Non-infectious complications of Primarily Antibody Deficiencies ("The CVIDc phenotype")

Manish Butte, MD PhD

E. Richard Stiehm Endowed Chair
Professor & Division Chief

June 2023

Learning Objectives

- What are the most common non-infectious complications for primarily antibody deficiencies?
- What are ways to monitor for lung diseases?
- What are ways to monitor for GI diseases?
- What is the role of IgA in the GI tract in reducing autoimmunity?

Connor: Unresolved issues

- “A 35-year-old man with recurrent pneumonia”
- You have diagnosed him with CVID and started him on Ig replacement

- Now what?
- What are his future risks?
- How often will you see him in follow-up?
- How will you monitor him?
- What tests will you routinely order, and how often?

Non-infectious complications of PADs are life-threatening

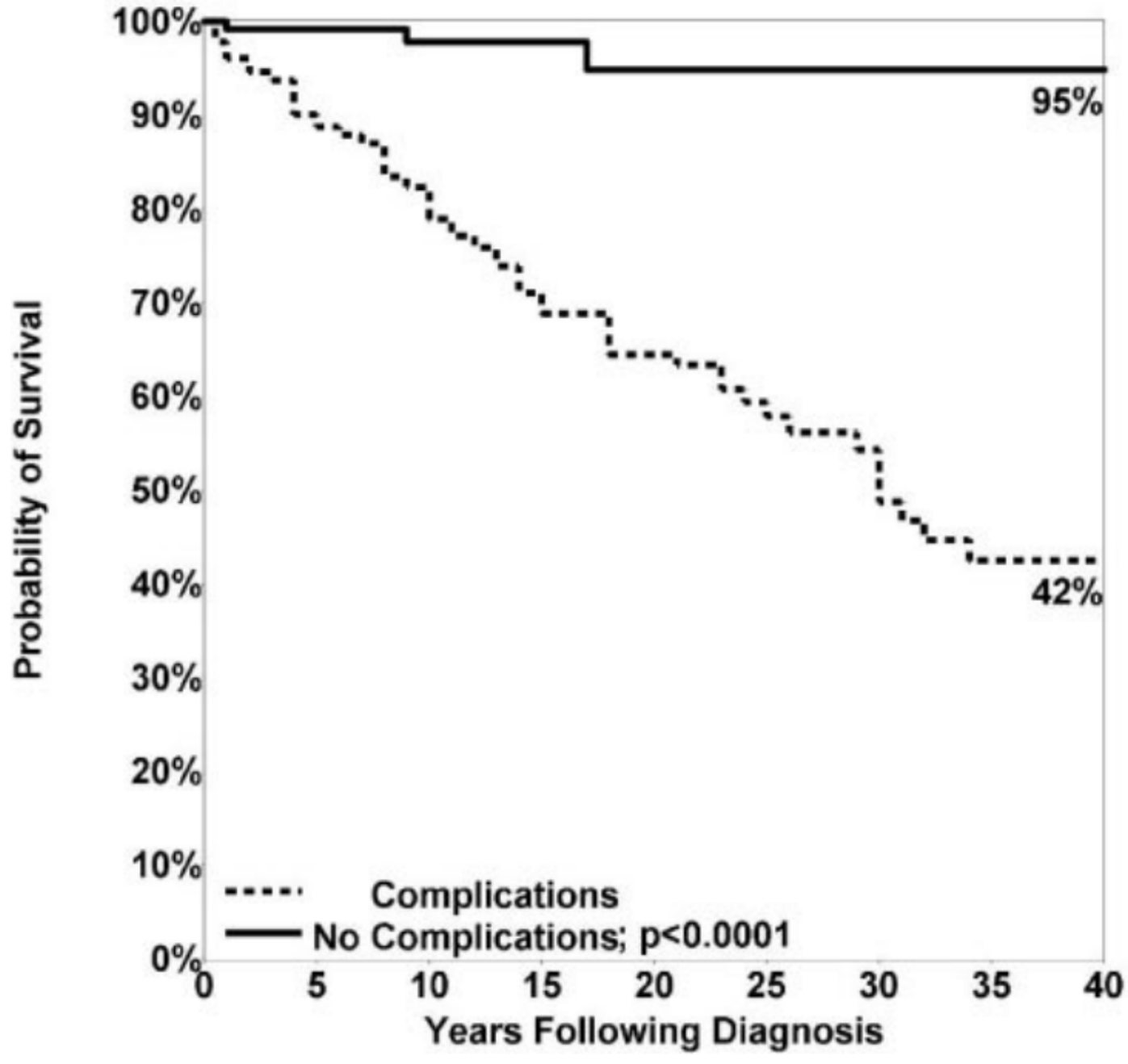


Figure 2. Kaplan-Meier curve for patients with and without noninfectious complications. Patients with noninfectious complications were significantly more likely to die than those with infections only ($P < .0001$).

Resnick et al, Blood 2012

Complicated PADs

- **Pulmonary complications**
- **Gastrointestinal complications**
- Autoimmune / inflammatory complications
- Cancers
- Mental health complications
- Lymphoproliferative complications

Lung diseases are the most common complication of IEI

- *What kind of signs and symptoms does one look for?*
- *How do we test for lung diseases in IEI?*

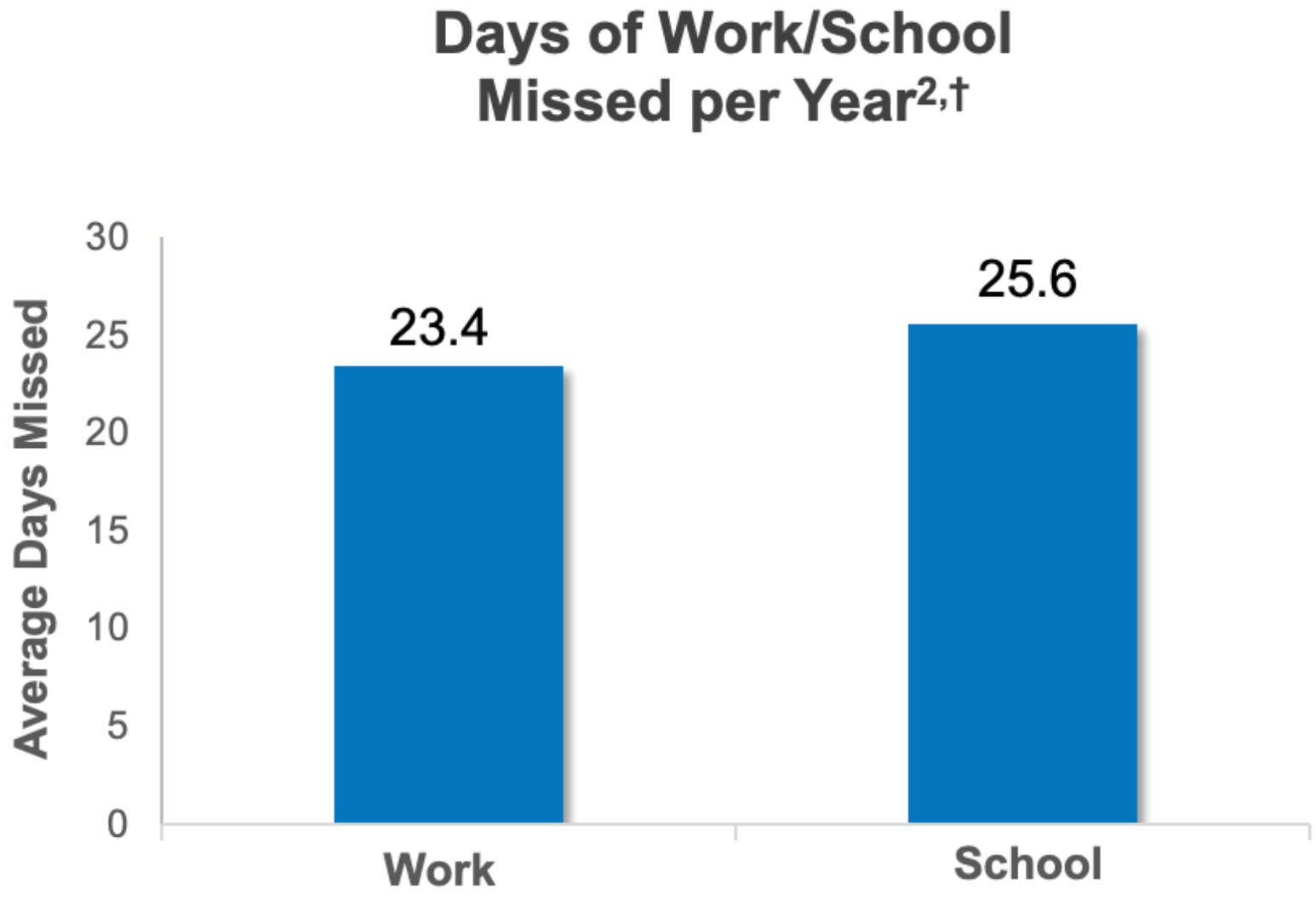
Covered today

- **Inflammation**
  - Asthma
  - Bronchiectasis
- **Infections**
- **Autoimmunity**
  - GLILD

Not covered today

- **Pulmonary hypertension**
- **Pulmonary Alveolar Proteinosis**
- **Malignancy**

Impact: Missed work and school



(despite immunoglobulin replacement)

Symptoms of lung disease

Ask about these in your History

- Missed school or work
- Decreased exercise ability
- Recurrent and prolonged infections

- Shortness of breath
- Cough (chronic)
- Low oxygen saturation
- Low energy
- Wheezing
- Tightness or pain with breaths

