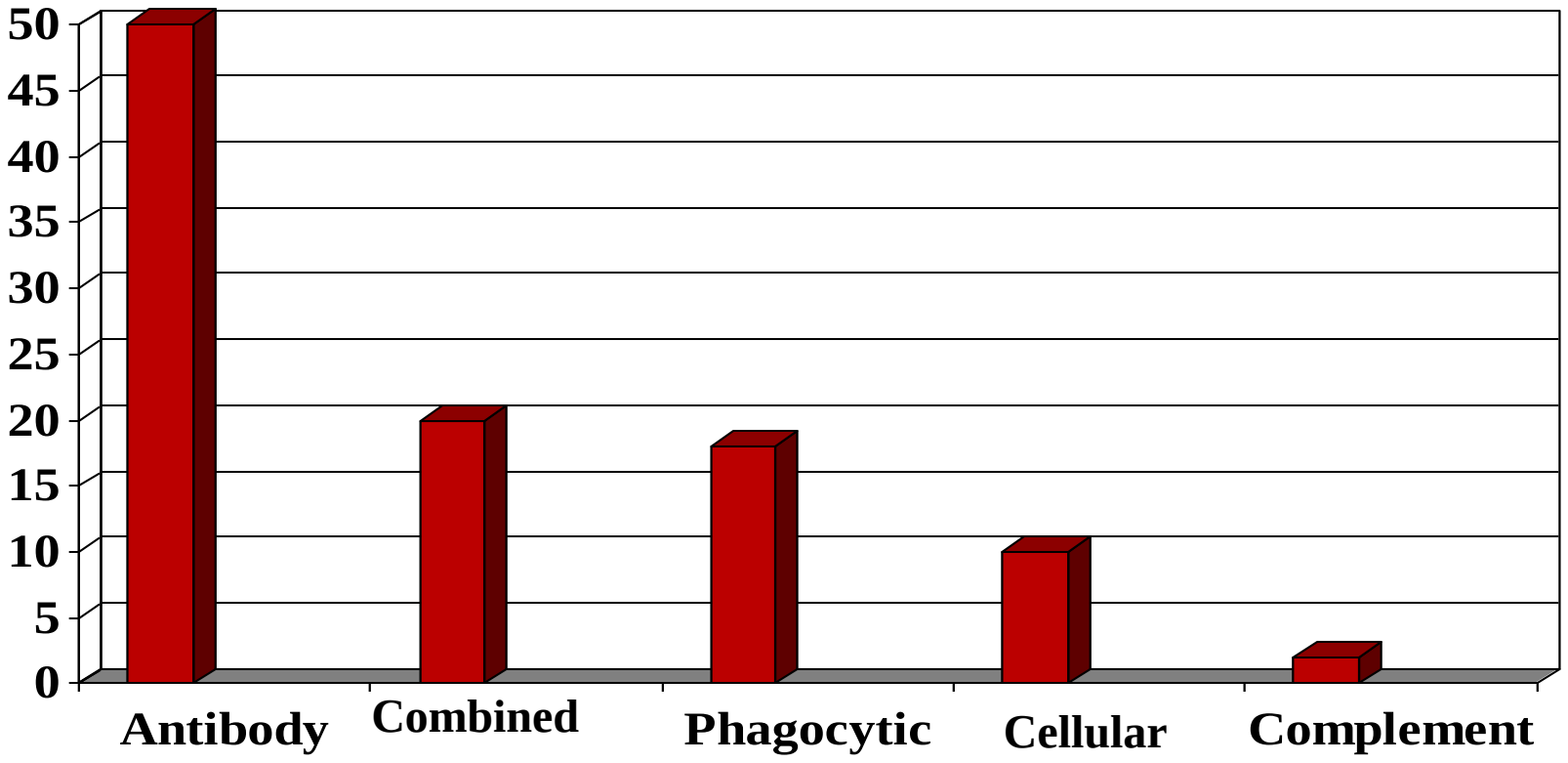
Immune system Components
Non specific

- Complement
  - Critical role against bacteria, fungi and virus
- Phagocytes
  - Macrophages, neutrophils, NK cells

Immune system Components
Specific: Lymphocytes

- Recognition: Antigen Specific
  - B-cell
  - T-cell
- Each receptor on cell is identical
- Need 10-100 million different and unique lymphocytes

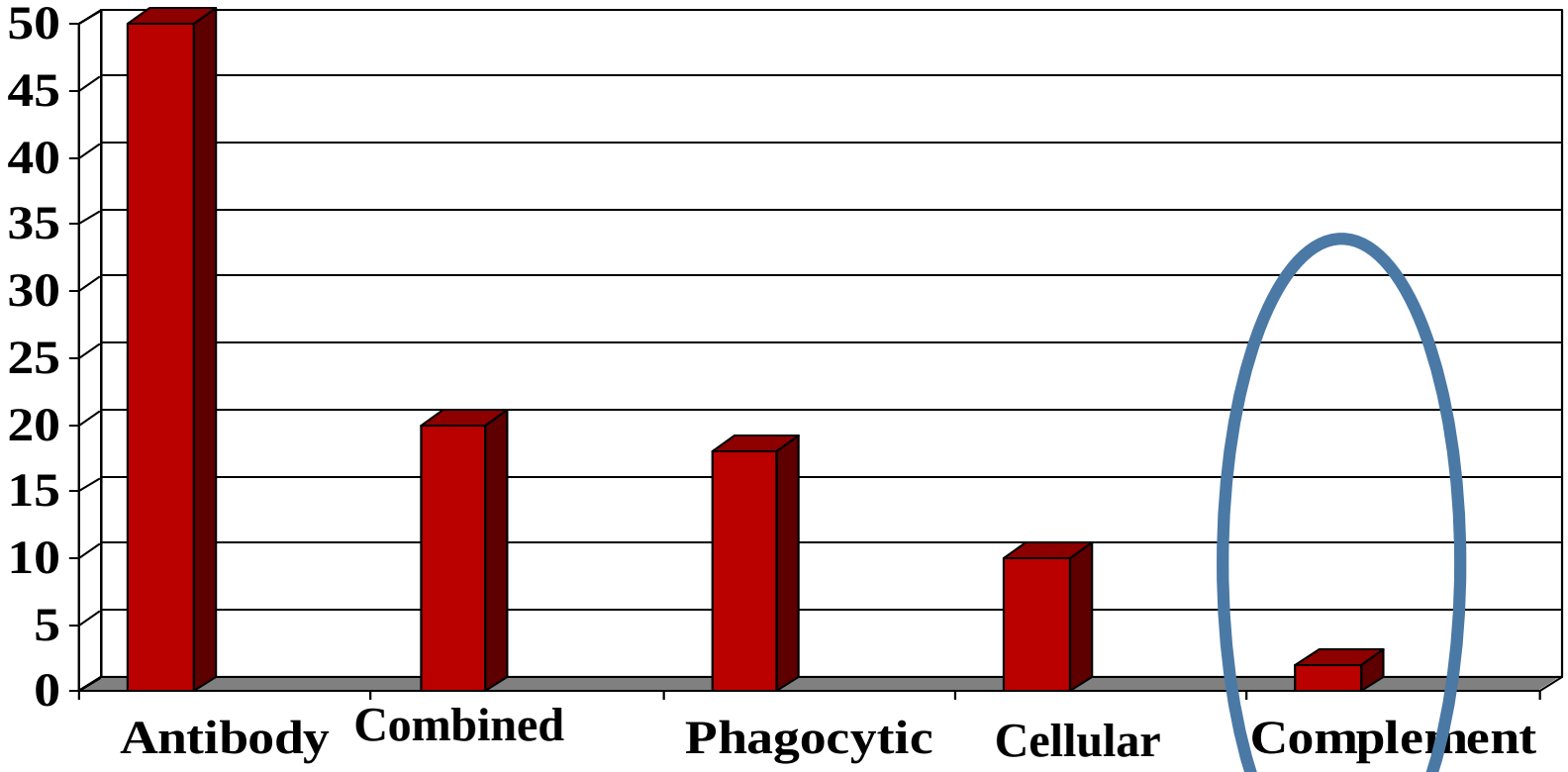
Primary Immunodeficiencies
Relative Distribution



