IPOPI 4TH REGIONAL ASIAN PID MEETING

19-20 NOVEMBER 2022

KUALA LUMPUR, **MALAYSIA**

an **IPOPI** event

CARE FOR RARE

GLOBAL ALLIANCE EDUCATIONAL SEMINAR

Care-for-Rare Foundation

IPOPI

IPOPI.ORG

SUPPORTING ORGANISATIONS

My POPI

SEAPID

SUPPORTED BY

Takeda

Management of Infectious Complications

Session 4:Optimal PID Management

Intan Hakimah Ismail
MD, MMed (Paeds), PhD
Advanced Medical Research in Allergy and Clinical Immunology (AMRAC)
Faculty Of Medicine and Health Sciences
Universiti Putra Malaysia

IPOPI
IPOPI.ORG

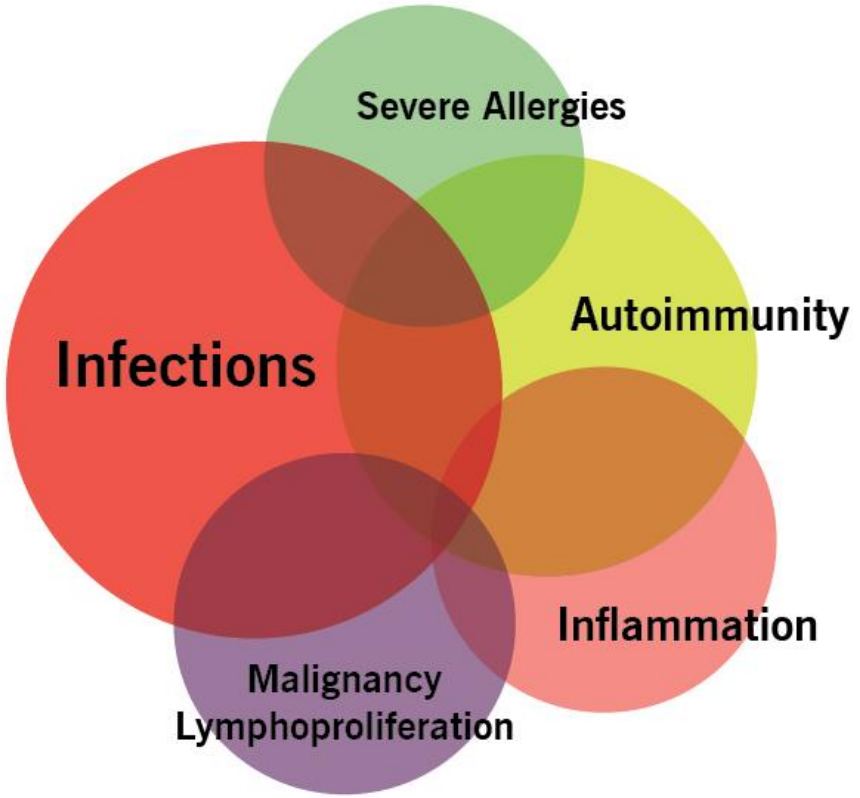
IPOPI
4TH REGIONAL
ASIAN PID MEETING
19-20 NOVEMBER 2022
KUALA LUMPUR, MALAYSIA
an IPOPI event

UNIVERSITI PUTRA MALAYSIA

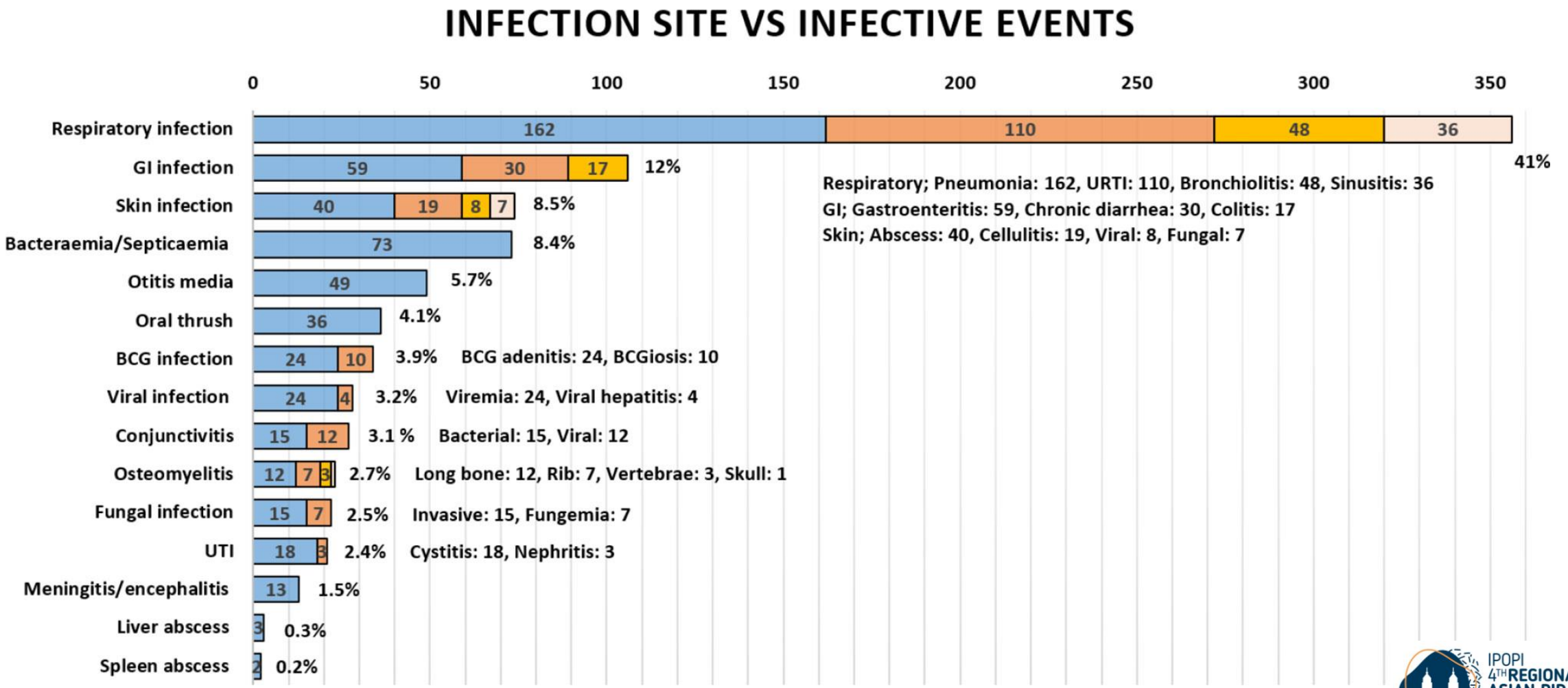
Contact immunology team HPUPM
immunoallergyupm@gmail.com
intanhakimah@upm.edu.my