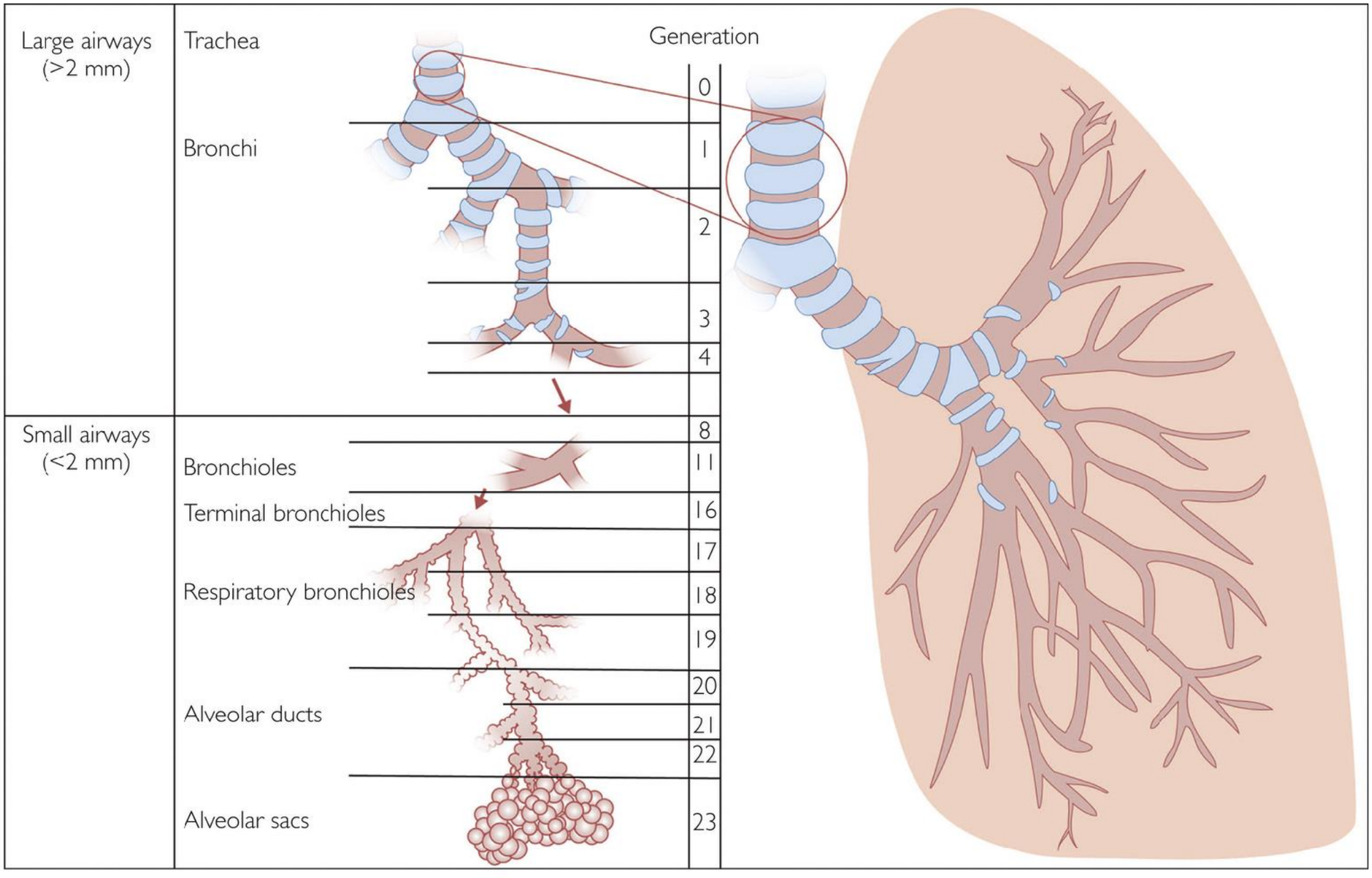
- Later stages: unintended weight loss

Diagnostic testing: Imaging

- X-ray
- CT scan
  - better views of the lungs and heart and vasculature
  - about 60 times as much radiation as X-ray

- Obtain HRCT initially to evaluate for
  - Bronchiectasis
  - Cavitary disease
  - Interstitial lung diseases
  - Lymphadenopathy
  - Nodules

Pulmonary Function Testing

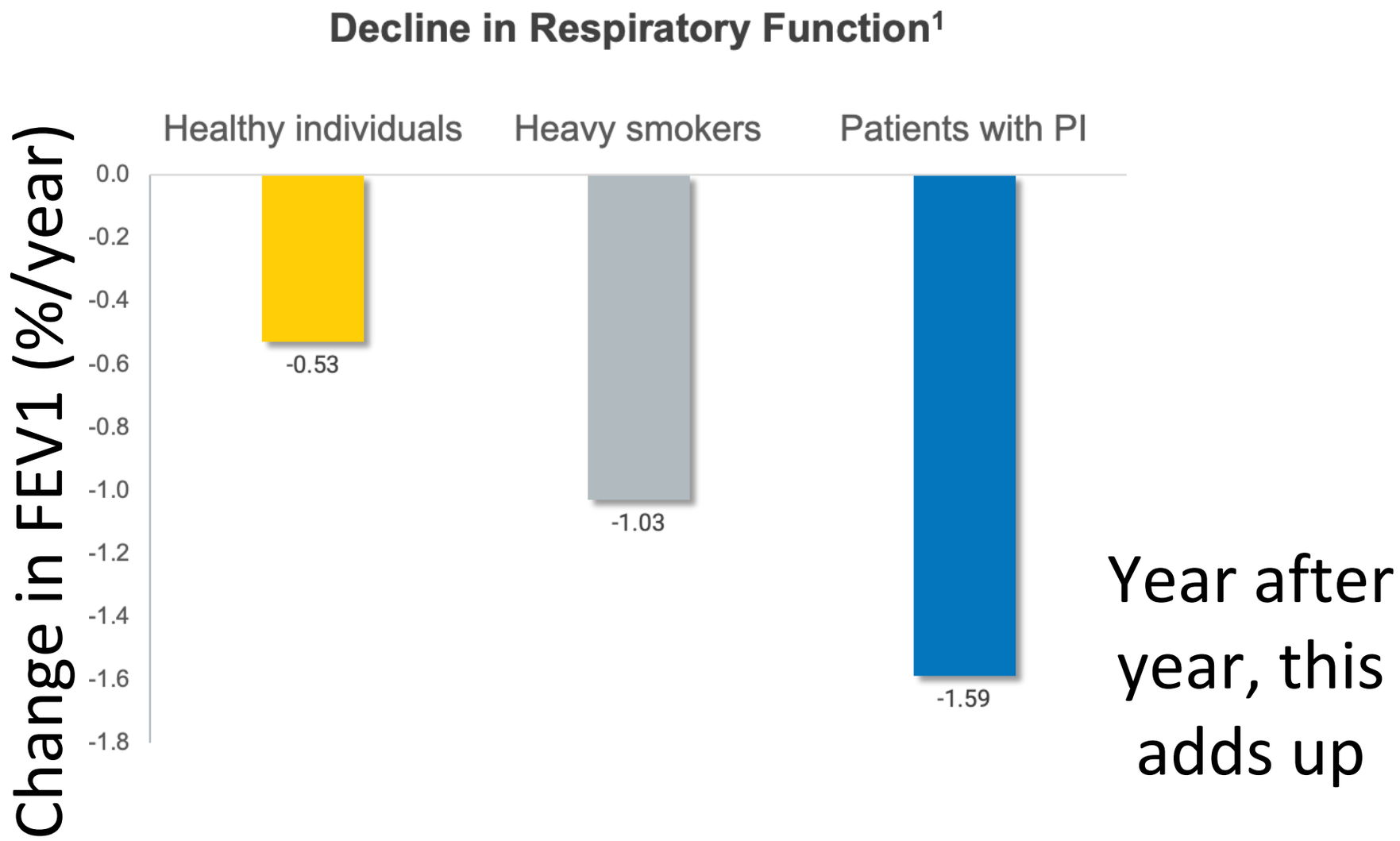


A

70-80% of the air is exhaled in the first second (FEV1)

PAD patients lose lung function over time

Worse than heavy smokers!