Clues Immunodeficiency

- Features associated with specific immunodeficiency disorders
- Recurrent bacterial otitis media and pneumonia: **Hypogammaglobulinemia**
- Fungal, protozoal and viral infections: **defective cell mediated immunity**
- Uncommon bacteria, typically of low virulence: **chronic granulomatous disease**

Primary Immunodeficiencies
Relative Distribution



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

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

Deficiency of early components

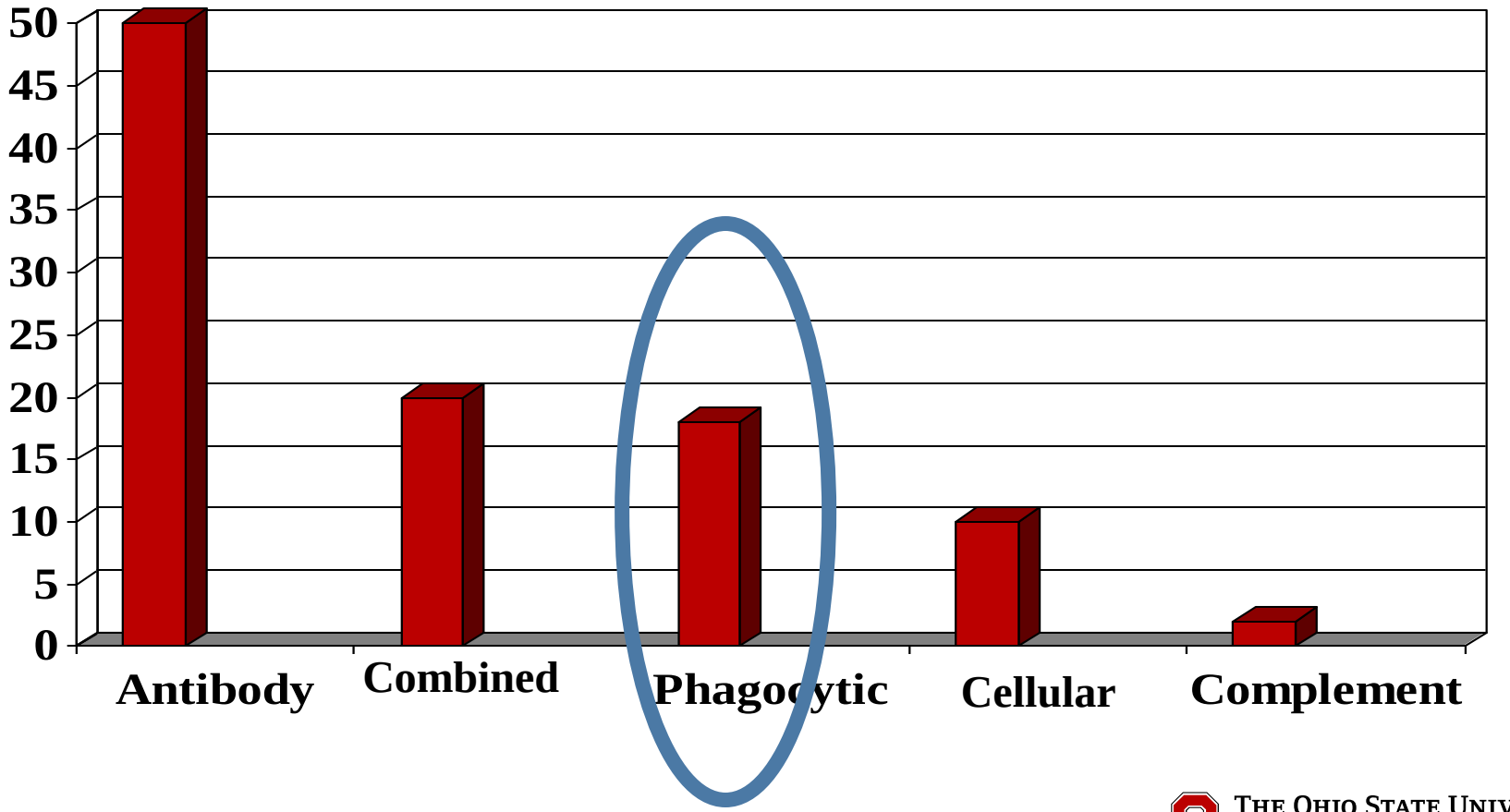
- C1,C4 or C2 deficiencies
  - Similar to C3 deficiency, as these components are necessary for activation of C3 via classical pathway
  - Not as susceptible as those with C3 deficiency
- Most common inherited complement deficiency is C2
  - Approximately 1 in 10,000

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



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

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

LAD I

- Lack the leukocyte integrin CD11/CD18 complex
- CELL SURFACE integrins LFA-1, CR3, p150,95 are deficient
- May be partial (2-8%) or complete
- Autosomal recessive: chromosome 21q22.3 (codes CD18)

LAD II

- Defect is on the endothelial cells, not leukocytes
- Normal levels of CD18
- defective expression of sialyl-Lewis X
- Very rare