Primary immunodeficiencies = Inborn error of immunity

- PIDs are no longer defined by tendency for infections alone
- PID patients with non-infectious complications are increasingly recognised with features of immune dysregulation:
  - Autoimmunity
  - Inflammation
  - Lymphoproliferation
  - Allergy
  - Malignancy



The frequency of infections according to infection site



Antimicrobial therapy in PID

- Antimicrobial therapy is important for the treatment of all forms of
- Infections are the most common forms of presentation, and depend on the type of immune defect present
- The treatment of infections in PID patients is complex, requiring long-term use of medication and often with a broad spectrum
- Due to the greater susceptibility to unusual agents, a greater effort must be made for the exact identification of pathogens, including the culture of affected tissues and molecular techniques to identify the pathogen

Pattern of infections associated with PID

T cells / combined

- Systemic (viral)
- Lung / GI etc
  - **Intracellular:** Viruses Mycobacteria
  - **Fungi:** Candida, Aspergillus
  - **Protozoa:** Cryptosporidium
  - **Opportunistic:** PCP

B cells / antibody

- Sinopulmonary
- GI / skin / joint
  - **Pyogenic bacteria:** Pneumococcus Haemo infl B Moraxella
  - Enterovirus (enceph)
  - Mycoplasma (joint)

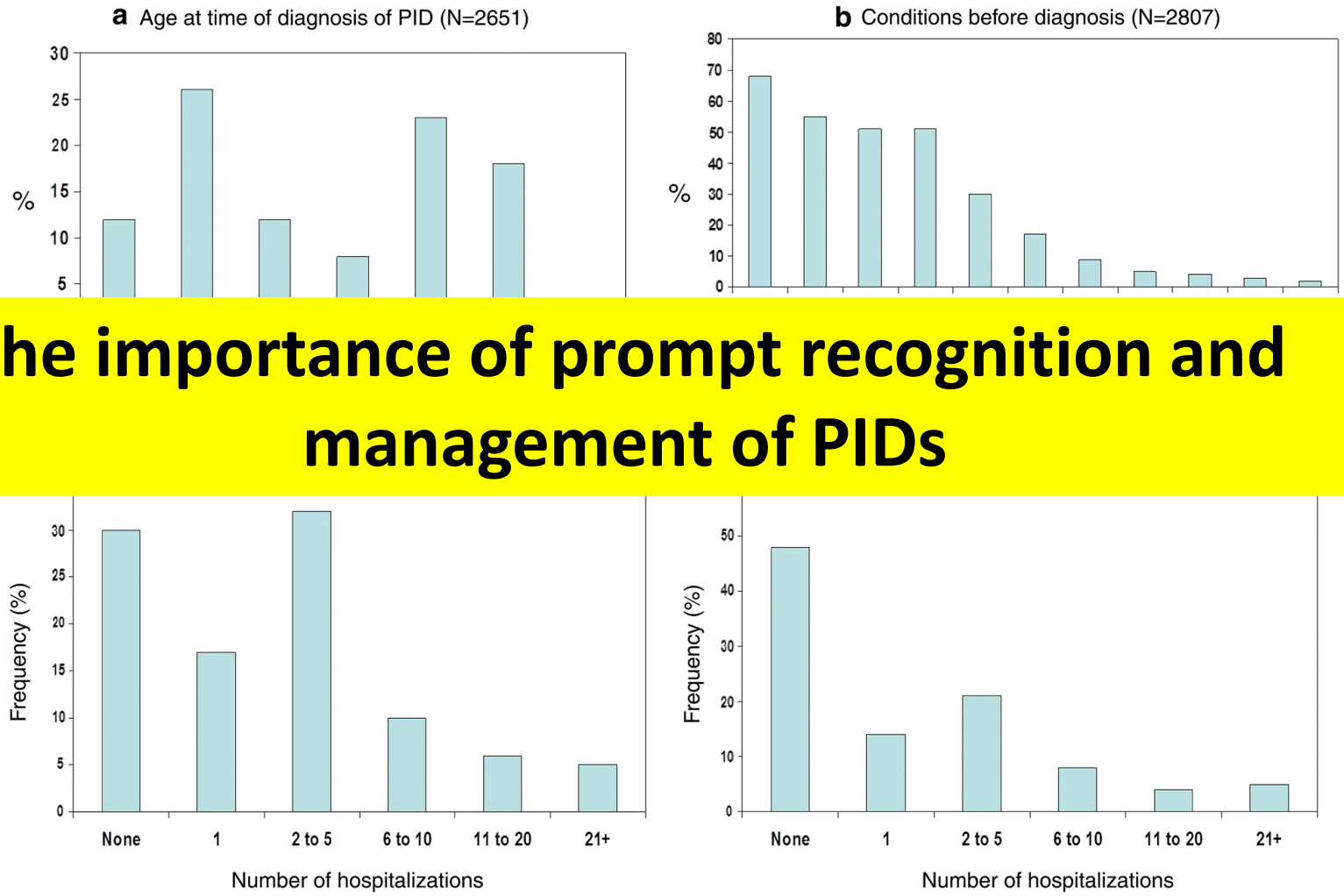
Innate / phagocytes

- Skin / lung / lymph
- GI / liver
  - **Bacteria:** Catalase + Staphylococcus Serratia E.coli/ Klebsiella B.cepacia
  - **Fungi:** Candida Aspergillus

Complement

- Systemic (bacteria)
  - **Neisseria** Meningococcus
  - **Pyogenic bacteria:** Pneumococcus Haemo infl B
  - CMV / HSV

