MAYO CLINIC

APPROACHES AND ASSESSMENT OF RECURRENT INFECTIONS IN CHILDREN

Avni Y Joshi, MD, MSc

Mayo Clinic, Rochester ,MN
Sept 11,2023

DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

- Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

All relevant financial relationships have been mitigated.

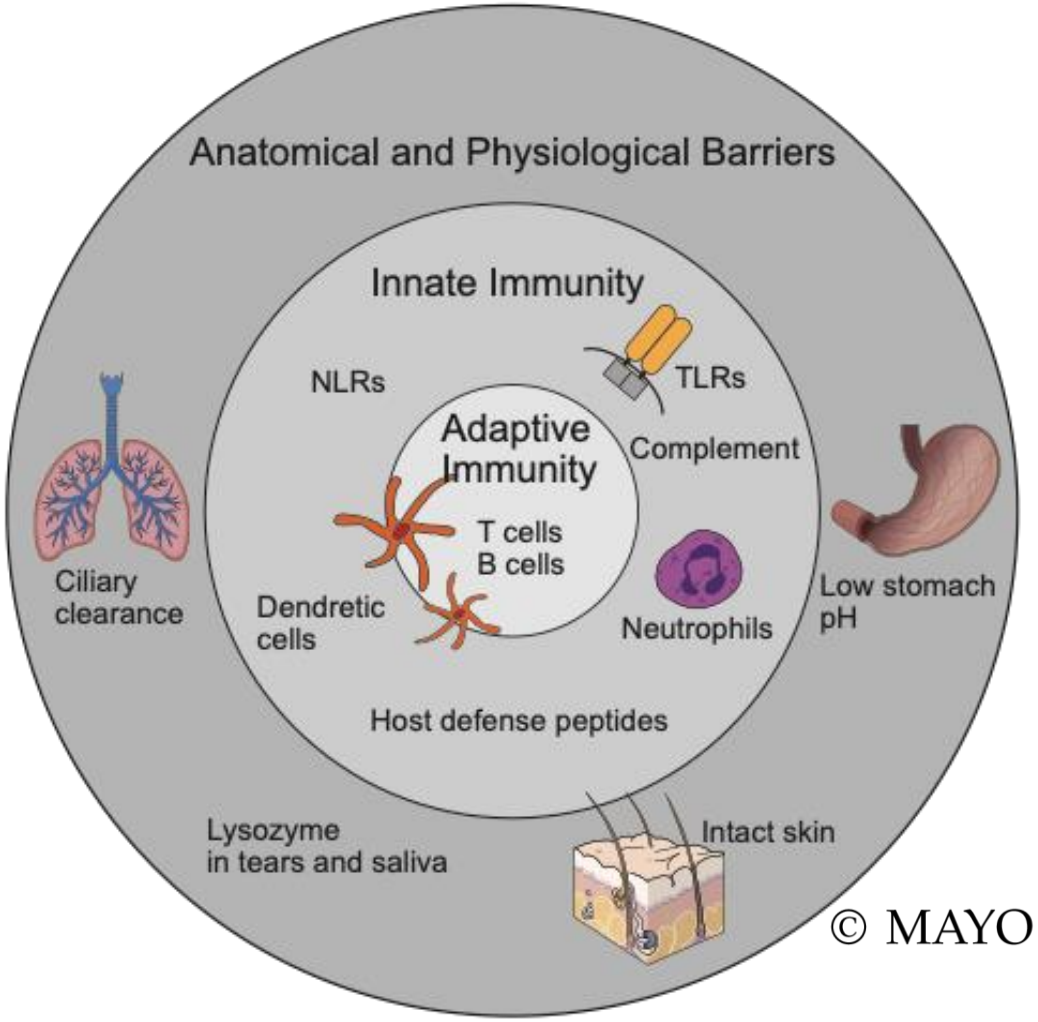
OBJECTIVES

- Recognize when to suspect a primary immune deficiency disorders (PIDD) in a child presenting with recurrent infections
- Decipher the different diagnostic tests available in if you suspect a primary immune deficiency disorders
- Analyze when to seek subspecialty care for recurrent infections

OUTLINE OF THE TALK:

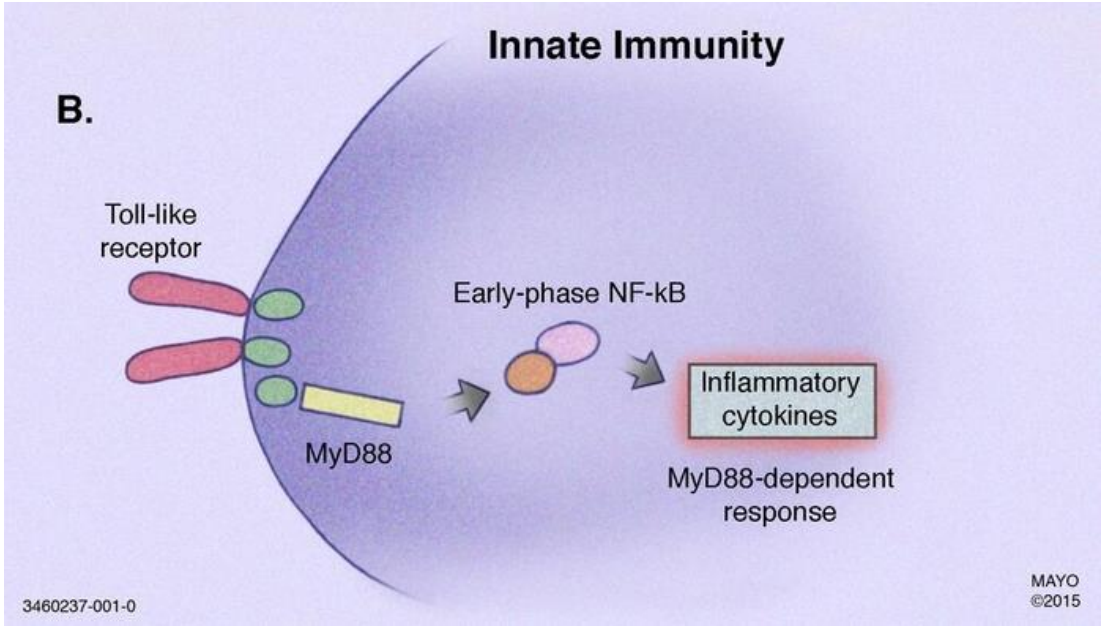
- Overview of the Immune System
- 3 cases: discuss ***less severe*** **and** ***more severe*** forms of recurrent infections
- What a busy primary care physician need to know about investigating recurrent infections

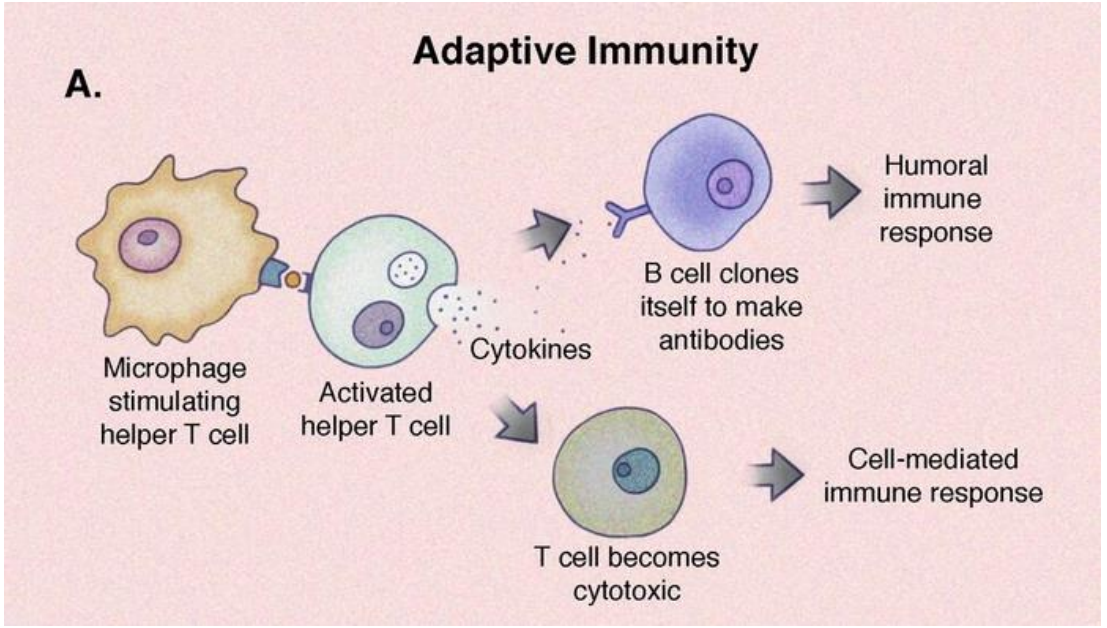
THREE LEVELS OF HUMAN DEFENSE AGAINST INFECTION



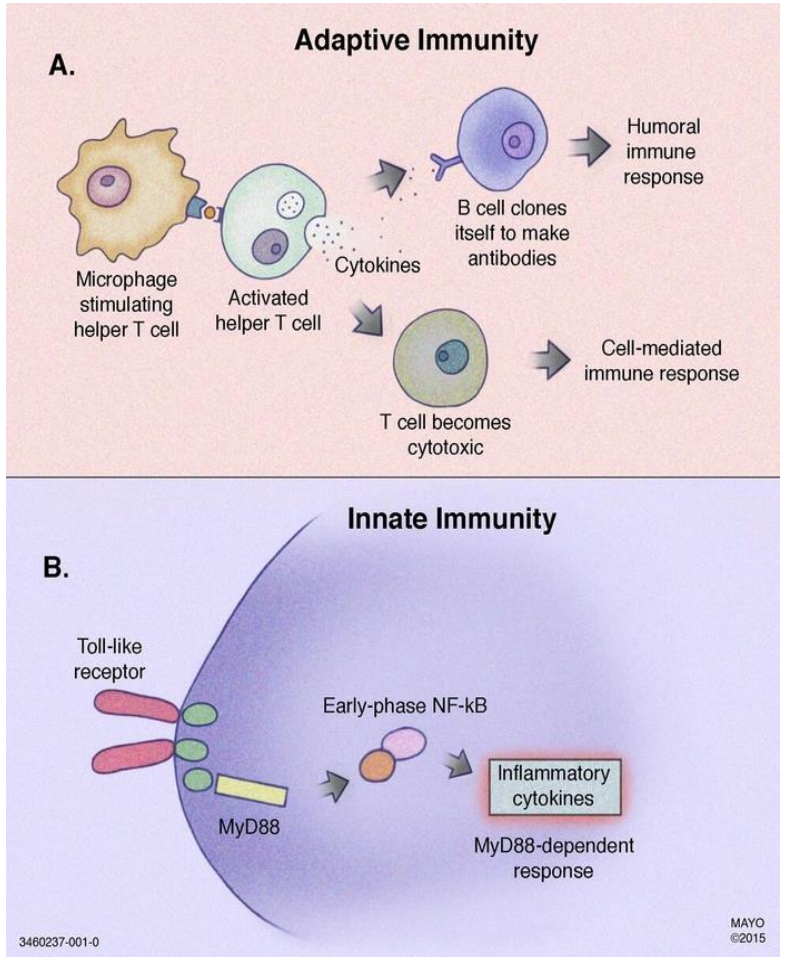
Redrawn from; S Jyothi et al. Arch Dis Child Educ Pract Ed 2013;98:186-196

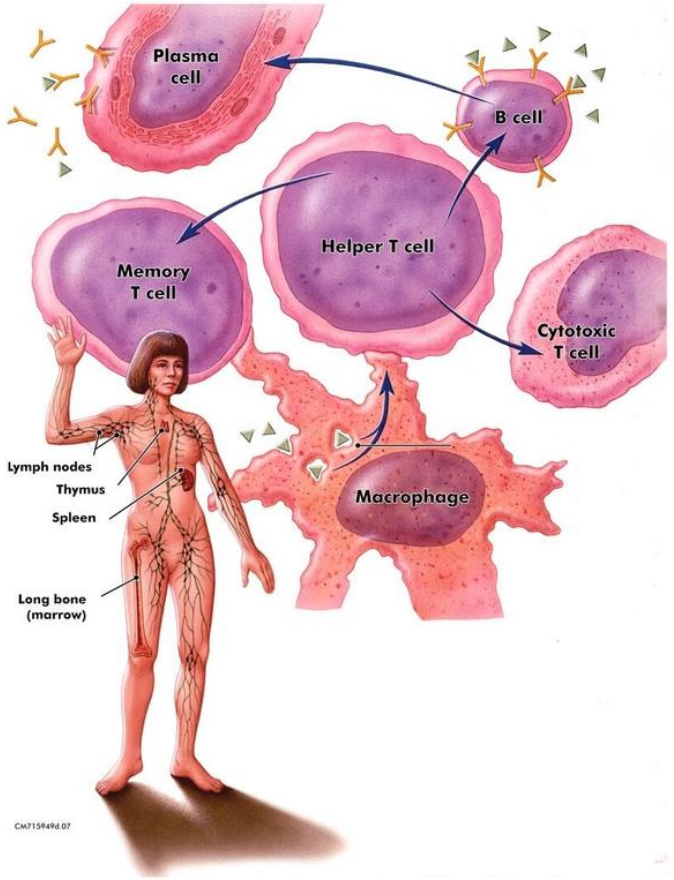
INNATE AN ADOPTIVE IMMUNE SYSTEMS

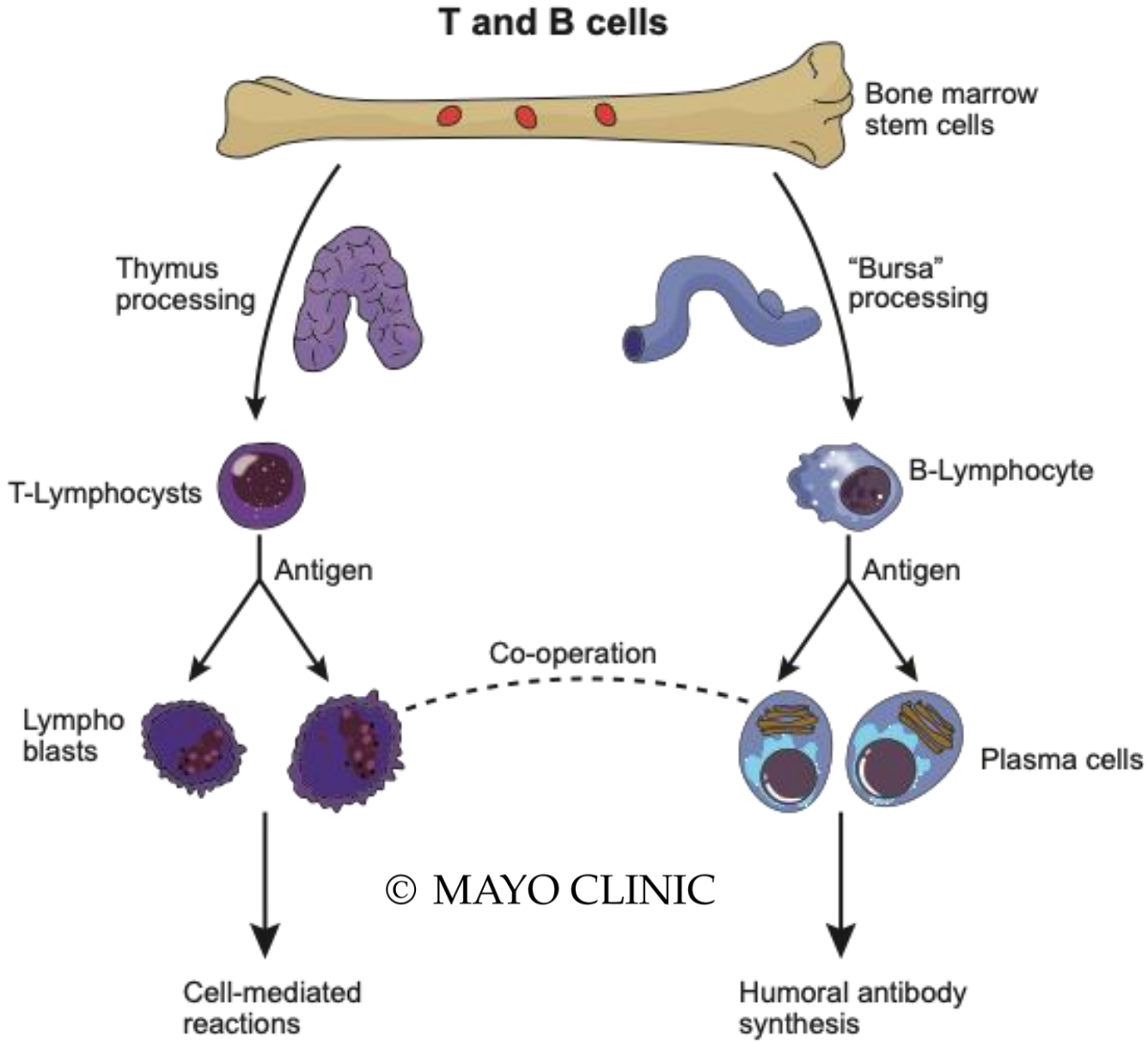




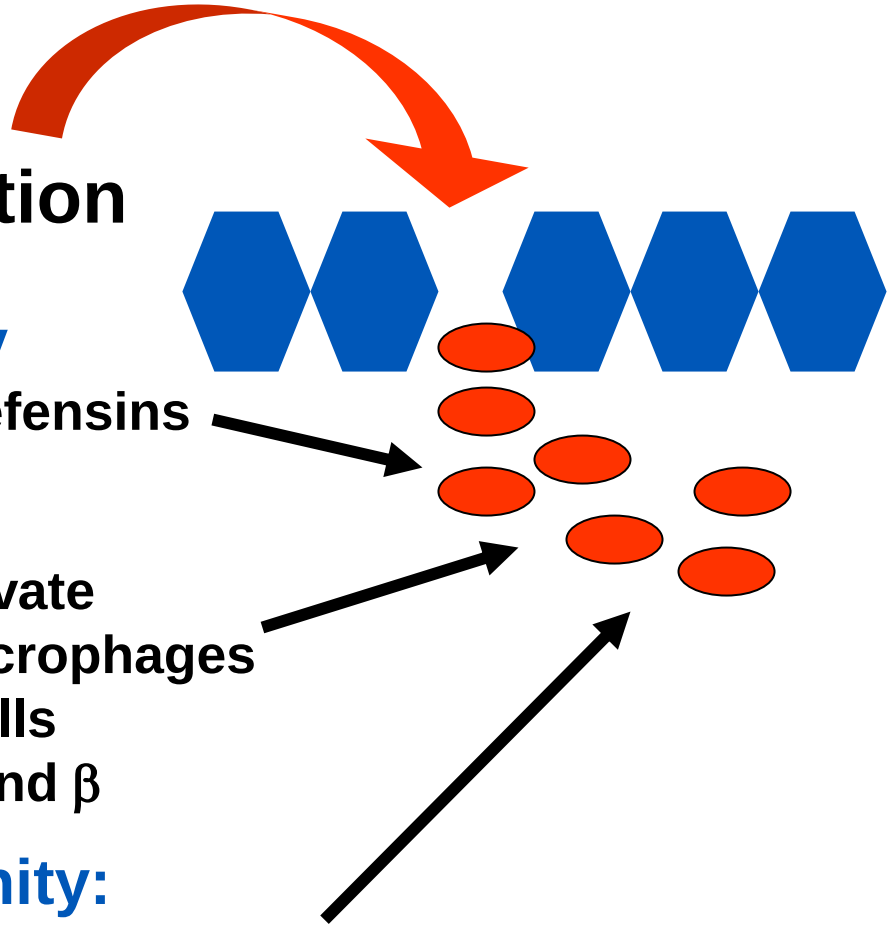
CROSS TALK BETWEEN THE INNATE AND ADAPTIVE IMMUNE SYSTEM







Redrawn from presenter-supplied original; no source supplied.