LAD III

- Doubt this will be tested
- Previously considered LAD I variant
- Affects beta-1, beta-2 and beta-3 integrin families
  - Both leukocytes and platelets affected
- LAD + bleeding complications
- Poor prognosis without BM transplantation

Phagocytic Dysfunction

- Chronic Granulomatous Disease
- Glucose-6 phosphate dehydrogenase deficiency
- Chediak-Higashi Syndrome
- Job's Syndrome

Phagocytic Dysfunction: Clinical Characteristics

- Range from mild skin infections to severe systemic infections
- Mainly susceptible to low grade virulent bacterial infections
- Skin infections, furunculosis, organ abscess, lymphadenitis
- Delayed separation of the umbilical cord

Chronic Granulomatous Disease

- Most cases are X-linked
  - Affected gene codes for gp91
  - 2006: 2 cases treated with gene therapy and stem cell transplant
    - cleared infections (difficult due to indolent infections)
    - Guarded outlook
- Autosomal recessive similar treatment and prognosis

Screening Tests: Phagocytosis

- Leukocyte count with differential: measures total number of neutrophils
- Nitro Blue Tetrazolium (NBT), chemiluminescence: measures neutrophil metabolic function
  - Blue is good: Normal neutrophils turn NBT to blue
- Dihydrorhodamine 123 (DHR) is a newer test
  - Dihydrorhodamine is reduced to rhodamine by normal cells
- Cytochrome c reduction assay

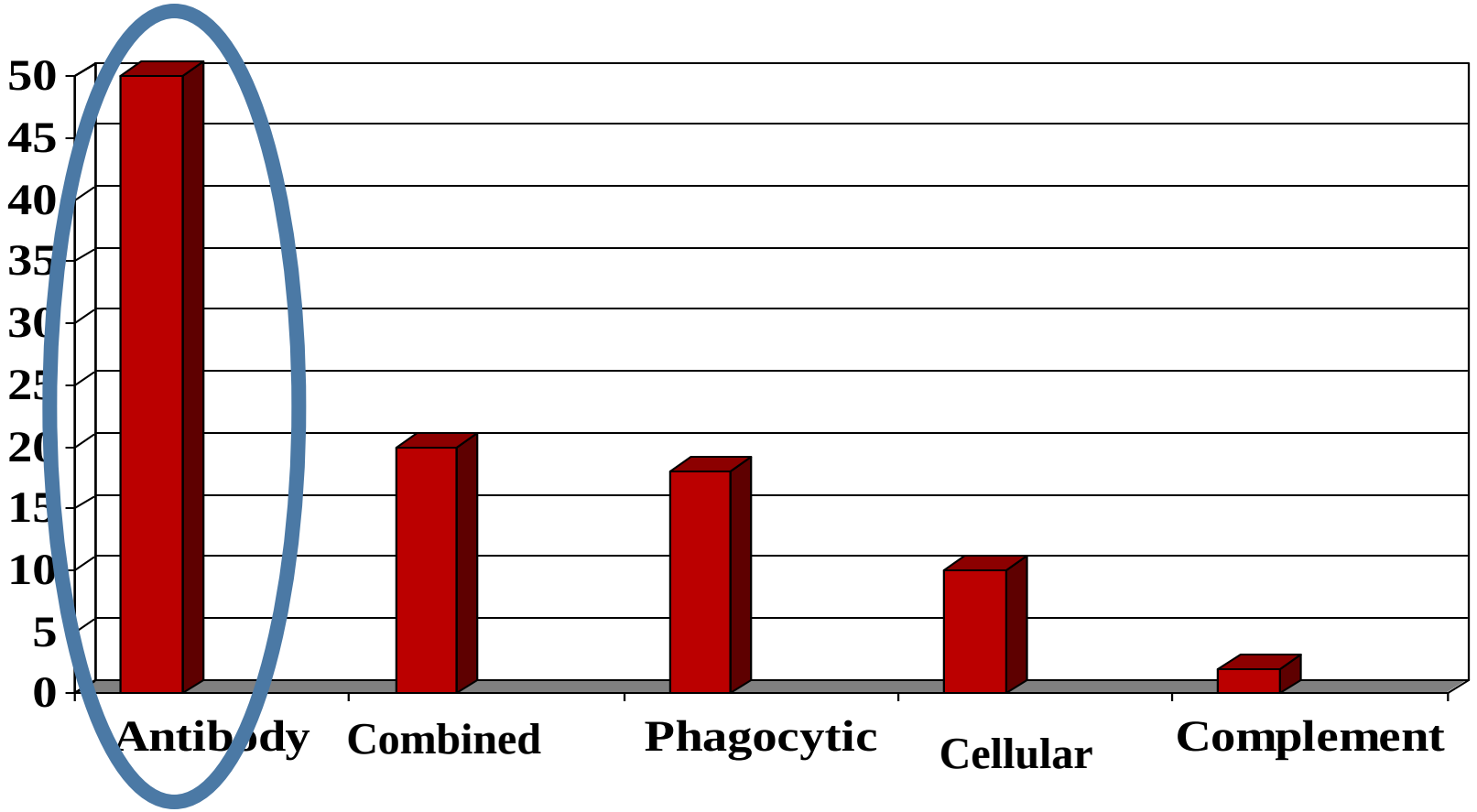
Chronic Granulomatous Disease

- Nitroblue tetrazolium test, quantitative killing curve, superoxide generation or chemiluminescence
  - Functional defect in respiratory burst
- X-linked (autosomal variant)
- Symptoms by 2 years of age
- May survive into second decade and beyond with TMP-SMX prophylaxis

Chediak-Higashi Syndrome

- Phagocytic Dysfunction
- Characteristic abnormality: **Giant cytoplasmic granular inclusions in leukocytes and platelets on routine peripheral blood smears.**
- Autosomal recessive
- Poor prognosis, but may live into 3rd decade

Primary Immunodeficiencies
Relative Distribution



Antibody (B-Cell) Immunodeficiency Disorders

- Transient hypogammaglobulinemia of infancy
- Common Variable immunodeficiency
- X-linked (congenital) hypogammaglobulinemia
- Immunodeficiency with hyper-IgM
- Selective deficiencies
  - IgA; IgM; IgG subclasses
- X-linked lymphoproliferative disease
- Duncan's Syndrome: X-linked lymphoproliferative syndrome
- Secondary (drugs, protein losing states)

B-Cell Deficiencies
Clinical Characteristics

- Onset of symptoms: 7-9 months
- Recurrent infections--high grade bacterial pathogens
- Chronic sinopulmonary infections
- Few problems with fungal or viral pathogens
- No growth failure, survival with treatment
- May or may not lack palpable lymph nodes/lymphoid tissues
- Increased allergy/autoimmune diseases