Rate of hospitalisations pre- and post diagnosis

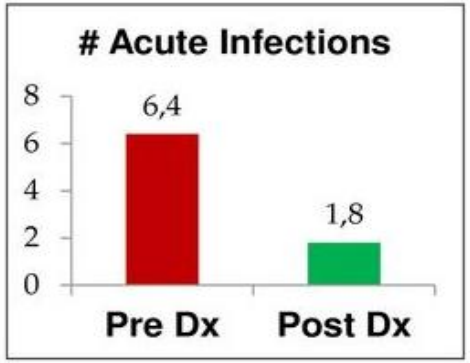


The importance of prompt recognition and management of PIDs

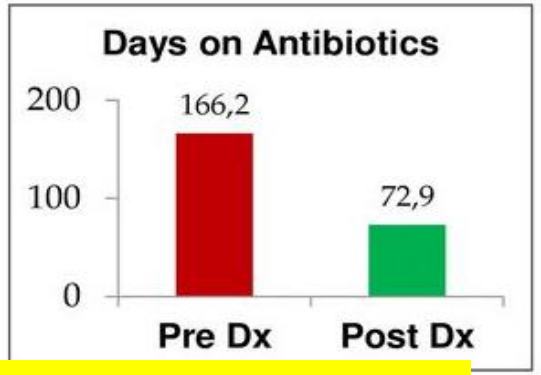
McCusker, C., Upton, J. & Warrington, R. Primary immunodeficiency. *Allergy Asthma Clin Immunol* **14** (Suppl 2), 61 (2018)

IPOPI 4TH REGIONAL ASIAN PID MEETING 19-20 NOVEMBER 2022 KUALA LUMPUR, MALAYSIA an IPOPI event

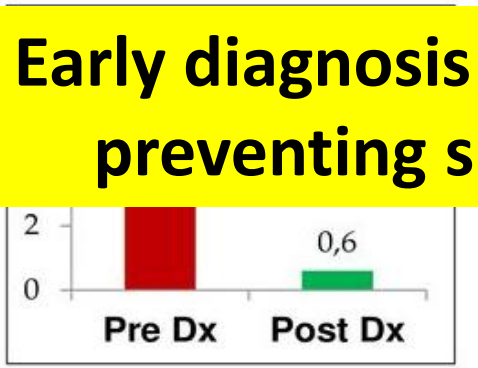
Improvement after diagnosis of PID

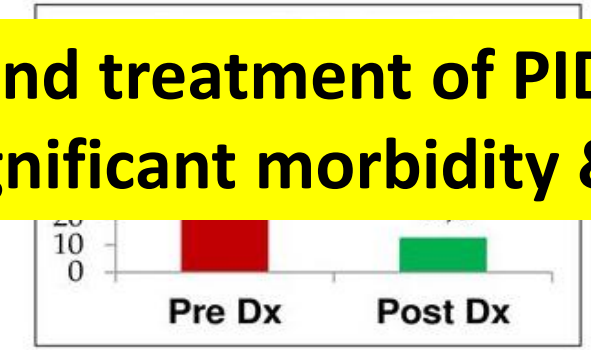


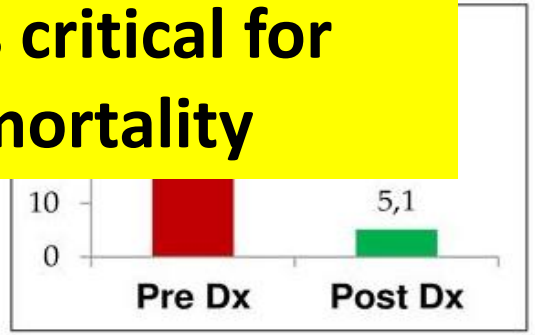
- Comparing quality of life data per year for undiagnosed vs. diagnosed patients with PID
- Modell et al, Immunol Res 2011 51:61-70

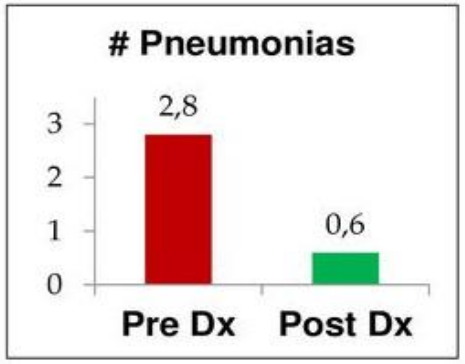


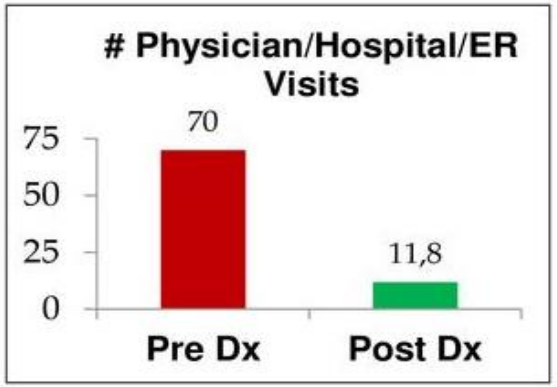
Early diagnosis and treatment of PID is critical for preventing significant morbidity & mortality

