Immunodeficiency: Pulmonary manifestations and how to assess

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Learning Objectives

Upon completion of this learning activity, participants should be able to:

1) Describe the pulmonary complications of immunodeficiency disorders
2) Identify the antibody deficiencies and their diagnostic workup
3) Recognize the association of COPD exacerbations and antibody deficiency

Outline

I. Primary Immunodeficiency and Pulmonary Disorders

II. The Antibody Deficiency Syndromes

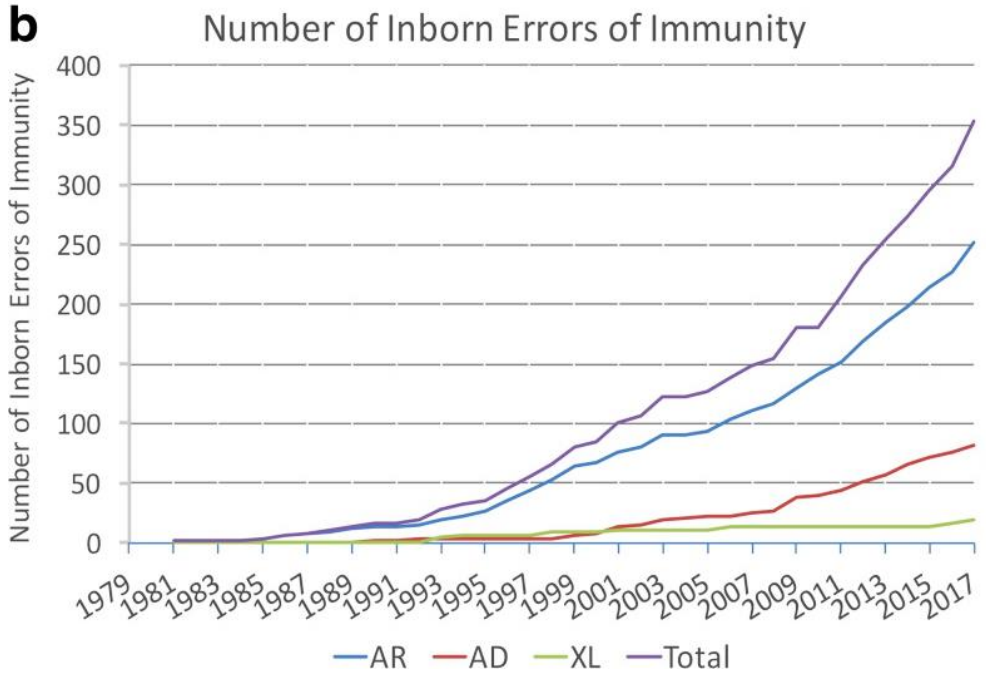
III. Granulomatous Lymphocytic Interstitial Lung Disease – GLILD

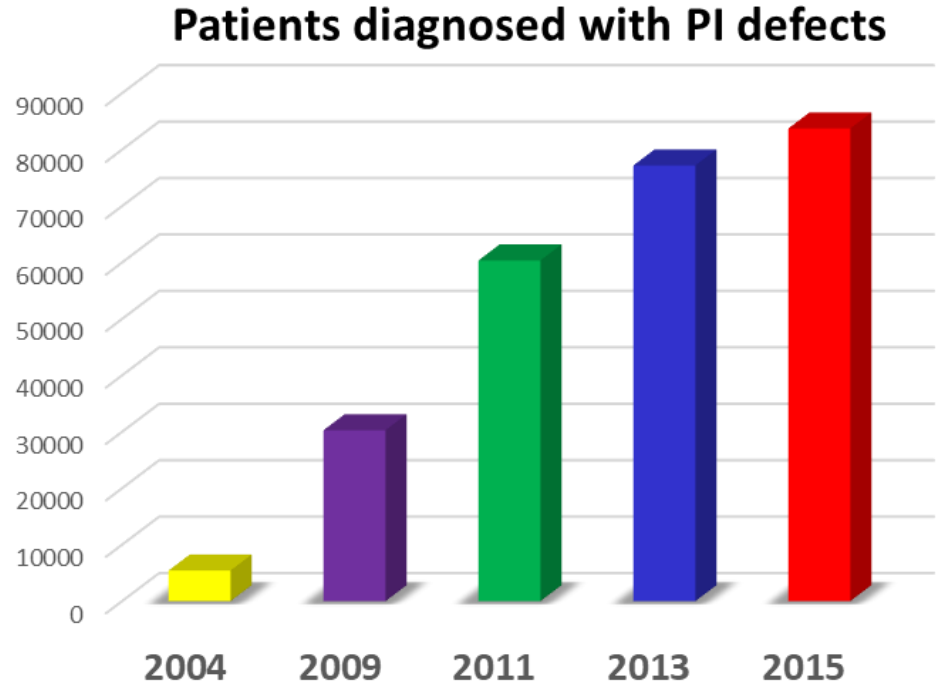
IV. COPD - the “Frequent Exacerbator” Phenotype

Primary Immunodeficiency Disorders (PID) aka Inborn Errors of Immunity (IEI)

- Genetically heterogeneous group of disorders
- Defects in different components of the immune system
- Prevalence ~ 1:1200 in US
  - Selective IgA Deficiency ~ 1:500
- ~ 500 genes identified

Significant increase in number of disorders, and patients diagnosed with PID





J Clin Immunol 2018; 38(1): 96–128
Modell V. et al. Immunol Res (2011) 51:61–70
Modell V. et al. Immunol Res (Jan 2016)