Timeline:

0-4 hours

Innate immunity

- Complement, defensins

4-96 hours

- Recruit and activate
- neutrophils, macrophages and dendritic cells
- Produce INF α and β

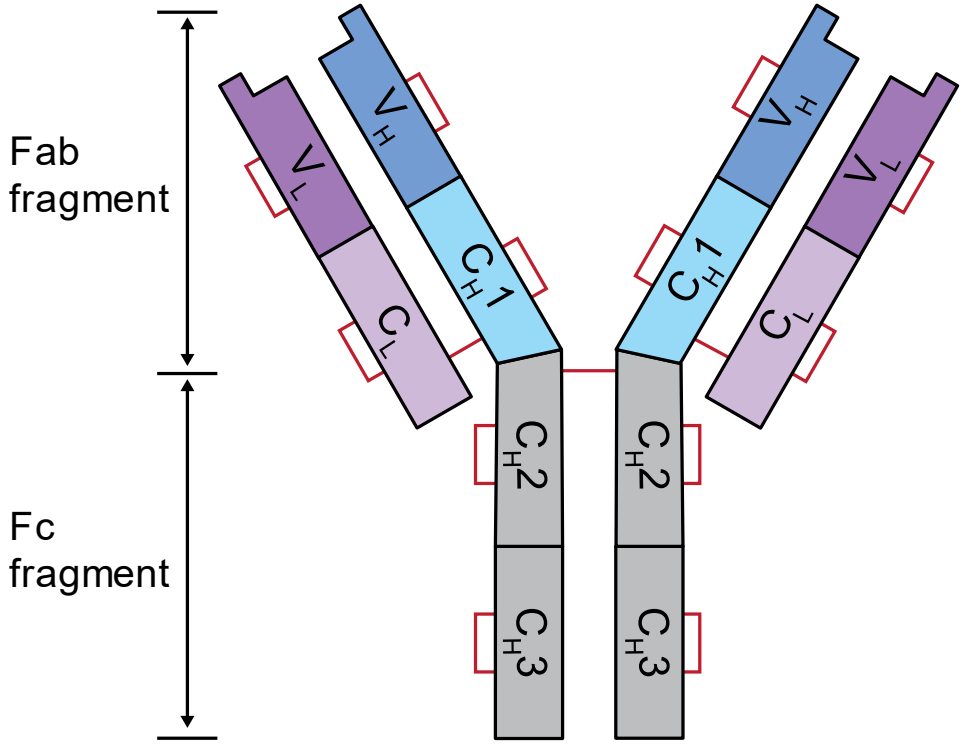
Adaptive immunity:

> 24 hours

- Transport antigen to lymph nodes; activate B and T lymphocytes
- Clonal expansion and differentiation of effector B and T lymphocytes

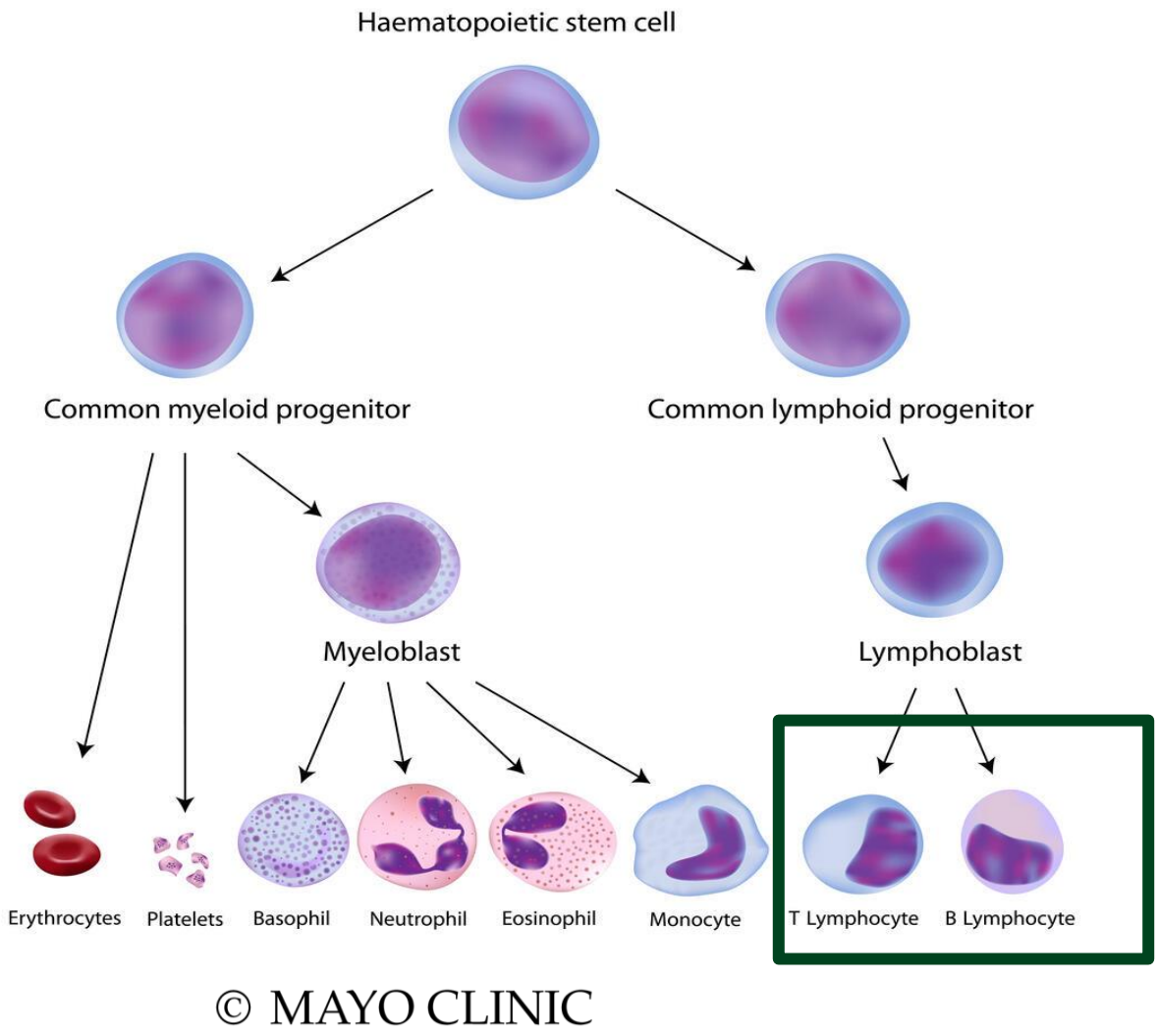
B CELL COMPARTMENT: IMMUNOGLOBULIN SUB-CLASSES FAMILY OF MOLECULES

- Classes (isotypes) of heavy chains:
  - IgM
  - IgG
    - IgG1, IgG2, IgG3, IgG4
  - IgA
    - IgA1, IgA2
  - IgD
  - IgE



Redrawn from presenter-supplied original; no source supplied.

ADAPTIVE IMMUNE SYSTEM



IMPORTANT POINTS TO CONSIDER:

- Physical exam
- Family history
- Response to standard therapy
- Unusual presentation
- Severe presentation

Editorial

The lost art of the clinical examination: an overemphasis on clinical special tests

Chad Cook

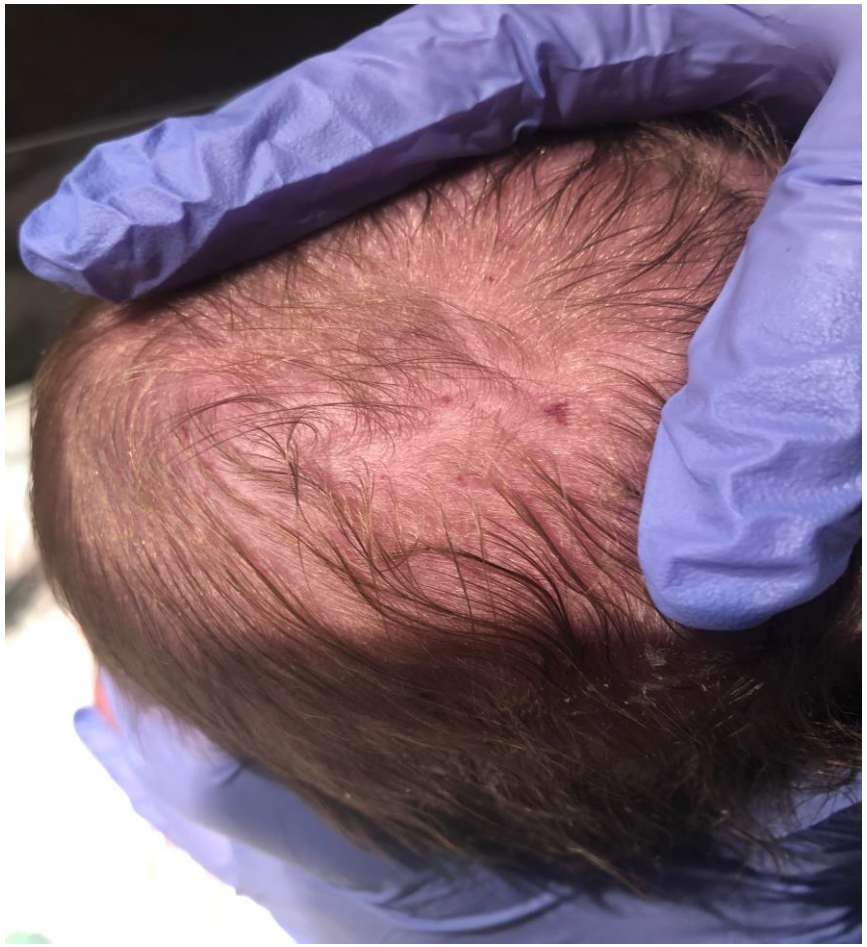
Duke University, USA

Special tests have assumed the role of the double edged sword or the Catch 22 of the clinical examination. Special tests include imaging, clinical specialties. Ordering imaging appears to be the primary consequence of the intolerance.[10]

To be fair, an emphasis on laboratory and imaging

- J Man Manip Ther. 2010 Mar; 18(1): 3–4.

PHOTO CASE #1: SCALP RASH AT BIRTH



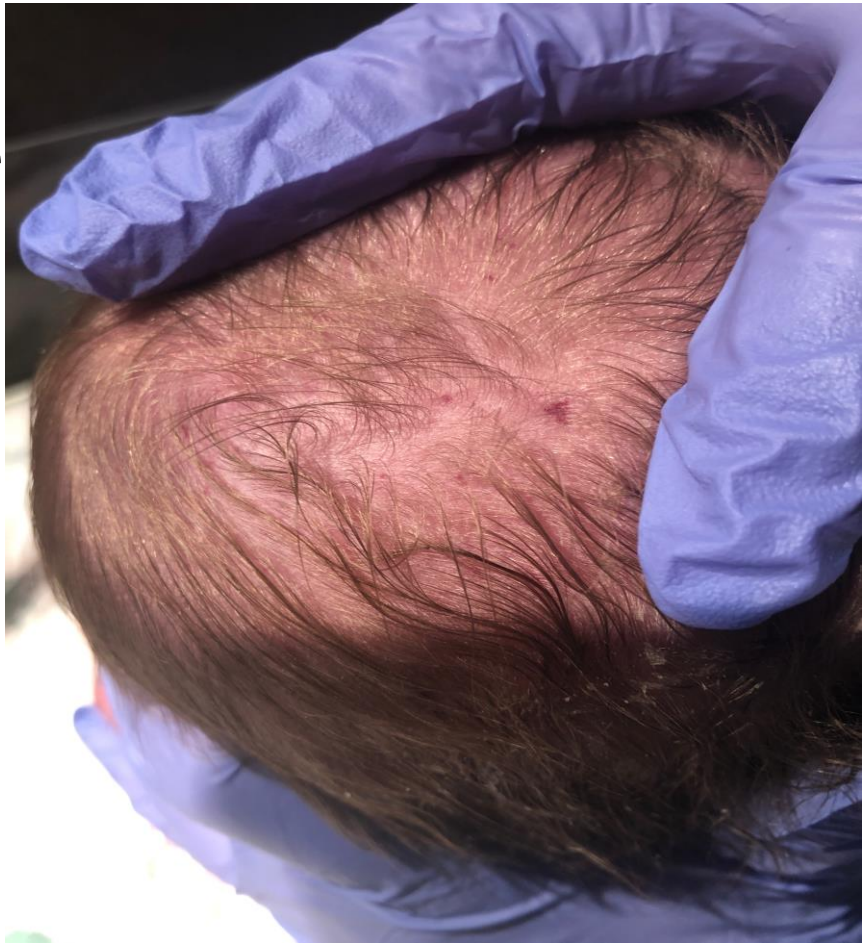
What is the likely diagnosis?

1) Neonatal Thrombocytopenia
2) Wiskott Aldrich Syndrome
3) Birth instrumentation injury
4) Neonatal pustulosis

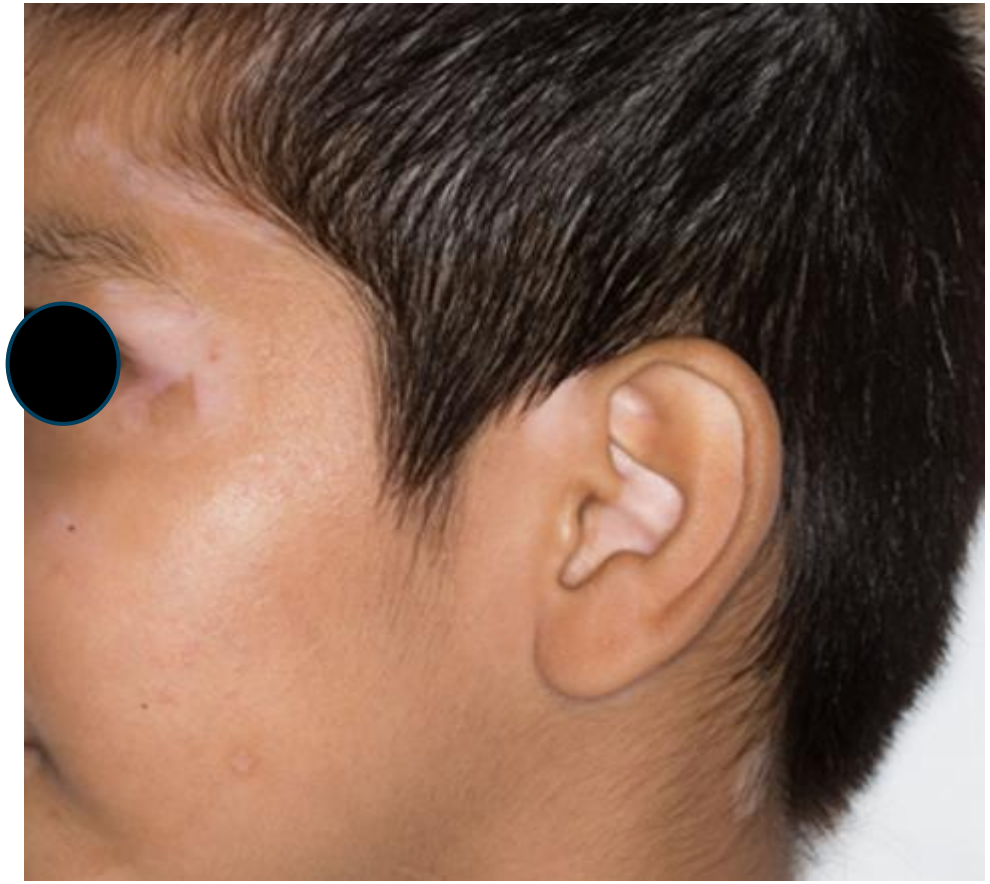
SCALP PETECHIAE

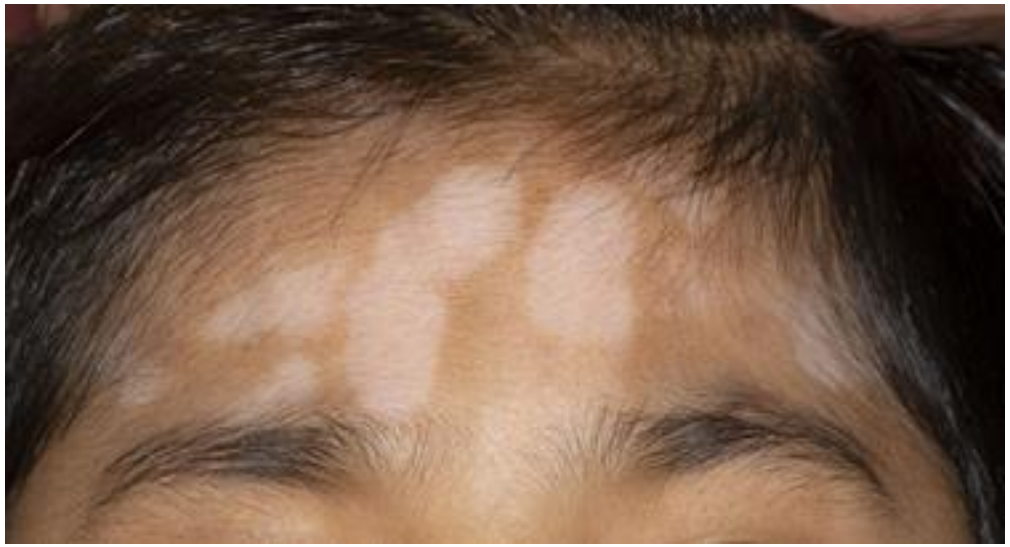
- Platelet count: 40,000
- Family History of Wiskott Aldrich syndrome
- Wiskott Aldrich Syndrome

- Take home point:
- Keen clinical exam
- Dwell into detailed family history



THE LOST ART OF PHYSICIAN EXAM



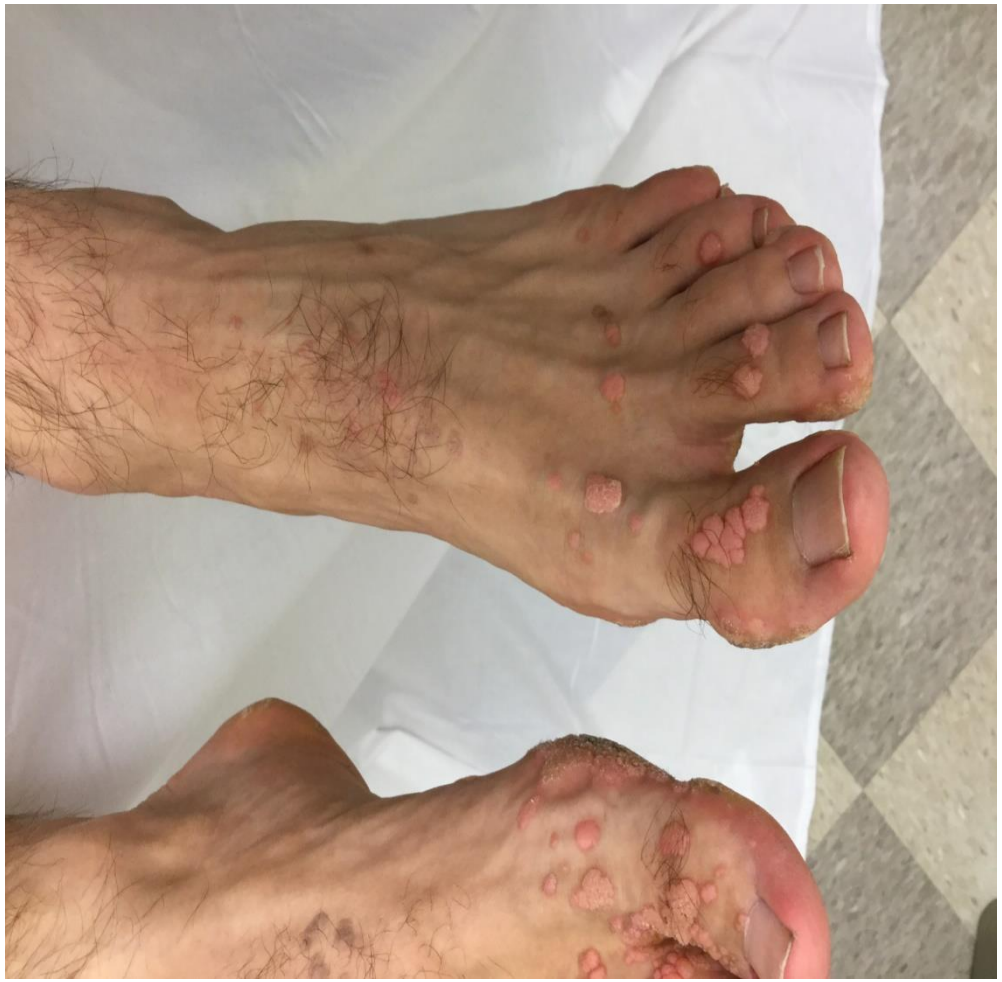


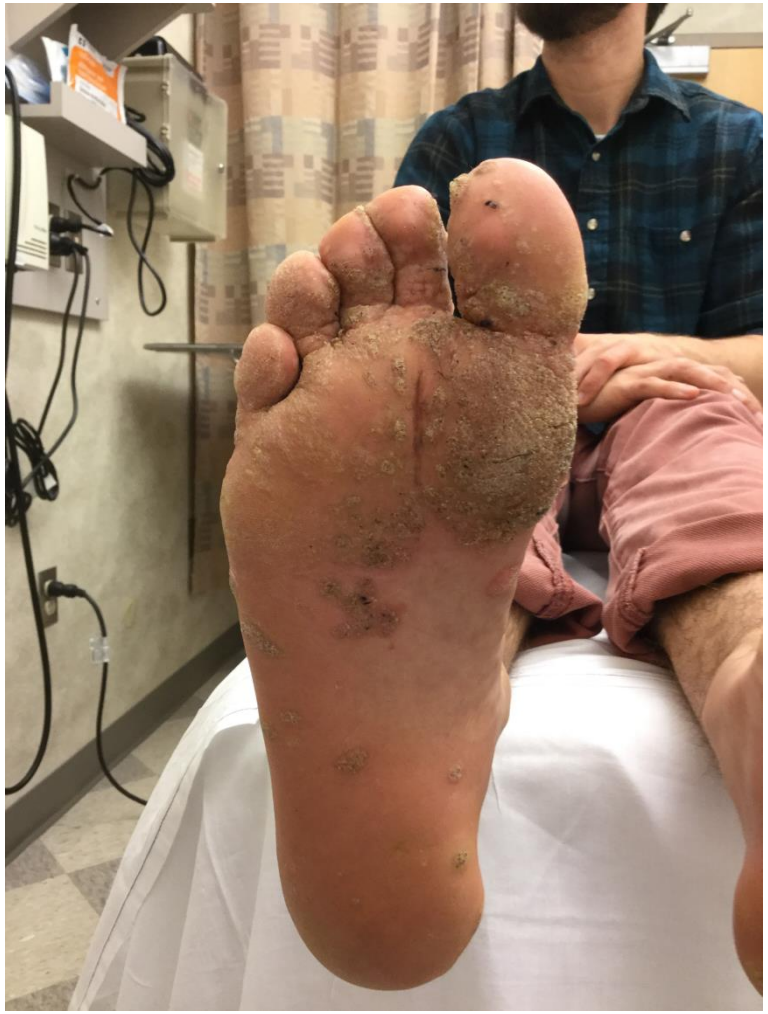
Images Approved for use.