Antibody-mediated Immunity Tests

- Quantitative Immunoglobulins
  - IgG, IgM, IgA
- Isohemagglutinin titer (anti-A and Anti-B): measure IgM antibody function primarily
- Specific antibody levels following immunization
  - Look for 4 fold increase in titer

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

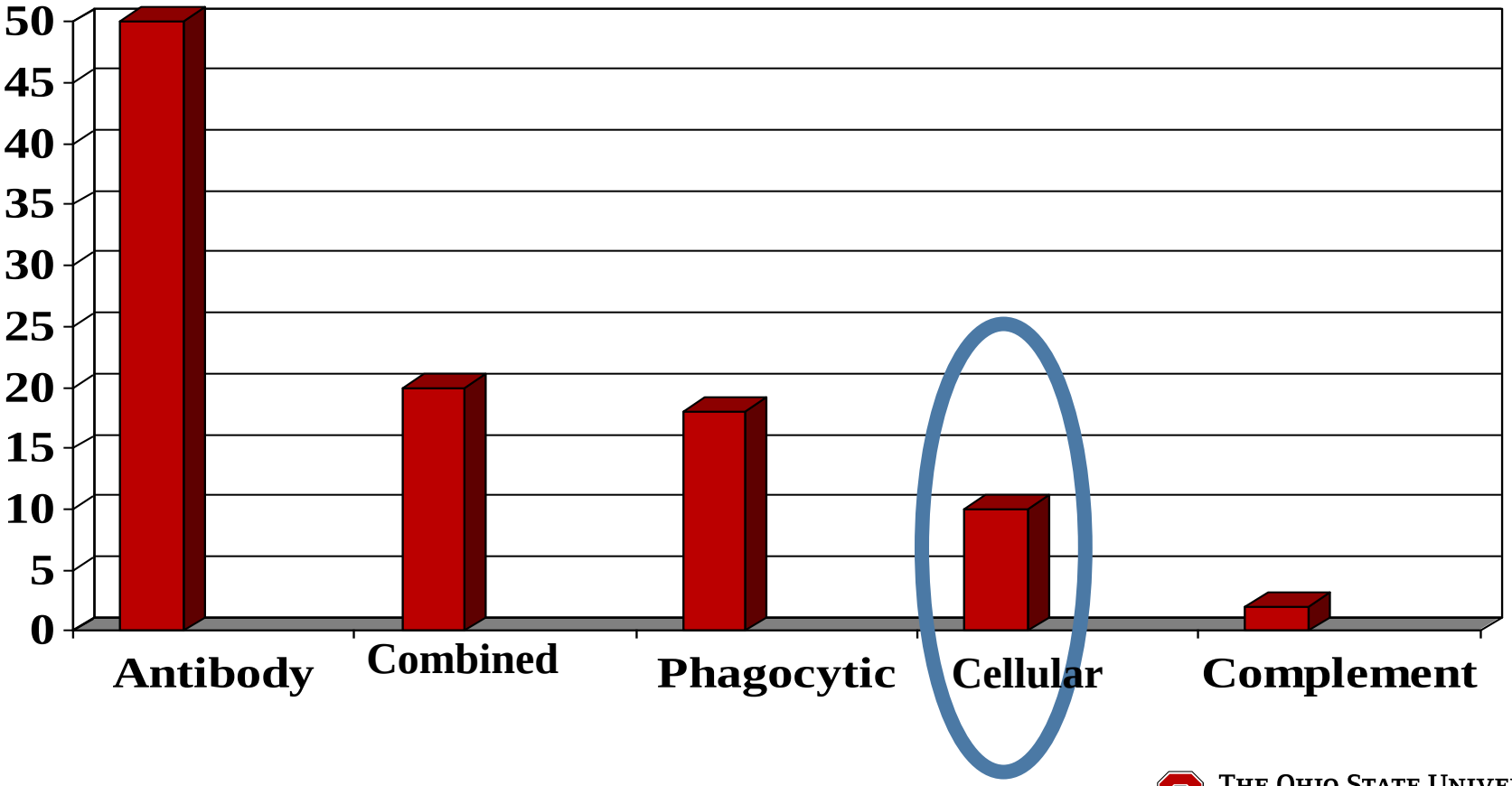
Common Variable Immunodeficiency

- 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

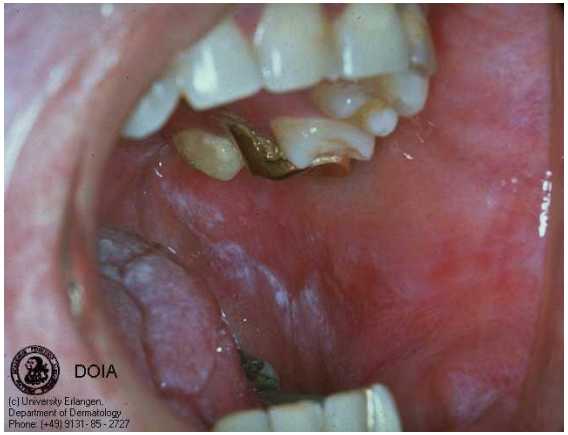
Primary Immunodeficiencies
Relative Distribution