Under-Diagnosed

250,000

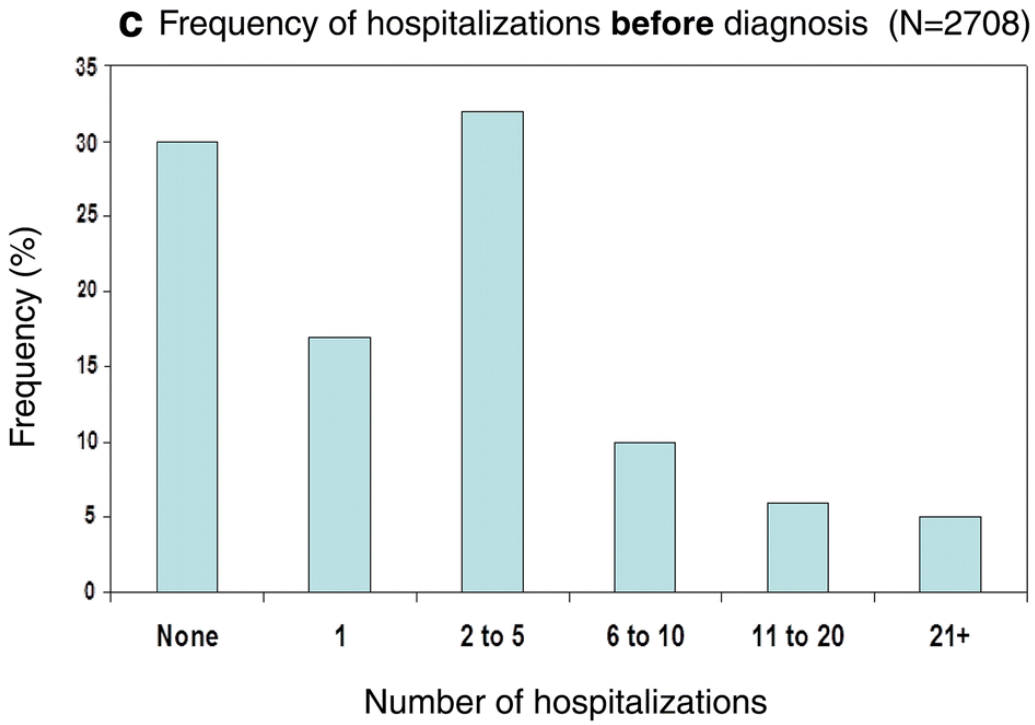
- Diagnosed in the US

500,000

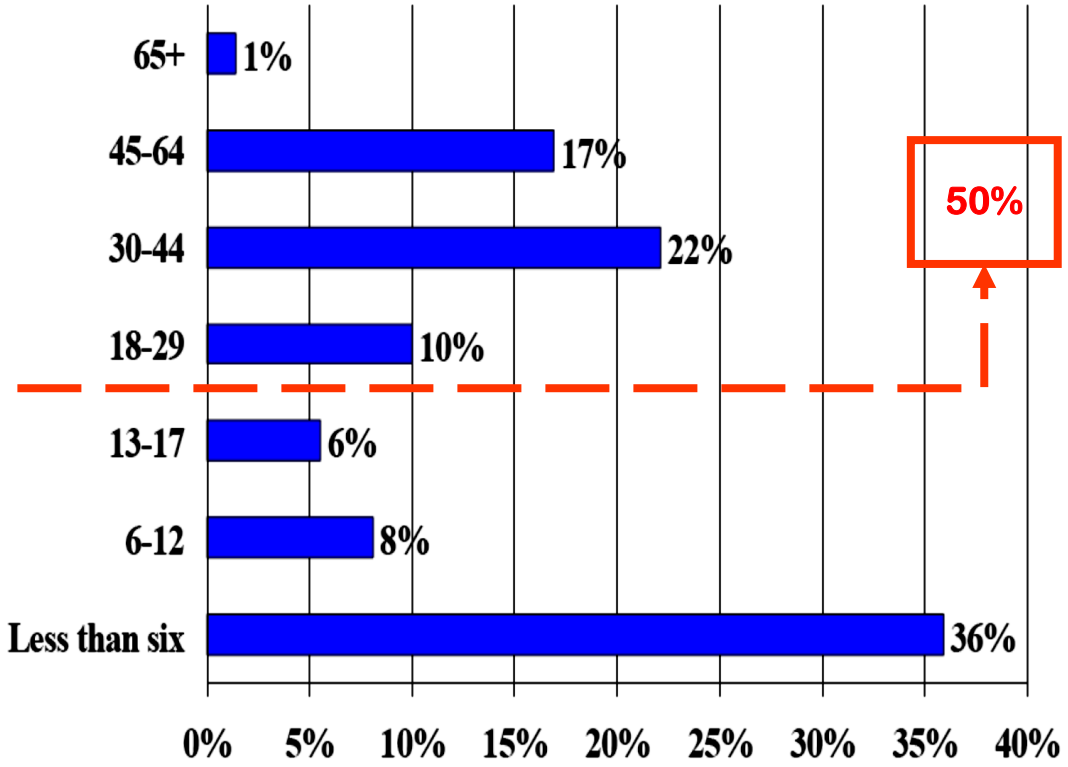
- Estimated undiagnosed

12.4 years

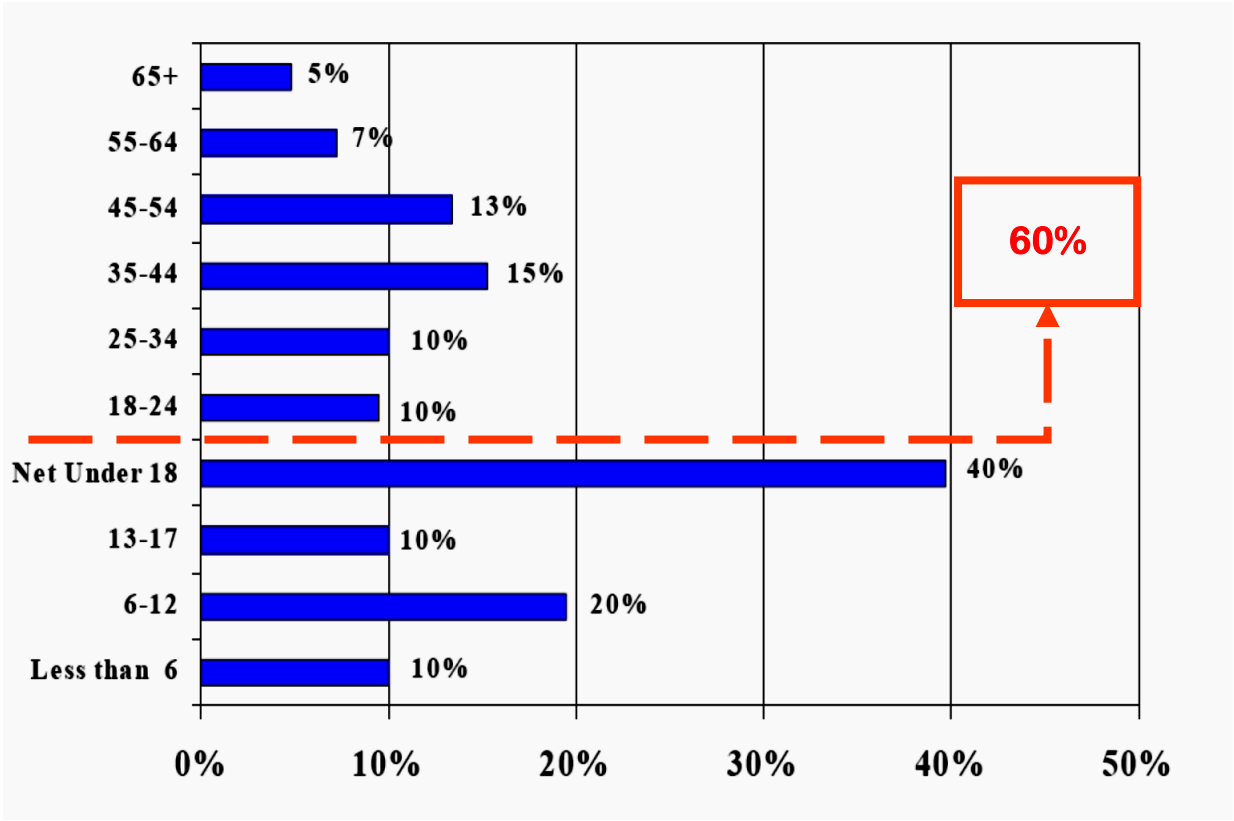
- Average time to diagnosis



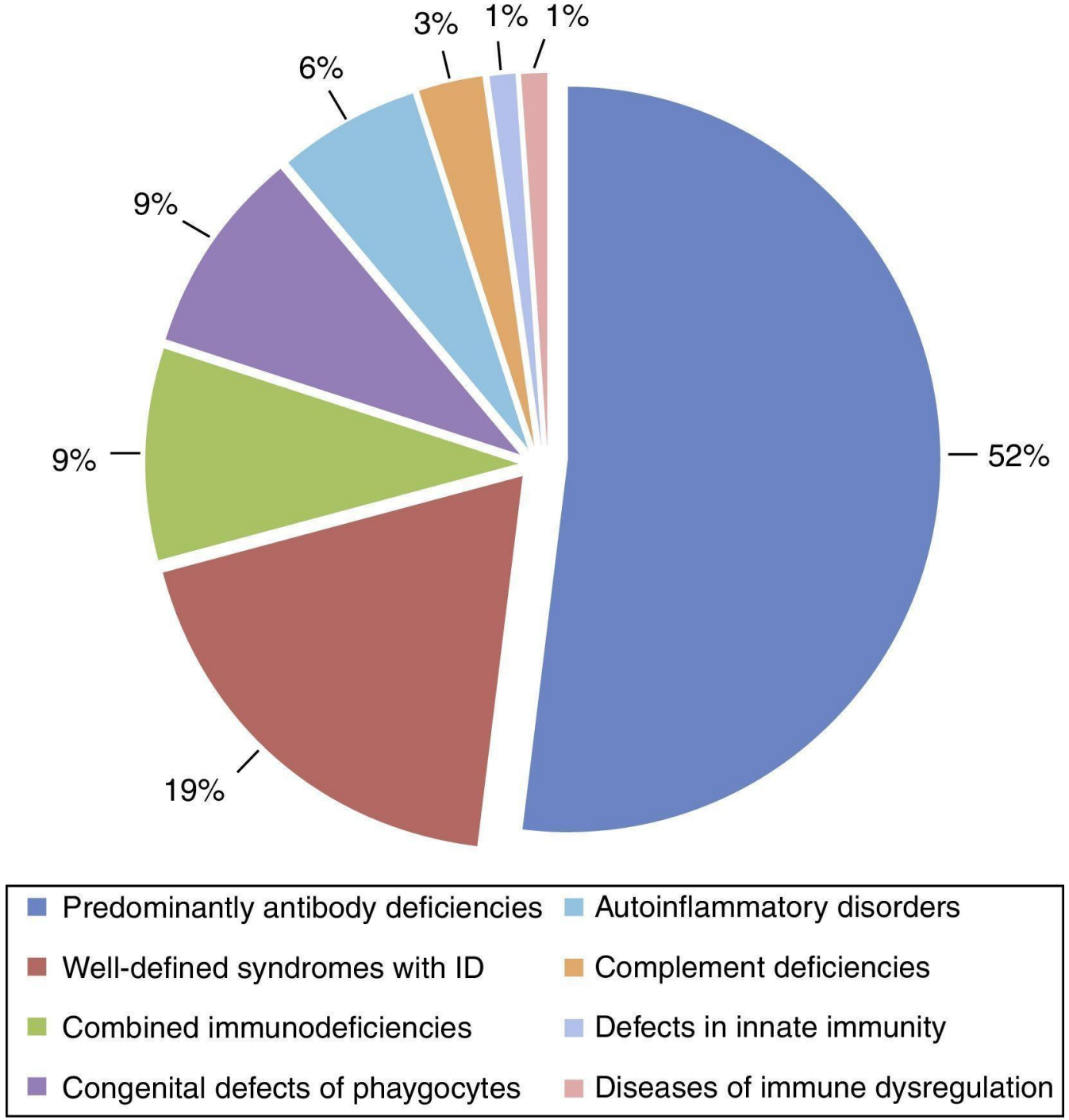
Age at Diagnosis of PID



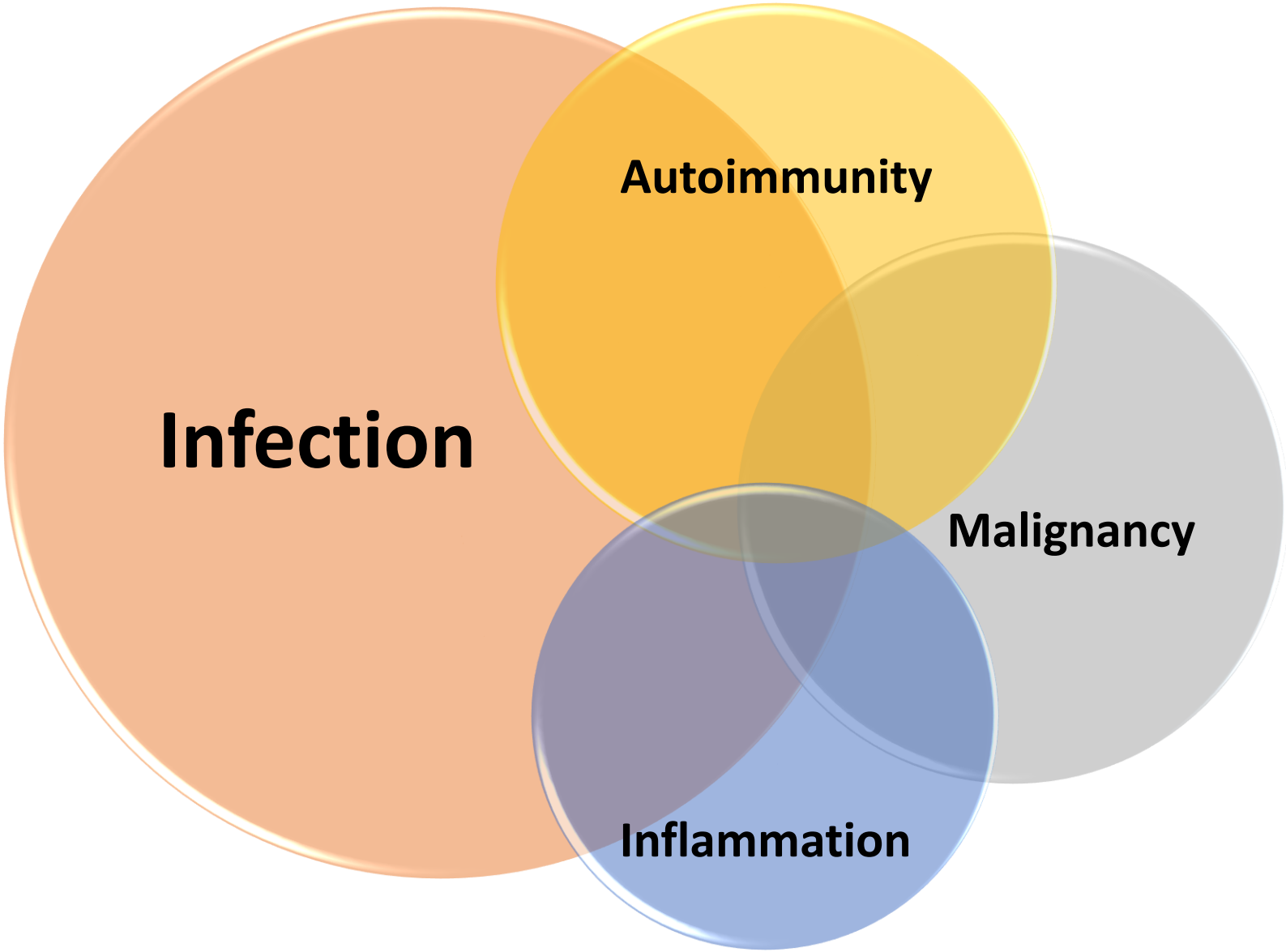
Current Age of PID Patients

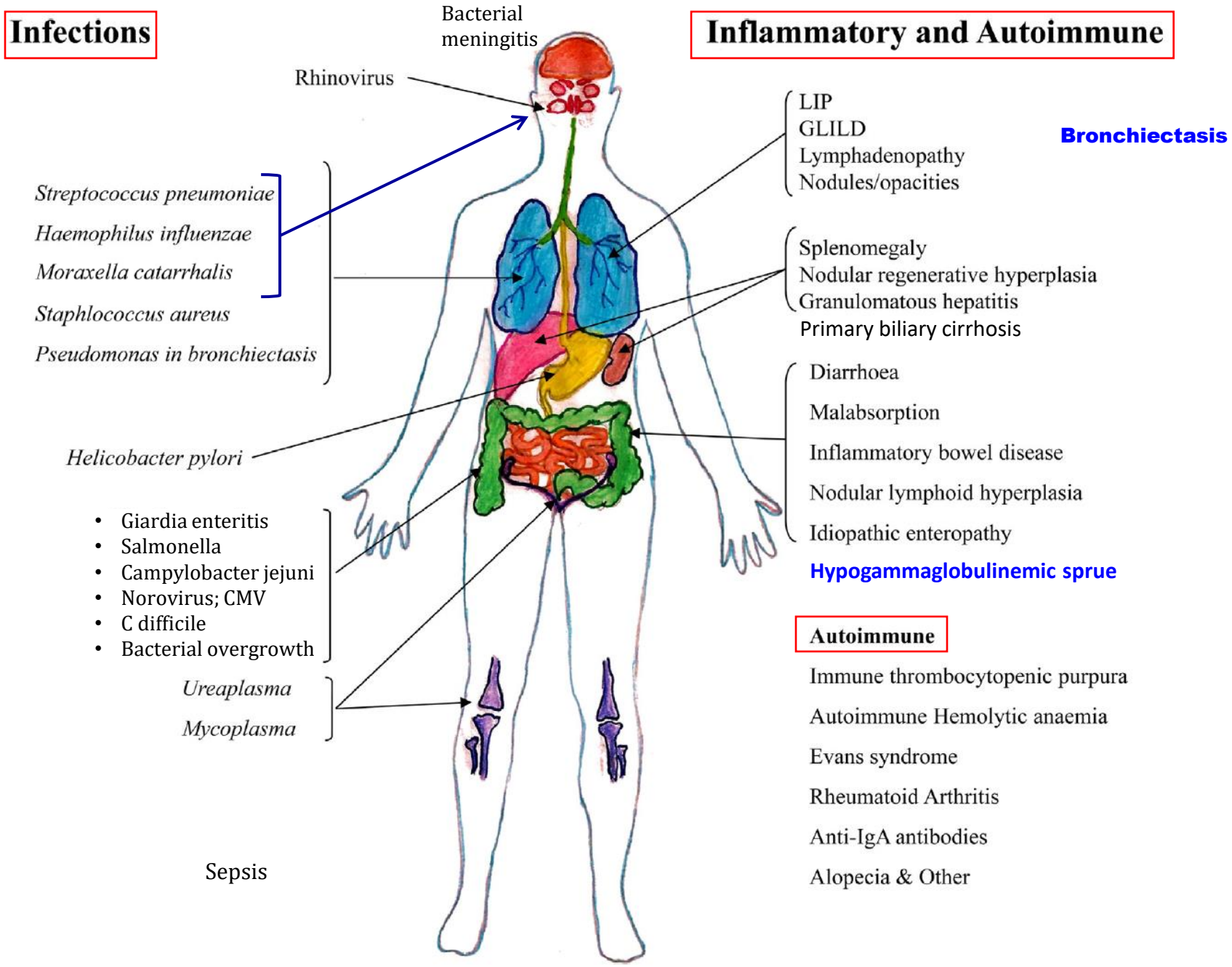


Immune Deficiency Foundation (IDF) patient survey 2003, N = 1499


3%
1%
1%
6%
9%
9%
52%
19%
Predominantly antibody deficiencies
Autoinflammatory disorders
Well-defined syndromes with ID
Complement deficiencies
Combined immunodeficiencies
Defects in innate immunity
Congenital defects of phaygocytes
Diseases of immune dysregulation

Primary Immunodeficiency - Manifestations





Modified from: Jolles, S. JACI Pract. 2013 (6):545-56

Pulmonary Disease in PID/IEI

- Most common cause of end-organ damage!
- May be the initial manifestation of a PID
- Certain clinical and radiographic findings should prompt an immunologic evaluation for an underlying PID, regardless of patient age

Pulmonary Infections

- **Unusual frequency**
  - Recurrent pneumonia (ie >2/lifetime) is unusual in healthy individuals
- **Unusual severity**
  - Multilobar opacities
  - Protracted courses of antibiotics
  - Inpatient hospitalization or surgical intervention
- **Unusual (opportunistic) organisms**
  - Eg *Pneumocystis jirovecii*, *Pseudomonas*, *Burkholderia*, *Aspergillus*, CMV
- **Unusual complications**
  - Empyema, lung abscess
  - Eg pneumatoceles, cavitary lesions

Pulmonary Infections

- Recurrent pneumonias in a specific lobe suggest structural abnormalities
  - Anatomical abnormality, neoplasm, foreign body
- Pneumonias confined to dependent lobes suggest recurrent aspiration
  - GERD, swallowing disorders
- Other differential: CF, ciliary dyskinesia
  - Often associated with sinus disease

Thoracic Lymphadenopathy

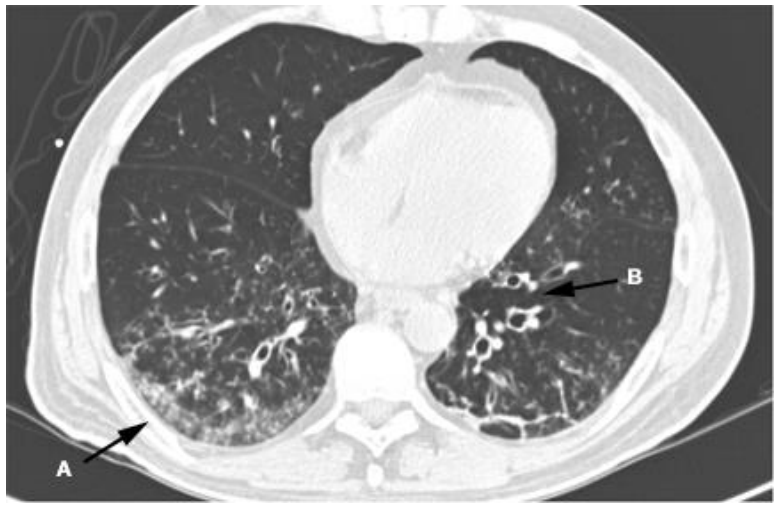
- Thoracic lymph nodes >1 cm in diameter are considered enlarged
- Nodes >2 cm in diameter are almost always abnormal
  - Infection (eg tuberculosis, histoplasmosis)
  - Malignancy
  - Granulomatous inflammation
- Malignancy increased in CVID, Wiskott-Aldrich syndrome, ataxia-telangiectasia (AT), cartilage-hair hypoplasia