OCULAR TELANGIECTASIA

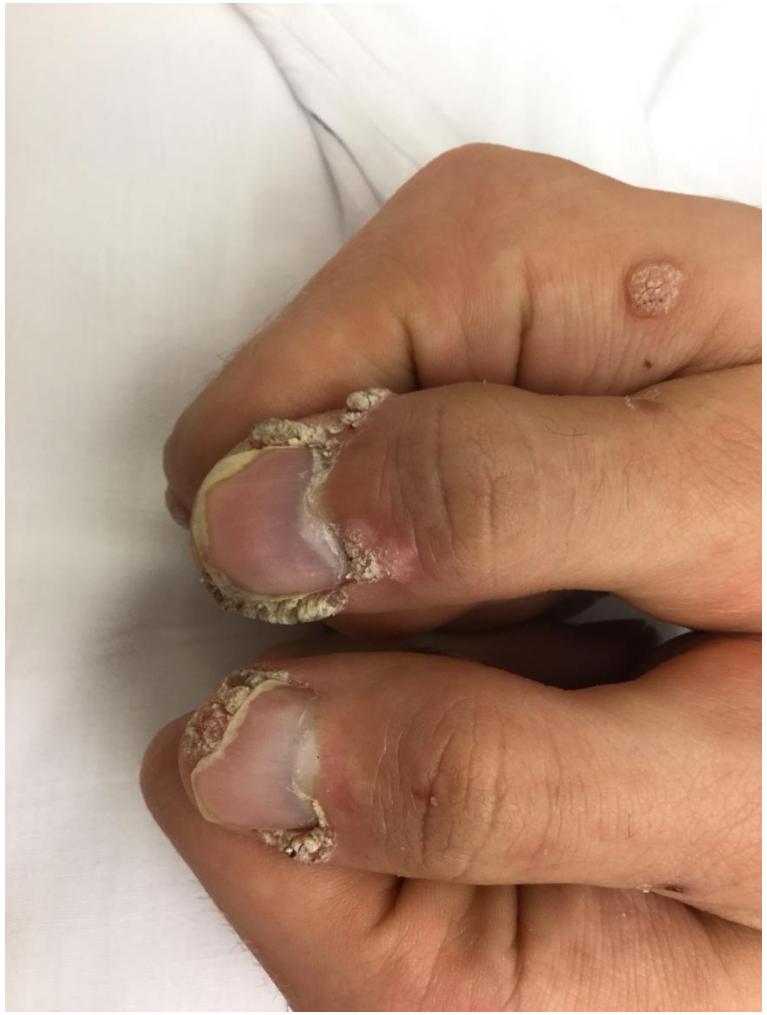
Images Approved for use.

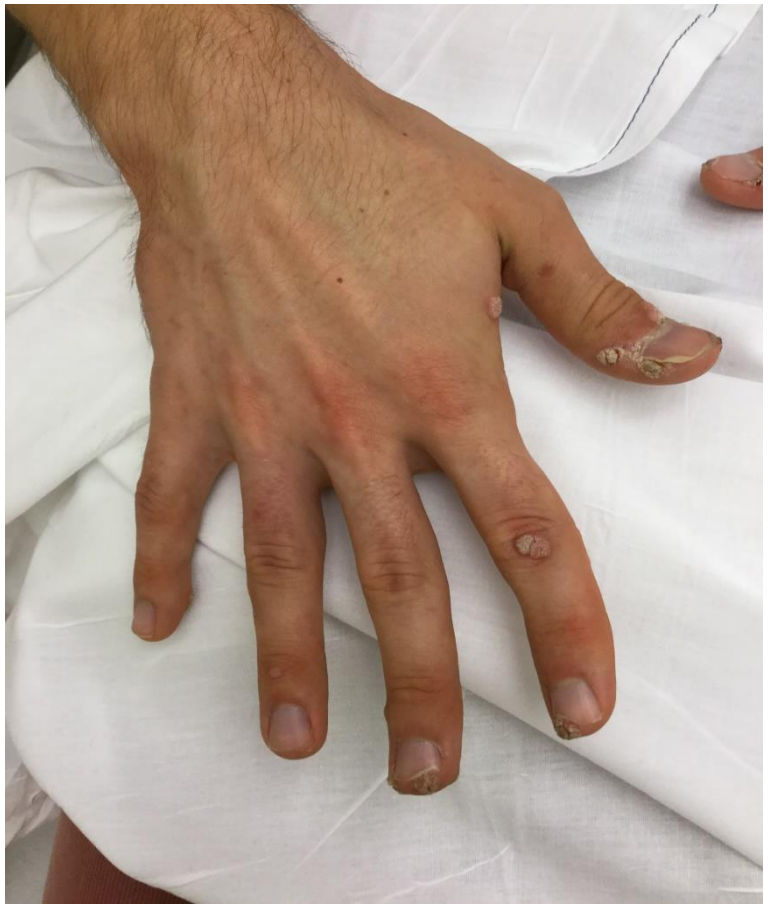
PHOTO CASE #2:RECURRENT WARTS IN A TEENAGER





Images Approved for use.



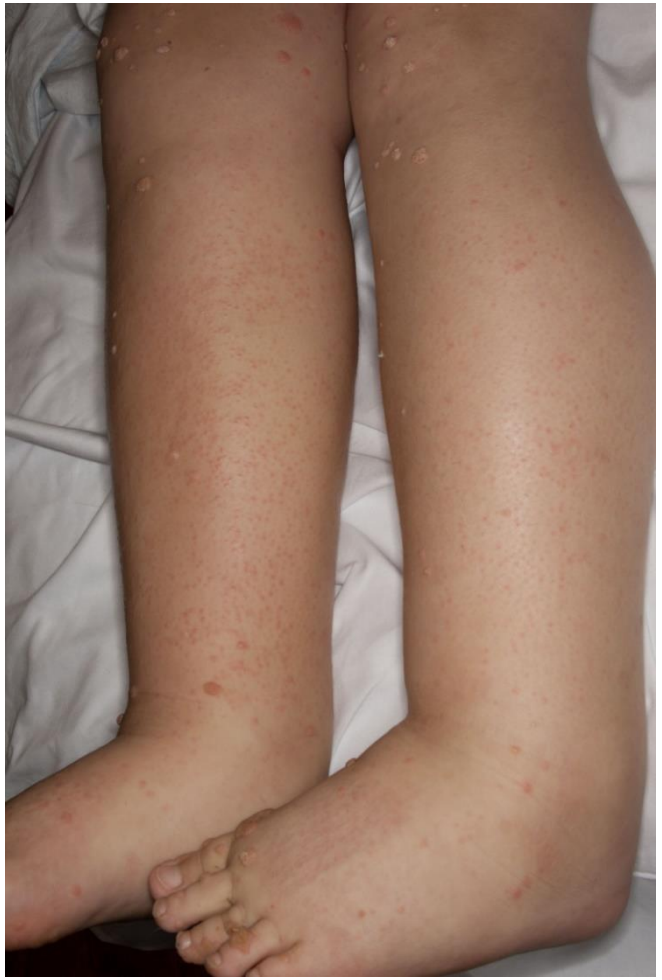


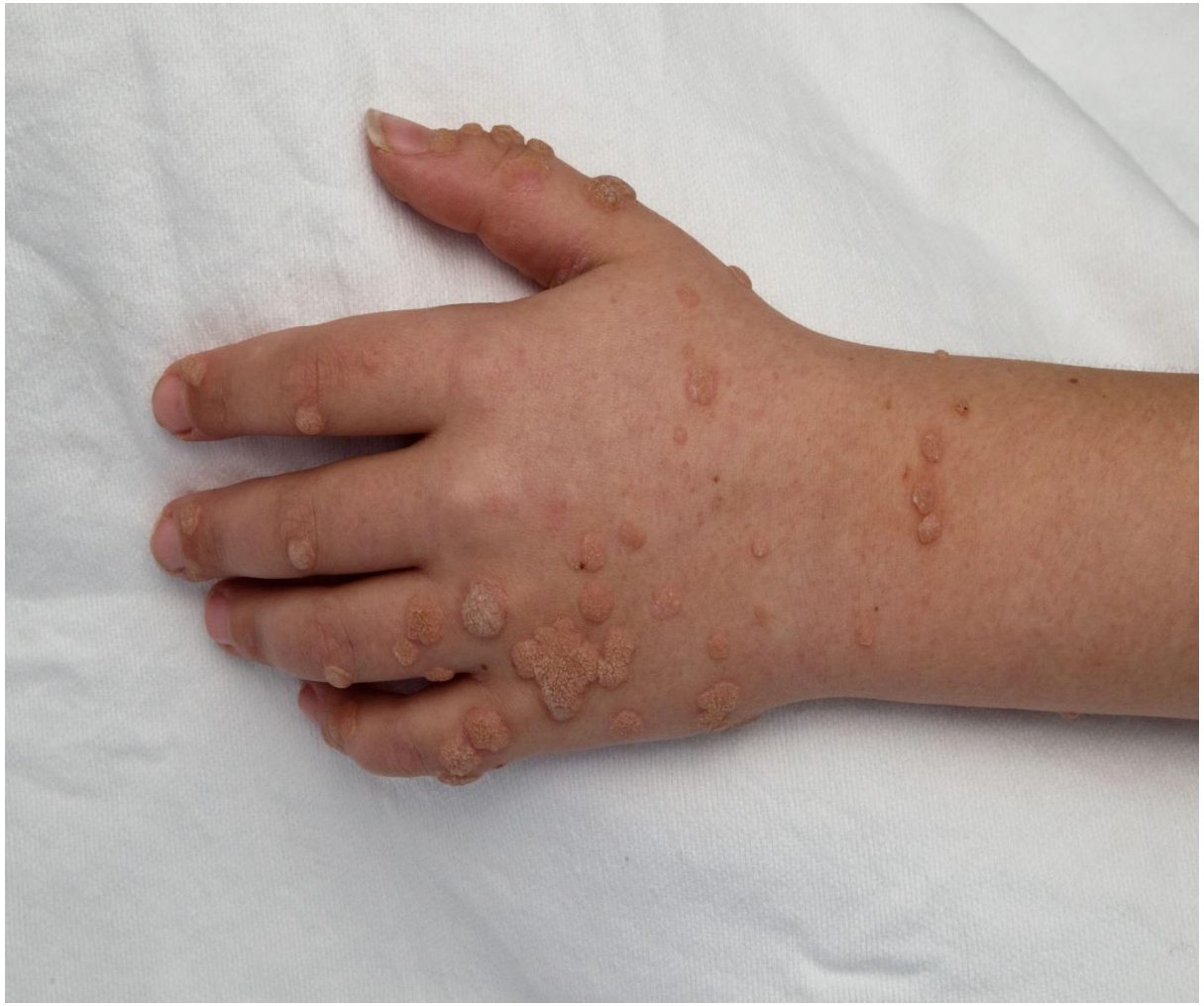
Images Approved for use.

CASE #2: WHAT IS LEAST LIKELY DIAGNOSIS?

- 1) Familial Warts
- 2)Defects in HPV immunity
- 3) Primary immune deficiency
- 4)HSV associated disease

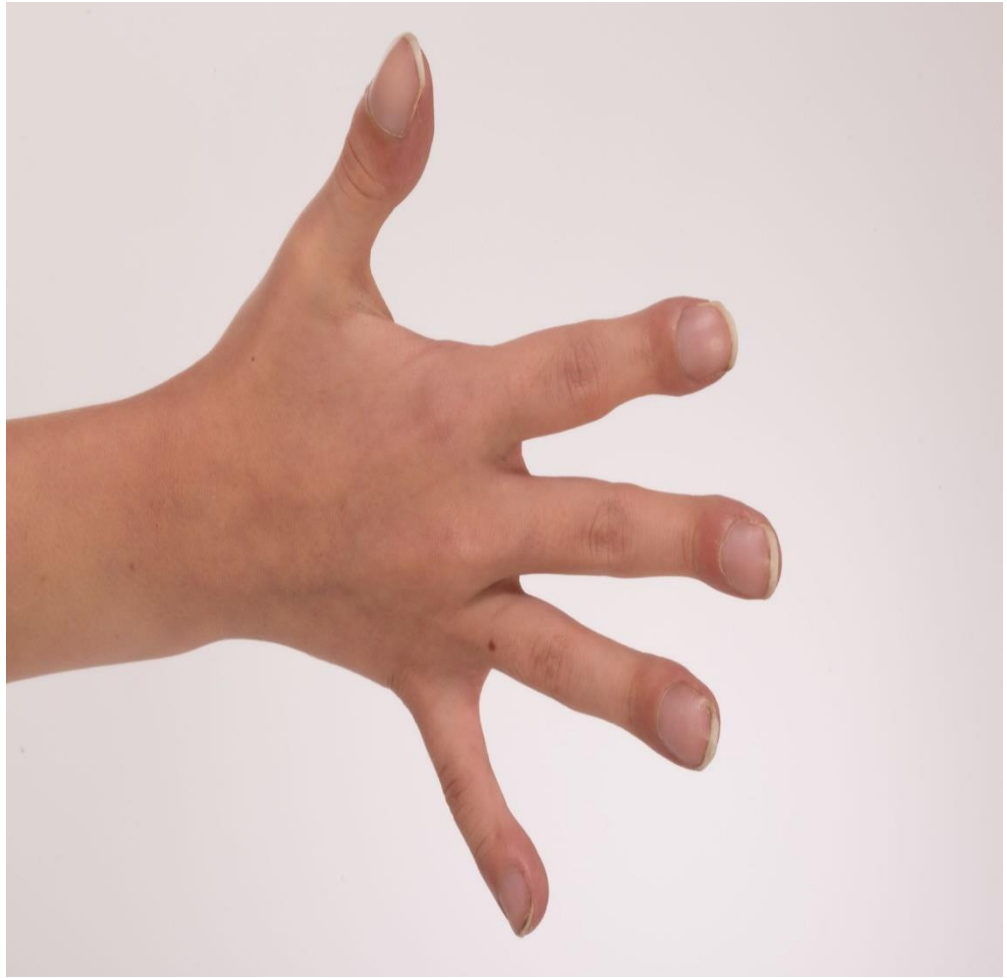
SAME FAMILY

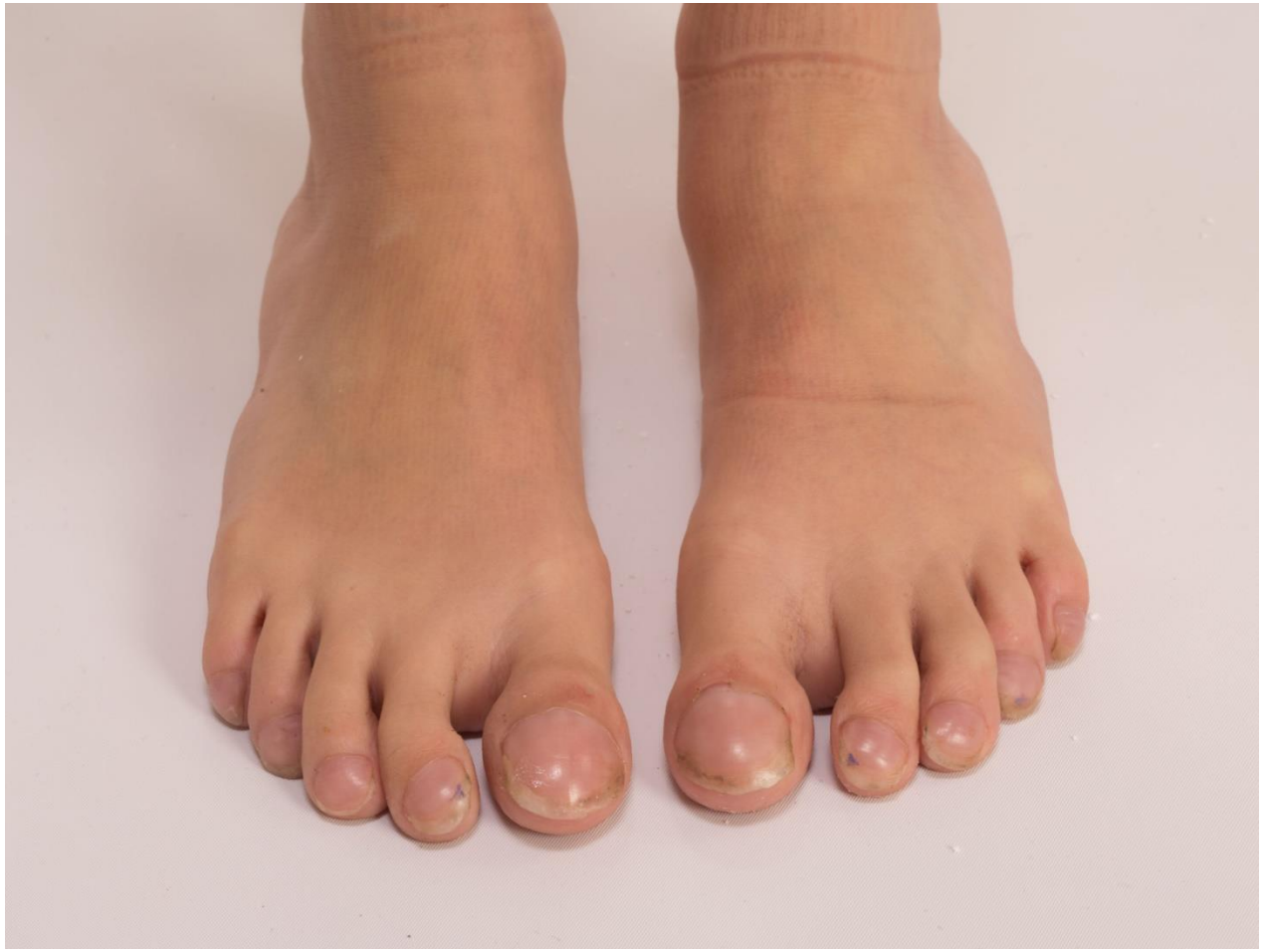




Images Approved for use.