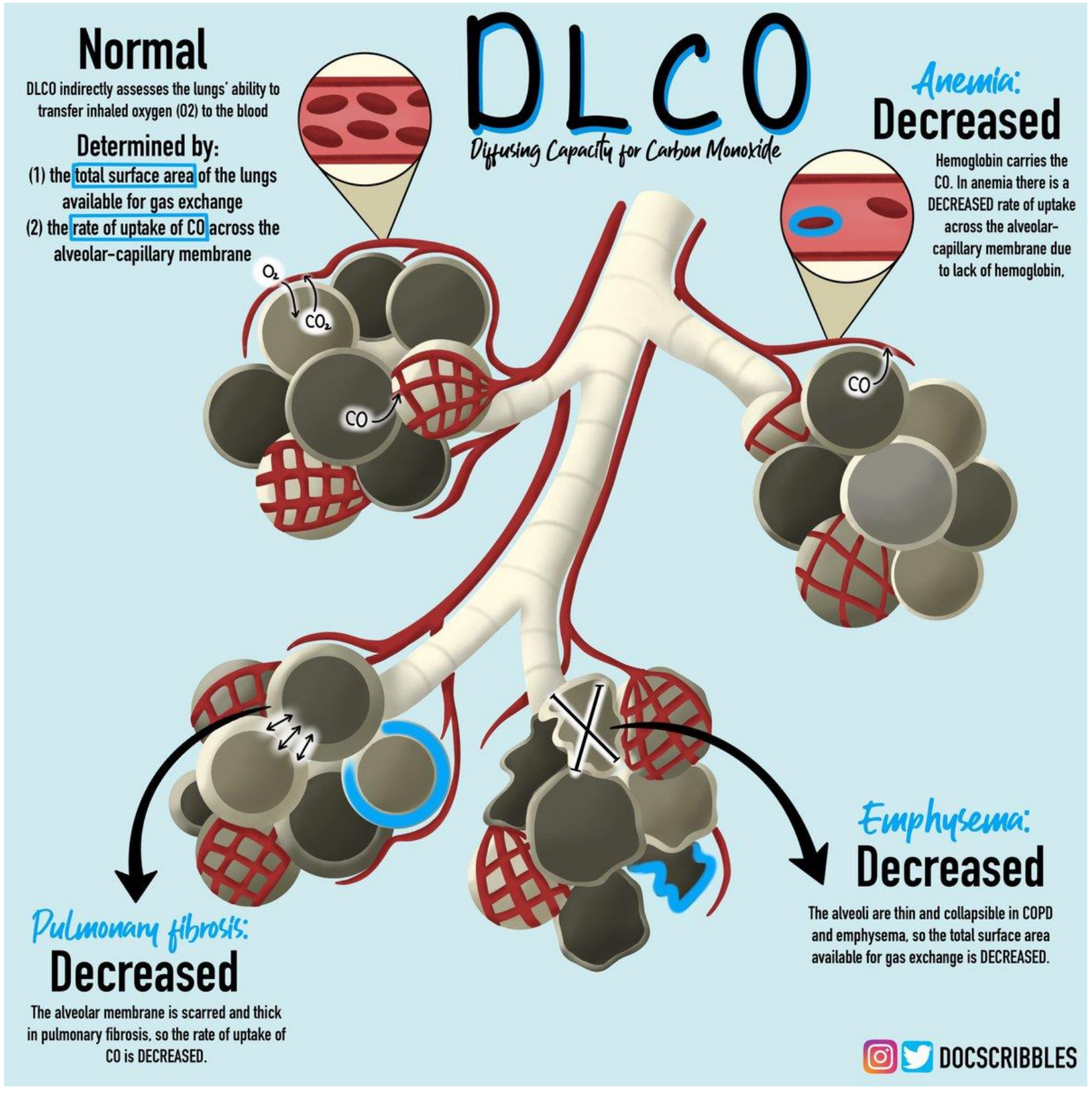


Year after year, this adds up

Worse if the Ig replacement dose isn't adequate

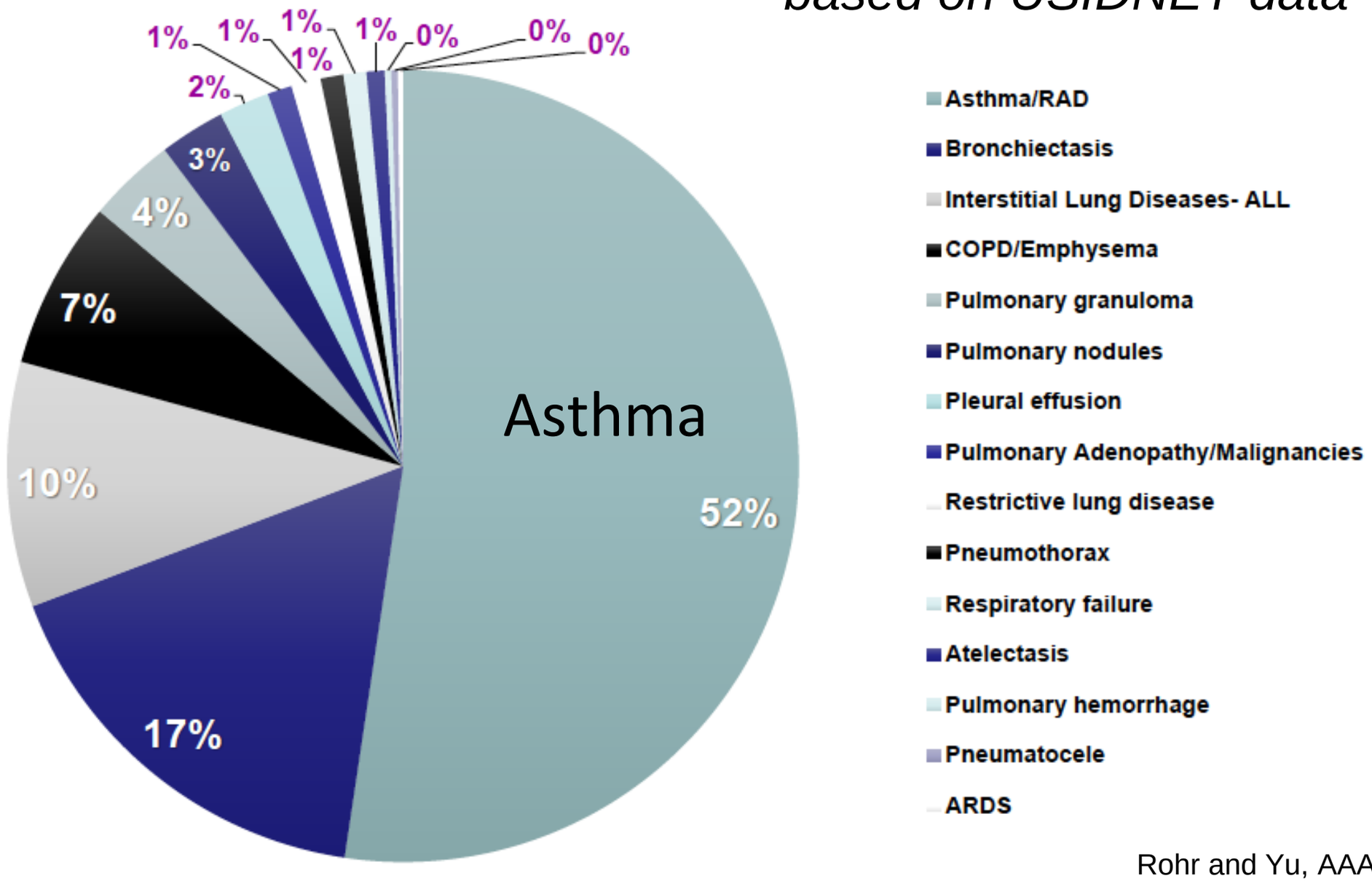
Baumann U, et al. *Front Immunol*, 2018;9:1837

Diffusion of gasses (DLCO)



Asthma is common

based on USIDNET data



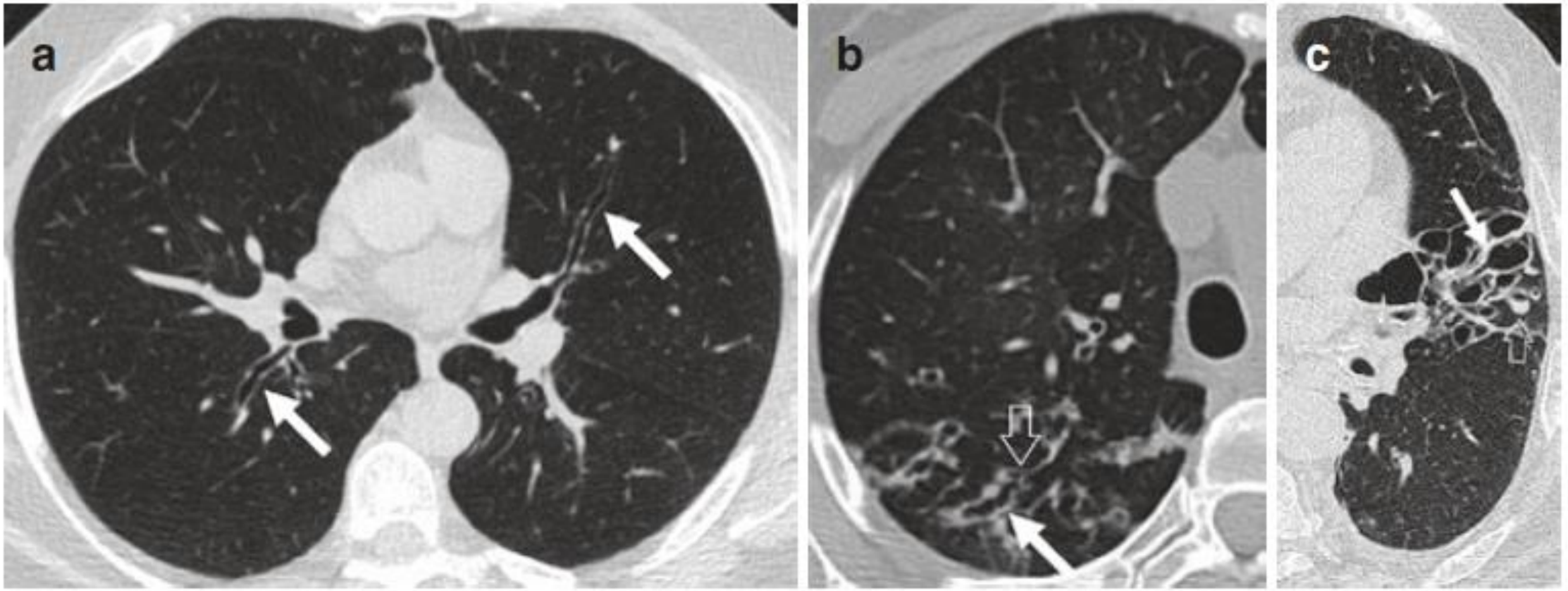
Rohr and Yu, AAAAI 2018

Figure 3. Relative frequency of non-infectious pulmonary disease across all PIDDs. Asthma/reactive airways disease (RAD) was by far the most common complication (52%).

May not be IgE-mediated

Rubin et al, J Asthma 2021

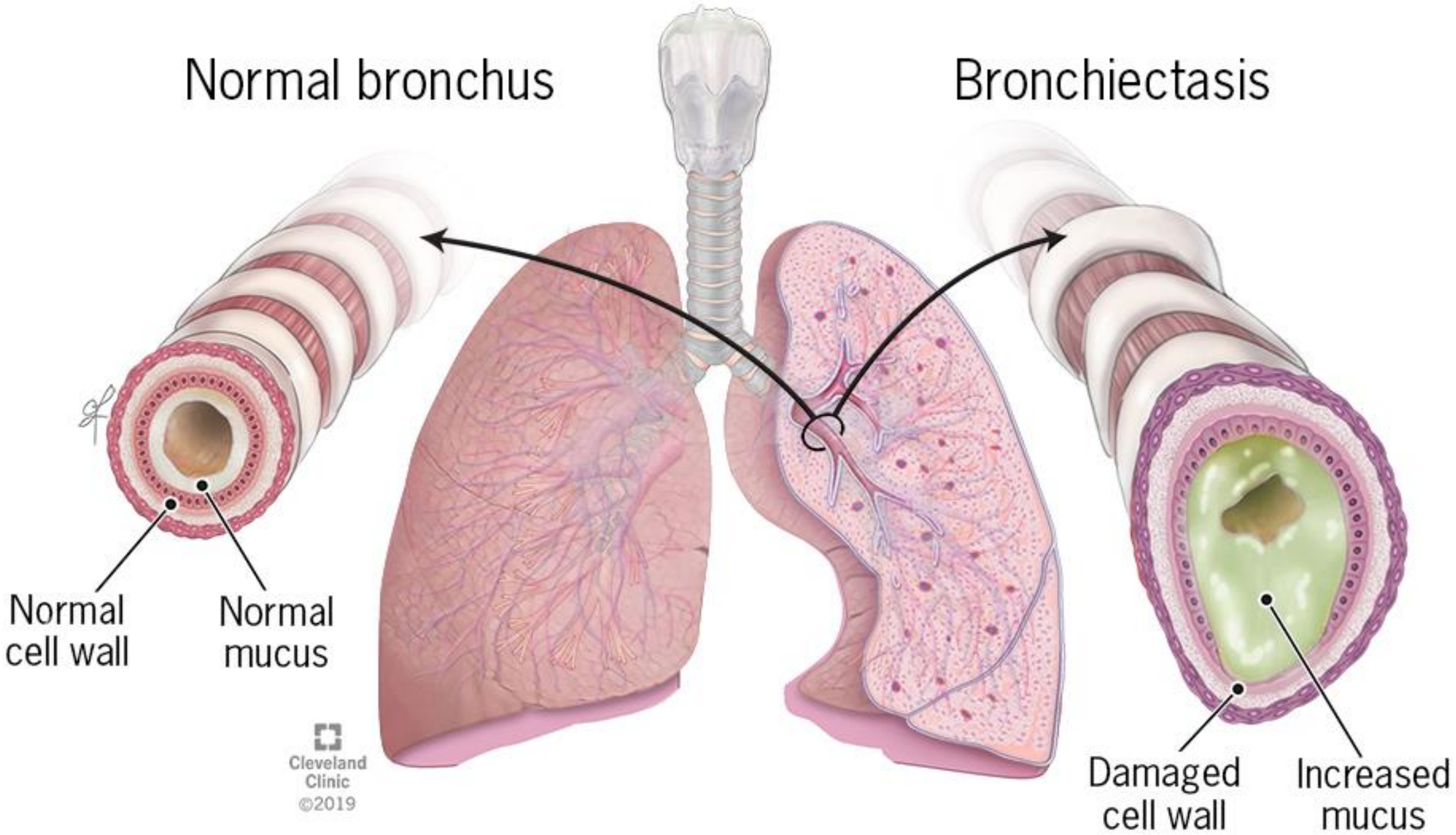
Bronchiectasis



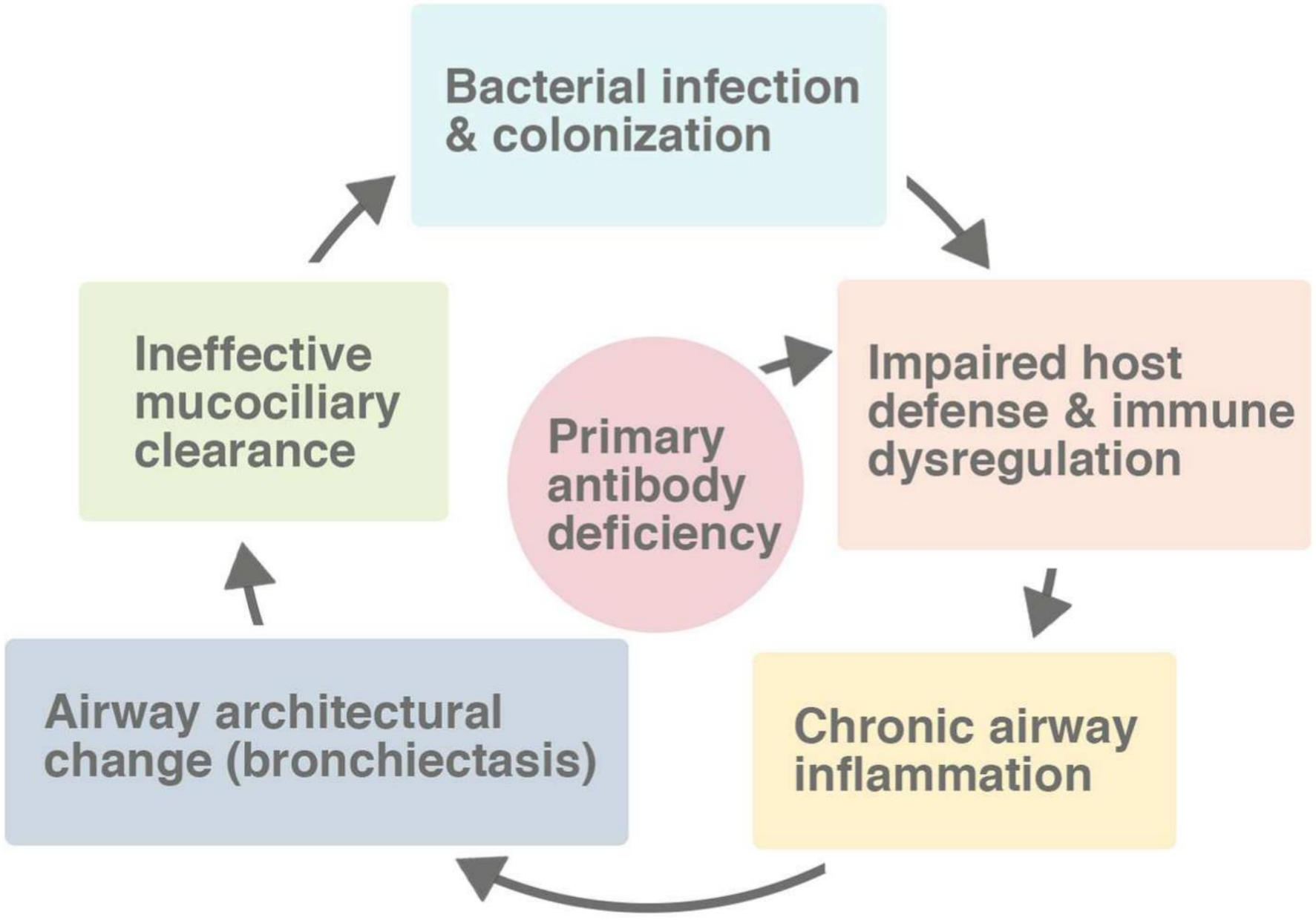
Affects 23% of CVID patients (up to 66% in some centers)