  - Primary (eg lymphoma) or secondary (eg metastatic gastric carcinoma)
- Granulomatous inflammation – CVID, CGD

Bronchiectasis

- Permanent lung damage caused by recurrent infections
- PFTs show obstructive disease
  - ↓ FEV_1, ↓- normal FVC, ↓ FEV_1/FVC
- Differential:
  - Cystic fibrosis
  - Ciliary dysfunction
  - Recurrent aspiration
  - Alpha-1 antitrypsin deficiency
  - Scarring from prior infections
  - ABPA

Bronchiectasis

- CXR: insensitive in detecting bronchiectasis
  - May see increased peribronchial markings may occasionally be present
- HRCT: gold standard
  - Parallel (tram) lines, dilated bronchi ~1.5 times wider in diameter than pulmonary artery branch - "signet ring sign" (B)
  - Tree-in-bud pattern" opacities (A)



Diagnostic Evaluation

- CXR: initial imaging for acute pneumonia

- HRCT: much more sensitive than CXR (or PFTs) and better defines lung abnormalities (eg, bronchiectasis, ground-glass opacities, nodular opacities, consolidation, adenopathy)

  - Screening: consider for all CVID patients

  - Monitoring:
    - Decrease in lung volumes or DLCO
    - Abnormal CXR requiring further workup
    - Bronchiectasis eval
    - Parenchymal lung disease
    - Hemoptysis

Diagnostic Evaluation

- PFTs: spirometry, lung volumes, DLCO
  - Baseline and monitoring (6-12 months)
- Serology: can be falsely negative in patients with antibody defects
- Histology
  - Transbronchial biopsy
  - Surgical lung biopsy typically needed for ILD, bronchiolitis, or suspected malignancy

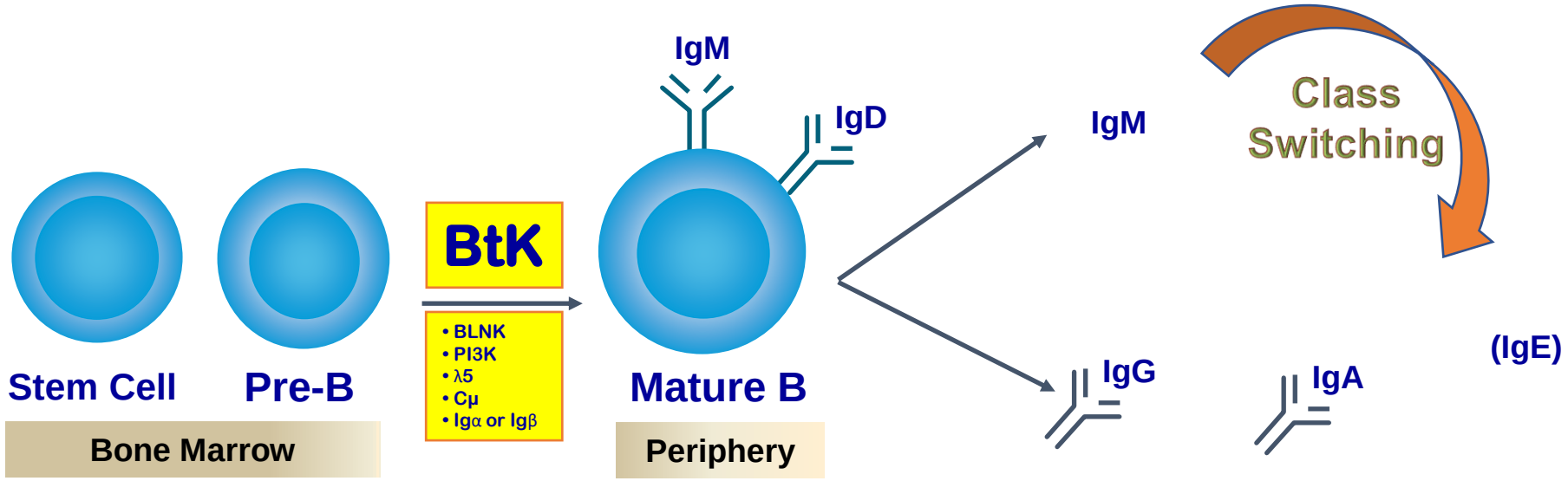
Outline

I. Primary Immunodeficiency and Pulmonary Disorders

II. **Antibody Deficiency Syndromes**

III. Granulomatous Lymphocytic Interstitial Lung Disease – GLILD

IV. COPD – the “Frequent Exacerbator” Phenotype


IgM
IgD
Class
Switching
IgM
BtK
• BLNK
• PI3K
• λ5
• Cμ
• Igα or Igβ
Stem Cell
Pre-B
Mature B
IgG
IgA
(IgE)
Bone Marrow
Periphery

Common Variable Immunodeficiency "CVID"

- **Most common <u>symptomatic</u> PID: ~ 1:25,000**

- **<u>Definition:</u>**

1) **↓ serum IgG (> 2 SD below mean)**
2) **↓ serum IgA and/or IgM**
3) **Impaired production of specific antibodies (poor responses to vaccines)**
4) **Exclude other causes of hypogammaglobulinemia**

Bonilla et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015 Nov;136(5):1186-205

Specific Antibody Deficiency (SAD)