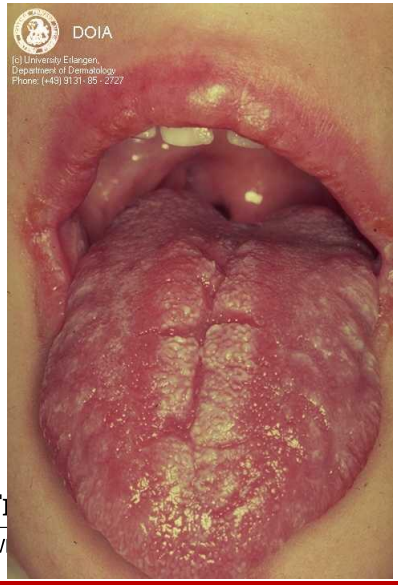


T-cell Immunodeficiency Disorders

- DiGeorge's Syndrome: Congenital Thymic Aplasia

- Chronic Mucocutaneous Candidiasis

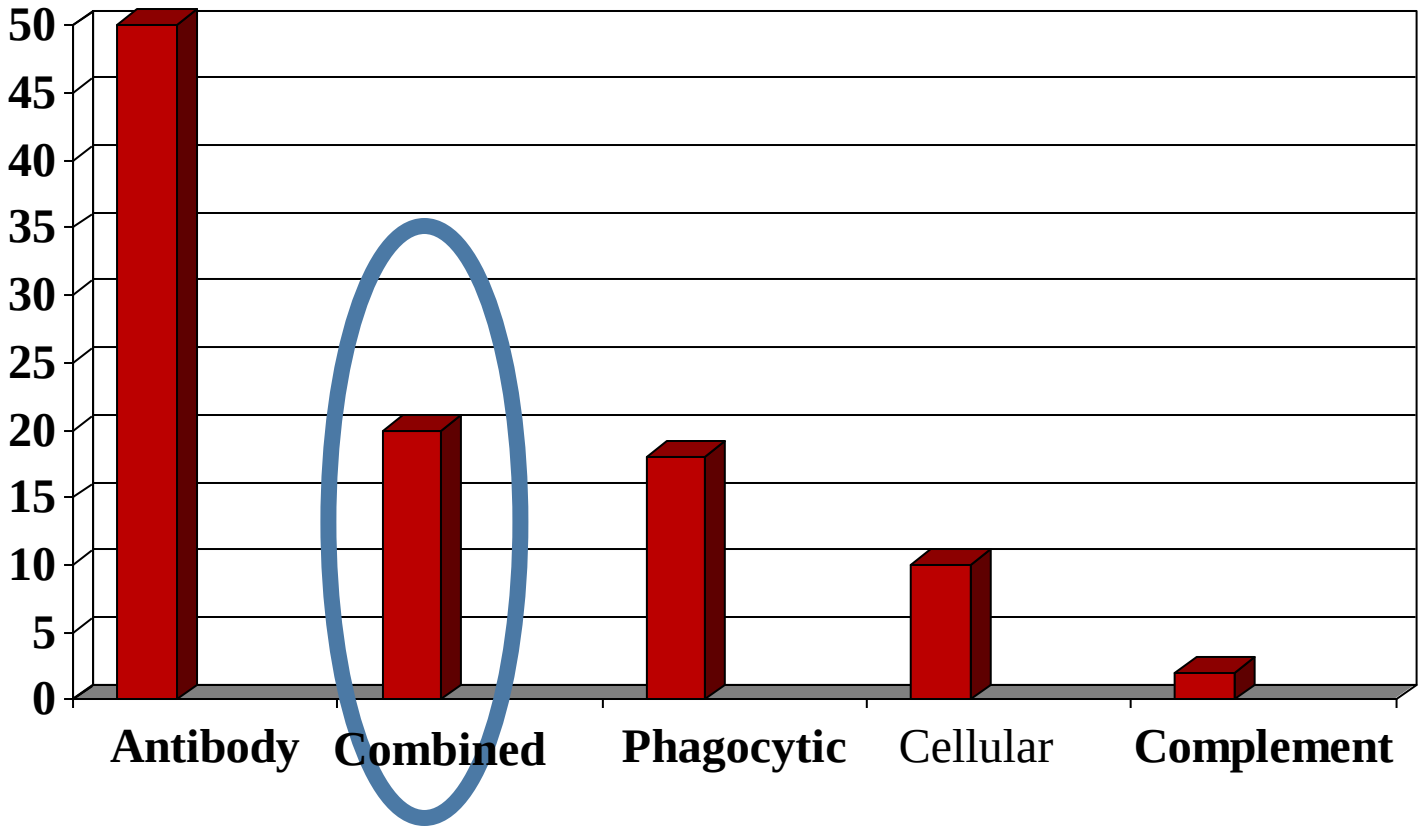




Chronic Mucocutaneous Candidiasis

- 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

Primary Immunodeficiencies
Relative Distribution



T-Cell Deficiencies
Clinical Characteristics

- Onset frequently early infancy (4-5 months)
- Recurrent infections
- Opportunistic infections
- Failure to thrive, often fatal in childhood
- Fatal infections--Live virus vaccines or BCG vaccination
- Graft vs. Host disease following blood transfusions
- Increased incidence of malignancy

T-cell Immunity Screening Tests

- Absolute lymphocyte count
- Chest x-ray for thymus shadow in the newborn period
- Delayed skin hypersensitivity to recall antigens
- Quantitation of T-cell subsets

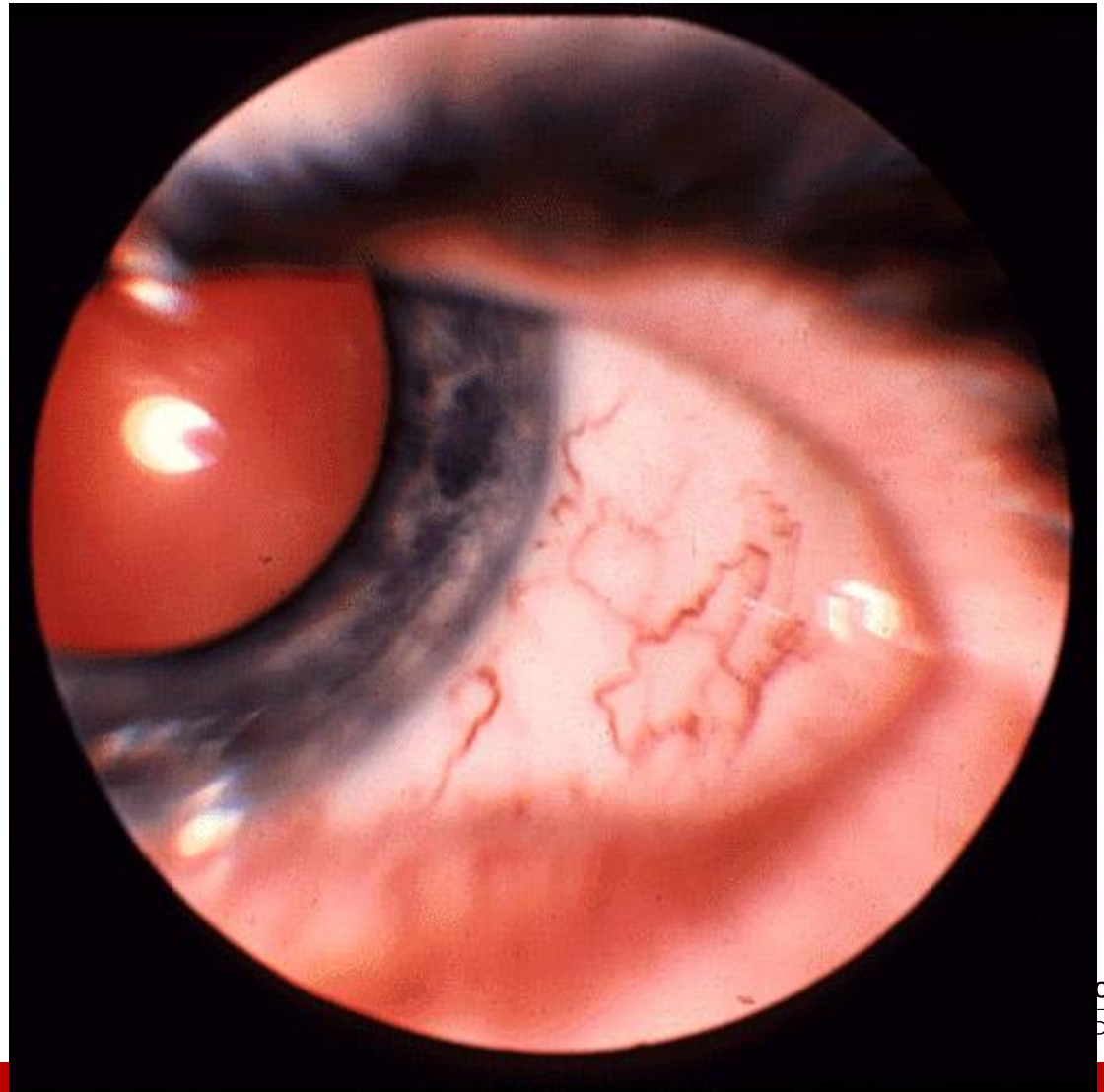
Combined B and T cell Immunodeficiency disorders