Wall … Sorensen. Frontiers in immunology 2020.

Bronchiectasis



Viscous cycle leading to bronchiectasis



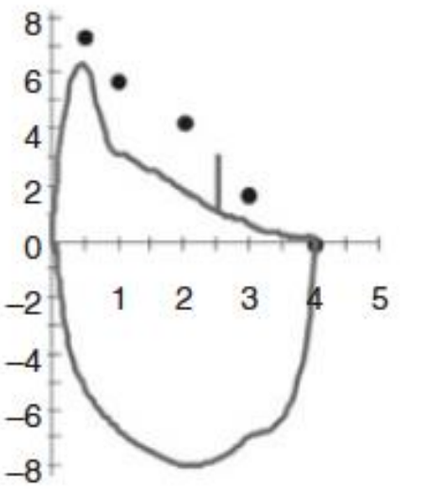
Wall … Sorensen. Frontiers in immunology 2020.

Bronchiectasis Lung function

Table 4.3 Pulmonary function test features of patients with bronchiectasis

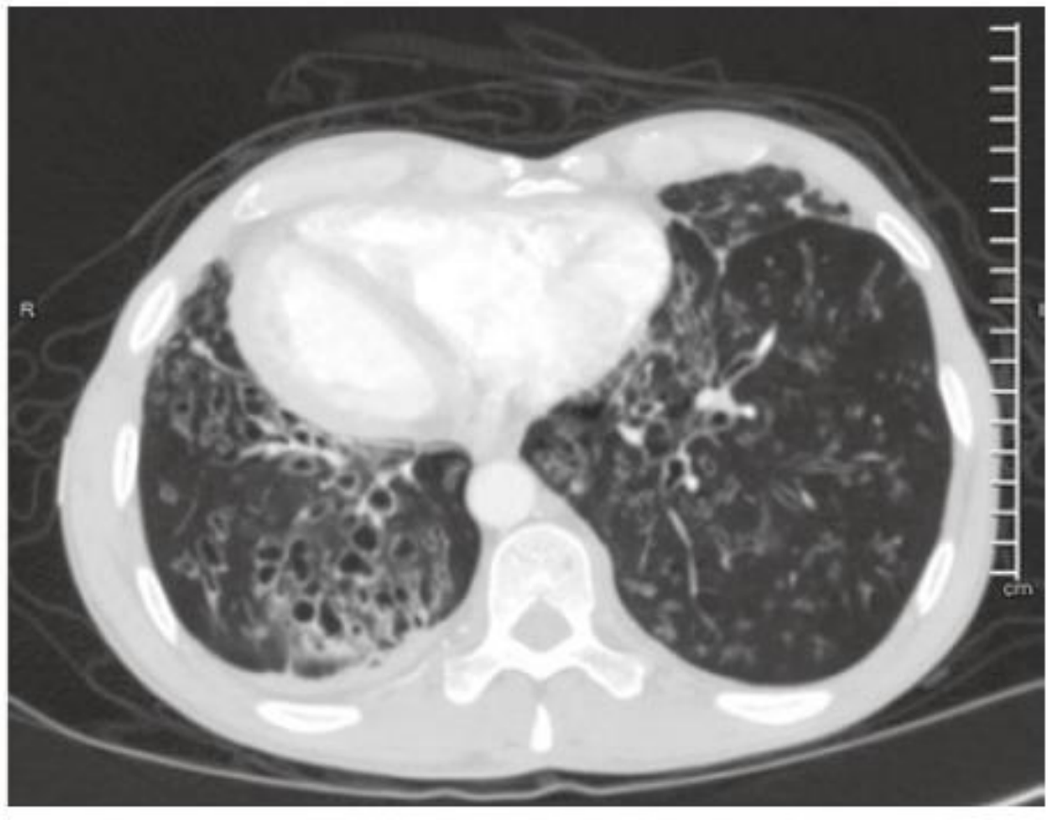
Feature	%
Normal	22–38
Obstructive pattern	43–60
Restrictive pattern	7–8
Mixed obstructive/restrictive	11–24
Positive bronchodilator response	9–22
Reduced diffusion capacity (<80%))	24

low FEV1
low FEV1/FVC



Flow/Volume Loop

	Predicted	Actual	% Predicted
FVC (L)	3.98	2.35	59
FEV (L)	3.27	1.38	42
FEV1/FVC		59	70
TLC	5.35	6.10	113
RV	1.62	2.34	144

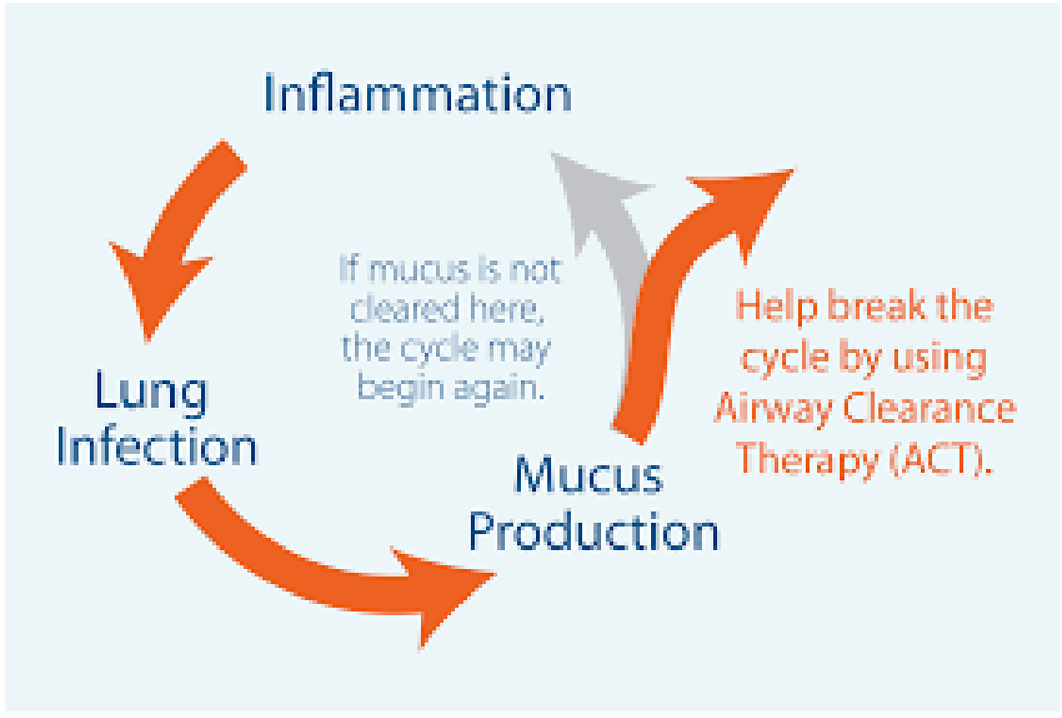


In late stages, diffusion falls

Fig. 4.1 Pulmonary function testing and chest tomography of a 57-year-old man with bronchiectasis and Kartagener syndrome. Pulmonary function testing shows severe obstruction and air trapping. Chest tomography reveals dextrocardia and advanced cystic bronchiectasis

Bronchiectasis, Chambers et al eds. 2018

Vest therapy



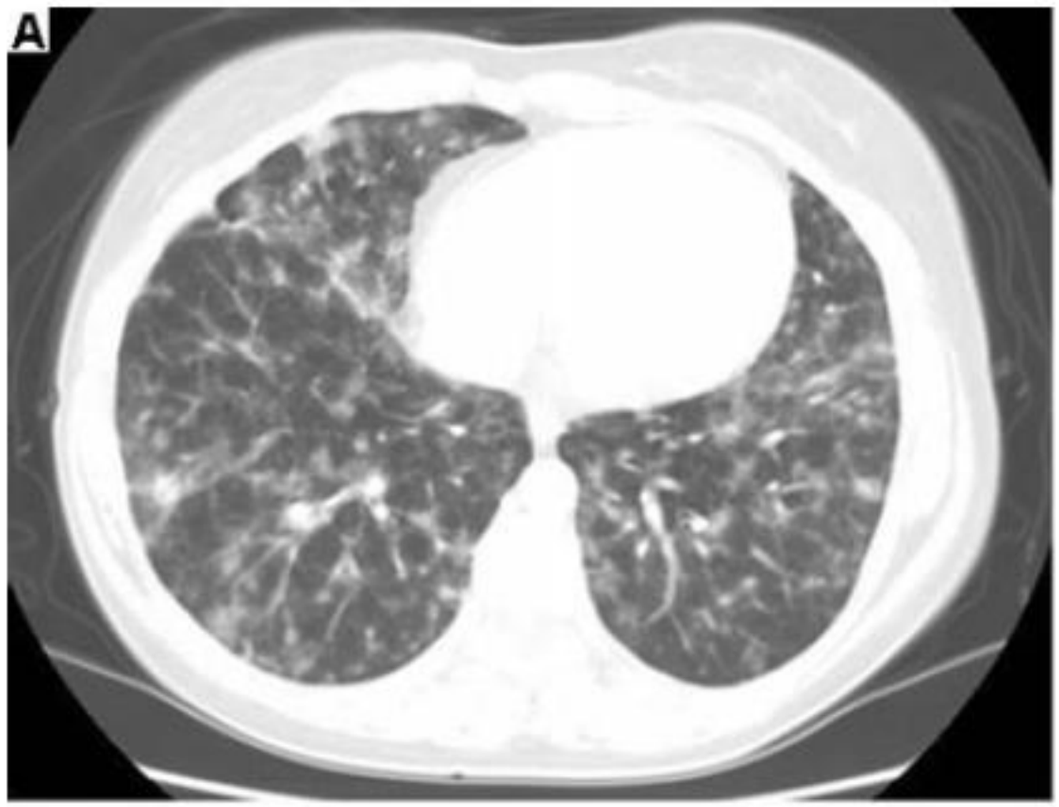
To mobilize mucus:
Add hypertonic saline
while doing the vest therapy