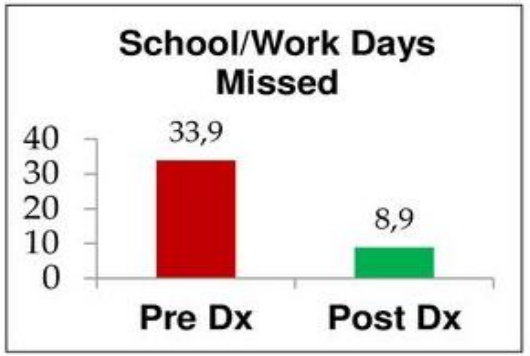






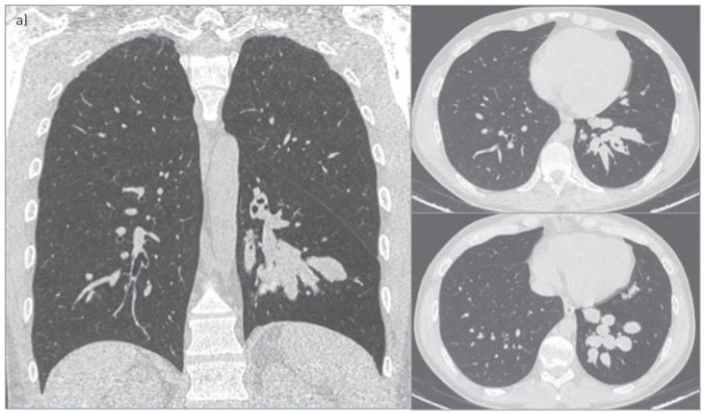






IPOPI 4TH REGIONAL ASIAN PID MEETING
19-20 NOVEMBER 2022
KUALA LUMPUR, MALAYSIA
an IPOPI event

Infectious complications – bronchiectasis



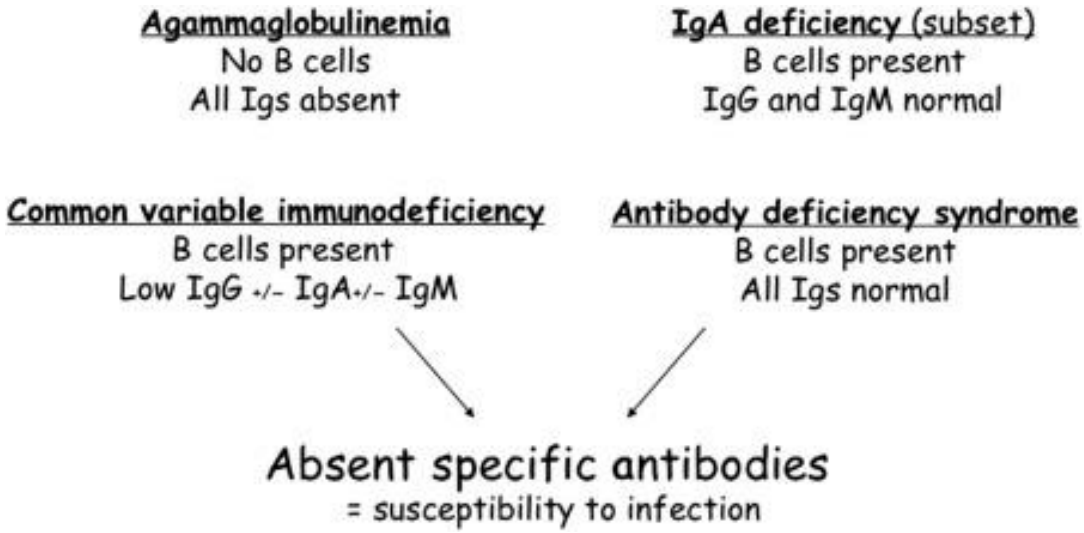
Factors associated with bronchiectasis in patients with antibody deficiencies

- Delayed diagnosis of antibody deficiency
- History of pneumonia
- Prolonged respiratory infectious
- Chronic wet or productive cough
- Protracted bacterial bronchitis, > 3 episodes per year
- Abnormal or worsening pulmonary function testing
- Difficulty maintaining sufficient IgG trough on IgRT
- CD4 counts < 700 cells/microliter
- Low B cells and /or memory B cells
- In the setting of CVID: very low IgA level (<7 mg/dl) or very low IgM

Wall LA, Wisner EL, Gipson KS, Sorensen RU. Bronchiectasis in Primary Antibody Deficiencies: A Multidisciplinary Approach. Front Immunol. 2020 Mar 31;11:522

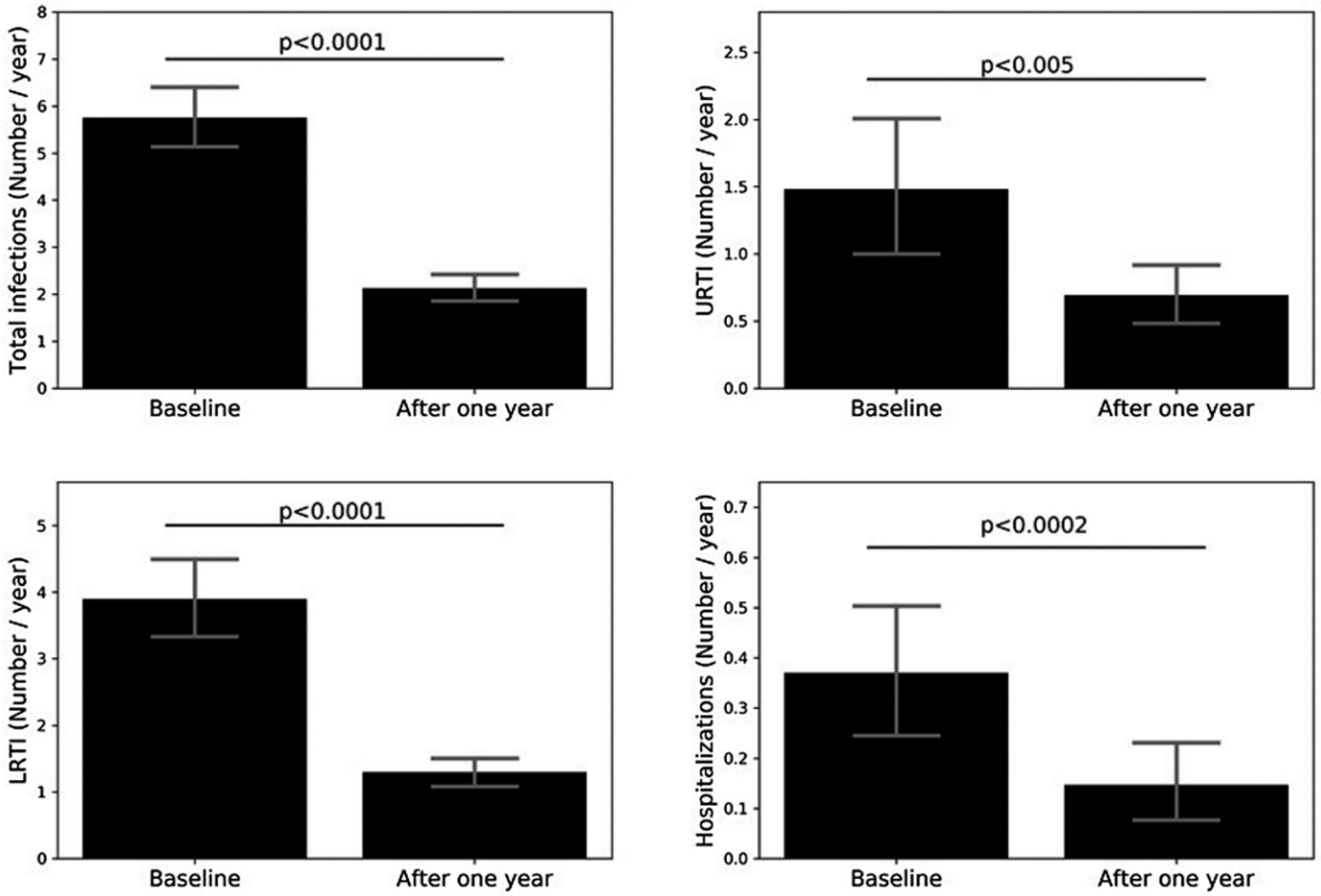
Immunoglobulin replacement therapy (IRT)