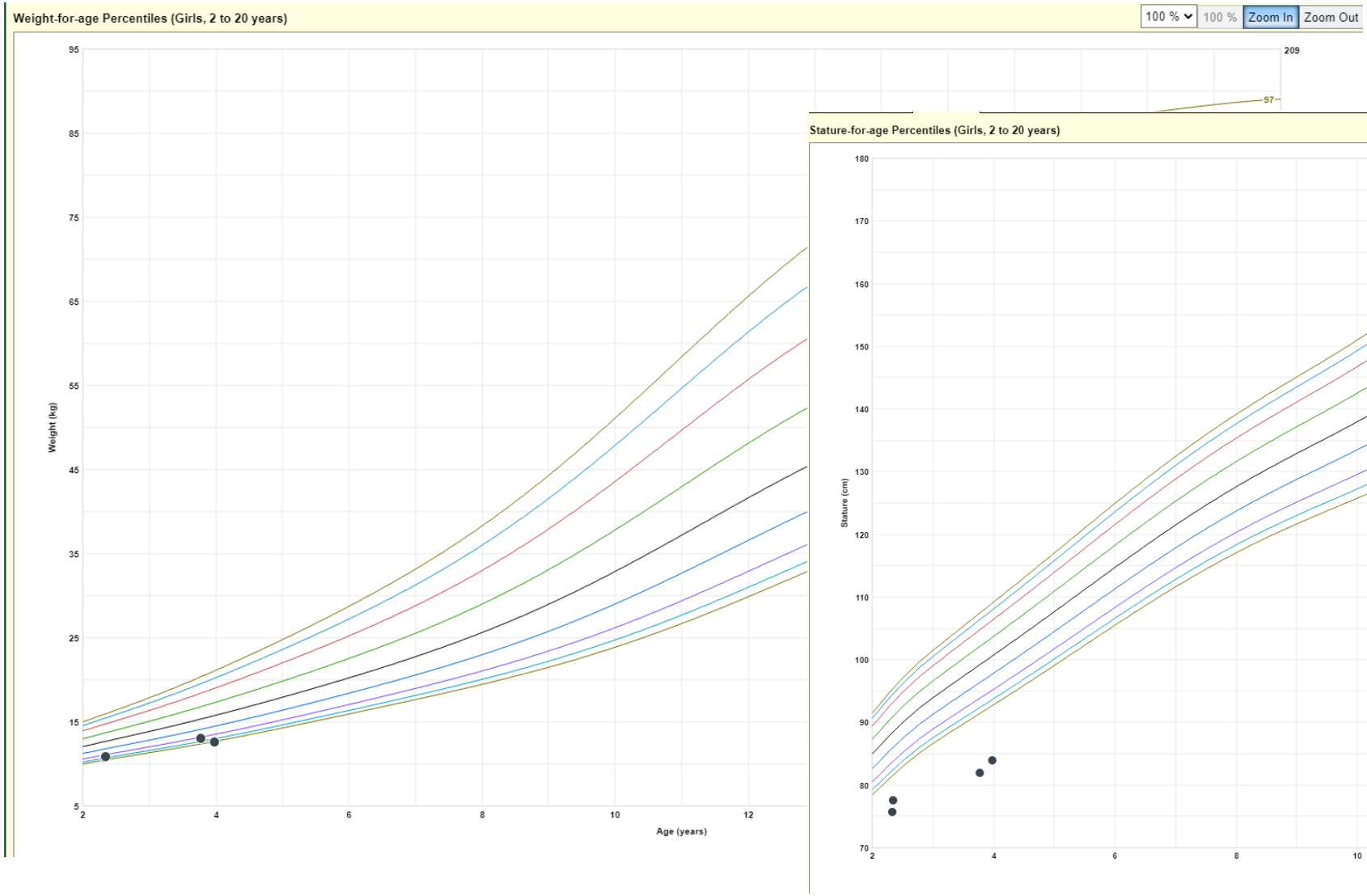
SAME FAMILY

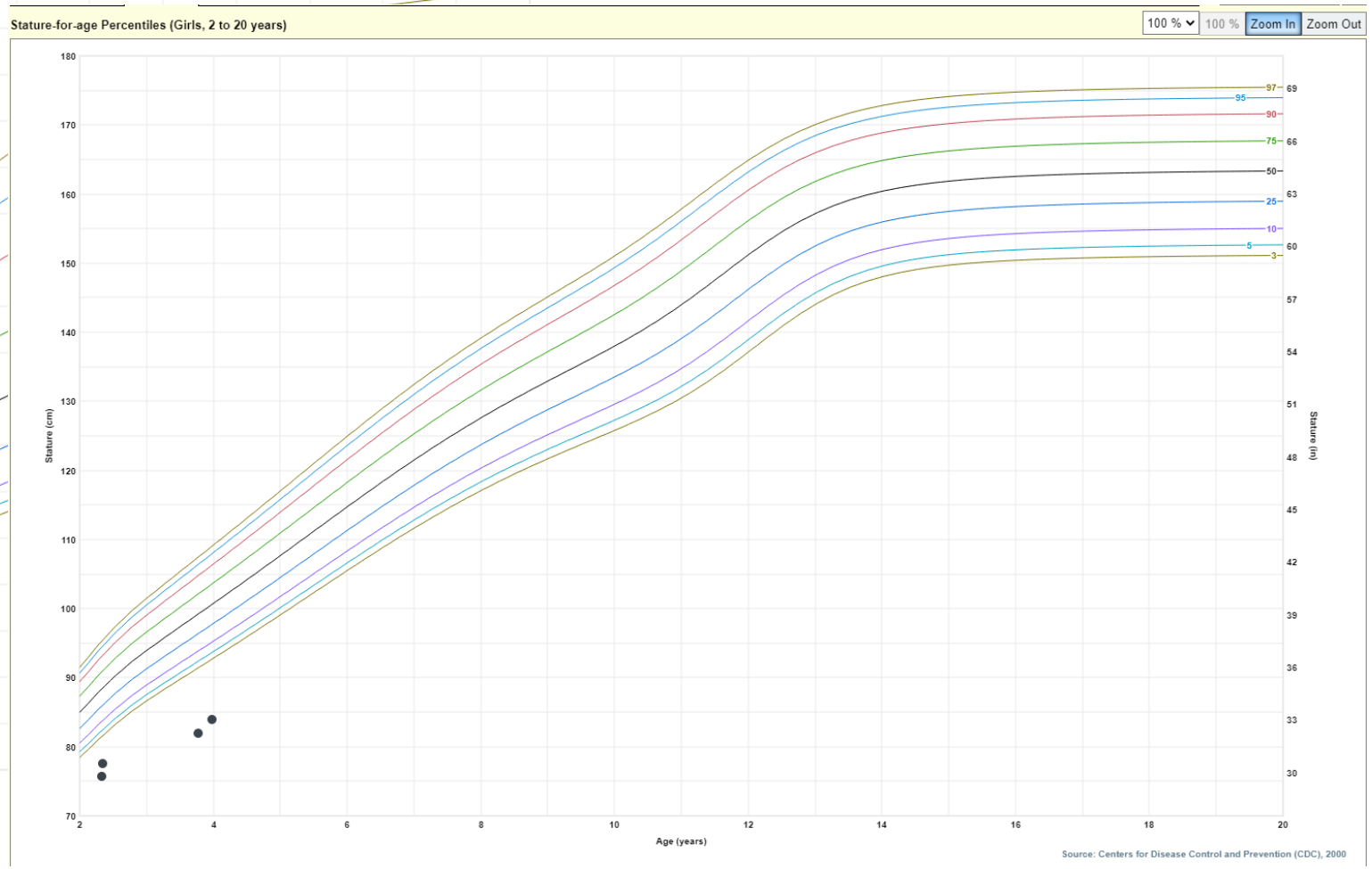




Images Approved for use.

PAY CLOSE ATTENTION TO GROWTH PARAMETERS





MASQUERADERS OF IMMUNE DEFICIENCY

HOW COMMON ARE PIDD?

ORIGINAL ARTICLE

Incidence and Temporal Trends of Primary Immunodeficiency: A Population-Based Cohort Study

AVNI Y. JOSHI, MD; VIVEK N. IYER, MD, MPH; JOHN B. HAGAN, MD; JENNIFER L. ST. SAUVER, PHD; AND THOMAS G. BOYCE, MD, MPH

OBJECTIVE: **To determine the incidence and temporal trends of primary immunodeficiency diseases (PIDs) and examine whether an association exists between delayed diagnosis and increased morbidity.**

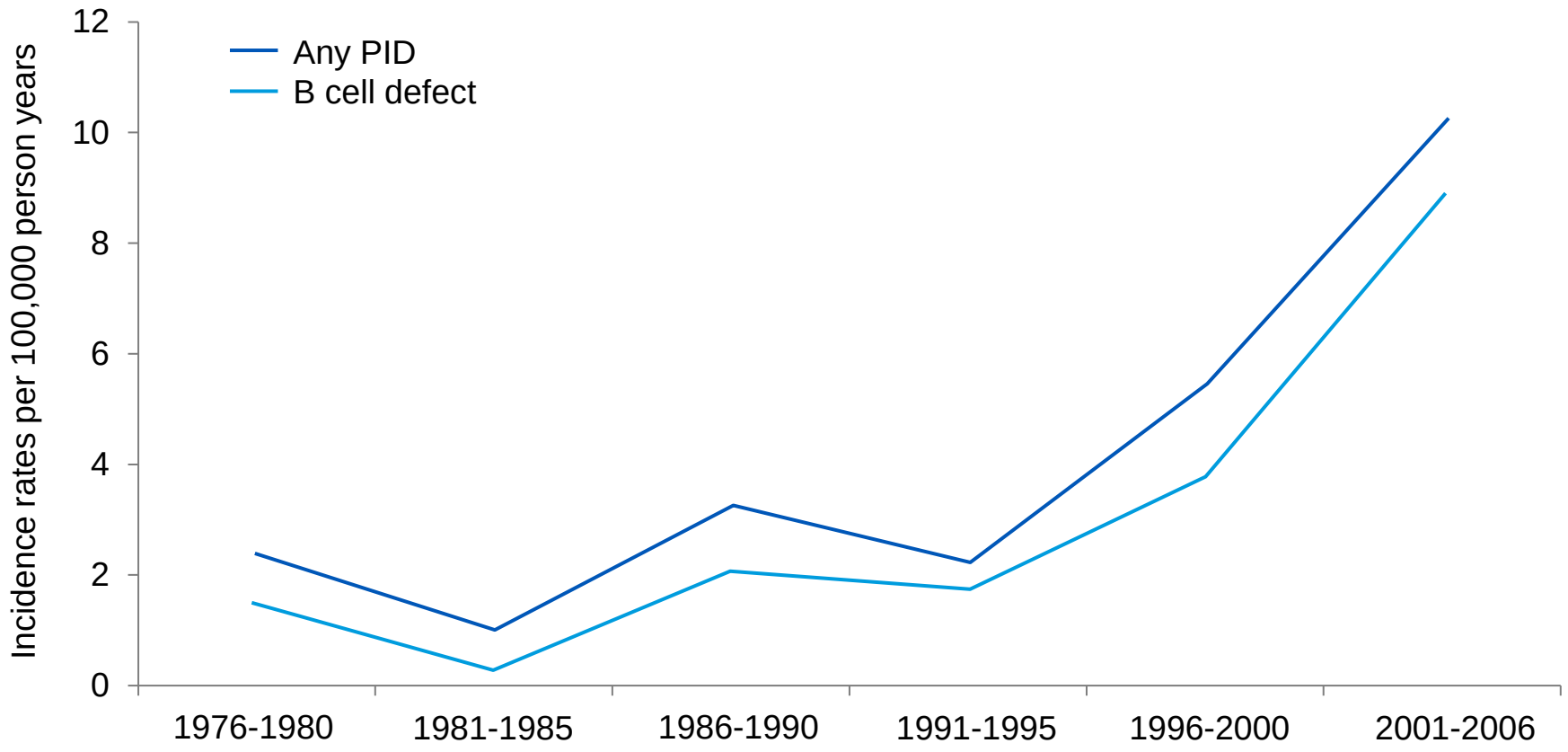
PATIENTS AND METHODS: **We performed a historical cohort study to describe the epidemiology of PIDs in Olmsted County, Minnesota, during a 31-year period from January 1, 1976, through December 31, 2006, using the Rochester Epidemiology Project. Incidence and trends over time, presence of comorbid conditions, and trends in management were determined.**

RESULTS: **During the 31-year study period, 158 new cases of PIDs were diagnosed, with an overall incidence rate of 4.6 per 100,000 person-years. The rate of PIDs from 2001 through 2006 (10.3 per 100,000 person-years) was nearly 5 times higher than that from 1976 through 1980 (2.4 per 100,000 person-years). The associations between continuous variable(s) and categorical outcome(s)**

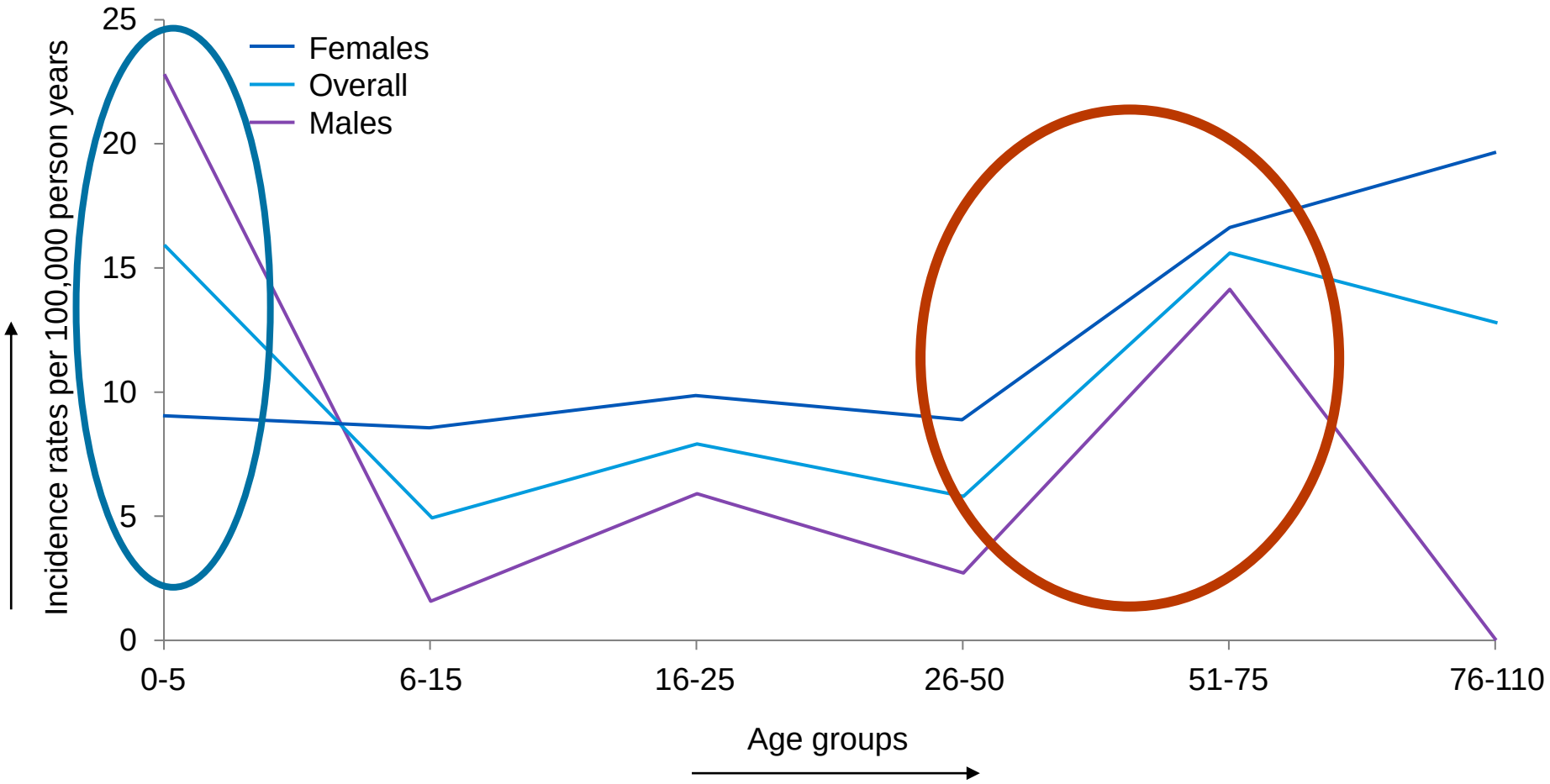
growing for a newborn screen for PIDs, especially severe combined immunodeficiency.[5-7] We need estimates of the incidence and prevalence of the disease in the population to determine the cost-effectiveness of routine screening. Some estimates have been made of the incidence and prevalence of PIDs based on PID registries in various countries[8-13]; however, the incidence of PIDs in the United States is unknown. Boyle and Buckley[1] conducted a telephone interview study by random-digit dialing to evaluate the prevalence of PIDs in 2006-2007, but the numbers are approximate and may not correspond to the true incidence and prevalence of PIDs in the population. Our objectives in this study were to (1) describe the epidemiology of PIDs in

Mayo Clin Proc. 2009;84(1):16-22

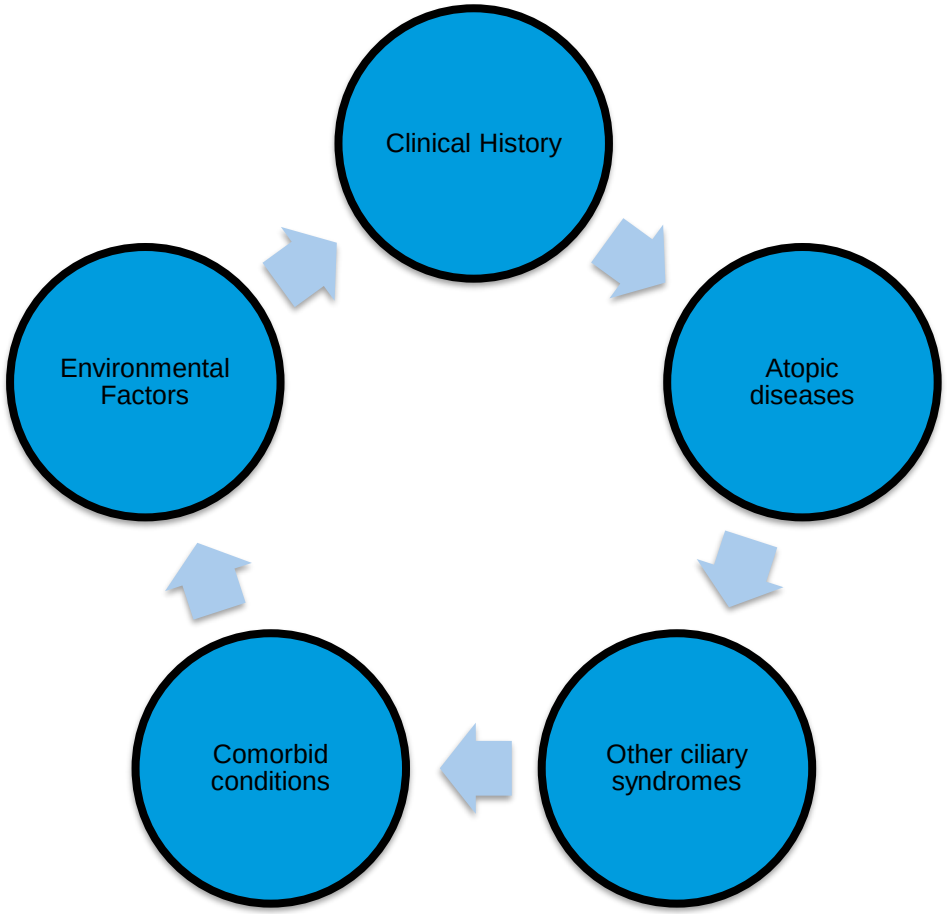
INCIDENCE RATE OF PID OVER THE PAST 40 YEARS



INCIDENCE RATES OF ALL PIDS OVER VARIOUS AGE GROUPS



Redrawn from presenter-supplied original; no source supplied.



RECURRENT INFECTIONS? HOW MANY ARE TOO MANY?

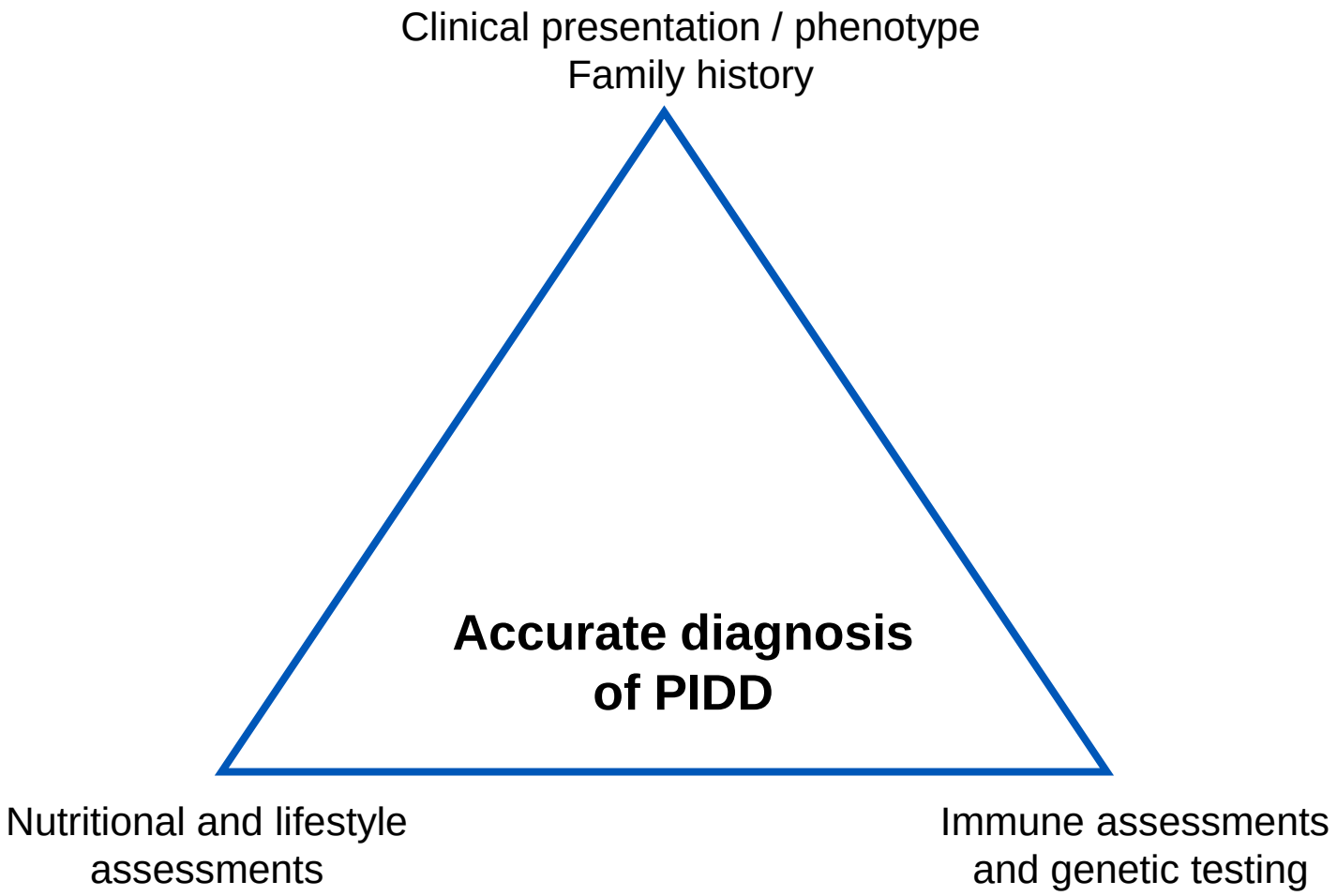
- • Need more than four courses of antibiotic treatment per year
- • Experience more than four new ear infections in one year after 4 years of age.
- • Develop pneumonia twice over any time?
- • Have more than three episodes of bacterial sinusitis in one year or the occurrence of chronic sinusitis?
- • Need preventive antibiotics to decrease the number of infections?
- • Develop unusually severe infections that started as common bacterial infections?