Table 1
ESID and US practice parameters for the diagnosis of SAD

	SAD	
	ESID Criteria[3]	**US Practice Parameters**[6]
Clinical presentation	Recurrent or severe bacterial infections	Recurrent respiratory tract infections
Antibody levels	Normal IgG, IgA, and IgM and IgG subclasses	
Response to vaccines	Profound alteration of the antibody responses to polysaccharide vaccine	Impaired response to pneumococcal capsular polysaccharide
B cells	Not considered	Normal B-cell levels
T cells	Exclusion of T-cell defect	Not considered
Other diagnostic criteria	None	Patients older than 2 y

Perez, Ballow. Immunol Allergy Clin N Am 40 (2020) 499–510

Specific Antibody Deficiency (SAD)

Pneumococcal Serotype	Pre-Pneumovax (Ug/ml)	Post-Pneumovax (Ug/ml)
1	0.03	0.03
3	0.09	0.06
4	0.04	0.04
5	0.06	0.04
6B	0.09	0.08
7F	0.05	0.05
8	0.11	0.10
9N	0.38	0.95
9V	0.36	0.76
12	0.09	0.08
14	0.28	0.19
18C	0.01	0.01
19F	0.13	0.09
23F	0.07	0.06
Diphtheria	0.32 IU/mL	0.45 IU/ML
Tetanus	7.18 IU/ML	7.79 IU/ML

Degree of polysaccharide unresponsiveness

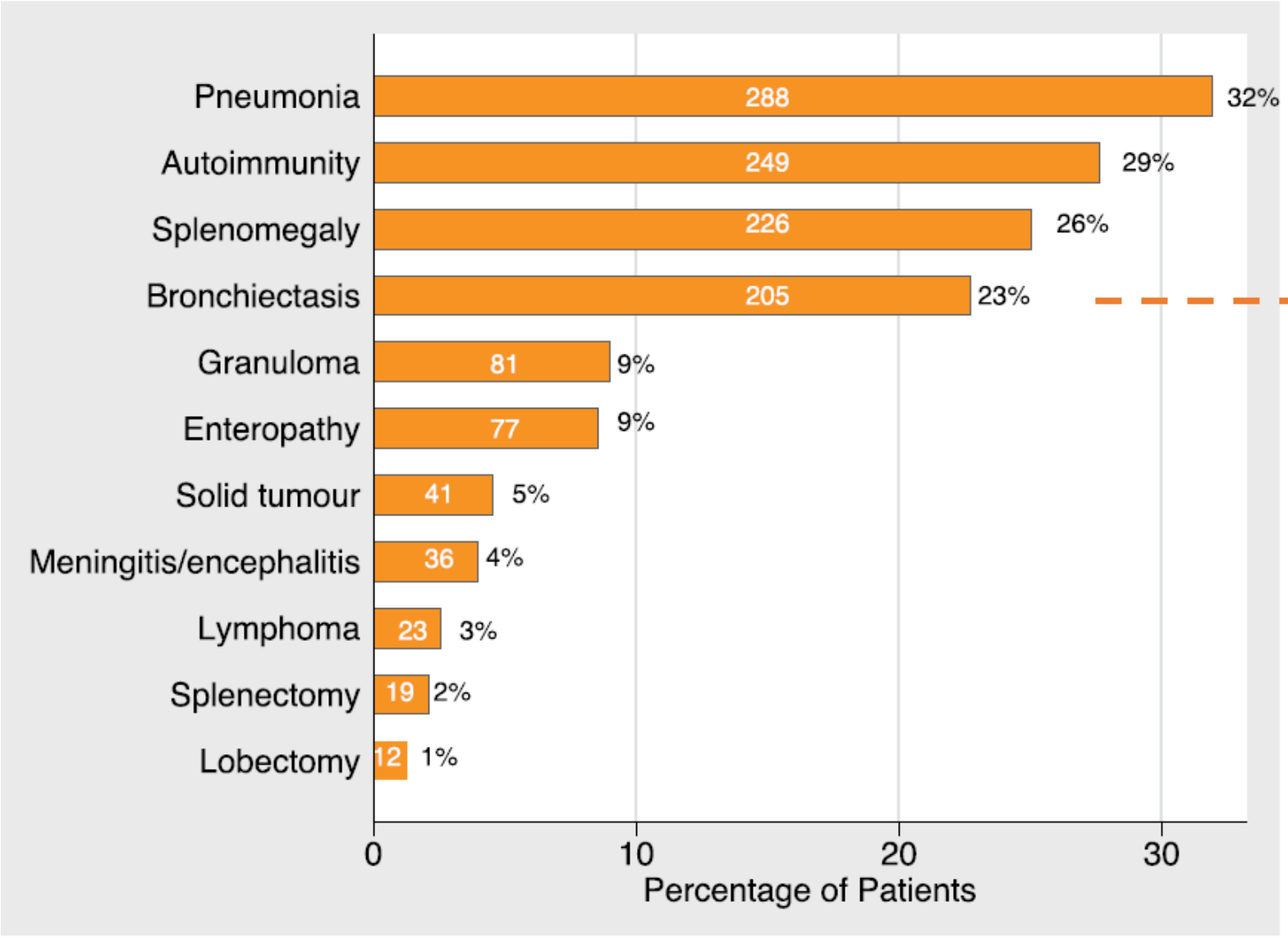
Phenotype*	PPV23 response, age >6 y	PPV23 response, age <6 y
Severe	≤2 protective titers (≥1.3 μg/mL)	≤2 protective titers (≥1.3 μg/mL)
Moderate	<70% of serotypes are protective (≥1.3 μg/mL)	<50% of serotypes are protective (≥1.3 μg/mL)
Mild	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 70% of serotypes	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 50% of serotypes
Memory	Loss of response within 6 mo	Loss of response within 6 mo

*All phenotypes assume a history of infection.

Pre-immunization titer > 4 μg/mL: very unlikely to increase

- *Orange et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: A working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2012; 130:S1-24*
- *Hare ND, Smith BJ, Ballas ZK. Antibody response to pneumococcal vaccination as a function of preimmunization titer. J Allergy Clin Immunol 2009;123: 195-200.*

CVID manifestations
(ESID cohort - 902 patients)



47% (801 UK patients)

Gathmann B et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. JACI – 2014 Jul;134(1):116-26

Pulmonary Complications in CVID

1. **Recurrent pneumonia and bronchitis**

2. **Airway Disease; Bronchiectasis**
   - Prevalence gradually increases with age and number of infections
   - Central or distal
   - RML (77%) > lower lobes >> upper lobes

3. **Interstitial Disease ~15-30%**

Interstitial Disease

Types of interstitial lung disease pathology seen in primary antibody deficiency

Pathology	Characteristics
Follicular bronchiolitis	Benign lymphoid hyperplasia bordering the airways
Lymphocytic interstitial pneumonia	Pulmonary lymphoid hyperplasia involving lung interstitium with expansion of alveoli septa. Considered progression of follicular bronchiolitis. Granulomas may be present
Nodular lymphoid hyperplasia	Well-demarcated lymphoid follicles considered a precursor to MALT lymphoma
Non-necrotizing granulomatous inflammation	Inflammation containing circumscribed macrophages lacking a central area of necrosis
Organizing pneumonia	Production of granulation tissue within the alveolar space in response to lung injury. Formerly called bronchiolitis obliterans with organizing pneumonia or BOOP
GLILD	Broadly encompassing term typically implying the presence of granulomatous inflammation together with pulmonary lymphoid hyperplasia and sometimes also organizing pneumonia

Maglione PJ. Immunology and Allergy Clinics of North America. 40,3: 437-459

Outline

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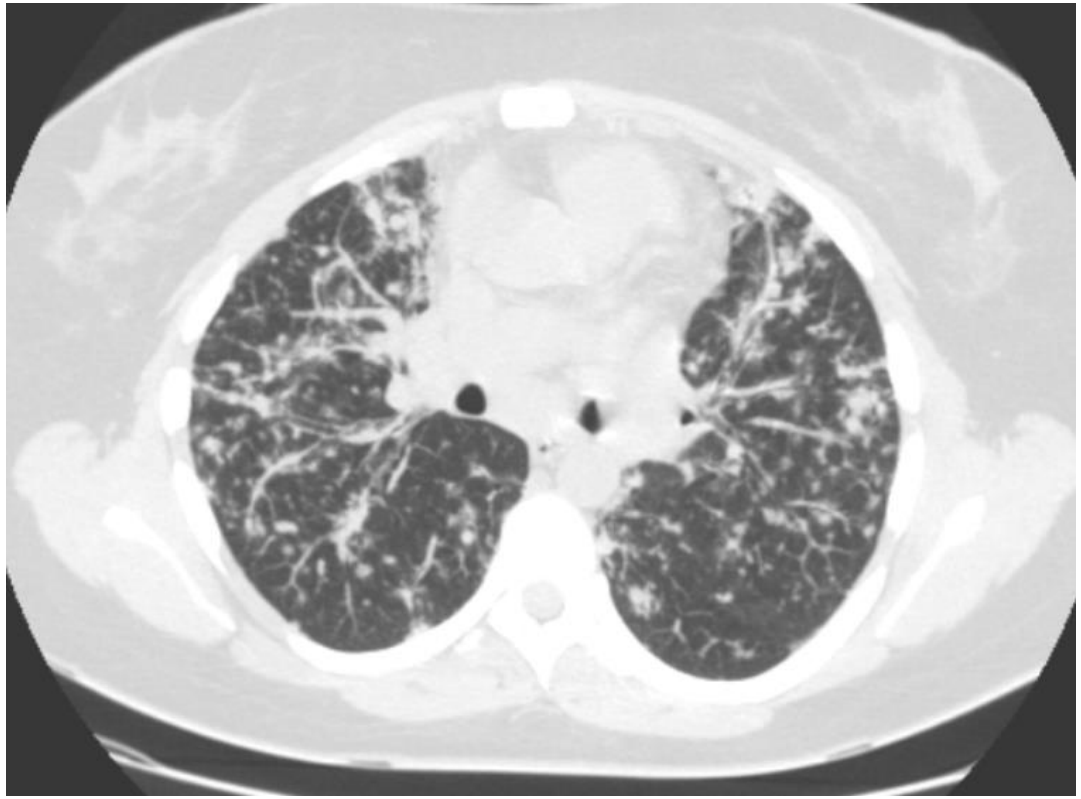
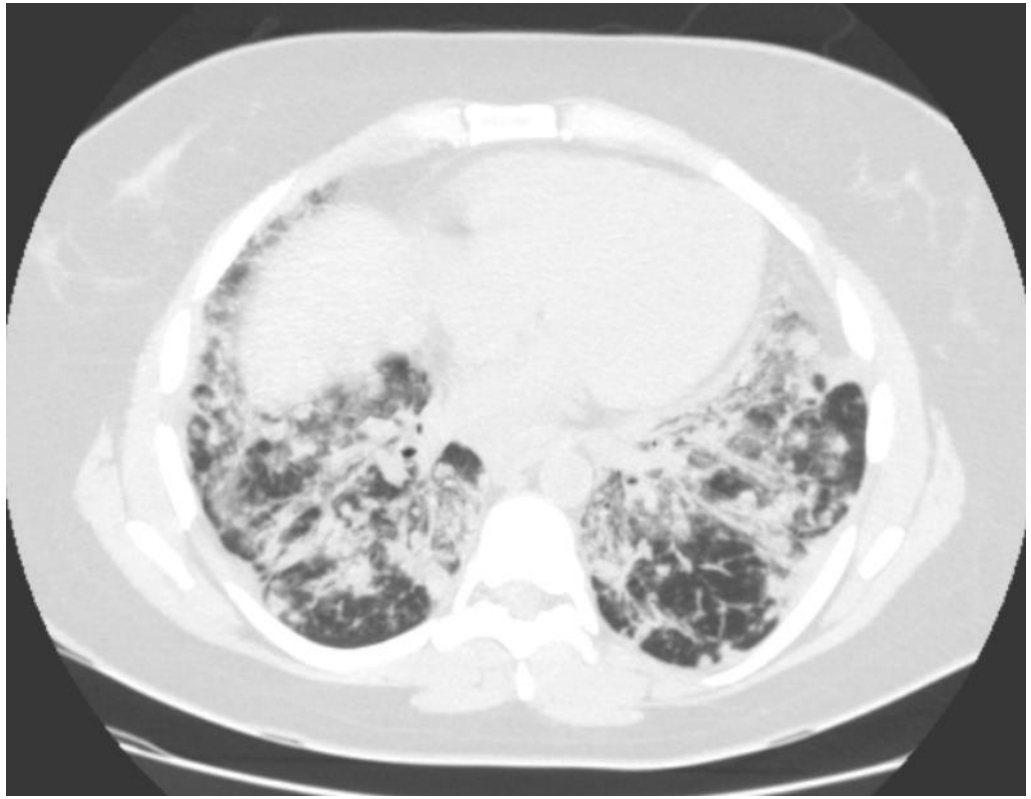
IV. COPD – the “Frequent Exacerbator” Phenotype