- Lifelong IVIg or SCIg replacement therapy for patients with PAD, especially XLA and CVID has led to :
  - Decrease in the incidence of infections
  - Reduce severity of infections
  - Decrease the rate of hospitalization
  - Prevent long-term deterioration in organ function
  - Reduced mortality from acute bacterial infections

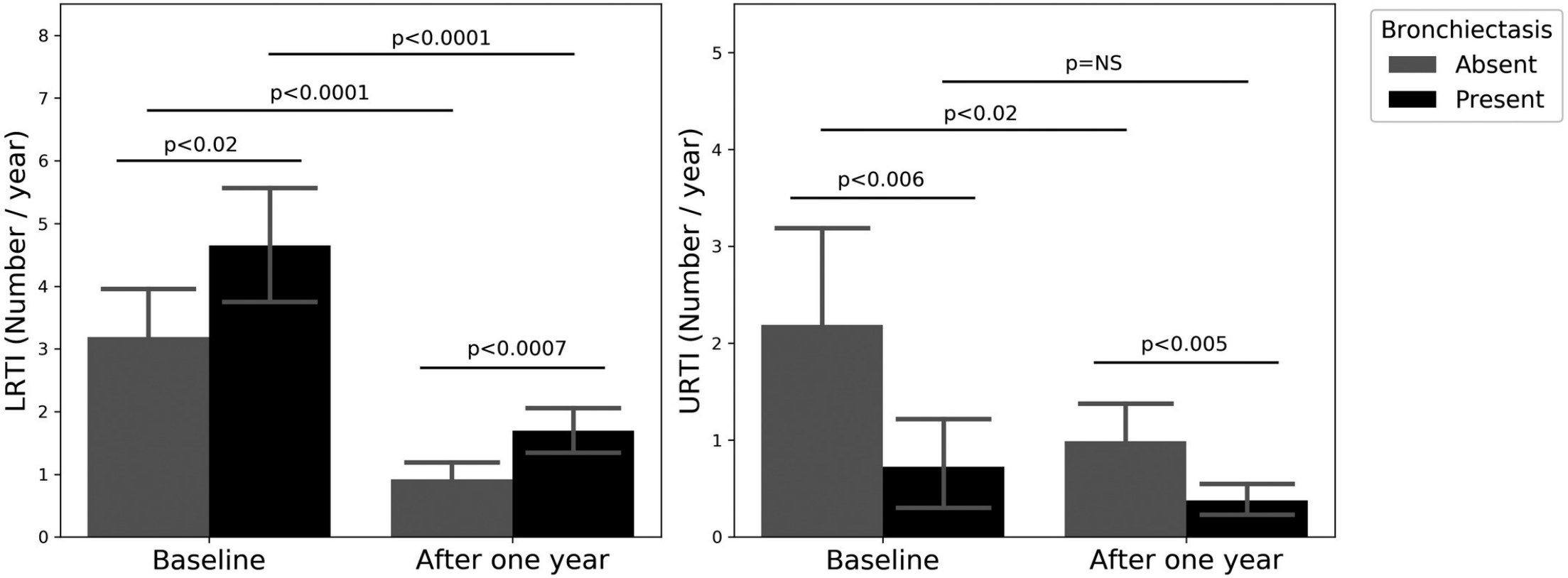


Jolles S, Orange JS, et al. Current treatment options with immunoglobulin G for the individualization of care in patients with primary immunodeficiency disease. Clin Exp Immunol. 2015 Feb;179(2):146-60.

Effectiveness of low-dose IVIG therapy in minor primary antibody deficiencies



Effectiveness of low-dose IVIG therapy in minor primary antibody deficiencies



Clinical Commentary Review

Antibiotic Prophylaxis in Primary Immune Deficiency Disorders

Merin Kuruvilla, MD, and Maria Teresa de la Morena, MD *Dallas, Tex*

frontiers in Immunology

REVIEW
published: 09 August 2017
doi: 10.3389/fimmu.2017.00937

Primary Immunodeficiency Diseases: Current and Emerging Therapeutics

*Beatriz E. Marciano and Steven M. Holland**

IMMUNOCOMPROMISED HOSTS INVITED ARTICLE

David R. Snydman, Section Editor

Prevention of Infections During Primary Immunodeficiency

Claire Aguilar,[1,2,3] Marion Malphettes,[1,4] Jean Donadieu,[1,5] Olivia Chandesris,[1,3,6] Hélène Coignard-Biehler,[1,2,3] Emilie Catherinot,[1,7] Isabelle Pellier,[1,8] Jean-Louis Stephan,[1,9] Vincent Le Moing,[1,10] Vincent Barlogis,[1,11] Felipe Suarez,[1,3,6] Stéphane Gérart,[3] Fanny Lanternier,[1,2,3] Arnaud Jaccard,[1,12] Paul-Henri Consigny,[2] Florence Moulin,[13] Odile Launay,[14] Marc Lecuit,[1,2,3] Olivier Hermine,[1,3,6] Eric Oksenhendler,[1,4] Capucine Picard,[1,3,15,16,a] Stéphane Blanche,[1,3,16,a] Alain Fischer,[1,3,16,17,a] Nizar Mahlaoui,[1,3,16] and Olivier Lortholary[1,2,3]

Antimicrobial prophylaxis for primary immunodeficiencies

Alexandra F. Freeman and Steven M. Holland

Laboratory of Clinical Infectious Diseases, NIAID, NIH, Bethesda, Maryland, USA

Correspondence to Dr Alexandra F. Freeman, NIH, Building 10 Room 11N234, 10 Center Dr, Bethesda, MD 20892, USA
Tel: +1 301 594 9045; fax: +1 301 496 0773;
e-mail: freemaal@mail.nih.gov

Current Opinion in Allergy and Clinical Immunology 2009, 9:525–530

Purpose of review
Antibiotic prophylaxis is one of the mainstays of therapy of primary immunodeficiencies. We aim to summarize what is known about antibiotic prophylaxis for select primary immunodeficiencies.
Recent findings
In recent years, there has been a push towards more evidence-based practices for antimicrobial prophylaxis for many conditions such as antifungal prophylaxis for extremely premature neonates and antibiotic prophylaxis for neutropenia associated with chemotherapy. However, there are remarkably few data regarding antibiotic prophylaxis in primary immunodeficiencies and regimens vary greatly between practices.