PRIAMRY IMMUNE DEFICIENCIES

- **Severe** primary immune deficiency
- Emergency/urgency

- **Less severe** immune deficiency
- Window of opportunity

DIAGNOSIS OF PIDDS



BASIC IMMUNE WORKUP

Tier 1 testing:

CBC with diff: Pay close attention to differential

Neutrophil (ANC) and Lymphocyte counts (ALC)

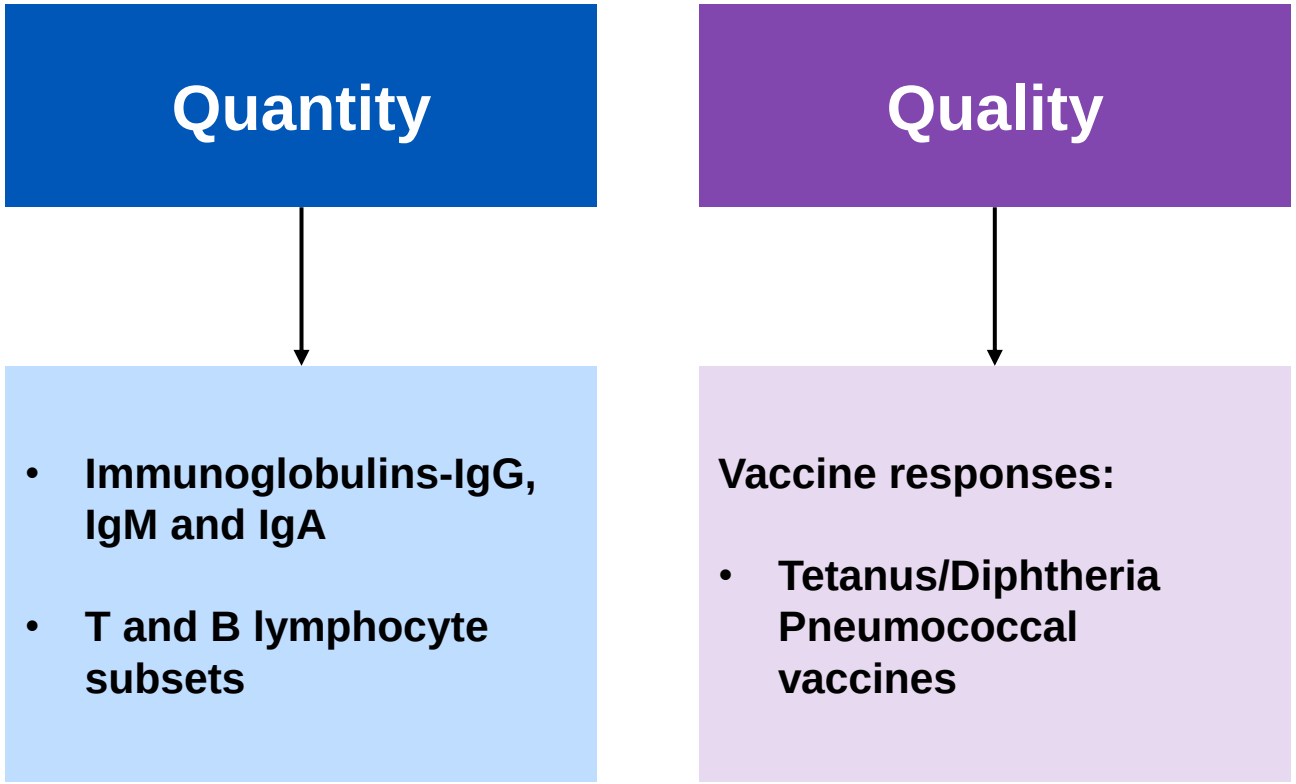
- Immunoglobulins, T and B lymphocytes quantitation

- Tier 2 testing:
- Functional assessments

- Tier 3 testing:
- Gene testing: NGS panel

Whole Genome Sequencing (WGS):Ideally trio- parents and the affected child

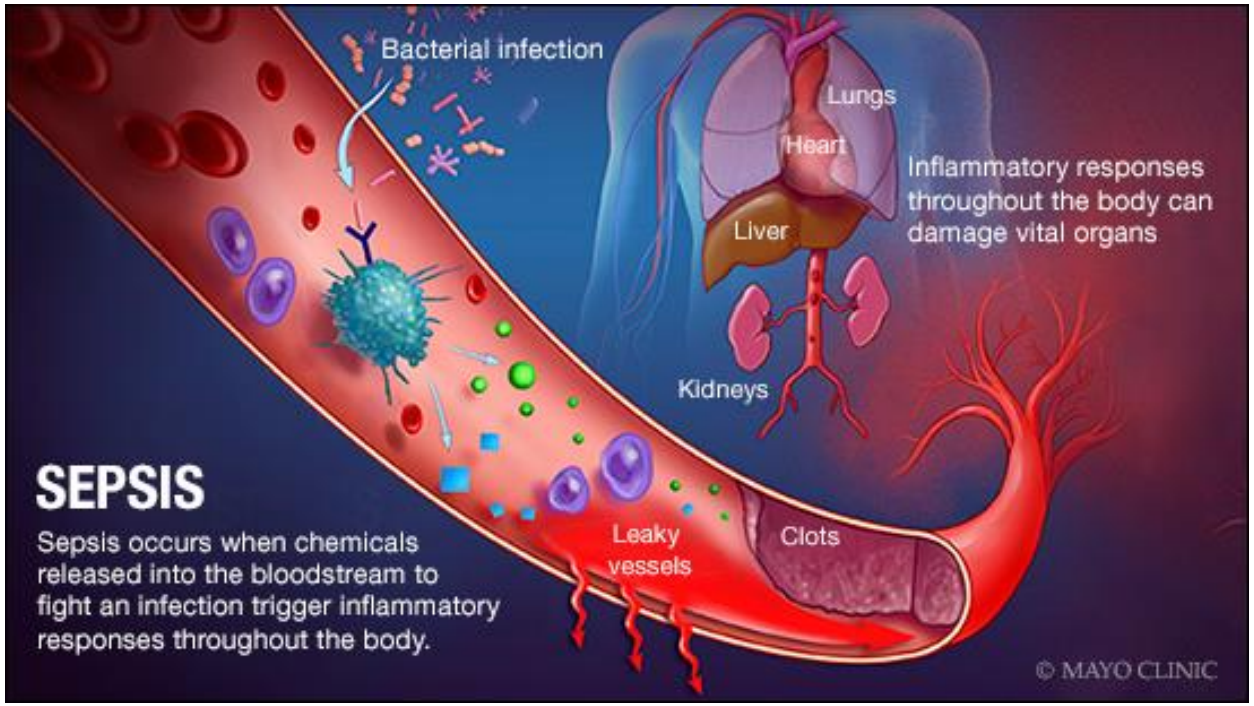
ASSESSING IMMUNE COMPETENCE: TIER 1



MORE SEVERE FORMS OF IMMUNE DEFICIENCY#1

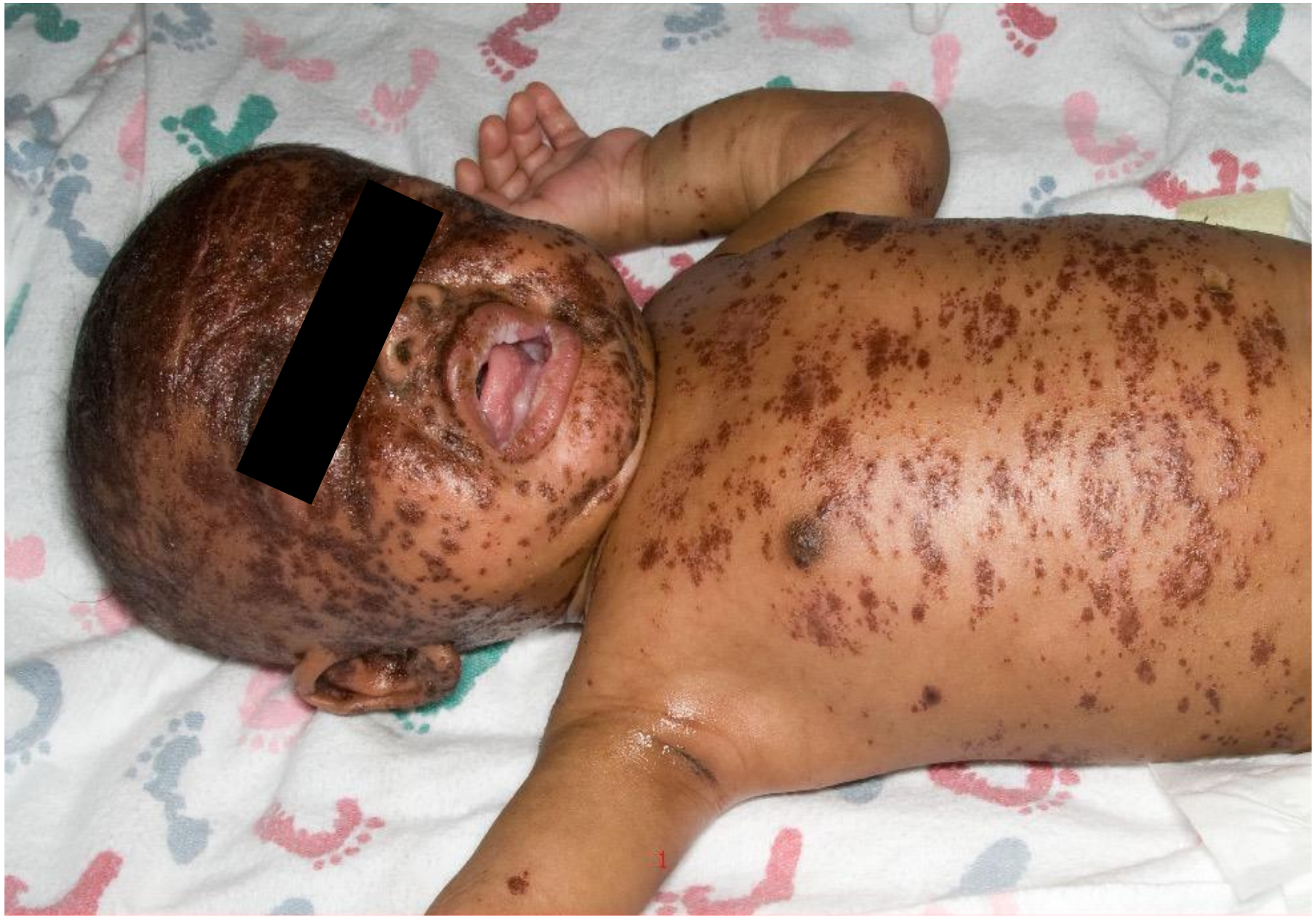
CASE NO 1:

- 2-month-old Somali male
- Presenting complaints: fever, rash and irritability
- Suspicion for meningitis at PCP visit
- Full Sepsis work-up initiated with blood, urine cultures
- Broad Spectrum IV antibiotics initiated

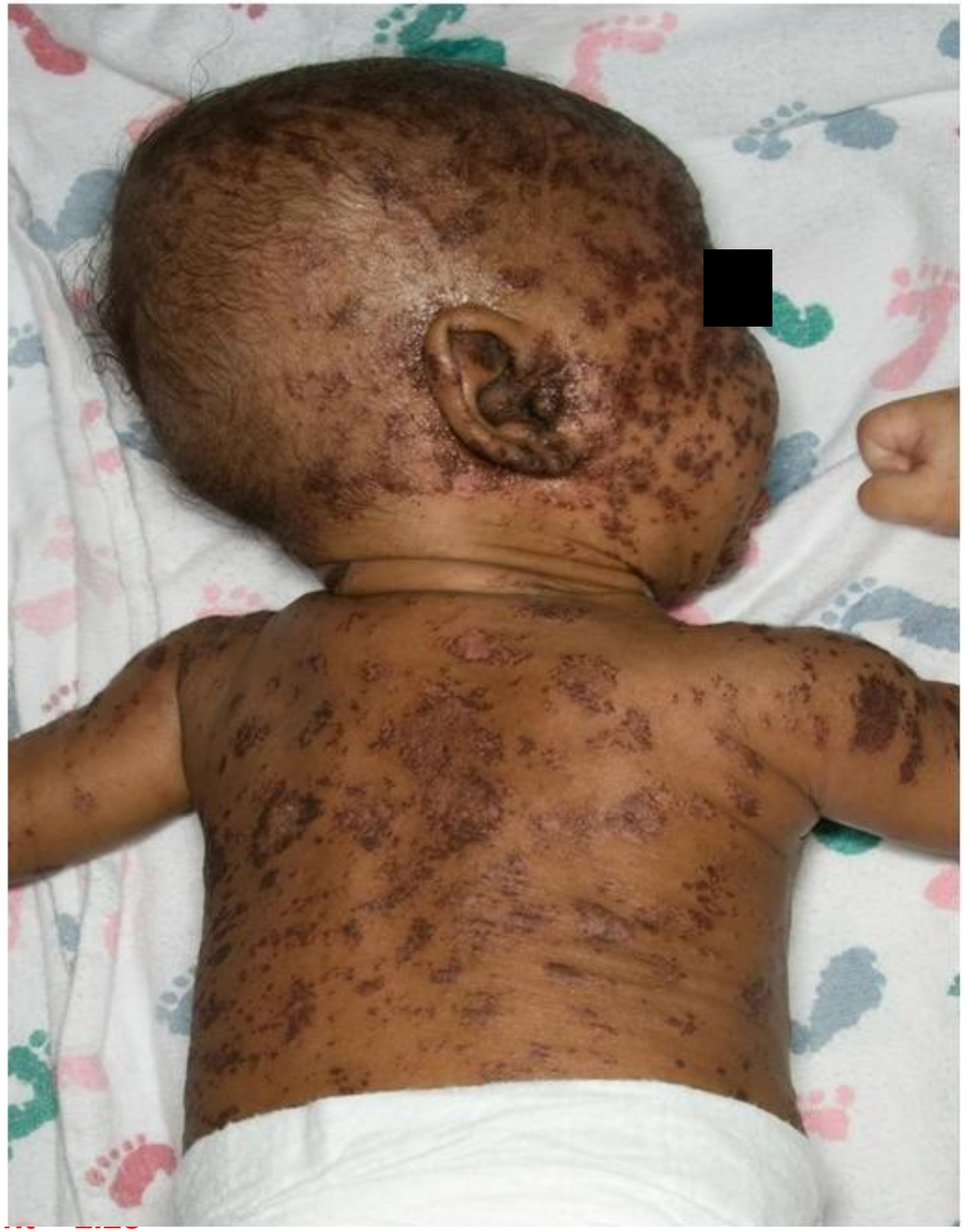


CASE #1 (CONTD.):PAST MEDICAL AND FAMILY HISTORY

- CBC at birth: Petechiae - Platelet count: 150,000, discharged home
- WBC count: 4,000
- Absolute lymphocyte count: 100 (ALC= 0.1)
- FH: parents 1st degree cousins, 2-year-old sibling with congenital sensorineural hearing loss
- Growth parameters: weight and height <5th percentile

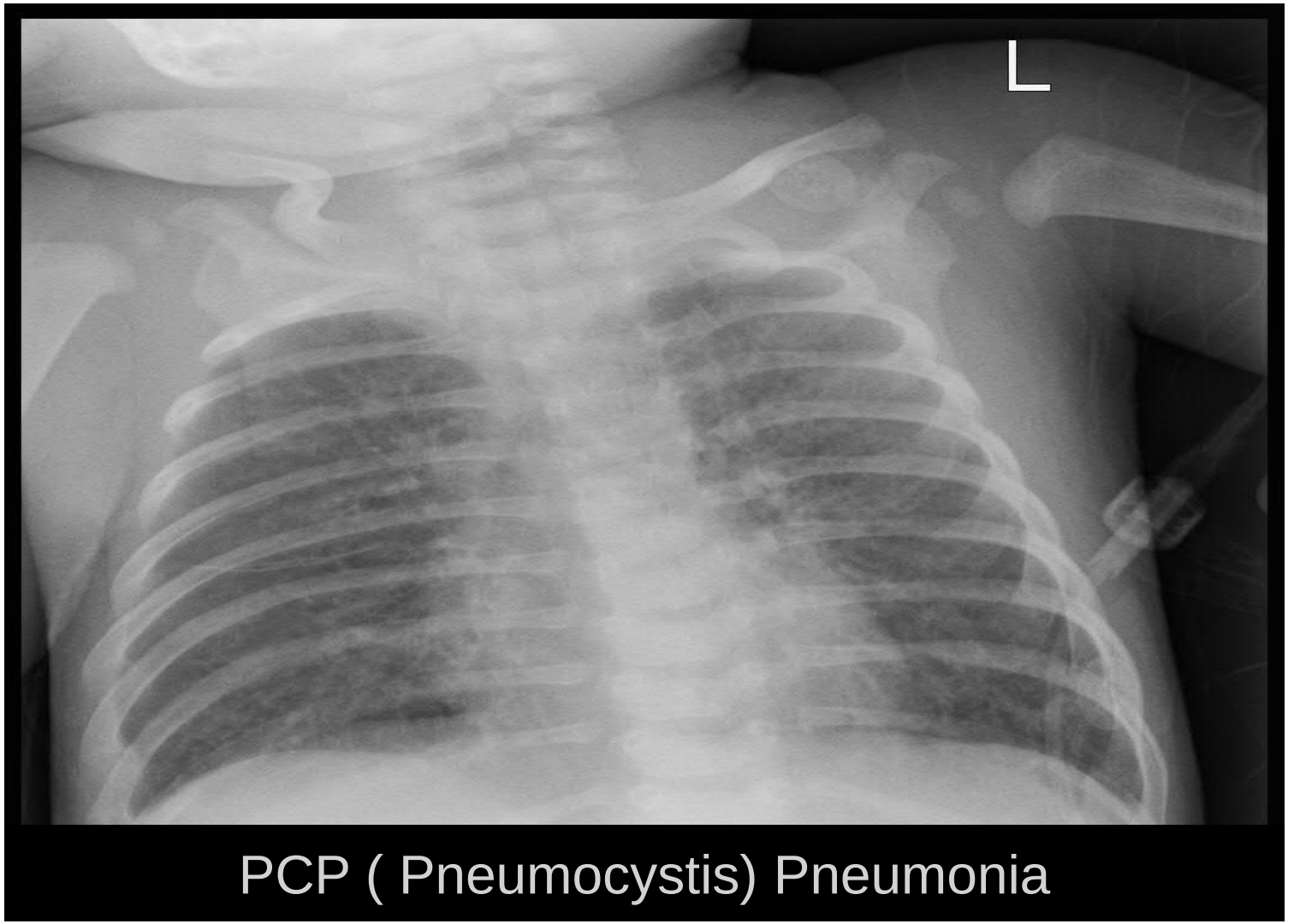


Images Approved for use.



Images Approved for use.

CHEST-X-RAY

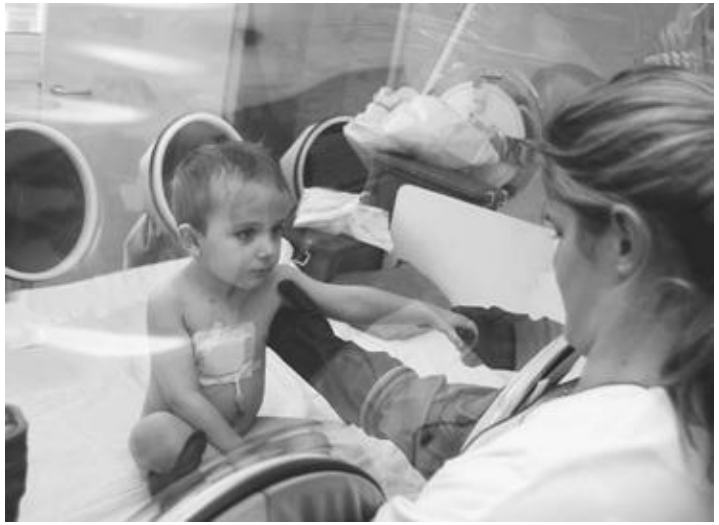


PCP (Pneumocystis) Pneumonia

Images Approved for use.

CBC CONTINUED TO SHOW PERSISTENT LYMPHOPENIA (ALC=0) DIAGNOSIS?