Consider also
Tobi (if pseudomonas)

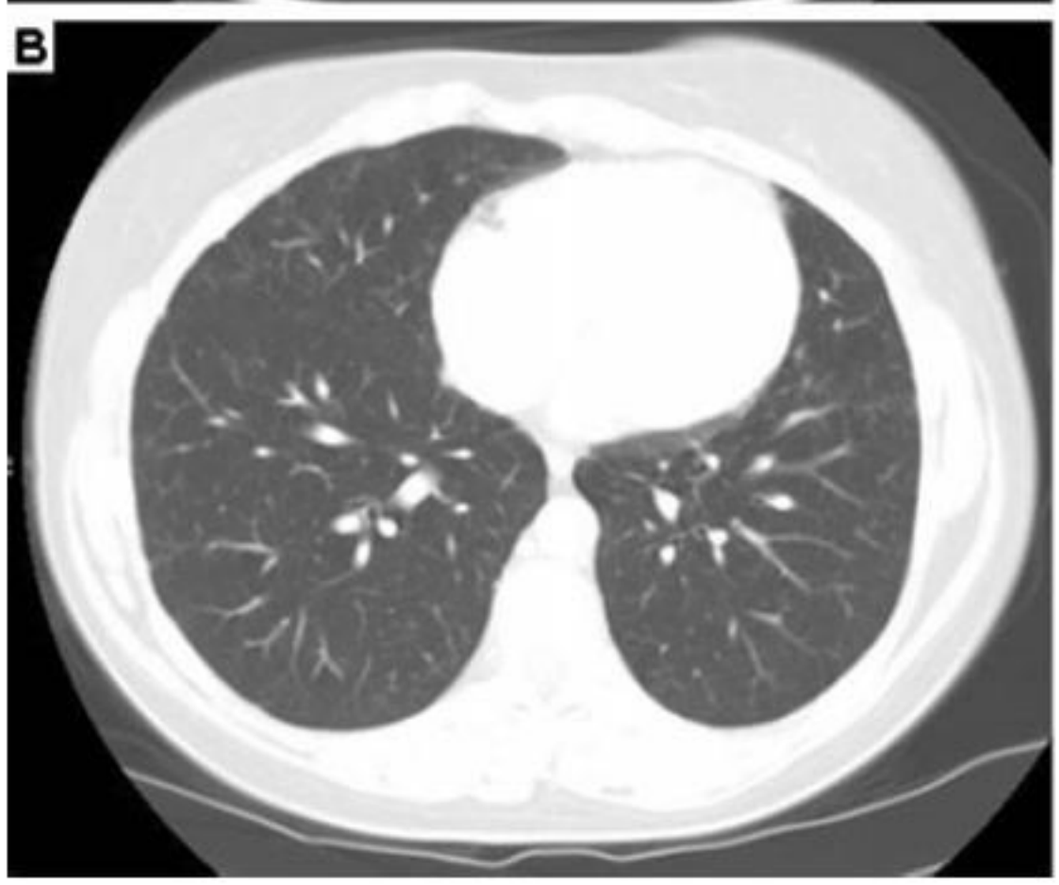
GLILD

- **Granulomatous Lymphocytic interstitial lung disease**
- Seen in **PADs and CIDs** (40% CTLA4, LRBA, Rag def)
- Often confused with *sarcoidosis*
  - But there are differences. In sarcoidosis:
    - no increase in infections
    - no enlargement of liver and spleen
    - IgG levels are high
    - More lung lymph adenopathy
- Biopsy is very important but sometimes is not definitive

GLILD



- patchy
- lower > upper
- ground glass



Recommendations to Monitor

Chest CT

PFTs with DLCO

Surgical lung biopsy

Tam and Routes, Am J Rhinol Allergy 27, 260 –265, 2013

Combination Treatment for GLILD

- Definitely optimize Ig replacement (increase dose)
- 1st line: corticosteroids (2 mg/kg)
  - “Corticosteroids did not achieve a remission in any case.”
    — Jack Routes

Trial of steroids
Move quickly to combination therapies with Rituximab

Sirolimus, azathioprine

Hurst et al, JACI 2017

GI Complications in PADs

- **Inflammatory GI disease**
  - Crohn-like disease
  - villous blunting / atrophy
- **Chronic diarrhea**
  - infections and non-infectious
- **Nodular lymphoid hyperplasia**
  - lymphoproliferative IEI phenotypes
- **Biliary tract disease** (PBC, *Cryptosporidium*)
- **Structural bowel disease**
  - Hirschprung (CHH), atresia (TTC7A, PI4KA)
- **Malignancy**

Take a good history

- Family history (many autosomal dominant diseases!)
  - consanguinity
- Food allergies (immediate-type reactions)
- Celiac disease (gliadin triggering)
- Necessity of TPN
- GI autoimmunity
- perianal abscess or fistulas
- splenomegaly / hepatomegaly
- Diarrhea, mucus, blood in stool

Tegtmeyer D, …, Klemann C. Peds All Imm 2017

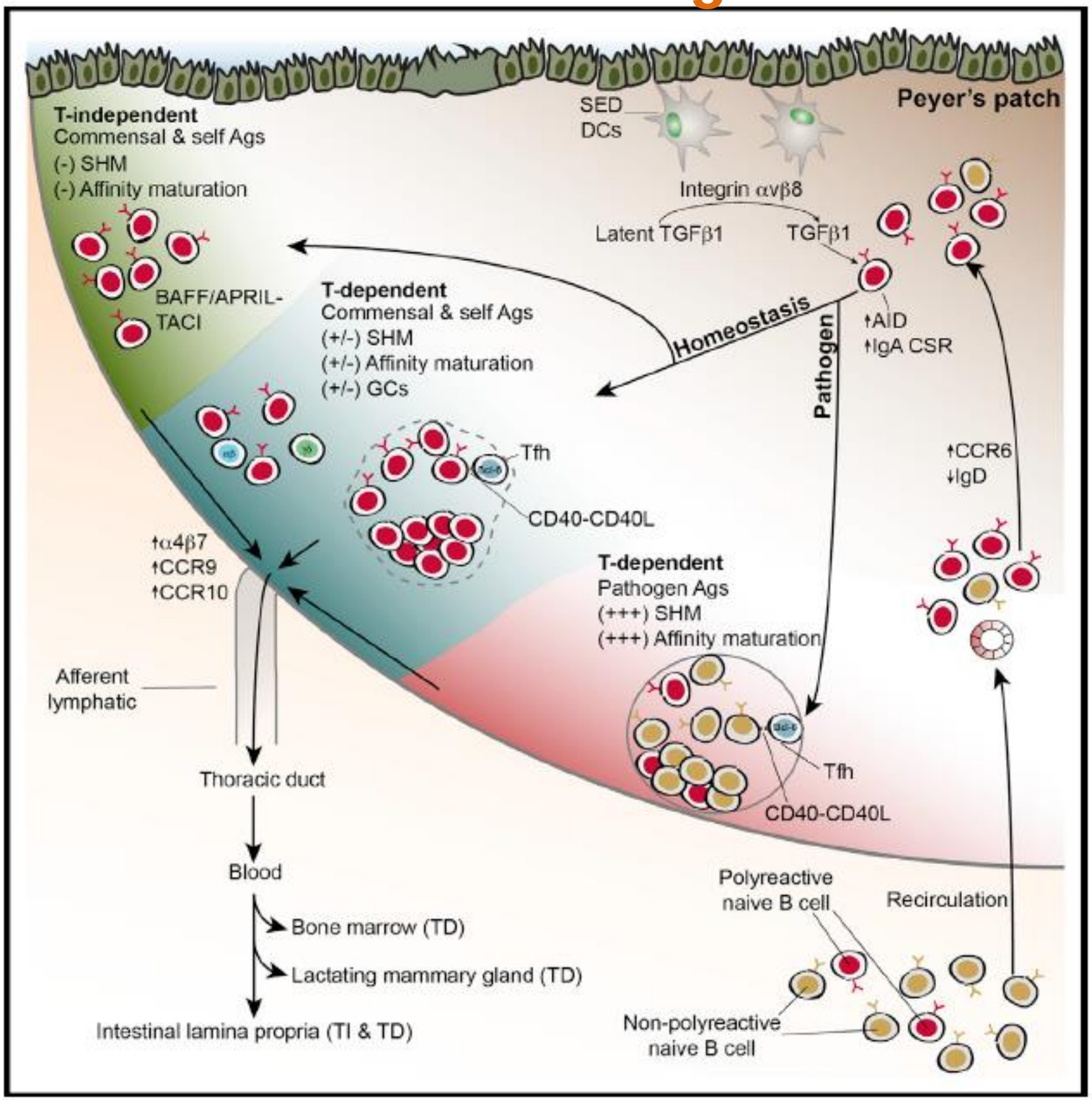
Chronic diarrhea

- Eval for Infectious causes; Refer to GI
- **Colonoscopy** for
  - Crohn's-like disease
  - lymphocytic infiltration (autoimmune)
  - lymphoma
  - CMV, EBV
- **Upper Endoscopy** for
  - villous blunting or loss
  - lymphocytic infiltration
  - sm. bowel biopsy for giardia
  - H. Pylori and ulcer disease
  - lymphoma
  - enterovirus and CMV
  - nodular lymphoid hyperplasia