30 yo female

FEV1 = 52%

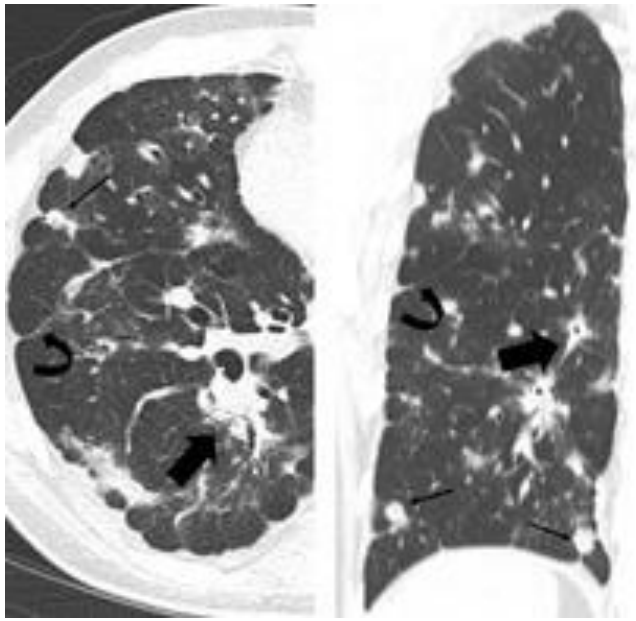




Granulomatous Lymphocytic Interstitial Lung Disease
GLILD

- Most common cause of diffuse parenchymal lung disease in CVID
- Lymphocytic infiltrate and/or non-caseating granulomas
- Increased risk for autoimmune diseases and malignancy (particularly non-Hodgkin lymphoma)
- Frequent splenomegaly, lymphadenopathy, and liver disease
  - Granulomas can also occur in bone marrow, GI tract, skin

GLILD

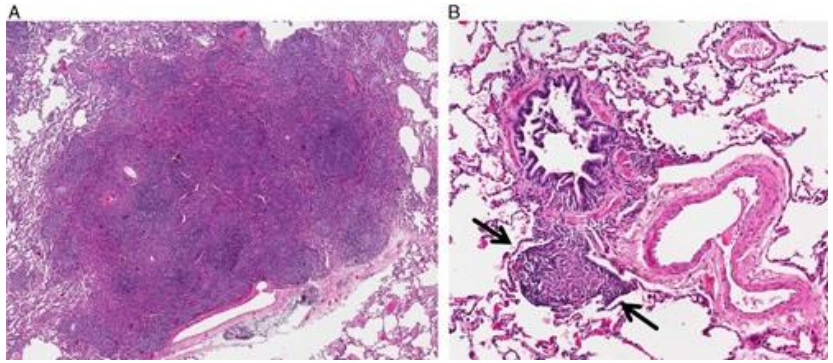


- **20-50 yo, F>M**
- **Gradual DOE, cough, fatigue, night sweats**
  - **May be asymptomatic (role of screening HRCT)**
- **Progressive impairment → respiratory failure**
- **HRCT scan:**
  - Lower lung predominant nodularity, consolidation, & interlobular septal thickening
  - Nodules may be solid or groundglass
  - Hilar and/or mediastinal adenopathy

Journal of Thoracic Imaging: November 2018 - 33 , 6. 377-383

GLILD

- **Diagnosis:** Lung biopsy + exclude other diagnoses
- **Differential:**
  - Sarcoidosis
  - ILD due to rheumatic disease (eg Sjögren, RA)
  - Hypersensitivity pneumonitis
  - Organizing pneumonia
  - Lymphomas
  - Granulomatous infections (Mycobacteria, fungi)



- **Rx:**
  - IG replacement (higher dose!)
  - Rituximab + Azathioprine (or Mycophenolate)
  - Others: Steroids; TNF-antagonists; Cyclosporine

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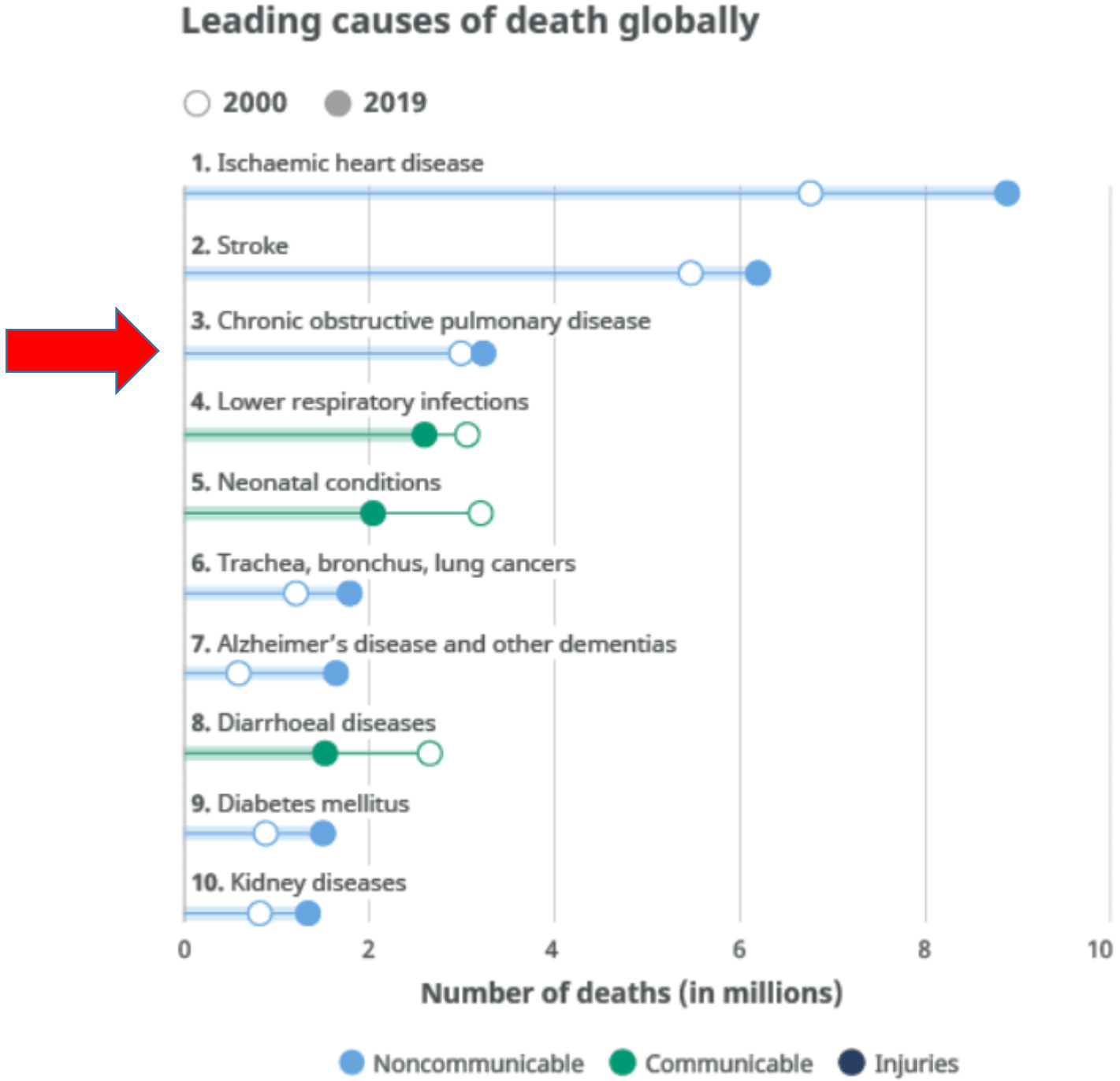
56 yo male with recurrent COPD exacerbations

- 4 COPD exacerbations over the past year, hospitalized 3 times. 2 exacerbations the year prior. These were treated with courses of systemic steroids and antibiotics. Stable in between
- FEV1 58%
- Smoked 2 ppd x 35 years; stopped smoking 3 years ago
- Meds:
  - High dose ICS, LABA, LAMA, roflumilast
  - Started Azithromycin 250 mg MWF a year ago

Chronic Obstructive Pulmonary Diseases COPD

- > 5% of the US population
- > 120,000 deaths/year
- $50 billion/year estimated cost in US (2010)