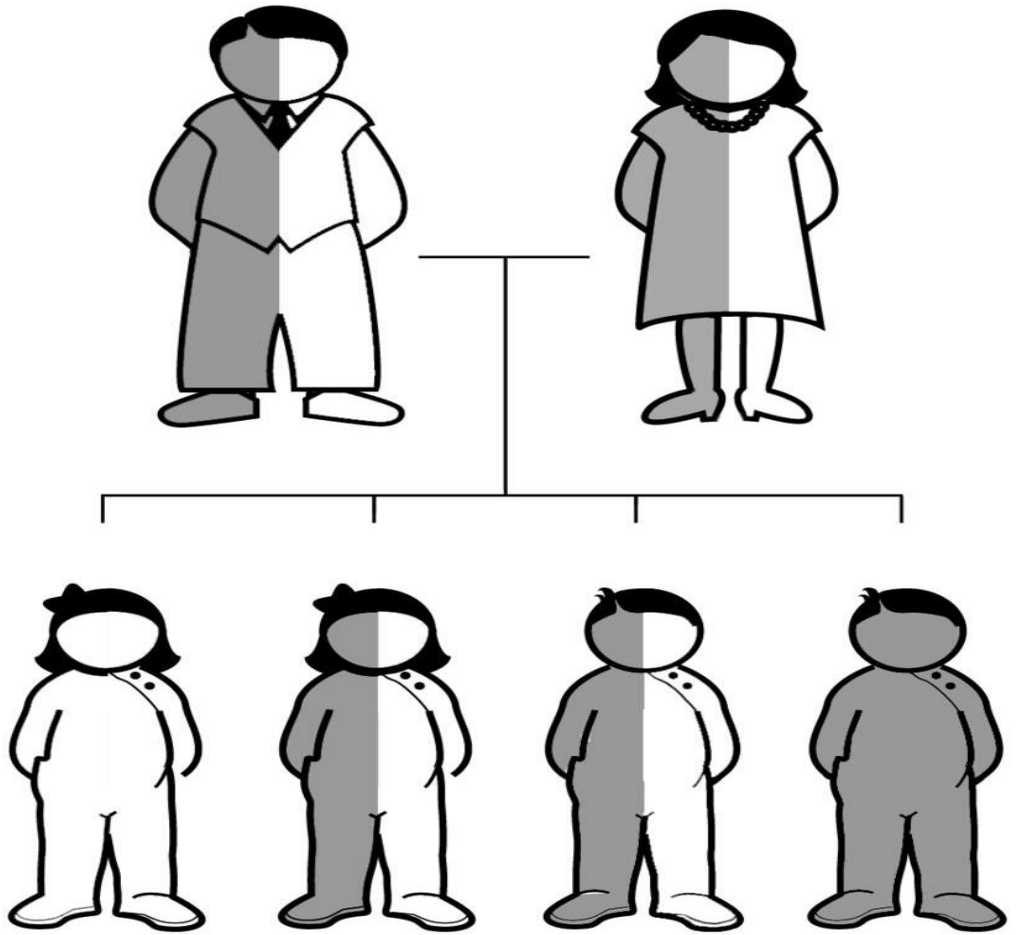
A. Common Variable Immune Deficiency (CVID)
B. Severe Combined Immune Deficiency (SCID)
C. Selective IgA Deficiency (SIgAD)
D. Chronic Granulomatous Disease (CGD)



SCID
Severe Combined Immune Deficiency

HOW COULD WE HAVE SAVED HIM?

FAMILY HISTORY IS CRITICAL



SCID CLASSIFICATION

Lymphocyte phenotype		Inheritance	Chromosome
1. T^-B^- SCID			
• NK^+	RAG 1/2 deficiency	AR	11p13
	DCLRE1C (Artemis deficiency)	AR	10p13
• NK^-	Adenosine deaminase deficiency	AR	20q13.11
	Reticular dysgenesis	AR	
2. T^-B^+ SCID			
• NK^+	IL7α deficiency	AR	5p13
	CD45 deficiency	AR	
	CD3δ/CDε/CD3ζ deficiency	AR	
• NK^-	Common gamma-chain deficiency	X-linked	Xq13.1
	JAK3 deficiency	AR	19p13.1

Redrawn from: Current Allergy & Clinical Immunology, March 2008 Vol 21, No. 1

SCID

- Unexplained lymphopenia
- Recurrent infections: thrush, RSV, VZV, HSV, measles, influenza or parainfluenza
- Failure to thrive
- Chronic diarrhea
- Adverse reactions to live vaccines

INCIDENCE

- 1 in 50,000-70,000 births
- 100 new cases per year in US

IMMEDIATE MANAGEMENT

- Protective isolation
- Irradiated blood
- No exposure to live vaccines
- Antimicrobial prophylaxis: bacteria, fungi and viruses
- PCP prophylaxis
- IVIG

DEFINITIVE MANAGEMENT

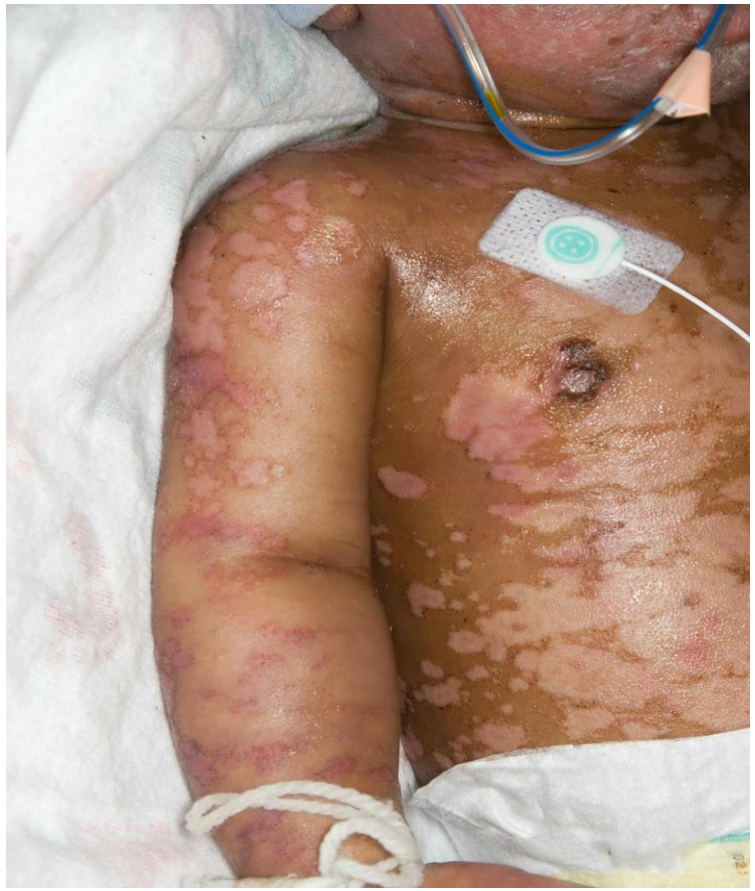
- **Bone marrow transplantation**
- Gene therapy
- Enzyme replacement (Peg-ADA)

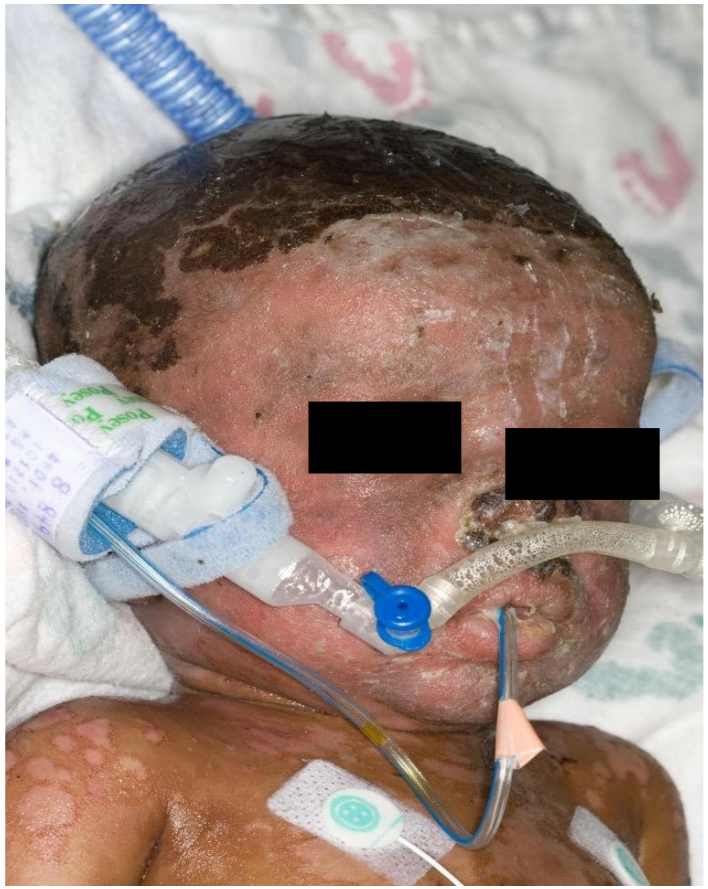
CASE 1: LYMPHOPENIA: ALC :0

- Diagnosed with SCID
- T-/B-/NK- SCID
- ADA enzyme = 0
- ADA deficient SCID
- Started Peg-ADA enzyme replacement

ADA DEFICIENT SCID

Worsening resp. status, withdrew support



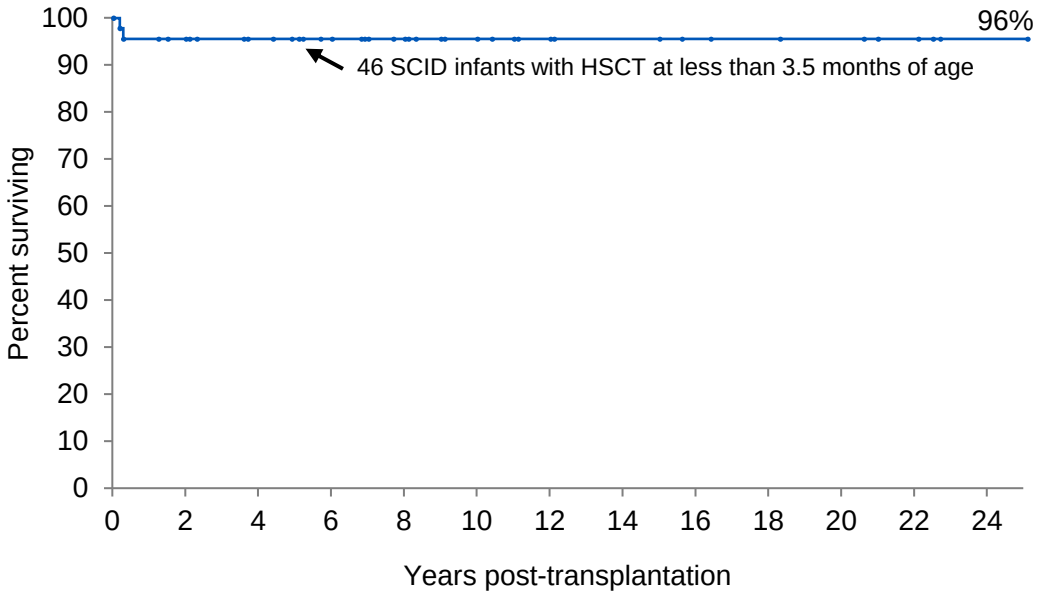


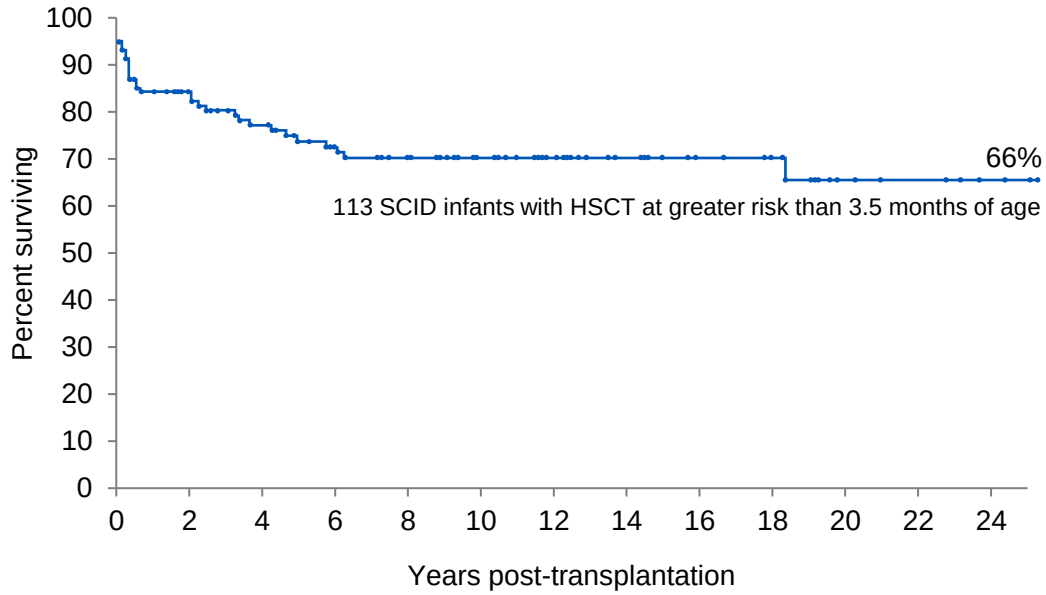
Images Approved for use.

HOW COULD WE HAVE SAVED THIS INFANT?

EARLY DIAGNOSIS IS LIFE SAVING

Kaplan-Meier plot of severe combined immunodeficiency patients transplanted at Duke University Medical Center





Diagnosed before 3.5 months

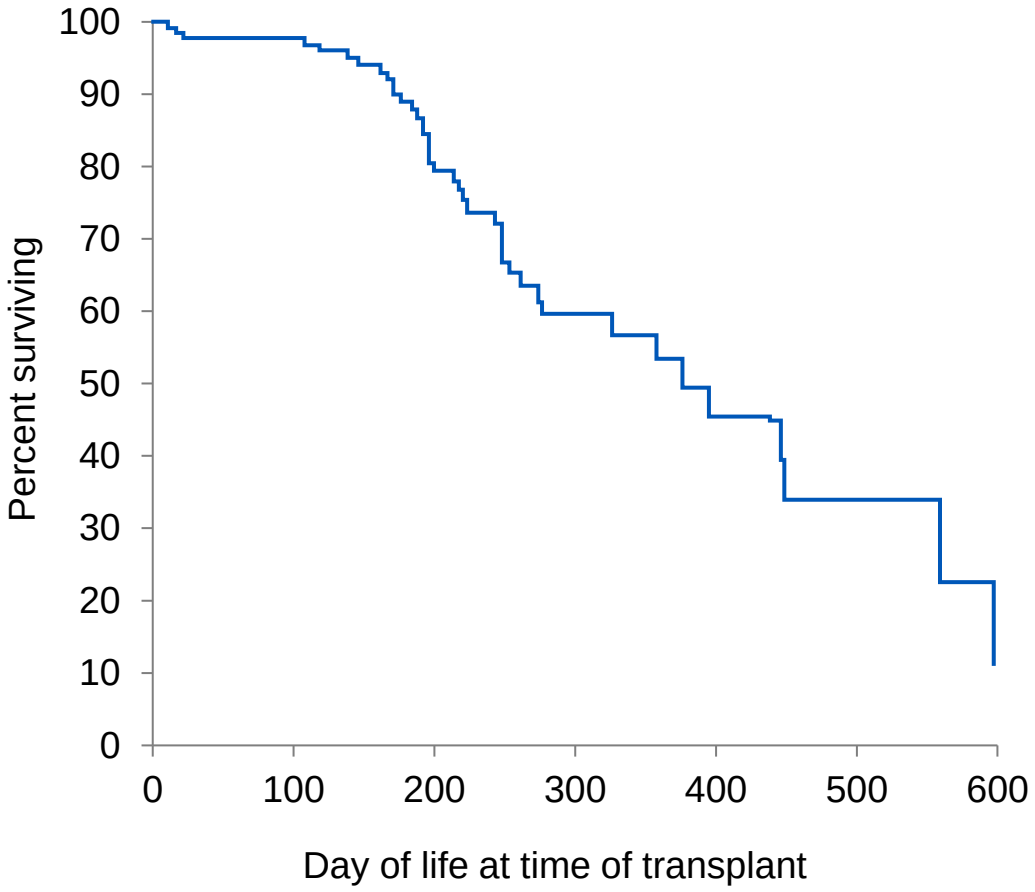
Forty-six infants diagnosed and treated in the first 3.5 months of life.

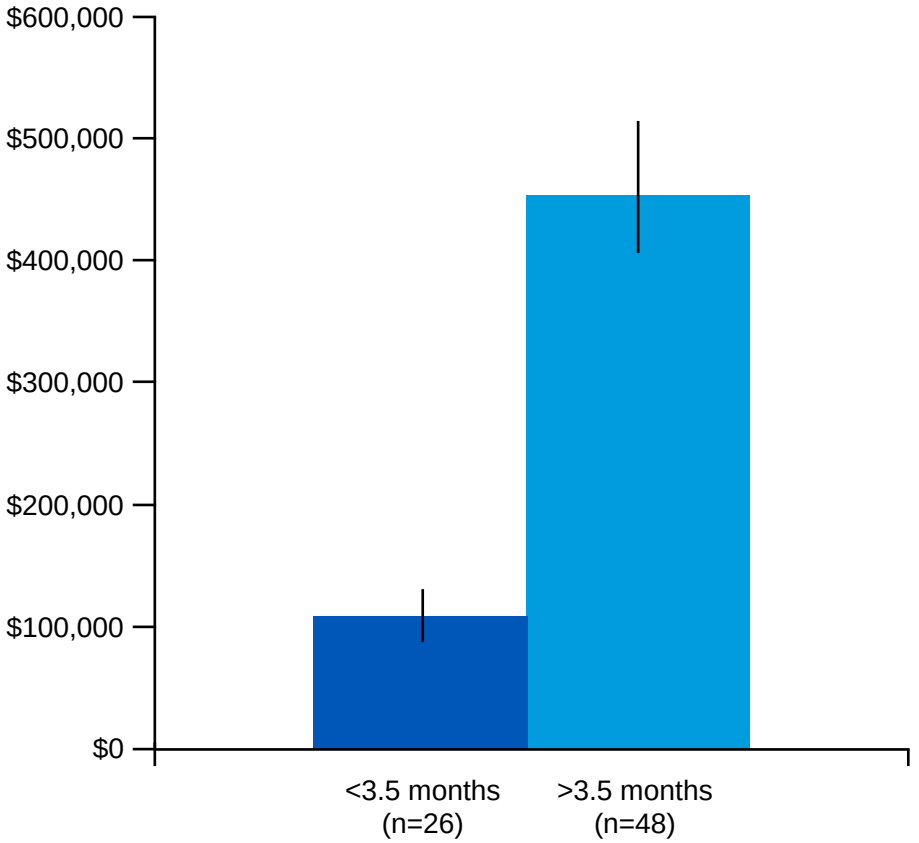
Diagnosed after 3.5 months

One hundred and thirteen infants treated after age 3.5 months.

Redrawn from: Rebecca Buckley. Reproduced with permission [15].

AGE AT THE TIME OF TRANSPLANT AND OUTCOMES





Redrawn from: Duke University Medical Center 1982-2011

NEWBORN SCREEN FOR IMMUNE DEFICIENCY

JANUARY 2010

Federal Advisory Committee Recommends SCID for Universal Newborn Screening

SCID Newborn Screening: Current Status of Implementation Map

As of December 10, 2018

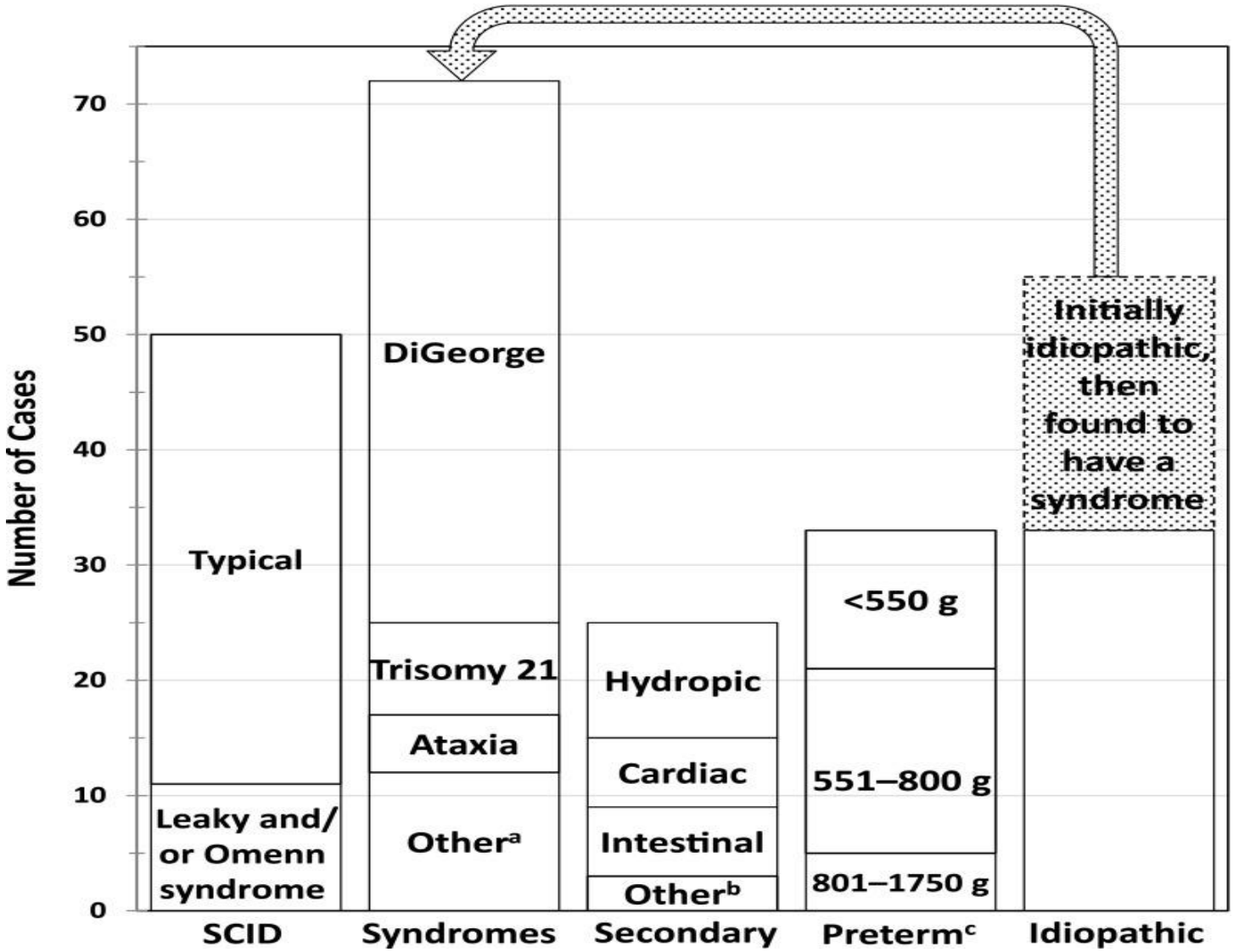
2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Wisconsin	Massachusetts	California	Delaware	Colorado	Minnesota	Illinois	Arkansas	Alaska	Arizona	Nevada
		New York	Michigan	Connecticut	Ohio	Iowa	Hawaii	Georgia	Kansas	Alabama
				Florida	Pennsylvania	Maine	Montana	Idaho	Missouri	Indiana
				Mississippi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

Timeline of SCID Newborn Screening implementation in U.S.

https://scidcompass.org/history-scid-newborn-screening

NEXT STEPS FOR POSITIVE NBS FOR SCID

- CBC with diff.
- T and B lymphocyte quantitation
- T cell receptor excision circle (TREC)
- Recent thymic emigrant study (CD4 RTE)



Amatuni GS, Currier RJ, Church JA, et al. Newborn Screening for Severe Combined Immunodeficiency and T-cell Lymphopenia in California, 2010-2017. Pediatrics. 2019;143(2):e20182300.