Autoimmunity and tolerance

Microbiome regulates B-cell repertoire

gut bacteria



B cells primed by commensal antigens

start here

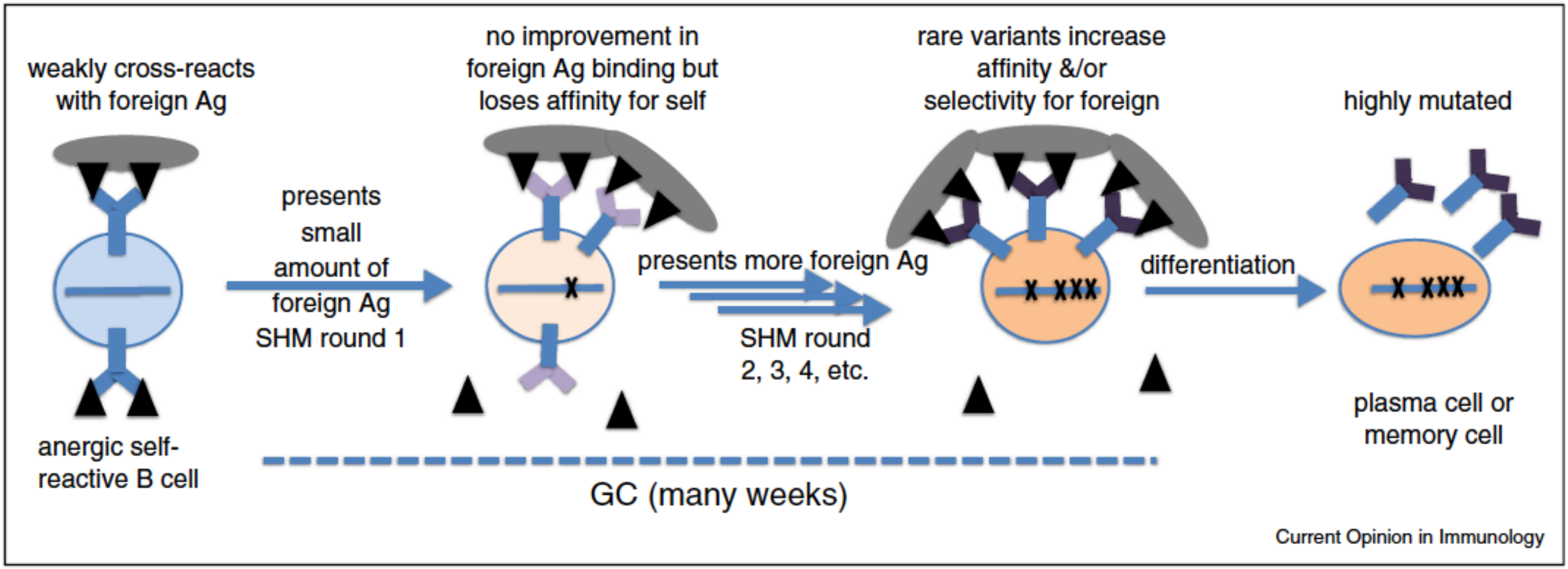
polyreactive B cells

Bunker Bendelac Immunity 2016

Clonal redemption

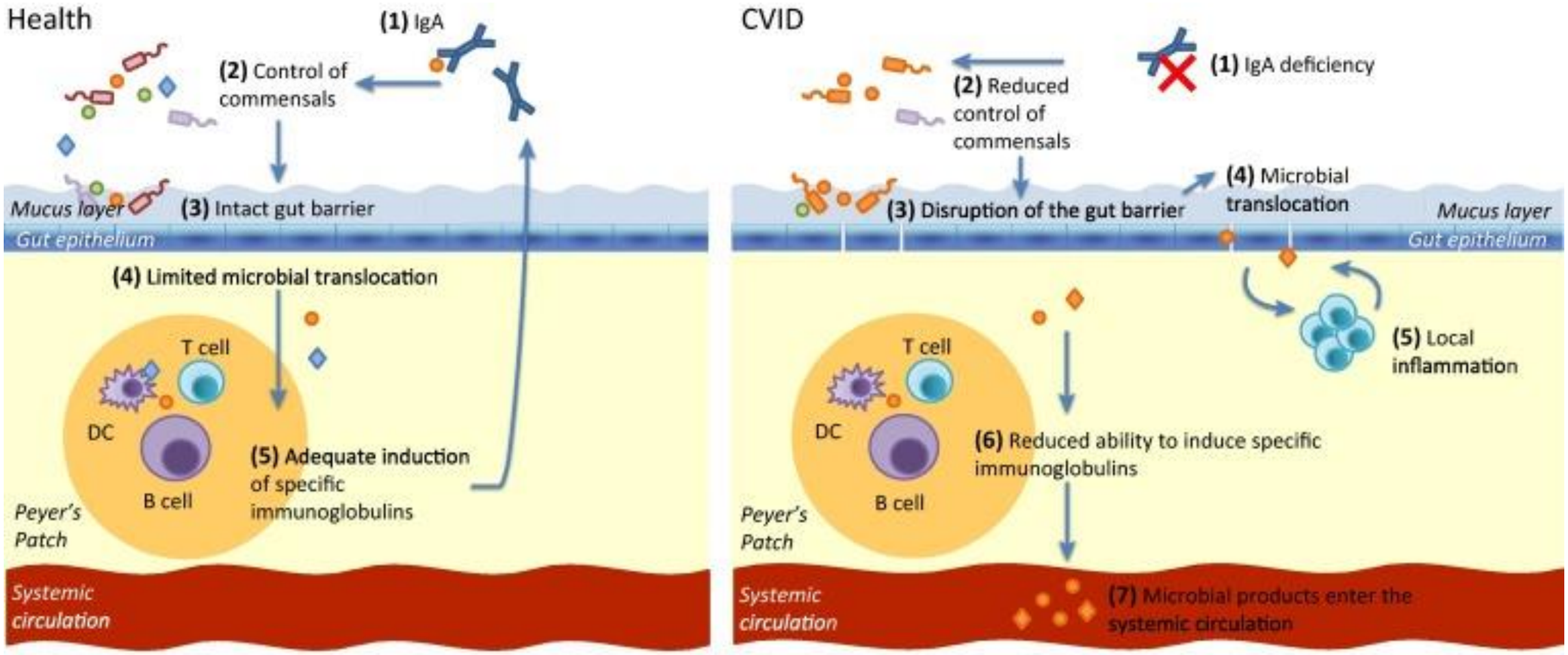
We are all born with auto-reactive B cells!

AIHA: Vh4-34 recognizes the I/i carbohydrate ag on RBCs



IgA bound to commensals
helps us get rid of autoimmunity

Inflammation / IBD



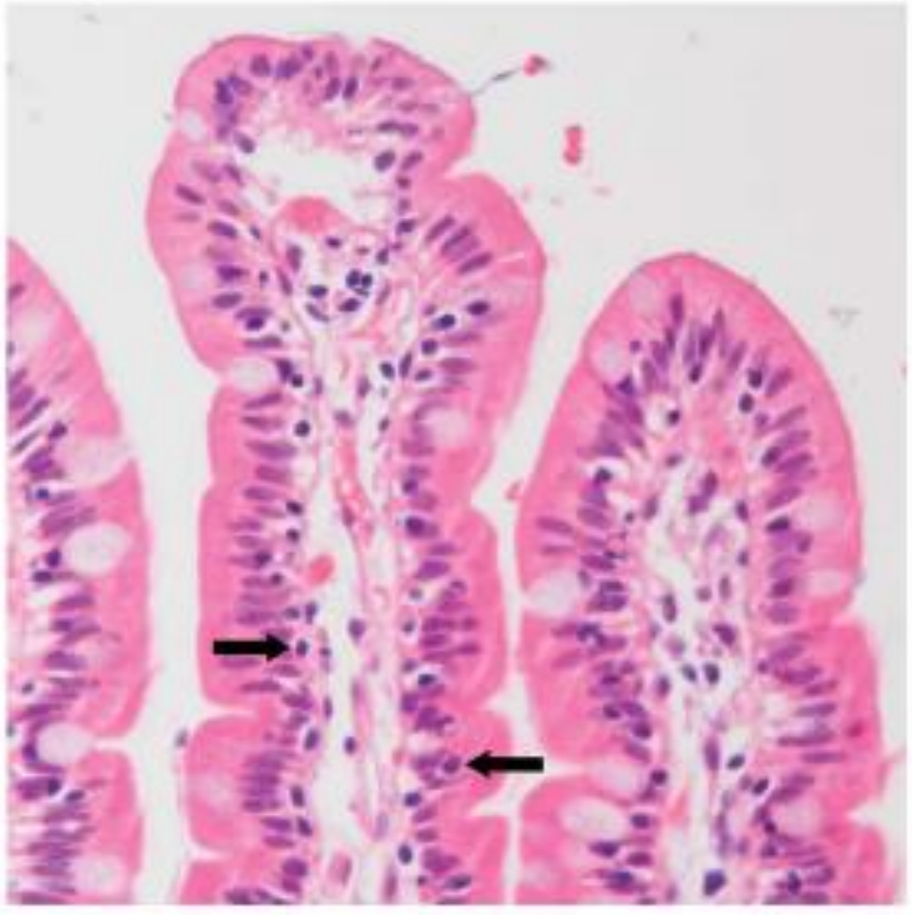
Berbers et al, Trends in Imm, 2017

Table 3. Percentage of patients with histopathological finding

Histopathological finding	Number of patients, *n* (%)
Increased IEL total	*32 (60%)*
Descending part of duodenum	23 (46%)
Reduced number of plasma cells	33 (62%)
Lymphoid hyperplasia	20 (38%)
Gastric metaplasia in duodenal bulb	13 (26%)
Fibrosis in the gastric mucosa	13 (26%)
Intestinal metaplasia in gastric mucosa	6 (12%)
Subacute inflammation	2 (4%)
Chronic/chronic active inflammation, total	*24 (45%)*
Stomach	20 (40%)
Colon	11 (22%)
Atrophic gastritis	9 (18%)
GVHD-like	1 (2%)
Eosinophilic inflammation	4 (8%)
Lymphocytic enteritis/colitis	4 (8%)
Collagenous enteritis/colitis	3 (6%)
Granulomatous inflammation	3 (6%)

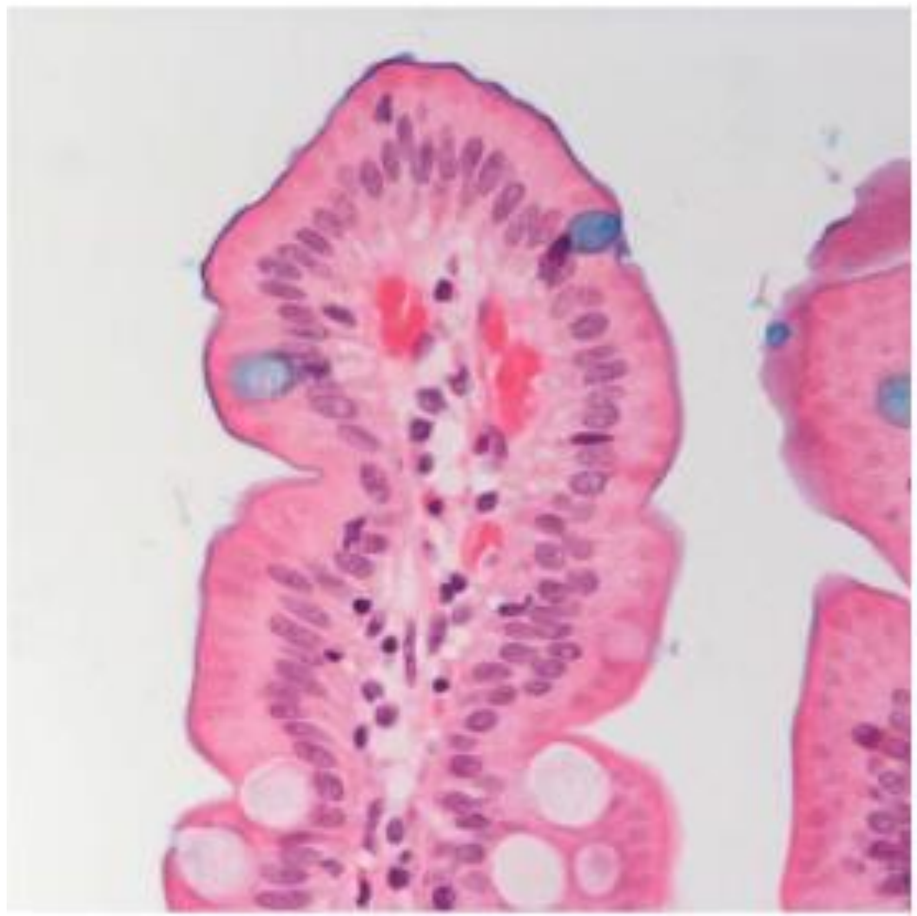
GVHD, graft-vs.-host disease; IEL, intraepithelial lymphocytes.
Text in bold relates to percentage of patients at each anatomical site.