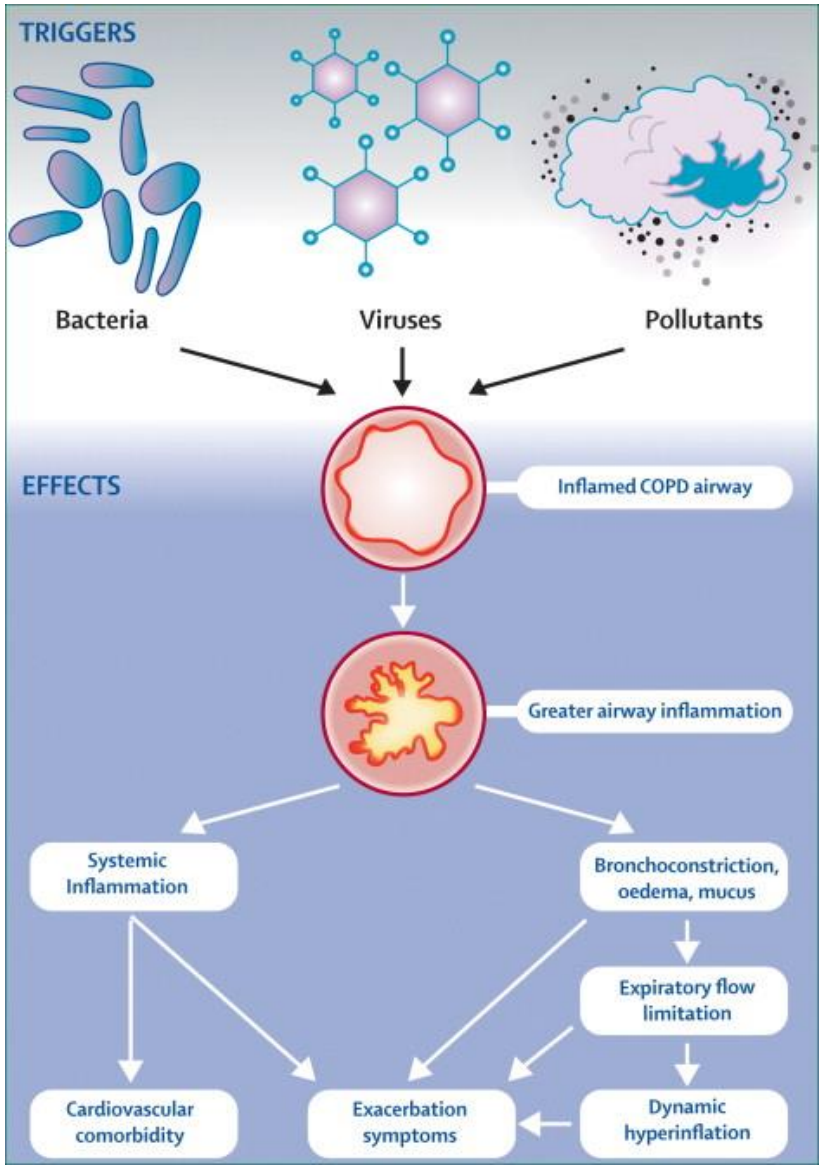
CDC; MMWR Nov 23, 2012


Leading causes of death globally
2000
2019
1. Ischaemic heart disease
2. Stroke
3. Chronic obstructive pulmonary disease
4. Lower respiratory infections
5. Neonatal conditions
6. Trachea, bronchus, lung cancers
7. Alzheimer's disease and other dementias
8. Diarrhoeal diseases
9. Diabetes mellitus
10. Kidney diseases
0
2
4
6
8
10
Number of deaths (in millions)
Noncommunicable
Communicable
Injuries

www.who.int

Acute Exacerbation of COPD "AECOPD"

- Acute worsening of respiratory sxs: Cough, Sputum, Dyspnea
- **Most important** contributor to QOL, morbidity & mortality of COPD
- **>50%** of cost of managing COPD
- **3.5%** of all Hospital admissions
  - 715,000 hospitalizations (2009)
- **1.5 million** ED visits/year



- Criner, J et al. Chest 2015; 147 (4): 894 - 942
- Wedzicha JA, Seemungal TA. Lancet. 2007 Sep 1;370(9589):786-96

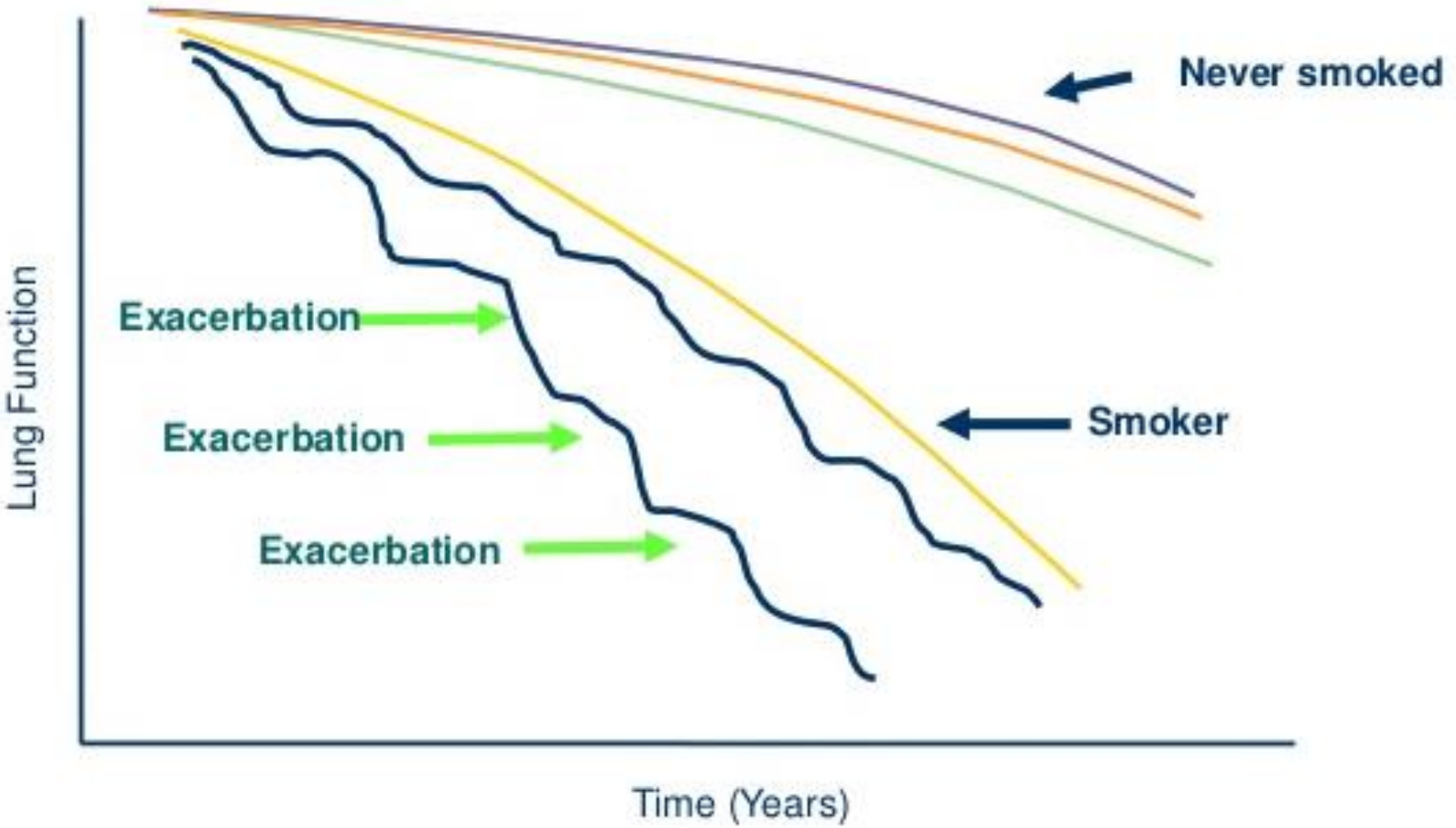
Burden per single AECOPD Admission

Mortality	Cost	LOS (days)	
0.9 %	**$7,242**	**4.5**	Simple admission
10.3 %	**$20,757**		ICU admission
26.5 - 39.1 %	**$44,909**	**16**	Intubation

Readmission rates within 30-60 days = 17.8%, 15.3% and 15.7%

for ED visits, simple admissions and complex admissions respectively

- Criner, J et al. Chest 2015; 147 (4): 894 - 942
- Wedzicha JA, Seemungal TA. Lancet. 2007 Sep 1;370(9589):786-96

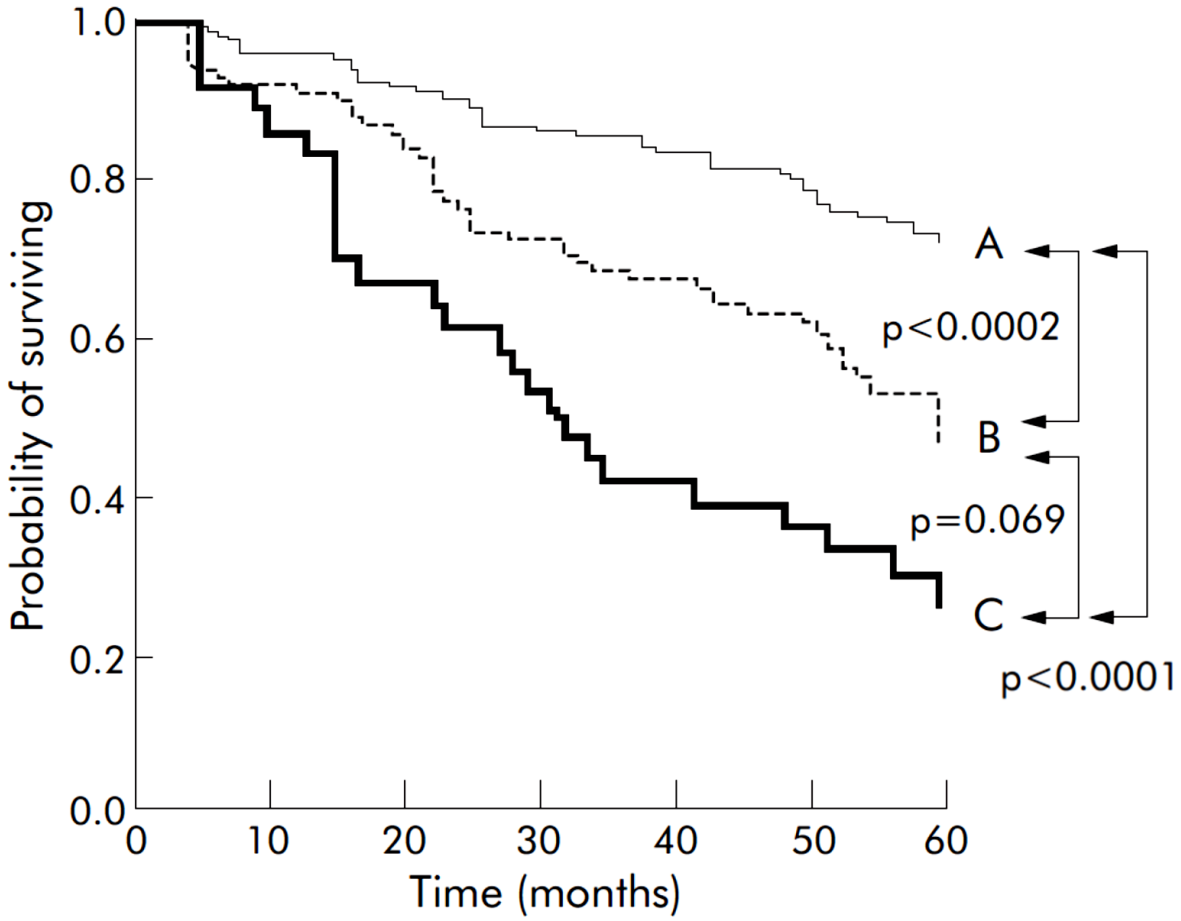


Fletcher C. Br Med J. 1977

“Frequent Exacerbator” Phenotype

- Irrespective of disease severity
- Subset of patients susceptible to frequent exacerbations ≥ 2x/year
- Single best predictor = history of prior exacerbation