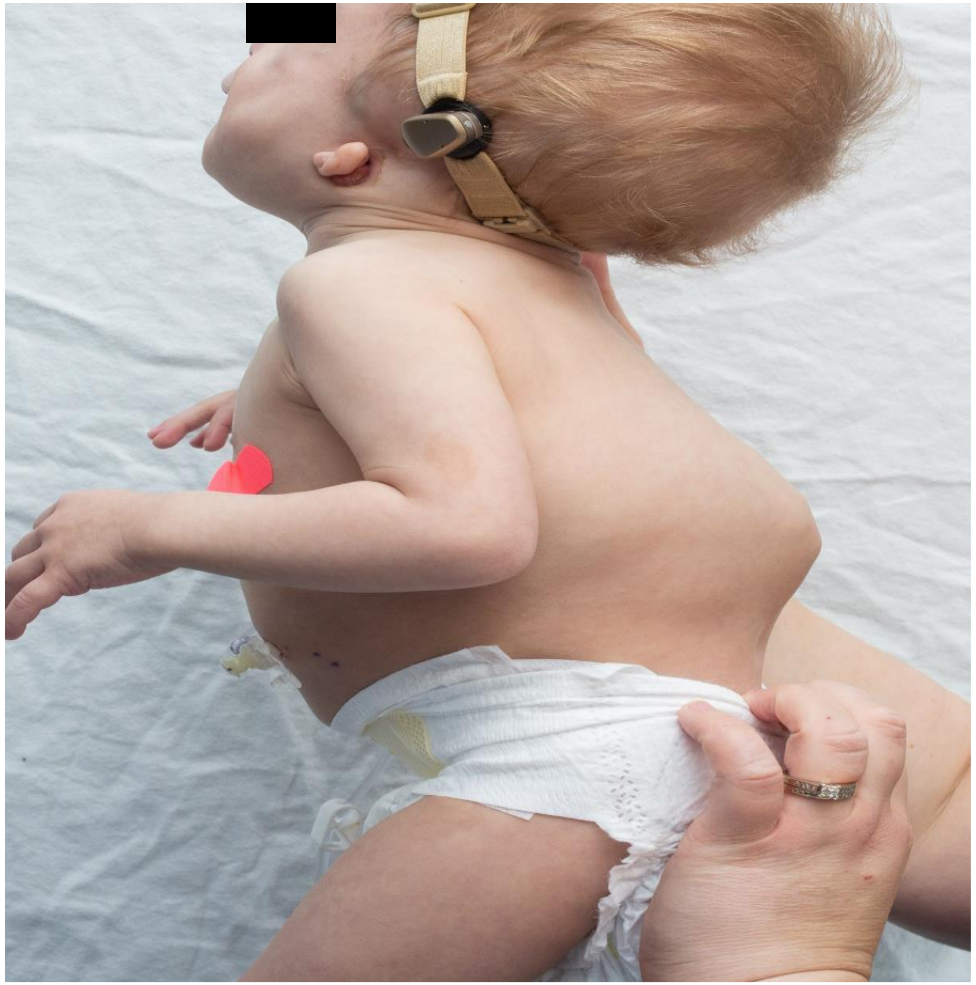
ETHICAL ISSUES ASSOCIATED WITH HSCT IN SCID

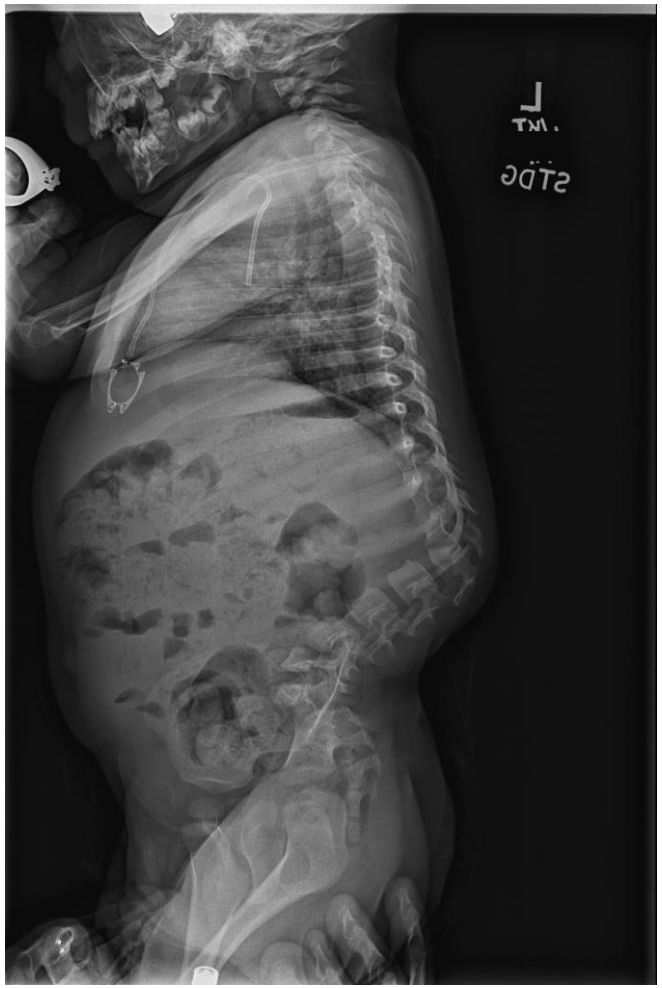
- May not be a complete fix
- Long-term sequelae

Question of:

- Chance of survival vs no chance of survival
- Quality of life for the child and the family

PHOTO QUIZ #3
ABSOLUTE LYMPHOCYTE COUNT :0





Images Approved for use.

WHAT IS THE DIAGNOSIS?

A. SCID
B. Thymic defect
C. Trisomy 21
D. Trisomy 18

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

THYMUS

PAX1 is essential for development and function of the human thymus

Yasuhiro Yamazaki[1], Raul Urrutia[2], Luis M. Franco[3], Silvia Giliani[4,5], Kejian Zhang[6,7], Anas M. Alazami[8,9], A. Kerry Dobbs[1], Stefania Masneri[4,5], Avni Joshi[10], Francisco Otaizo-Carrasquero[11], Timothy G. Myers[11], Sundar Ganesan[12], Maria Pia Bondioni[13], Mai Lan Ho[14], Catherine Marks[14], Huda Alajlan[8], Reem W. Mohammed[15], Fanggeng Zou[7,16], C. Alexander Valencia[7,17,18,19], Alexandra H. Filipovich[20], Fabio Facchetti[4], Bertrand Boisson[21,22,23], Chiara Azzari[24,25], Bander K. Al-Saud[15,26], Hamoud Al-Mousa[15,26], Jean Laurent Casanova[21,22,23,27,28], Roshini S. Abraham[29,30], Luigi D. Notarangelo[1]*

We investigated the molecular and cellular basis of severe combined immunodeficiency (SCID) in six patients with otofaciocervical syndrome type 2 who failed to attain T cell reconstitution after allogeneic hematopoietic stem cell transplantation, despite successful engraftment in three of them. We identified rare biallelic *PAX1* rare variants in all patients. We demonstrated that these mutant PAX1 proteins have an altered conformation and flexibility of the paired box domain and reduced transcriptional activity. We generated patient-derived induced pluripotent stem cells and differentiated them into thymic epithelial progenitor cells and found that they have an altered transcriptional profile, including for genes involved in the development of the thymus and other tissues derived from pharyngeal pouches. These results identify biallelic, loss-of-function *PAX1* mutations as the cause of a syndromic form of SCID due to altered thymus development.

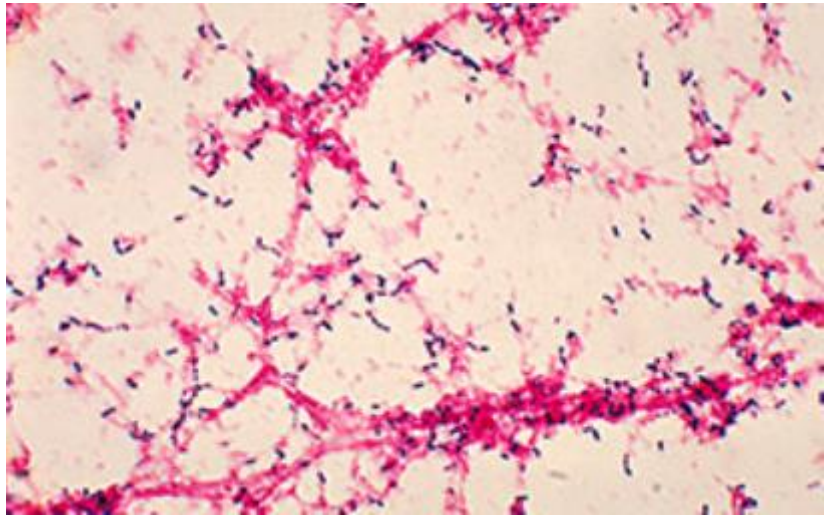
LESS URGENT/SEVERE FORMS OF IMMUNE DEFICIENCY






HUMORAL IMMUNE DEFICIENCY

- Recurrent sinopulmonary infections with encapsulated organisms
- Onset after 6 months of age



Streptococcus pneumoniae: Information for Clinicians | CDC

COMMON HUMORAL IMMUNE DEFICIENCY SYNDROMES

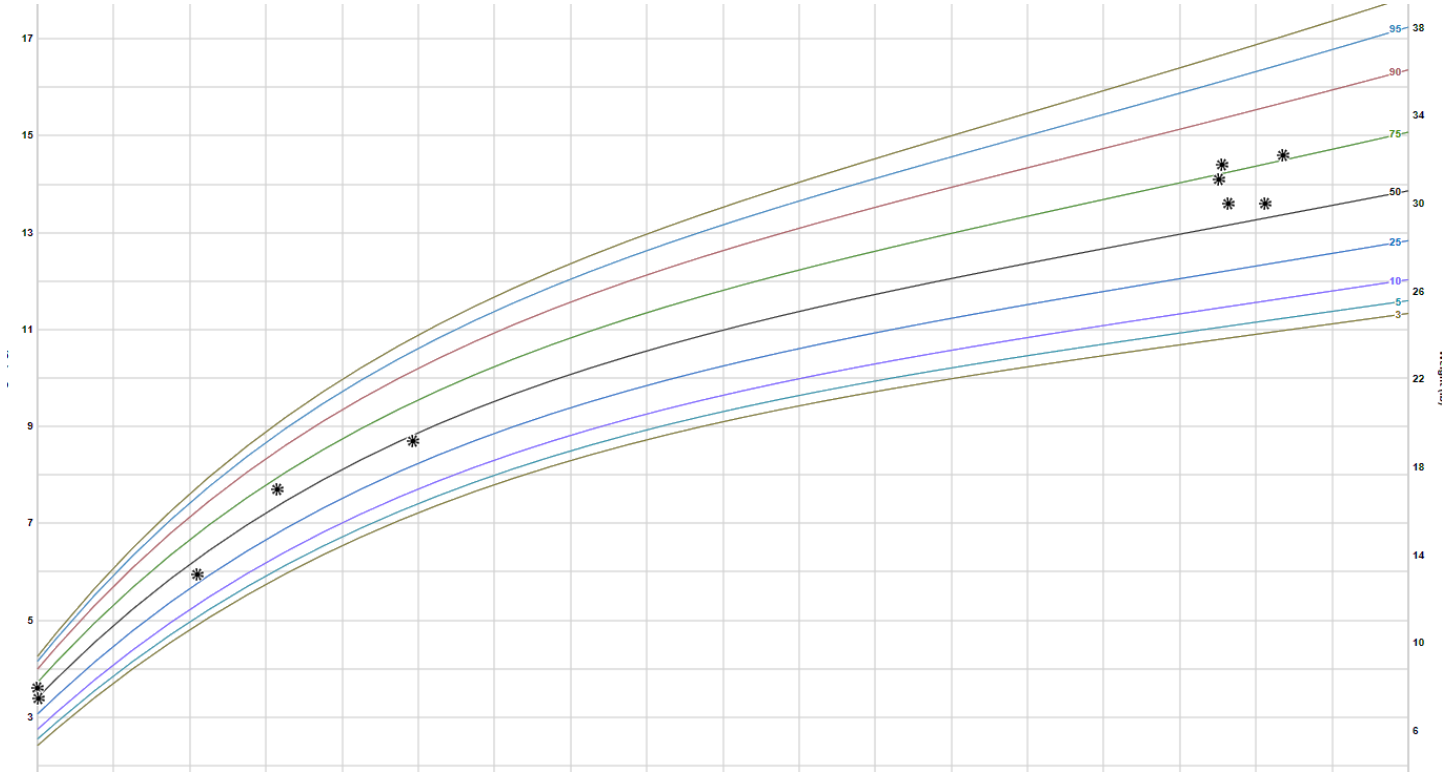
- X-linked agammaglobulinemia
- Transient hypogammaglobulinemia of infancy
- Common variable immunodeficiency
- Selective IgA deficiency

CASE 2

- 18-month-old/male: recurrent infections
- Infection H/O:

Recurrent Otitis Media

- Birth: uneventful
- Family History: Neg.
- Growth: 80th p for both weight and height



LAB TESTING

- IgG: **250**mg/dl
  (Normal range: 15-<24 months: 313-1,170mg/dL)
- IgA: **20**mg/dl
  (Normal range: 15-<24months: 36-79mg/dL)
- IgM: 50mg/dl
  (Normal range: 15-<24 months: 46-152mg/dL)

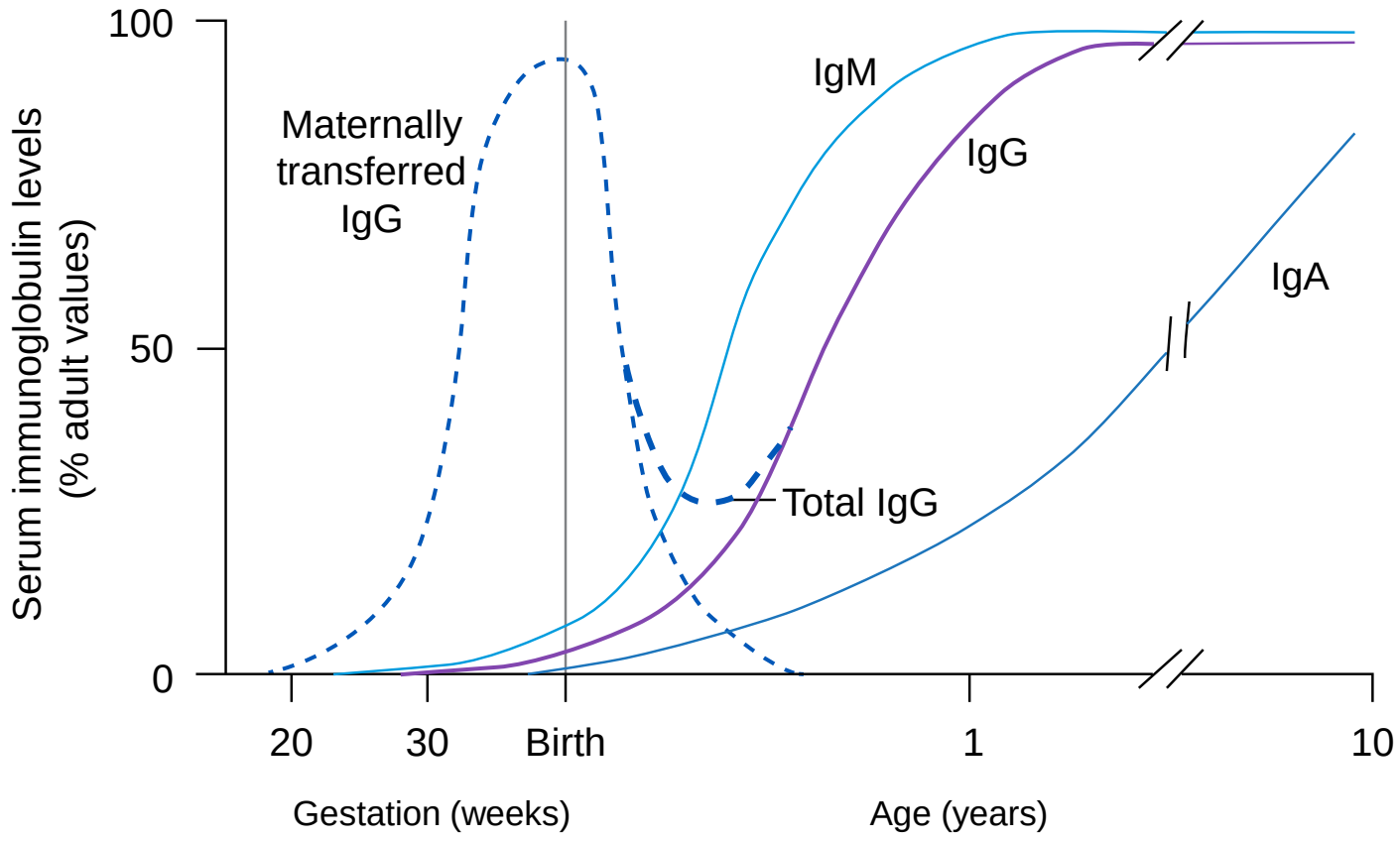
RECURRENT OTITIS MEDIA WITH LOW IGA/IGG. DIAGNOSIS?

A. Common Variable Immune Deficiency (CVID)
B. Transient Hypogammaglobinemia of infancy (THI)
C. Selective IgA deficiency (SIgAD)
D. Chronic Granulomatous Disease (CGD)

TRANSIENT HYPOGAMMAGLOBINEMIA OF INFANCY -THI

- Prolongation of the “physiologic” hypogammaglobulinemia of infancy
- The diagnosis is based upon IgG levels at least 2 SD below the mean for aged-matched controls
- No other immune deficiency

SERUM IMMUNOGLOBULIN LEVELS AND AGE



Redrawn from: S Jyothi et al. Arch Dis Child Educ Pract Ed 2013;98:186-196

WORK- UP FOR TRANSIENT HYPOGAMMAGLOBINEMIA OF INFANCY (CHILDHOOD)

- Baseline immunoglobulin assessment: IgG, IgM and IgA levels
- Vaccine responses: Routine childhood vaccines
- T and B lymphocyte subsets: To rule out combined humoral and cellular immune defects

TREATMENT FOR TRANSIENT HYPOGAMMAGLOBINEMIA OF INFANCY (CHILDHOOD)

- Usually, conservative
- If severe infections or significant hypogammaglobinemia:
  - Can consider IVIG
  - Self limited, usually outgrow by 4-5 yrs age

CASE #3: 9 YEAR/ F WITH RECURRENT INFECTIONS

- Uneventful first five years of life
- Recurrent sinus infections: at least 10 courses of antibiotics/year
- Age 9: S. pneumoniae sepsis
- Splenomegaly noticed for the first time

CASE # 3 (CONTD.)