Jorgensen et al Am J Gastroent 2016



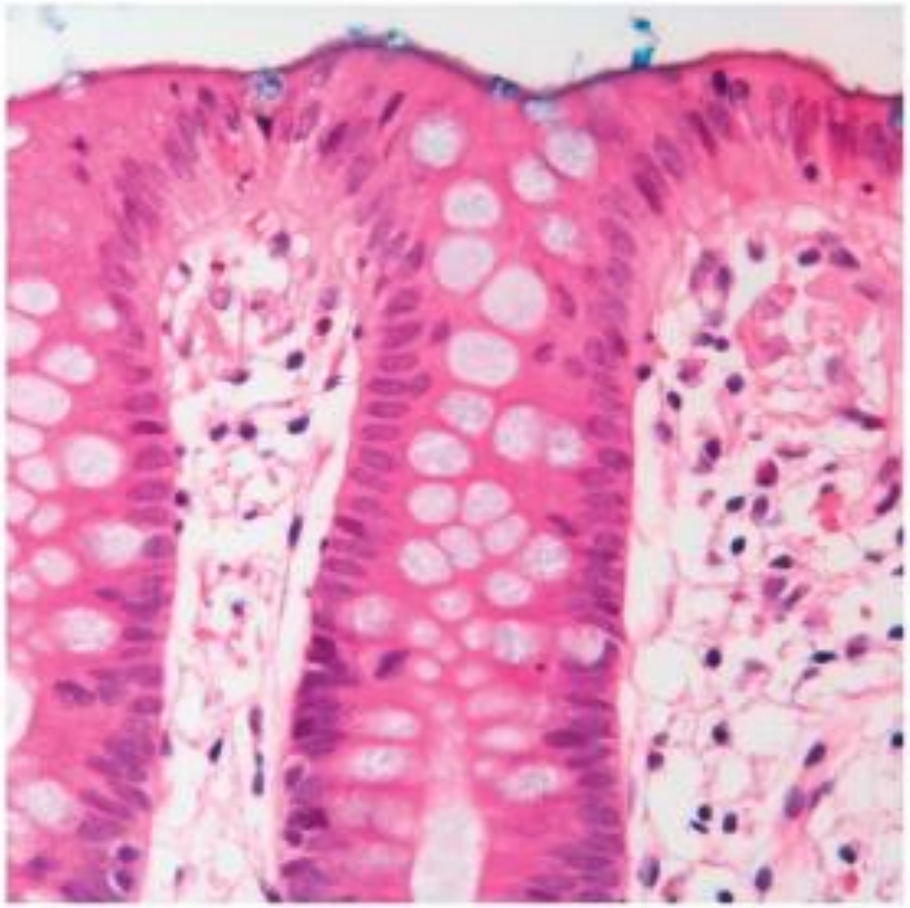
CVID

Increased IEL



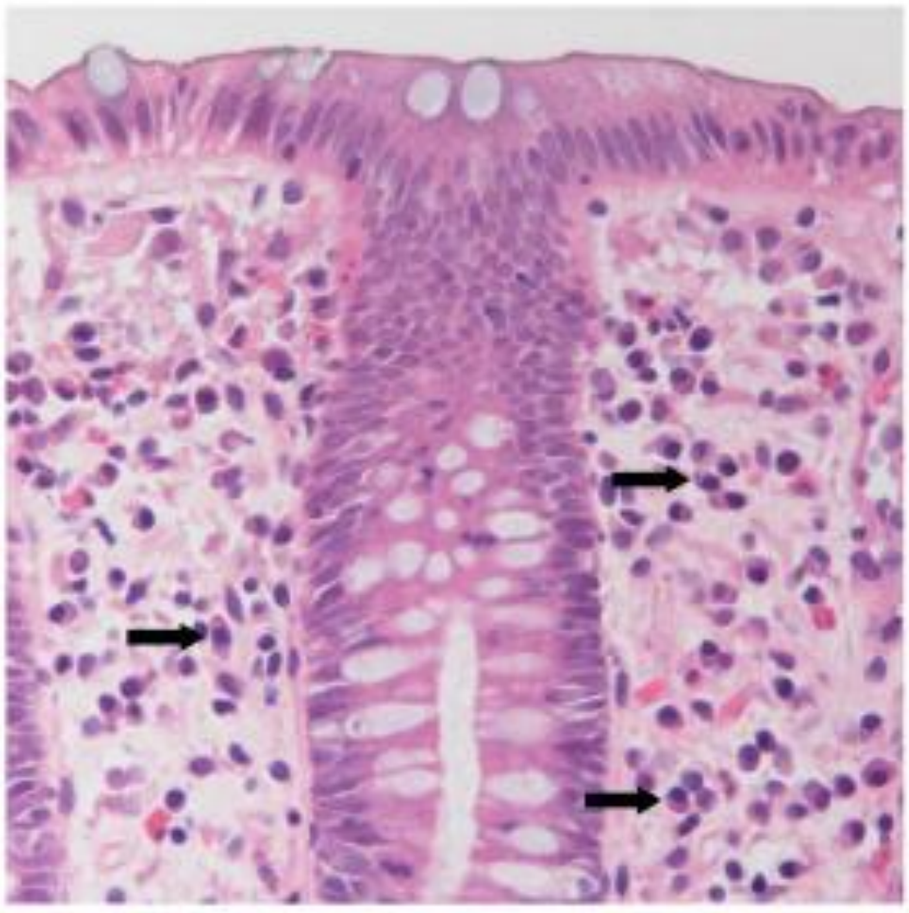
Control

Jorgensen SF et al Am J Gastroent 2016



CVID

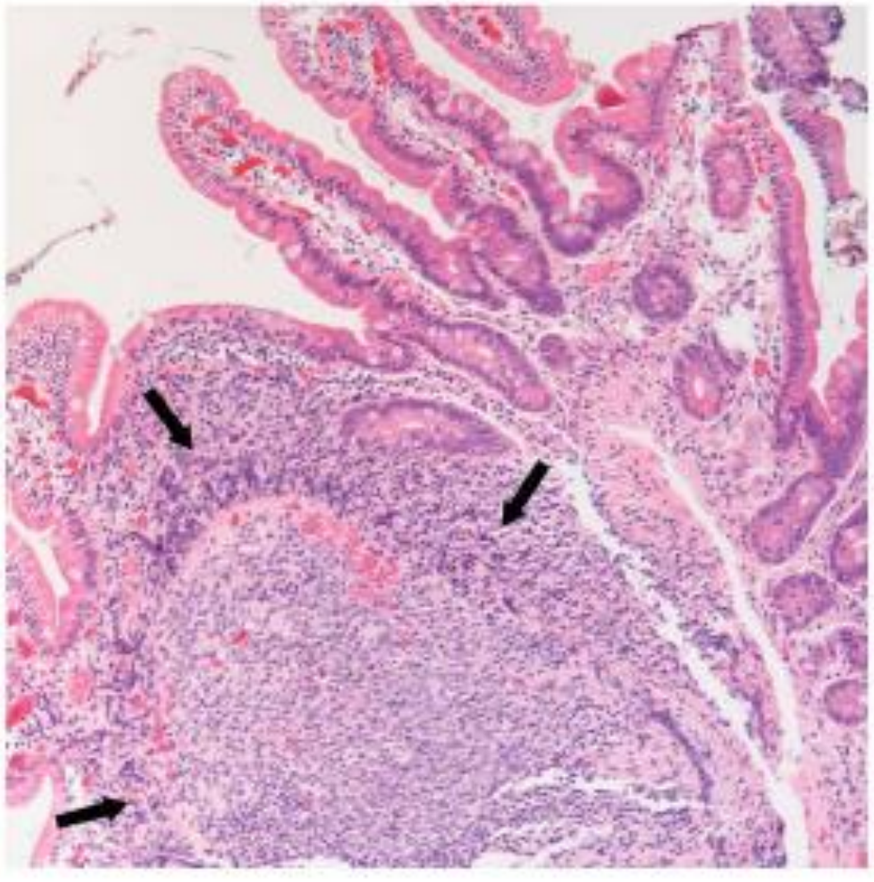
Decreased plasma cells



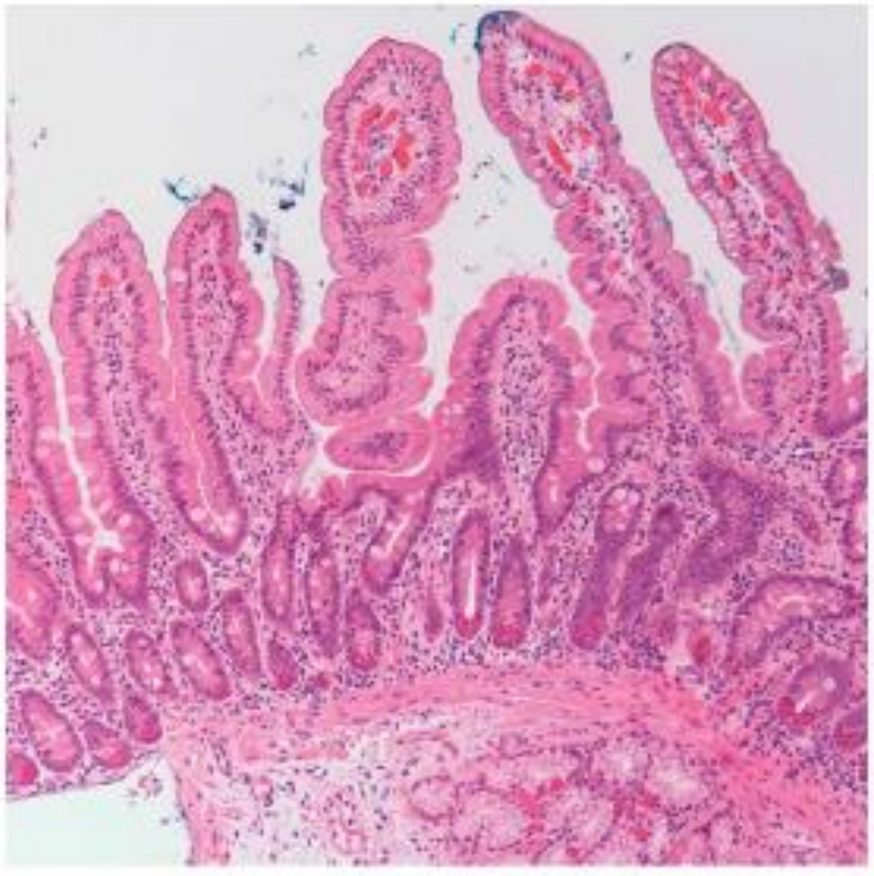
Control

Jorgensen et al Am J Gastroent 2016

Lymphoid aggregates



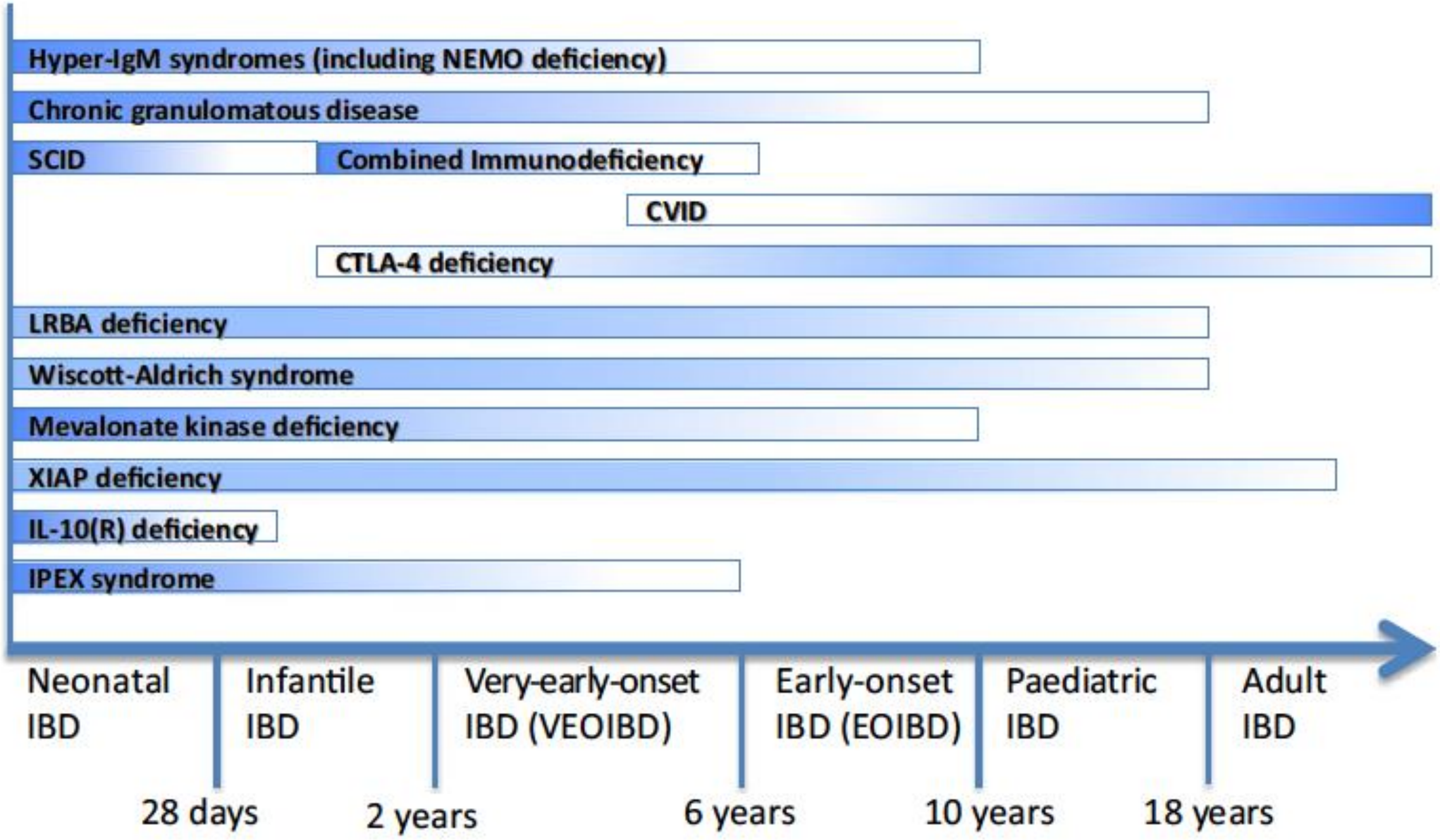
CVID



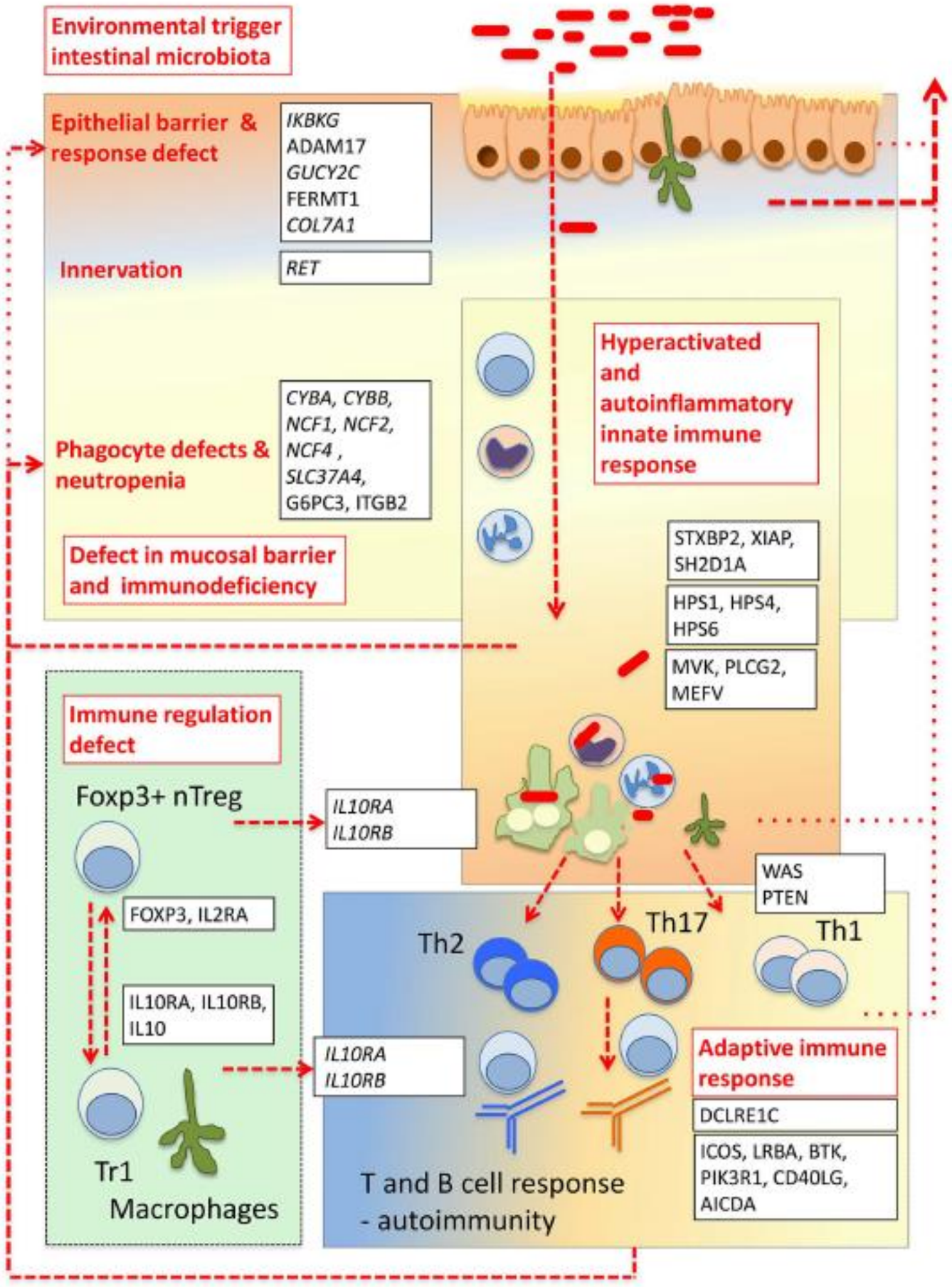
Control

Jorgensen et al Am J Gastroent 2016

Monogenic inflammatory diseases



Tegtmeyer D, …, Klemann C. Peds All Imm 2017



Categories of monogenic IBD

- Epithelial barrier
- Phagocyte Defects
- Hyperinflammation and autoinflammation
- T & B cell defects
- Immunoregulation
- Others

Uhlig HH, Gut 2013

Malignancy

Why malignancies in IEIs

- Chronic B cell activation (e.g., EBV)
  - leads to ROS damage
  - Somatic hypermutation (AID)
    - copy number changes
    - point mutations
    - **Genomic instability** is the result

- Stem cell developmental defects (e.g., GATA2)
- Defective telomere maintenance (e.g., DKC)