Mortality in AECOPD



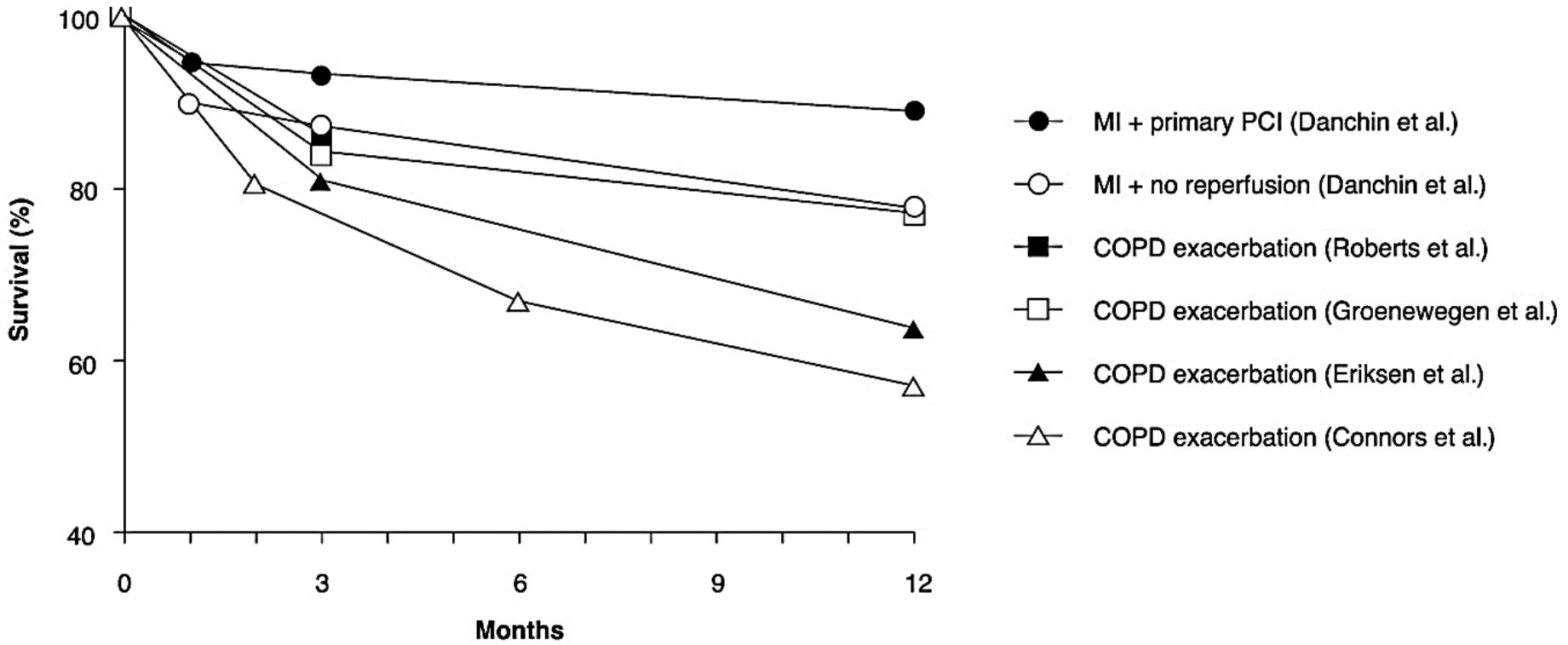
No AECOPD

1-2 AECOPD

≥ 3 AECOPD

Soler-Cataluna JJ, et al. Thorax 2005;60:925-931

AECOPD vs Acute MI



David Halpin; COPD: Journal of Chronic Obstructive Pulmonary Disease 2008, 5, 187-200.

Prevention of AECOPD

Pharmacologic Intervention	Nonpharmacologic Intervention
ICS	LVRS
LABA	Pulmonary rehabilitation
ICS/LABA combination	s
LAMA	
ICS/LABA + LAMA	
Phosphodiesterase-4 inhibitor	
Macrolide antibiotics	

ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LAMA = long-acting antimuscarinic agent; LVRS = lung volume reduction

Marchetti N et al. Preventing Acute Exacerbations and Hospital Admissions in COPD. CHEST 2013; 143(5):1444–1454

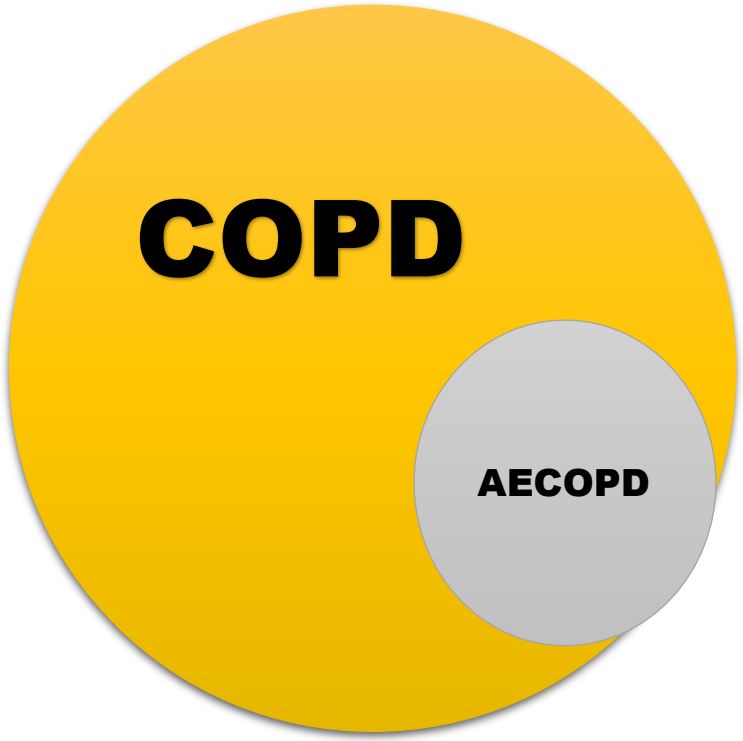
70-80% of **AECOPD** Triggered by Respiratory Infections

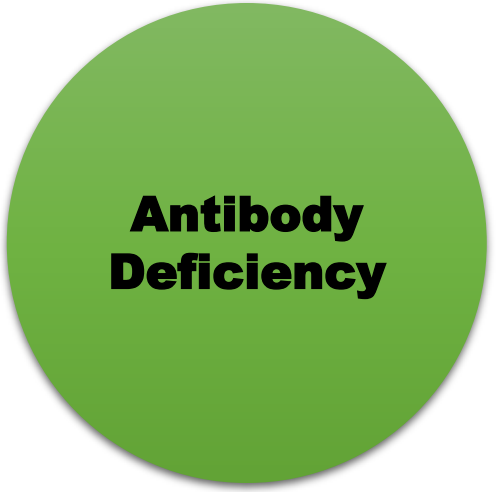
Bacteria 40-60%

Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis

Viruses ~ 56%

Rhinovirus
RSV





- *Sethi S. Chest 2000;117(5 Suppl 2):380S–5S*
- *Seemungal T et al. Am J Respir Crit Care Med 2001;164(9): 1618–23*

Lower serum IgA associated with COPD exacerbation in SPIROMICS cohort (n=1,049)