Prevention of infection in children and adolescents with primary immunodeficiency disorders

Efimia Papadopoulou-Alataki,[1] Amel Hassan[2] and E. Graham Davies[2]

(Asian Pac J Allergy Immunol 2012;30:249-58)

ELSEVIER

Archives of Medical Research 35 (2004) 359–360

Archives of Medical Research

LETTER TO THE EDITOR

Importance of Life-Long Continuous Antimicrobial Prophylaxis to Prevent Infections in Patients with Job's Syndrome*

Antimicrobial prophylaxis in PID

- Limited scientifically-based evidence for the use of antibiotic prophylaxis in PIDs, except for PAD, SCID and CGD.
- 39 patients at least 5 years old (6 female and 33 male; mean age, 14.9 years) were enrolled in this RDBPC study
- After the initially assigned treatment, each patient alternated between itraconazole and placebo annually
- Patients ≥ 13 years old or weighing ≥ 50 kg received a single dose of itraconazole 200 mg/day
- Those < 13 years old or weighing < 50 kg received a single dose of itraconazole 100 mg/day
- The primary end point was severe fungal infection, as determined by histologic results or culture

Table 1. Serious Fungal Infections.

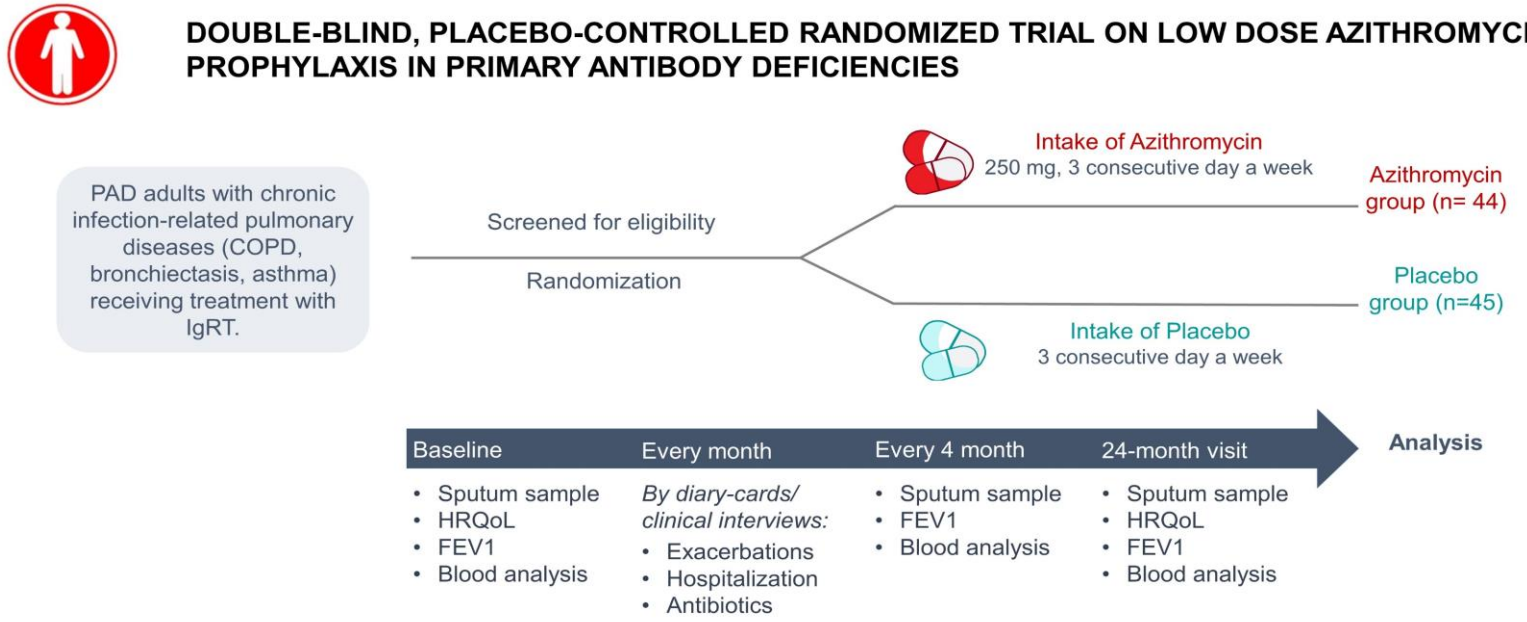
Patient No.	Age (yr)	Sex	Time from Randomization (yr)	Genotype	Infection
Itraconazole					
3*	19	M	3.7	p47^{phox}	*Aspergillus fumigatus* pneumonia
Placebo					
7	16	M	5.1	gp91^{phox}	*A. fumigatus* pneumonia
13	5	M	0.1	gp91^{phox}	Aspergillus species pneumonia
15	16	M	5.9	gp91^{phox}	*A. nidulans* pneumonia
28	7	M	0.3	gp91^{phox}	*A. nidulans* pneumonia
32	10	M	3.7	gp91^{phox}	*Paecilomyces lilacinus* soft-tissue abscess
34	25	M	4.3	gp91^{phox}	Fungal pneumonia†
37	16	M	0.4	gp91^{phox}	Aspergillus species pneumonia

* Itraconazole therapy failed in Patient 3, but the return of unused medication indicated that he probably was not taking the drug.
† Fungal elements were identified on lung biopsy, with no growth in cultu

Gallin, *et al.* Itraconazole to prevent fungal infections in chronic granulomatous disease. N Engl J Med, 348 (2003); 2416-2422

Low dose azithromycin prevents airway complications in primary antibody deficiencies

Milito C, et al. J Allergy Clin Immunol. 2019 Aug;144(2):584-593



Low dose azithromycin prevents airway complications in primary antibody deficiencies

Milito C, et al. J Allergy Clin Immunol. 2019 Aug;144(2):584-593

DOUBLE-BLIND, PLACEBO-CONTROLLED RANDOMIZED TRIAL ON LOW DOSE AZITHROMYCIN PROPHYLAXIS IN PRIMARY ANTIBODY DEFICIENCIES

PAD adults with chronic infection-related pulmonary diseases (COPD, bronchiectasis, asthma) receiving treatment with IgRT.