Immunoglobulins checked:

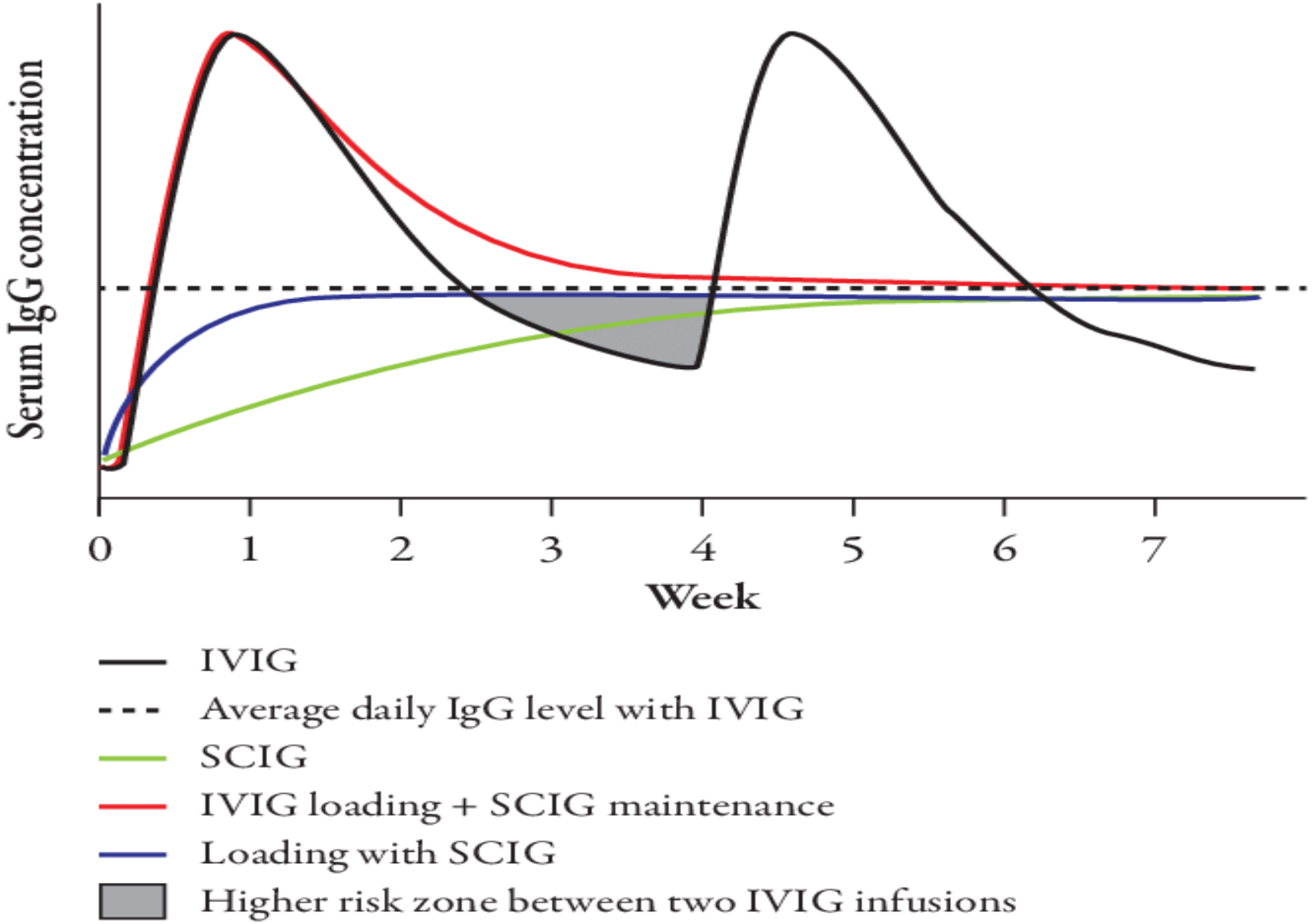
- IgA **<1**
  (Normal range: 7-<10 years: 34-274mg/dL)
- IgM **<1**
  Normal range: 7-<10 years: 38-251mg/dL)
- IgG: **33**
  (Normal range: 7-<10 years: 386-1,470mg/dL)

9 YR/F WITH SEPSIS, SPLENOMEGALY AND MARKEDLY DECREASED IMMUNOGLOBULIN LEVELS?

A. Common Variable Immune Deficiency (CVID)
B. HIV
C. Selective IgA deficiency (SIgAD)
D. Chronic Granulomatous Disease (CGD)

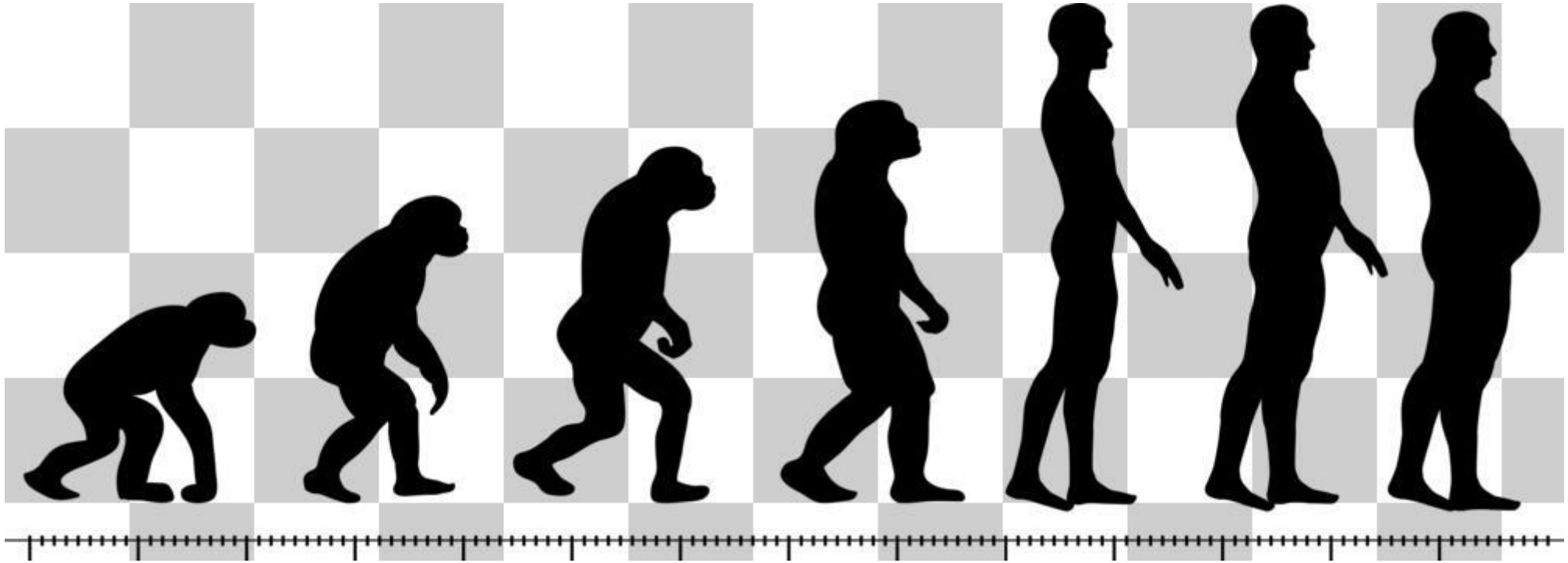
IVIG OR SQIG DOSING

- Historically= 100mg/kg
- Now : 400-600 mg/kg/month
- Peak- doesn’t seem to impact efficacy
- Trough levels: Most predictive



VACCIANTIONS

THE OBESITY EVOLUTION



https://mcmedia.mayo.edu/Dam/241HRGMSE4JDN?DownloadFormat=WebLow

ROLE OF DIET AND OBESITY IN IMMUNE COMPETENCE

Obesity

Innate and adaptive immune system

Adipose tissue

Systemic

Immune homeostasis

Trained innate immunity

Inflammaging / immunosenscence

Resistance to infection

Redrawn from: Front. Nutr., 19 November 2020

Association of vitamin D deficiency with COVID-19 infection severity: Systematic review and meta-analysis

Zhen Wang[1] | Avni Joshi[2,3] | Kaitlin Leopold[4] | Sarah Jackson[5] | Stephanie Christensen[4] | Tarek Nayfeh[1,6] | Khaled Mohammed[7] | Ana Creo[5] | Peter Tebben[5,8] | Seema Kumar[5]

[1]Division of Health Care Delivery Research, Robert D. and Patricia E. Kern Center for the Science of Health Care Division of Health Care Delivery Research, Mayo Clinic, Rochester, Minnesota, USA

[2]Division of Allergic Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA

[3]Division of Pediatric Allergy and Immunology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA

[4]Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA

[5]Division of Pediatric Endocrinology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA

[6]Mayo Clinic Evidence-based Practice Center, Rochester, Minnesota, USA

[7]Community Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA

[8]Division of Endocrinology and Metabolism, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA

Correspondence
Seema Kumar, Division of Pediatric Endocrinology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA.
Email: kumar.seema@mayo.edu

Abstract

Background: We sought to evaluate the association between vitamin D deficiency and the severity of coronavirus disease 2019 (COVID-19) infection.

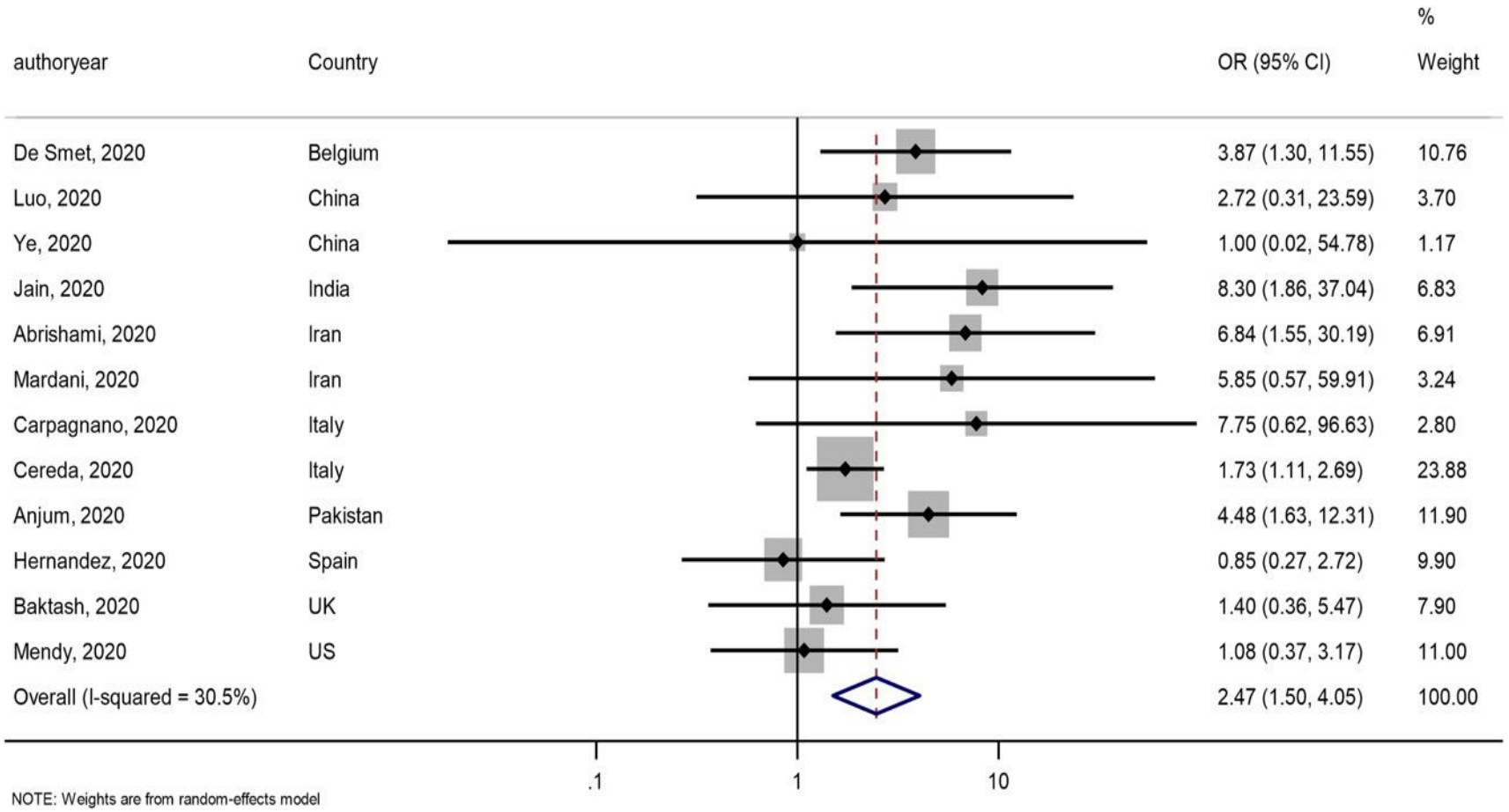
Methods: Multiple databases from 1 January 2019 to 3 December 2020 were searched for observational studies evaluating the association between vitamin D deficiency and severity of COVID-19 infection. Independent reviewers selected studies and extracted data for the review. The main outcomes of interest were mortality, hospital admission, length of hospital stay and intensive care unit admission.

Results: Seventeen observational studies with 2756 patients were included in the analyses. Vitamin D deficiency was associated with significantly higher mortality (odds ratio [OR]: 2.47, 95% confidence interval [CI]: 1.50–4.05; 12 studies; hazard ratio [HR]: 4.11, 95% CI: 2.40–7.04; 3 studies), higher rates of hospital admissions (OR: 2.18, 95% CI: 1.48–3.21; 3 studies) and longer hospital stays (0.52 days; 95% CI: 0.25–0.80; 2 studies) as compared to nonvitamin D deficient status. Subgroup analyses based on different cut-offs for defining vitamin D deficiency, study geographic locations and latitude also showed similar trends.

Conclusions: Vitamin D deficiency is associated with greater severity of COVID-19 infection. Further studies are warranted to determine if vitamin D supplementation can decrease the severity of COVID-19.

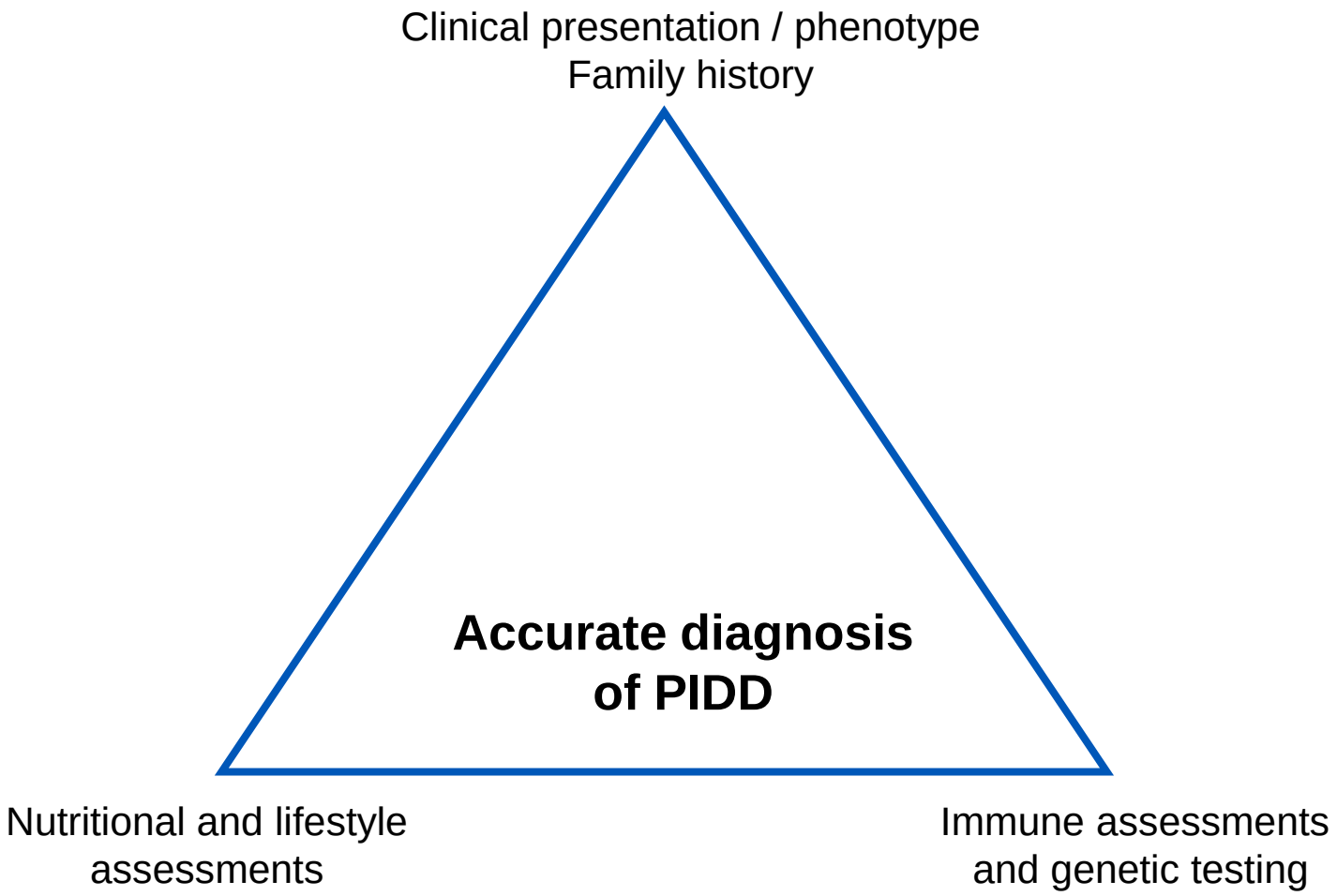
KEYWORDS
COVID-19, hospital admission, mortality, vitamin D

ASSOCIATION OF VITAMIN D DEFICIENCY WITH COVID-19 INFECTION SEVERITY: SYSTEMATIC REVIEW AND META-ANALYSIS

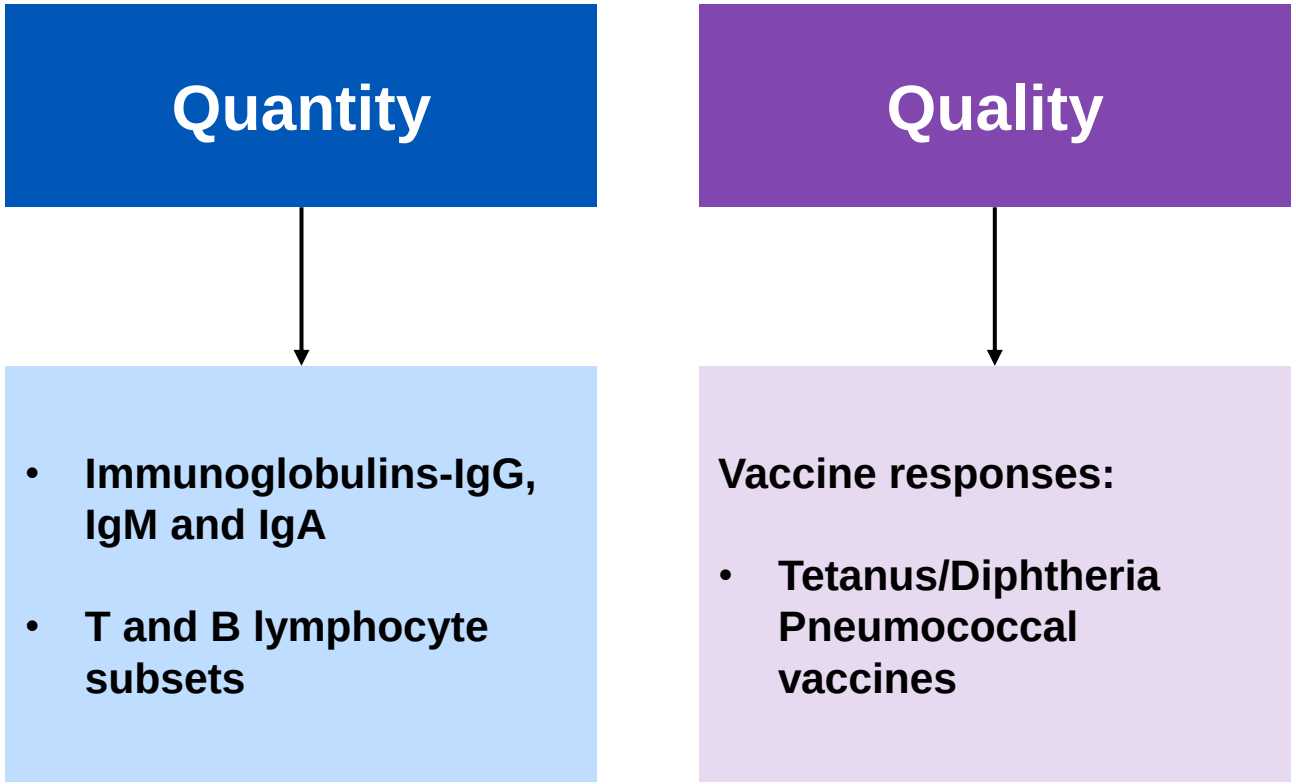


Redrawn from: Clinical Endocrinology, Volume: 96, Issue: 3, Pages: 281-287, First published: 23 June 2021, DOI: (10.1111/cen.14540)

DIAGNOSIS OF PIDDS



ASSESSING IMMUNE COMPETENCE: TIER 1



SUMMARY

- Immune deficiency can have **severe** and **less severe** presentations
- Inherited defects: **family history** is critical
- Pay close attention to **physical exam/dysmorphism** and **growth parameters**
- **Autoimmunity** and immune deregulation is increasingly being recognized with immune deficiency disorders

HIGH LEVEL SUMMARY

- Not everyone with recurrent infections needs immune assessment
- No everyone with subtle defect in immune assessments needs supplemental immunoglobulin therapies
- Stress Vaccination(s) at each visit
- Strong correlation with immune functioning with lifestyle:

Diet, Sleep and Nutrition

QUESTIONS & DISCUSSION