- Defective DNA repair (e.g., ATM)

- 17% of CVID its develop malignancy
  - mostly B cell lymphoma
  - watch for extra-nodal mucosal lymphoma

Baloh et al, JACI 2019

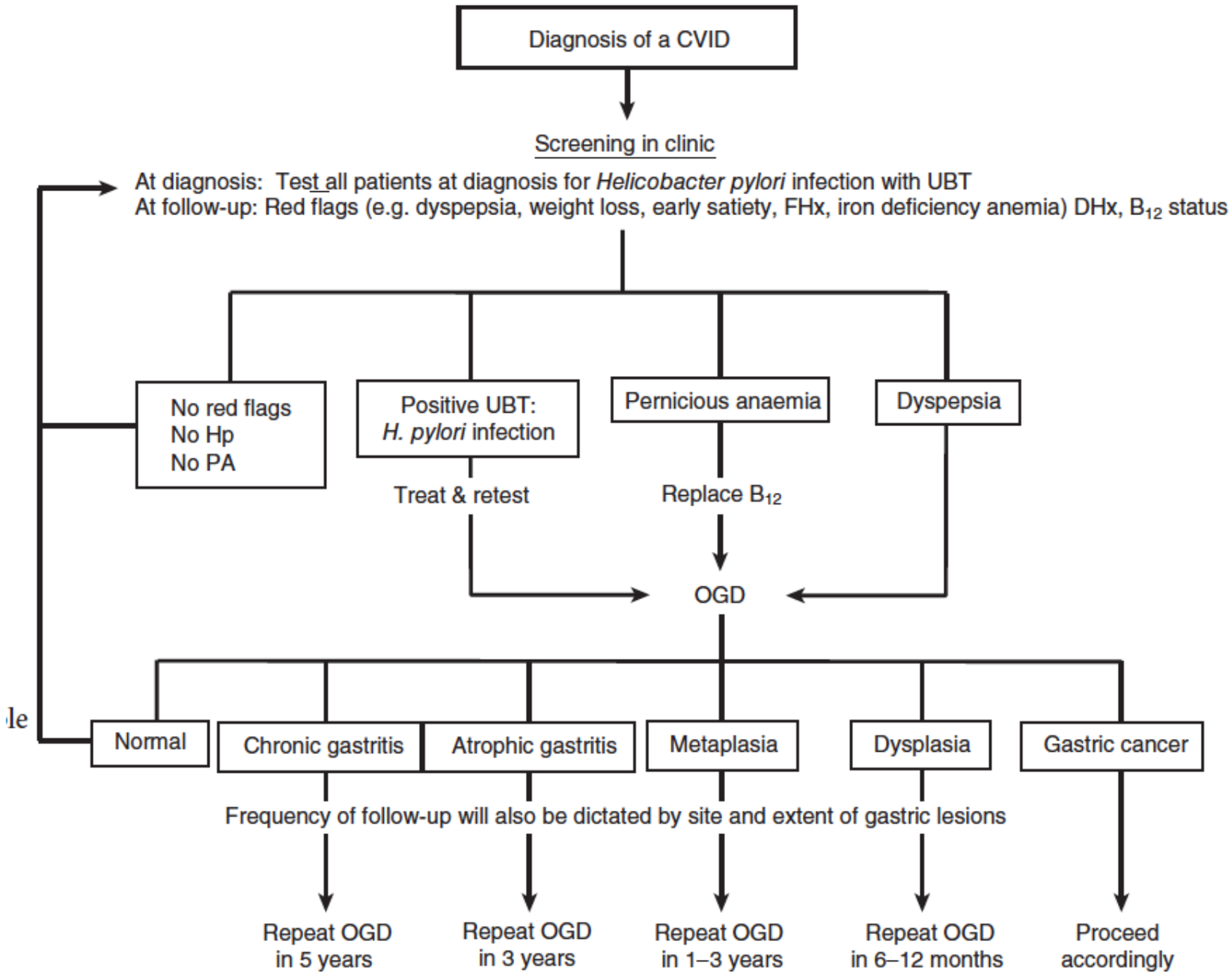
- H. pylori associated with 90% of these

Wootherspoon Lancet 1991

- 10% of Ataxia telangiectasia develop GI malignancy
  - average age 24 y

H pylori

All patients with IEI should be screened for H pylori and treated



Dhalla … Chapel Clin Exp imm 2011

Take home points

- Lung and GI diseases are common in CVID
- Order HRCT at least once
- Frequent pulmonary function testing
- Bronchiectasis needs daily treatment
- GLILD requires T and B cell suppression
- Endoscopy and colonoscopy help tremendously

Long Term Management Plan for Connor

- 35 y with recurrent pneumonias and CVID phenotype
  - Regular chest CT to monitor bronchiectasis and develop
    - How often?
  - Vest physiotherapy plus hypertonic saline
  - Sputum cultures during exacerbations to screen for *Pseudomonas*

- GI surveillance — regular history and physical exam
  - Monitor weight
  - Check Albumin, LFTs

Thank you!

mbutte@mednet.ucla.edu