Screened for eligibility

Randomization

Intake of Azithromycin
250 mg, 3 consecutive day a week

Azithromycin group (n= 44)

Placebo group (n=45)

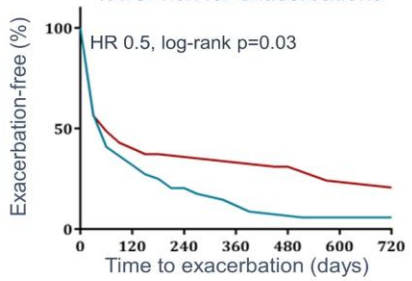
Intake of Placebo
3 consecutive day a week

Baseline	Every month	Every 4 month	24-month visit	Analysis
• Sputum sample • HRQoL • FEV1 • Blood analysis	*By diary-cards/ clinical interviews:* • Exacerbations • Hospitalization • Antibiotics	• Sputum sample • FEV1 • Blood analysis	• Sputum sample • HRQoL • FEV1 • Blood analysis	

COPD chronic obstructive pulmonary disease
HRQoL Health Related Quality of Life
FEV1 Forced Expiratory Volume 1st sec
IgRT Immunoglobulin Replacement Treatment
PAD Primary Antibody Defect

Primary outcome

In the Azithromycin group lower risk for exacerbations



Secondary outcomes

In the Azithromycin group:

- Lower risk for hospitalization
- Lower need for additional antibiotic courses
- No higher rate of macrolides resistant-carriage
- No drug-related toxicity
- Improved HRQoL
- No effect on FEV1
- Reduced count in blood of neutrophils

IPOPI 4TH REGIONAL ASIAN PID MEETING
19-20 NOVEMBER 2022
KUALA LUMPUR, MALAYSIA
an IPOPI event

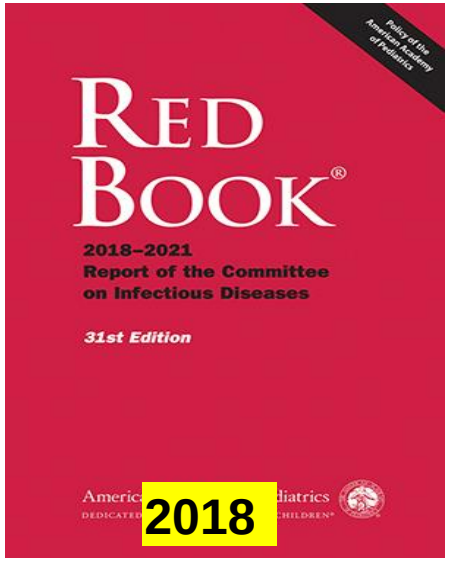
Disease	Agent	Dose	Route	Regimen
Common Variable Immunodeficiency	Trimethoprim-Sulphamethoxazole	5 mg/kg of Trimethoprim	P.O	1-2 divided doses daily, 3 days/week
	Azithromycin	10 mg/kg	P.O	Once daily
X-linked Agammaglobulinaemia	Trimethoprim-Sulphamethoxazole	5 mg/kg of Trimethoprim	P.O	1-2 divided doses daily, 3 days/week
Di George Syndrome	Trimethoprim-Sulphamethoxazole	5 mg/kg of Trimethoprim	P.O	1-2 divided doses daily, 3 days/week
	Fluconazole	3 mg/kg	P.O	Once daily
Wiskott-Aldrich Syndrome	Trimethoprim-Sulphamethoxazole	5 mg/kg of Trimethoprim	P.O	1-2 divided doses daily, 3 days/week
	Acylovir	80 mg/kg	P.O	Four times daily
	Fluconazole	3mg/kg	P.O	Once daily
	Penicillin if splenectomy	125 mg(<5years) 250 mg(>5years)	P.O	Twice daily
Chronic Granulomatous Disease	Trimethoprim-Sulphamethoxazole	6 mg/ kg of Trimethoprim	P.O	1-2 divided doses daily,
	Itraconazole	5 mg/kg	P.O	Once daily
Hyper IgE Syndrome STAT3 deficiency	Trimethoprim-Sulphamethoxazole	6 mg/kg of Trimethoprim	P.O	1-2 divided doses daily,
	Flucloxacillin	125-250 mg	P.O	Twice daily
	If bronchiectasis : Azithromycin Inh Tobramycin	 10 mg/kg 300 mg	 P.O Inhalation	 Once daily Twice daily
	If pneumatoceles: Itraconazole	 5 mg/kg	 P.O	 Once daily
Ataxia Telangiectasia	Azithromycin	10 mg/kg	P.O	3 days/week

Prophylaxis therapy in children with SCID

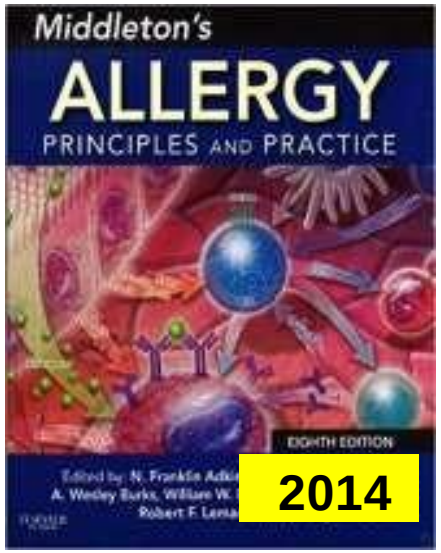
Against	Agent	Dose	Route	Regimen
Respiratory syncytial virus	Palivizumab	15 mg/kg	IM	Once monthly•
Pneumocystis jiroveci	Trimethoprim-Sulphamethoxazole	5 mg/kg of Trimethoprim	P.O	1-2 divided doses daily, 3 days/week
Pneumocystis jiroveci	*Pentamidine isetionate	300 mg	Inh	Once every 3 weeks
Pneumocystis jiroveci	*Dapsone	2 mg/kg	P.O	Once daily
Candida	Fluconazole	3 mg/kg	P.O	Once daily
Herpes family viruses	Acyclovir	80 mg/kg	P.O	Four times daily

IM, intramuscular; P.O, per os; Inh, Inhalation, •during respiratory syncytial virus season for children <2years * alternative to Trimethoprim-Sulphamethoxazole; TMP-SMX, 30 mg/kg total daily dose