- SCID: Severe Combined Immunodeficiency Disease
- Nezelof's Syndrome: Cellular Immunodeficiency with abnormal immunoglobulin deficiency
- Immunodeficiency with Ataxia-Telangiectasia
- Wiskott-Aldrich Syndrome: Immunodeficiency with **Thrombocytopenia**, Eczema and Recurrent Infection
- Graft vs Host

Immunodeficiency with Ataxia-Telangiectasia

- May reach 5th decade of life
- Predisposition to malignancies
- Autosomal recessive
- Progressive deterioration of neurologic and immunologic functions
- Cerebellar ataxia, oculocutaneous telangiectasias

Oculocutaneous Telangiectasia:
Immunodeficiency with Ataxia-Telangiectasia



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

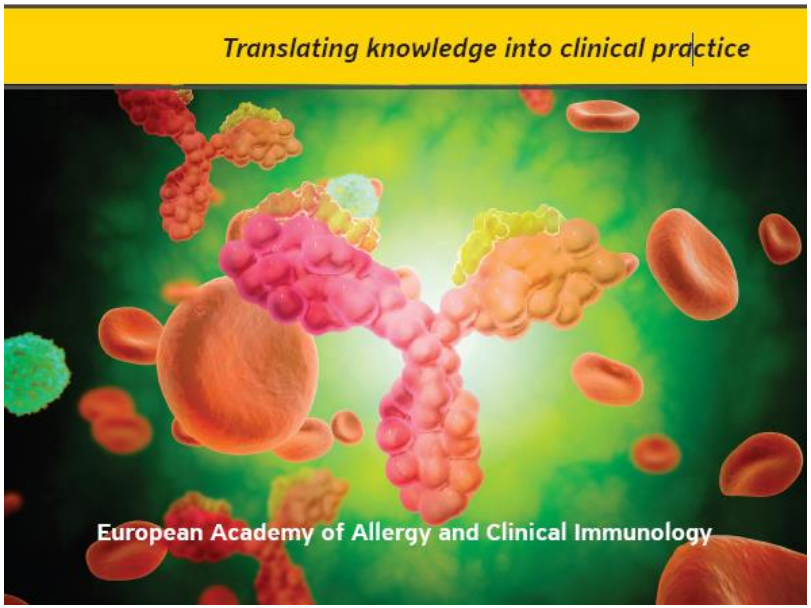
Graft vs Host

- **Hyperacute**
  - maculopapular rash with rapid progression to that resembling toxic epidermal necrolysis, associated with severe diarrhea: Death shortly after reaction
- **Acute**
  - Initial maculopapular rash
  - Diarrhea, hepatosplenomegaly, jaundice, cardiac irregularity, CNS irritability, pulmonary infiltrates
- **Chronic**
  - Chronic desquamation of skin, dysplastic nail growth, hepatosplenomegaly, chronic diarrhea

Anaphylaxis

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

Food Allergy and Anaphylaxis Guidelines



SUPPLEMENT ARTICLE

THE AMERICAN JOURNAL of MEDICINE®

Anaphylaxis: Underdiagnosed, Underreported, and Undertreated

David A. Sclar, BPharm, PhD,[a] Phillip L. Lieberman, MD, FAAAAI, FACAAI[b]
[a]Midwestern University, Glendale, Ariz; [b]University of Tennessee College of Medicine, Germantown, Tenn.

ABSTRACT

Diagnostic criteria and administrative codes for anaphylaxis have evolved in recent years, partly reflecting the challenges in recognizing anaphylaxis and understanding its symptoms. Before the diagnostic criteria were disseminated by the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network, several studies showed that a substantial proportion of anaphylaxis cases presenting

Practice parameter

The diagnosis and management of anaphylaxis practice parameter: 2010 Update

Chief Editors: Phillip Lieberman, MD, Richard A. Nicklas, MD, John Oppenheimer, MD, Stephen F. Kemp, MD, and David M. Lang, MD

Workgroup Contributors: David I. Bernstein, MD, Jonathan A. Bernstein, MD, A. Wesley Burks, MD, Anna M. Feldweg, MD, Jordan N. Fink, MD, Paul A. Greenberger, MD, David B. K. Golden, MD, John M. James, MD, Stephen F. Kemp, MD, Dennis K. Ledford, MD, Phillip Lieberman, MD, and Albert L. Sheffer, MD

Task Force Reviewers: David I. Bernstein, MD, Joann Blessing-Moore, MD, Linda Cox, MD, David A. Khan, MD, David Lang, MD, Richard A. Nicklas, MD, John Oppenheimer, MD, Jay M. Portnoy, MD, Christopher Randolph, MD, Diane E. Schuller, MD, Sheldon L. Spector, MD, Stephen Tilles, MD, and Dana Wallace, MD

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These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology.

New US Guidelines expected 2015

- 27 year old known asthmatic presents to your office with acute onset of hives, complaining of shortness of breath, and racing heart after eating shrimp for lunch. He denies any known food allergy. Your response

1. Nebulized beta-agonist
2. IM epinephrine
3. 50 mg benadryl
4. Sub cutaneous epinephrine

Answer: B

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Five More Things Physicians and Patients Should Question

Don't rely on antihistamines as first-line treatment in severe allergic reactions.

Don't perform food IgE testing without a history consistent with potential IgE-mediated food allergy.