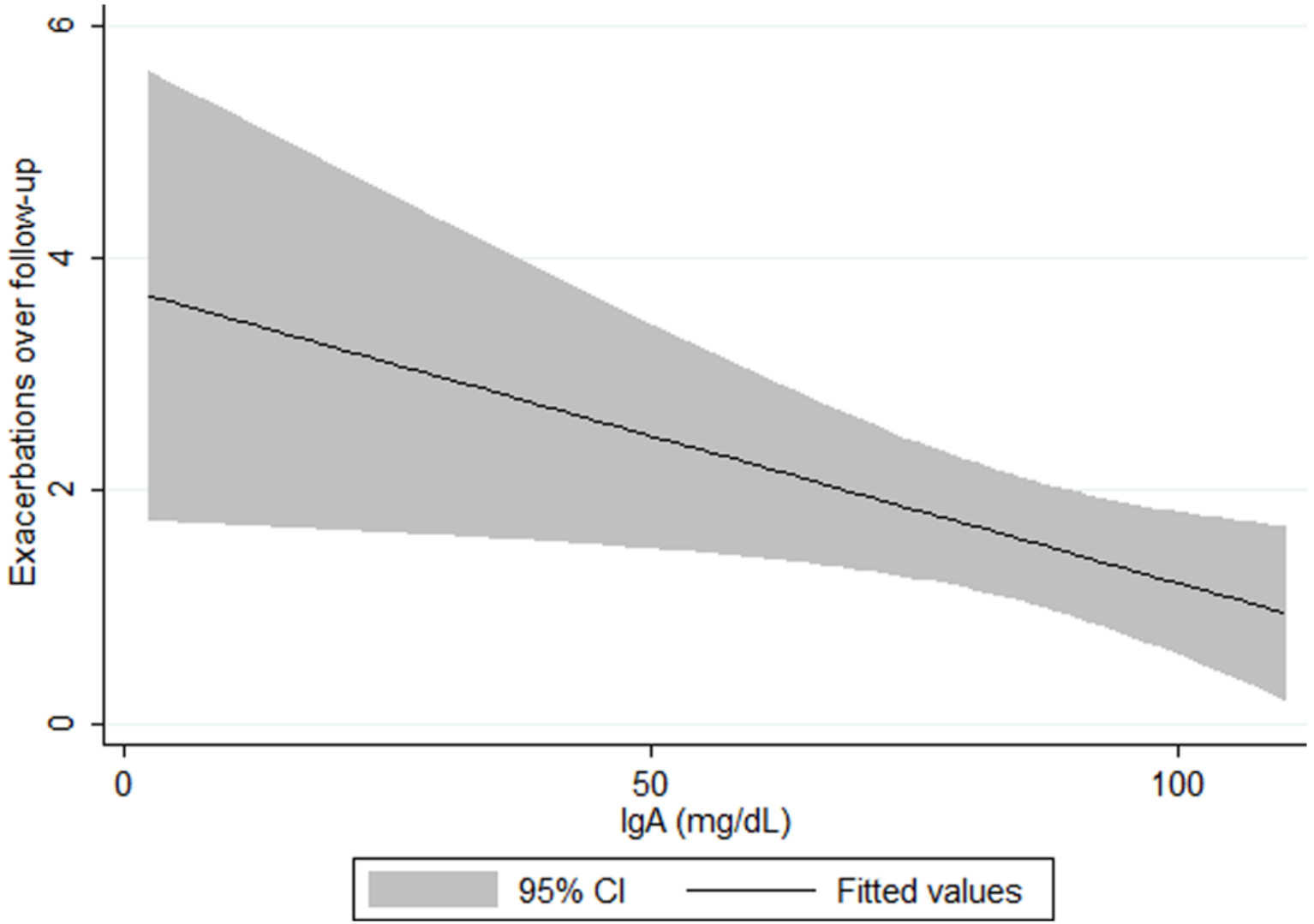
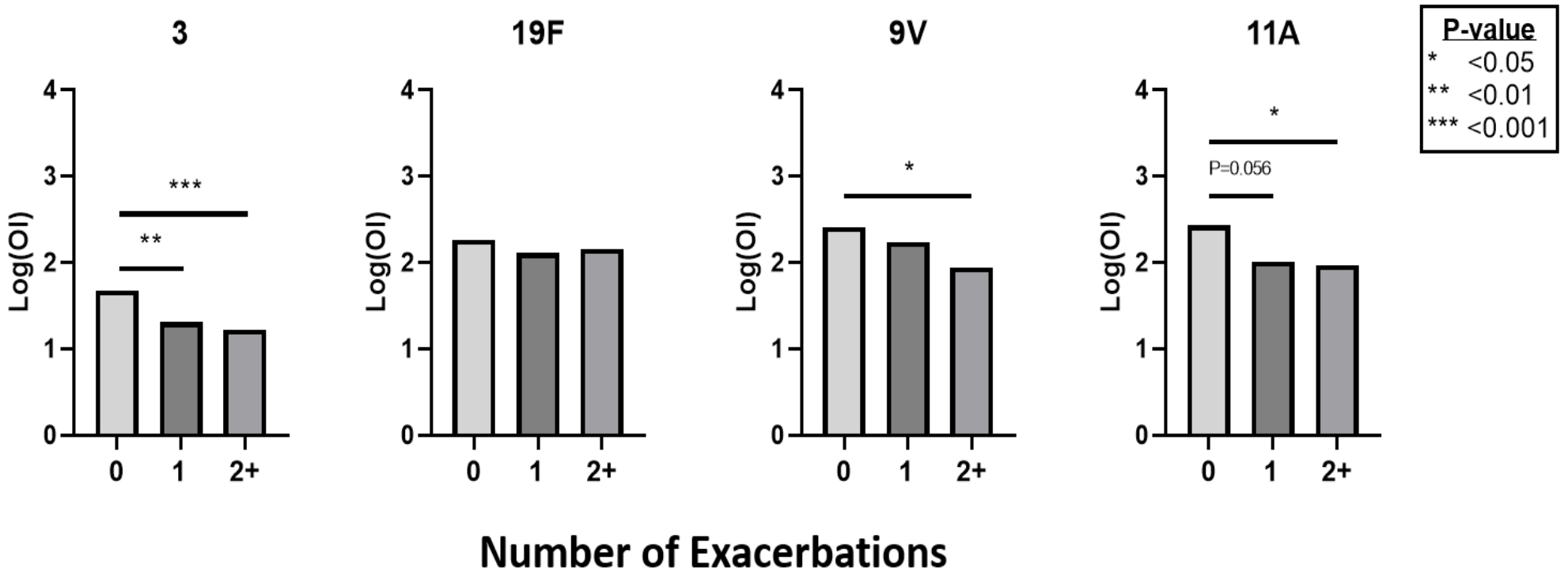
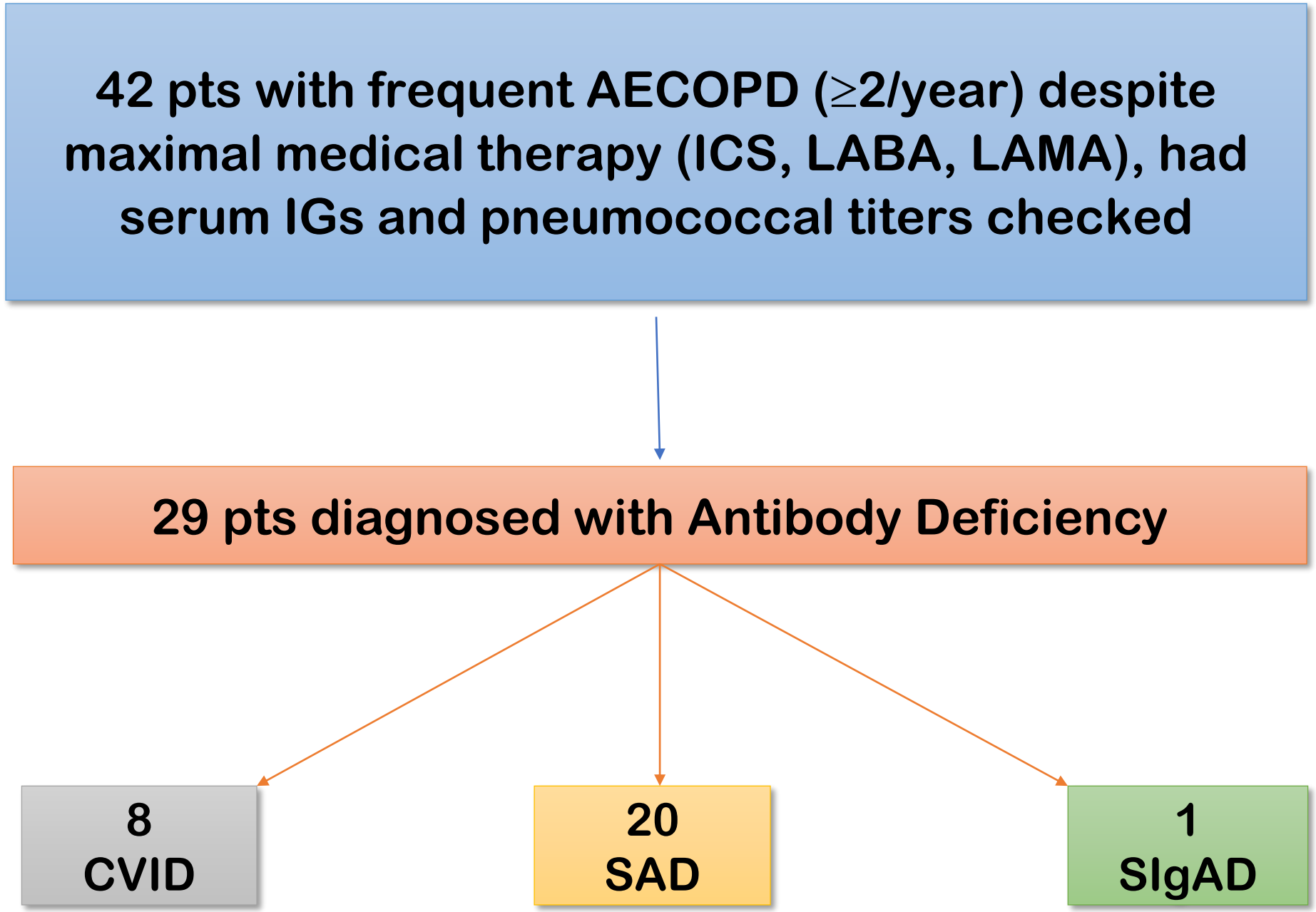


Fig 2. Unadjusted association of IgA with follow-up exacerbations among lowest decile IgA(0–120 mg/dL).

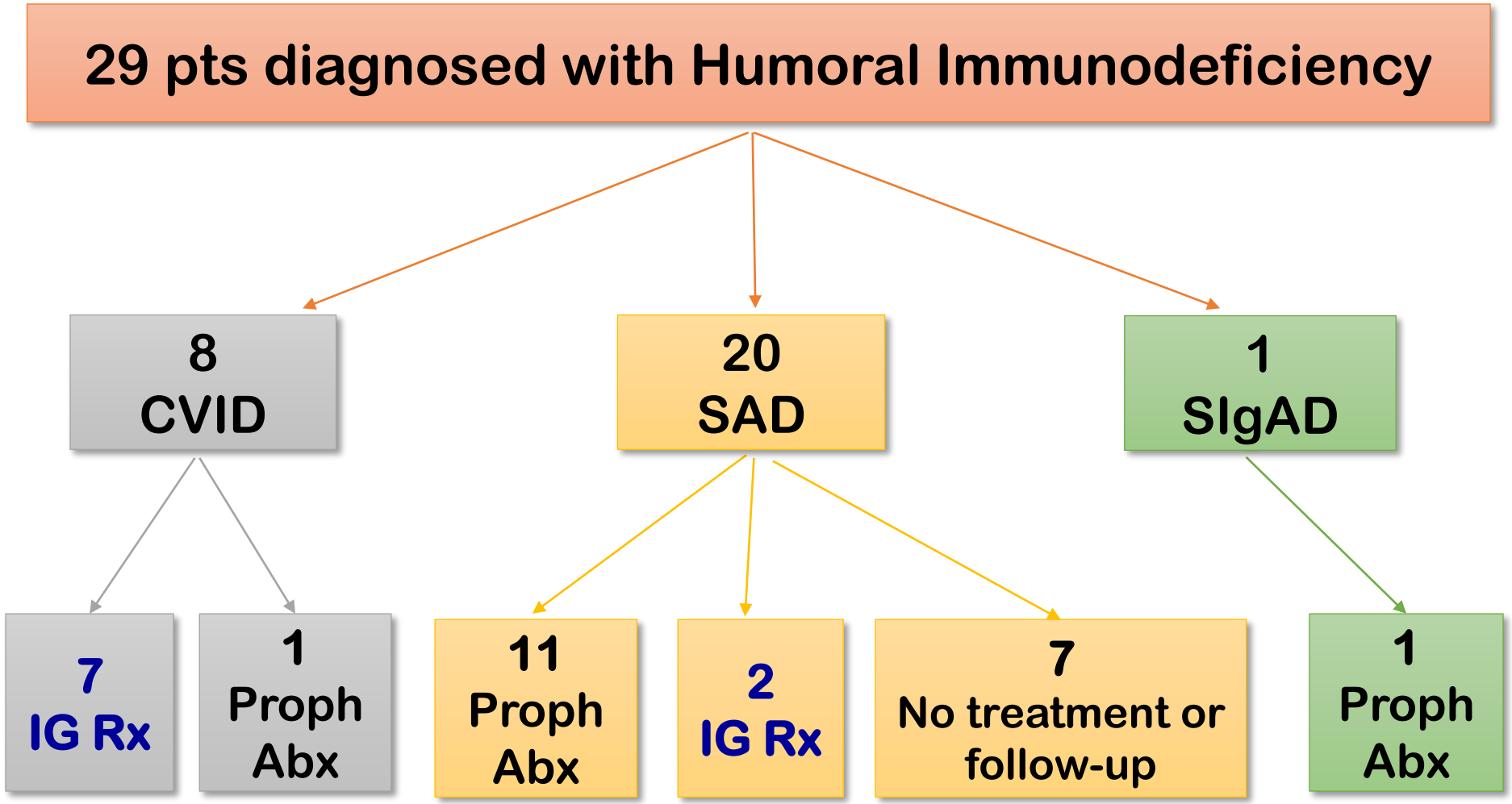
Putcha N, Paul G, Azar A et al. PLoS One. 2018; 13(4): e0194924

Opsonization index and exacerbation frequency for 4 pneumococcal serotypes commonly associated with acute respiratory infections in COPD





McCullagh BN, Azar AE PLoS One. 2017 Feb 17;12(2)



Proph Abx = Prophylactic Antibiotics
IG Rx = Immunoglobulin Replacement Therapy

Before/After Treatment of Antibody Deficiency

Variable	n	Before	After	Change	p-value
Exacerbations/year, median	18	4 [3-6]	1 [0-2]	-3.5 [-5 to -2]	<0.0001
Hospitalizations for AECOPD/year	17	1 [0-2]	0 [0-0]	-1 [-1 to 0]	0.037
ICU admissions	18	2 (11%)	0 (0%)		0.500
Prednisone cum annual dose	12	930 [0-3075]	0 [0-40]	-310 [-1990 to 0]	0.031
Average courses of prednisone/year	15	4 [0-12]	0 [0-1]	-3 [-11 to 0]	0.004
Average courses of rescue antibiotics/year	19	6 [4-12]	0 [0-1]	-6 [-10 to -3]	<0.0001
Oxygen use	20	7 (35%)	9 (45%)		0.157

McCullagh BN, Azar AE PLoS One. 2017 Feb 17;12(2)

Take Home Points

- Primary Immunodeficiency disorders are common and can present at any age
- Pulmonary disease is one of the most common manifestations of PID and can be the presenting finding
- Recognizing early signs of pulmonary disease in PID is essential for early diagnosis and treatment and improving long-term mortality and morbidity
- Patients with frequent COPD exacerbations (≥2 /year) warrant screening for underlying antibody deficiency disorder