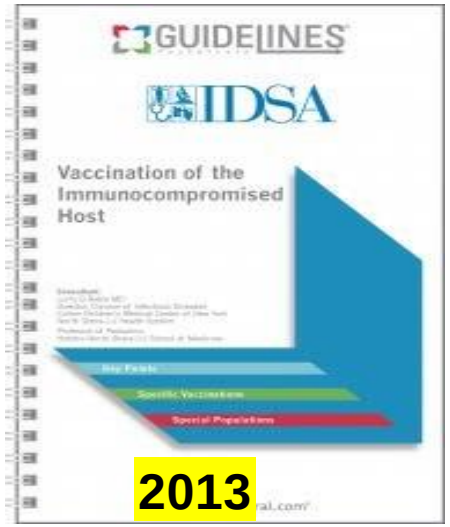
Guidelines



2018



2014



2013

Infectious Diseases Society of America

2016, update 2018

Current perspectives

Update: Vaccines in primary immunodeficiency

Francisco A. Bonilla, MD, PhD *Boston, Mass*

Francisco A. Bonilla, MD, PhD

Journal of Allergy and Clinical Immunology

2018;141:474-81 2018

Clinical Commentary Review

Vaccination in Primary Immunodeficiency Disorders

Ali Sobh, MD[a], and Francisco A. Bonilla, MD, PhD[b] *Boston, Mass*

Ali Sobh, MD, and Francisco A. Bonilla, MD, PhD

Journal of Allergy and Clinical Immunology: In Practice

2016;4:1066-75

IPOPI 4TH REGIONAL ASIAN PID MEETING
19-20 NOVEMBER 2022
KUALA LUMPUR, MALAYSIA
an IPOPI event

Immunisations of children and adolescents with primary immunodeficiencies

	Immune Deficiency Syndrome	Vaccine Contraindications	Vaccine Recommendations
B-lymphocyte defects	X-linked agammaglobulinaemia	All live vaccines	
	Common Variable Immunodeficiency	All live vaccines	Pneumococcal conjugated
	Selective IgA Deficiency	OPV	Haemophilus, meningococcal
	IgG subclass Deficiency	None	Trivalent influenza (non live)
T-lymphocytes defects	Severe Combined Immunodeficiency	All live vaccines	
	DGS	All live vaccines (except partial cases)	MMR if CD4+>400
	WAS	All live vaccines	Trivalent influenza (non live)
	HIGM-CD40 Ligand deficiency, A-T	All live vaccines	
Complement defects	Deficiency of Components C1-C9, properdin, factor B	None	Meningococcal, pneumococcal conjugated
Phagocytic defects	Chronic granulomatous disease	Live bacterial vaccines	Annual non live influenza
	Leukocyte Adhesion defects		
Cytotoxicity Defects	Chediak-Higashi syndrome	All live vaccines	
	Griscelli syndrome		
	Familial Haemaphagocytic lymphohistiocytosis		
	X-linked lymphoproliferative disease		
	Hyper IgE Syndrome	BCG	

Vaccinations in PID

- Risks of avoiding vaccination in PID may be greater than the benefits of vaccination
- Studies in pediatric PID patients are needed
- Distinguish the response as measured by antibody titer from the overall clinical effect of vaccination
- Think about PID in children with recurrent and/or atypical and/or severe infectious diseases

Ali Sobh and Francisco A Bonilla. JACI: In Practice 2016;4:1066-75; Francisco A Bonilla. JACI 2018;141:474-81 2018

Practice parameter for the diagnosis and management of PID

“ Live vaccines <u>should not be</u> administered to patients with severely impaired specific immunity ”

- Attenuated vaccines + severely immunocompromised patients → disseminated disease
- Live rotavirus vaccine + SCID (before their diagnosis) → severe diarrhea
- Should also be withheld in milder PIDs because lack of vigorous study
- Risk is low in some situations (e.g. partial DGS)
- IVIg provides circulating antibodies against polio, MMR, and varicella

Bonilla et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol 2015;136:1186-205, e1-78.

Practice parameter for the diagnosis and management of PID

"Non-viable vaccines can be administered to immunocompromised patients"

- No risk of disease
- There might be some protective immunity even in immunocompromised hosts
- Especially for pathogen that IVIg may not cover, such as influenza
- Immunisation beyond routine guidelines in some circumstances:
  - Patients with phagocytic cell defects and complement deficiency

Bonilla et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol 2015;136:1186-205, e1-78.

Specific recommendation for immunisation of PID patients

Category and Examples	Recommended	Contraindicated *(Should Not Receive)*
B-LYMPHOCYTE (HUMORAL) DEFECTS		
• Common Variable Immune Deficiency (CVID) • X-Linked Agammaglobulinemia (XLA) • Antibody Deficiencies	• Effectiveness of any vaccine is uncertain	• Oral Polio vaccine • Chickenpox, live influenza (inhaled) • Yellow fever • MMR
• Less severe antibody deficiencies • Selective IgA Deficiency • IgG Subclass Deficiencies	• All vaccines are probably effective • All routine vaccines are recommended • Live viral vaccine other than those contraindicated are probably safe	• Oral Polio vaccine • BCG vaccine • Yellow Fever
T-LYMPHOCYTE (CELLULAR) DEFECTS		
• Complete DiGeorge Syndrome	• All vaccines are probably ineffective	• Any live vaccine
• Combined defects - pre-transplant Severe Combined Immune Deficiency (SCID) and pre-transplant Combined Immune Deficiency	• All vaccines are probably ineffective	• Any live vaccines
• Post-Transplant Severe Combined Immune Deficiency (SCID)	• Effectiveness of vaccines depends on degree of immune suppression and reconstitution	• Any live vaccine
Partial defects such as: • Most patients with DiGeorge Syndrome • Wiskott-Aldrich Syndrom (WAS) • Ataxia Telangectasia (A-T)	• Effectiveness of vaccines depends on degree of immune competence	• Any live vaccine
COMPLEMENT DEFICIENCIES		
• C3, C4, C2 Deficiencies • Factor B Deficiency	• All routine vaccines are effective • Pneumococcal, meningococcal recommended	• None
PHAGOCYTIC FUNCTION DEFECTS		
• Chronic Granulomatous Disease (CGD) • Leukocyte Adhesion Defects • Myeloperoxidase Deficiency	• All inactivated vaccines are safe and probably effective • Live viral vaccines are probably safe and effective	• BCG and Salmonella

Adapted from "Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts," The Journal of Allergy and Clinical Immunology, April 20

Immune Deficiency Foundation
www.primaryimmune.org/immunizations

IPOPI 4TH REGIONAL ASIAN PID MEETING
19-20 NOVEMBER 2022
KUALA LUMPUR, MALAYSIA
an IPOPI event

Thank you for listening

IPOPI.ORG

IPOPI
4TH REGIONAL
ASIAN PID MEETING
19-20 NOVEMBER 2022
KUALA LUMPUR, MALAYSIA
an IPOPI event

IPOPI 4TH REGIONAL ASIAN PID MEETING

19-20 NOVEMBER 2022

KUALA LUMPUR, **MALAYSIA**

an **IPOPI** event

CARE FOR RARE

GLOBAL ALLIANCE EDUCATIONAL SEMINAR

Care-for-Rare Foundation

IPOPI

IPOPI.ORG

SUPPORTING ORGANISATIONS

My POPI

SEAPID

SUPPORTED BY

Takeda