Don't routinely order low- or iso-osmolar radiocontrast media or pretreat with corticosteroids and antihistamines for patients with a history of seafood allergy, who require radiocontrast media.

Don't routinely avoid influenza vaccination in egg-allergic patients.

Don't overuse non-beta lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation.

What is Anaphylaxis?

- 2003: WHO defines anaphylaxis as a severe, life-threatening generalized or systemic hypersensitivity reaction.
- 2005: US meeting sponsored by the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) established a consensus definition.
  - Enables researchers to work from a common definition

2005

- NIAID & FAAN consensus definition of anaphylaxis

Table 1 Definition of anaphylaxis

1. Acute onset of illness with cutaneous and/or mucosal involvement AND at least one of the following:
a. Respiratory compromise (e.g. dyspnoea, bronchospasm, stridor, hypoxia)
b. Cardiovascular compromise (e.g. hypotension, collapse)

2. Two or more of the following occur rapidly after exposure to a likely allergen (minutes to several hours):
a. Involvement of skin or mucosa (e.g. generalized hives, itch, flushing, swelling)
b. Respiratory compromise
c. Cardiovascular compromise
d. Or persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

3. Hypotension after exposure to known allergen for that patient (minutes to several hours): age-specific low blood pressure† or greater than 30% decline from baseline (or less than 90 mm Hg for adults).

†Hypotension for children is defined as systolic blood pressure <70 mm Hg from 1 month to 1 year, <(70 mm Hg+[2Xage]) from 1 to 10 year, and <90 mm Hg from 11 to 17 year.

Ben-Shoshan & Clarke, *Allergy* (2011); 66:1-14

Clinical Criteria for Anaphylaxis

Lieberman, Amer J Med. (2014) 127, S6-S11

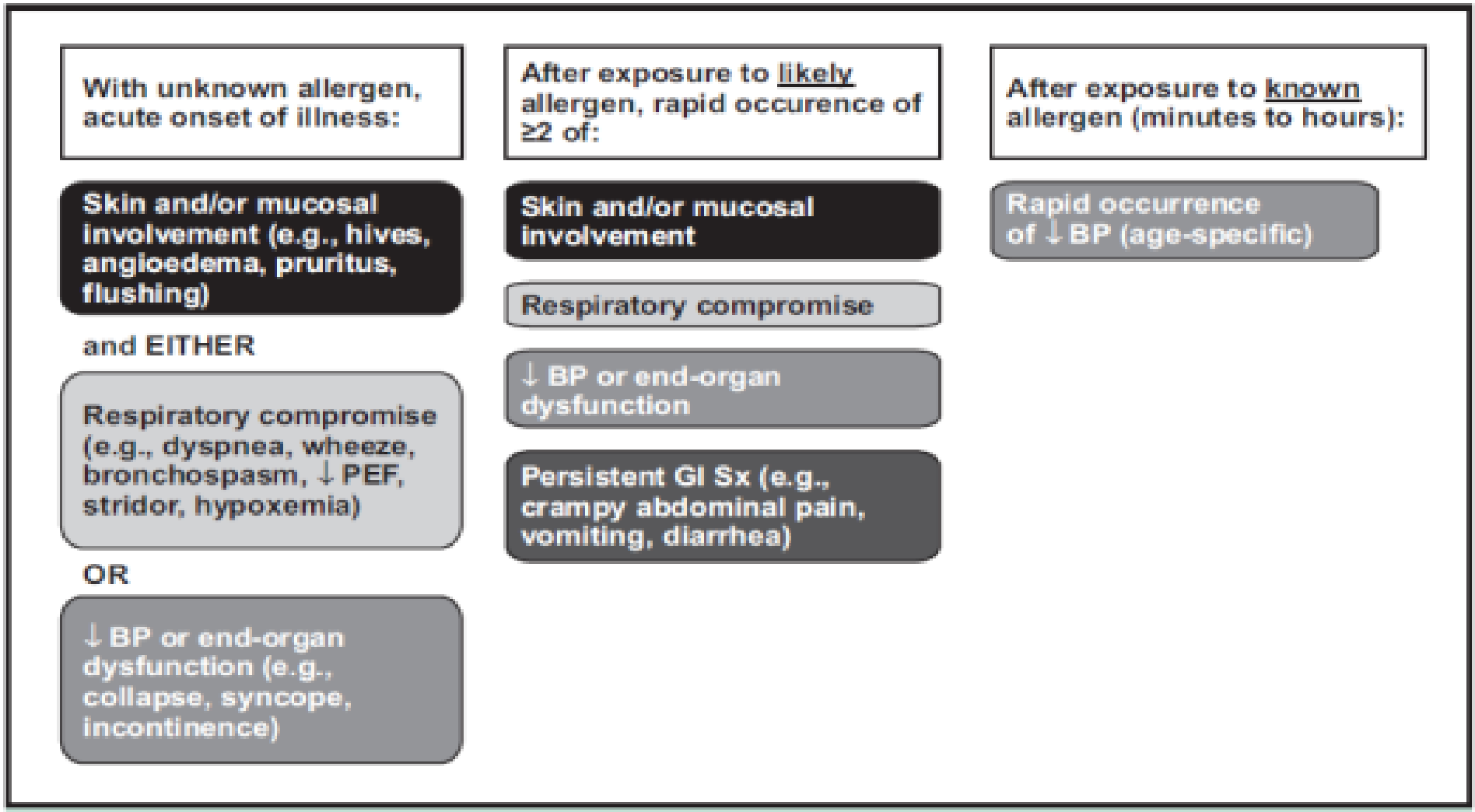

Figure 2 Clinical criteria for the diagnosis of anaphylaxis.[1]

Anaphylaxis Signs & Symptoms

Table 1 Signs and Symptoms of Anaphylaxis

Signs and Symptoms	Frequency (%)
Urticaria, angioedema	88
Dyspnea, wheeze	47
Dizziness, syncope, hypotension	33
Nausea, vomiting, diarrhea, cramping abdominal pain	30
Flush	46
Upper airway edema	56
Headache	15
Rhinitis	16
Substernal pain	6
Pruritus without rash	5
Seizure	2

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Lieberman, *Amer J Med* (2014) 127, S6-S11

Vasovagal Reaction

- Stress or fright
- Slow pulse
- Maintain blood pressure
- Pale, cold clammy skin
- Recumbancy alleviates symptoms
- No urticaria or pruritis

DDX Anaphylaxis

System	Anaphylaxis	Vaso-Vagal Rxn
Cutaneous	Urticaria, erythema	Pale, clammy
Respiratory	Globus, SOB wheezing, SPO2 ↓	Hyperventilation SPO2: ↑
Cardiovascular	Tachycardia, hypotension	Bradycardia, normotensive
G.I.	N, V, D	N, V, D
C.N.S.	"Feeling of impending doom"	Light headed, confused

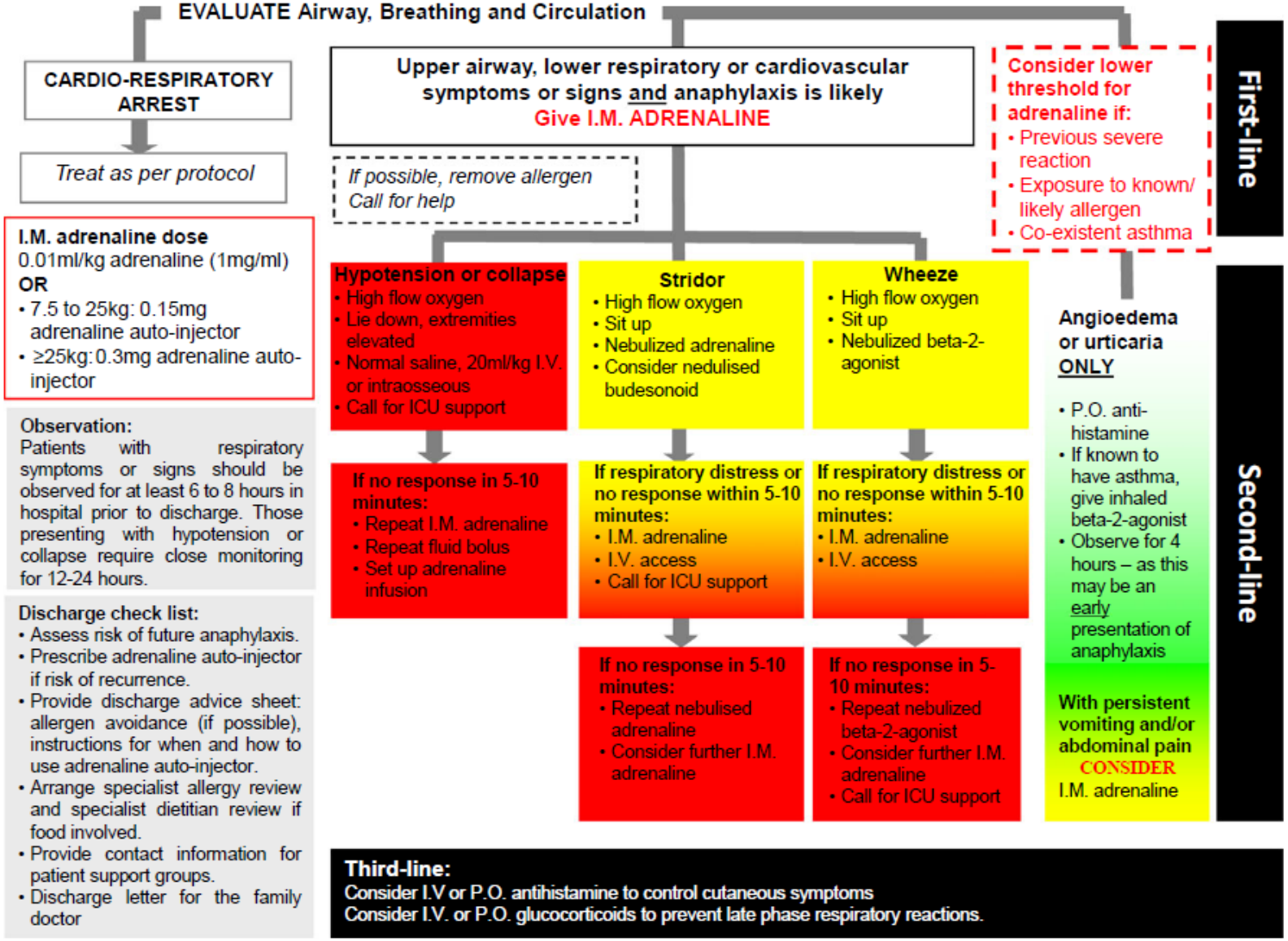

Figure 2 Schematic illustration of the initial management of anaphylaxis.

Anaphylaxis: Treatment

- Stabilize airway
- ***IM Epinephrine***
  - 0.01 mg/kg
- O2
- Large gauge IV
- Benadryl 50-100 mg IV or IM
- Cimetidine 300 mg IV
- Methyprednisolone 125mg IV

Anaphylaxis Management After Initial Assessment

- Antihistamine
- Corticosteroids
- Beta-Agonists for wheezing
- Fluids, Vasopressors
- **Glucagon**
  - Used for nonresponsive anaphylaxis in **patients on beta-blockers**
- Atropine

Anaphylaxis While Receiving Beta-blocker Therapy

- Unusual severity
- Bradycardia during profound hypotension
- Severe sustained bronchospasm
- Total body angioedema
- Refractory to usual treatment
  - Glucagon is used for refractory cases

Treatment of Anaphylaxis: in presence of Beta-blockade

- Aggressive and prompt support
- Epinephrine
- Large volume IV
- **Glucagon**
- Atropine
- Increased dopamine or beta-agonist
- Antishock trousers

Anaphylactoid Reaction

- Resemble anaphylaxis but not immunologically mediated
  - Not IgE mediated
- **Does not require prior sensitization**
  - Reaction may occur on first exposure
- Symptoms = anaphylaxis
- Treatment = anaphylaxis

Anaphylactoid Reactions
Non IgE mediated causes

- Complement-mediated
- Direct activation of mast cell-mediator release
- Arachidonic acid metabolism
- Unknown

Complement Mediated Anaphylactoid Reactions

- Human plasma and blood products
- Dialysis membranes

Direct activation of Mast Cell mediator release

- Opiates
- Vancomycin
- Muscle-depolarizing drugs
- Aminoglycosides
- Radiocontrast media

Direct activation of Mast Cell mediator release

- Radiocontrast media
  - Increased risk with IV administration and high osmolality
  - Sensitization not required
  - Previous reaction increases probability of reaction on rechallenge
  - Anaphylaxis in 1-10% of initial exposures
  - Pretreatment can be given to decrease risk

Modulators of Arachidonic Acid Metabolism

- Aspirin and Nonsteroidal drugs
  - Generally progresses more slowly
  - Less often hypotension
  - Bronchoconstriction, wheezing often begin within 30 minutes and progress for several hours

Anaphylaxis: Differential Diagnosis

- Vasodepressor Reaction
- Flush syndrome
- Restaurant Syndrome
- Other forms of shock
- Endogenous overproduction of histamine
- Red-man syndrome
- Pseudoanaphylaxis

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