



# Lung Disease in Primary Antibody Deficiency

*State of the Art*



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# Overview

PID, PAD and the (adult) lung

The Vulnerable Lung

Acute Infections

Chronic Complications

GLILD: state of the art

## Why are the lungs affected?

12

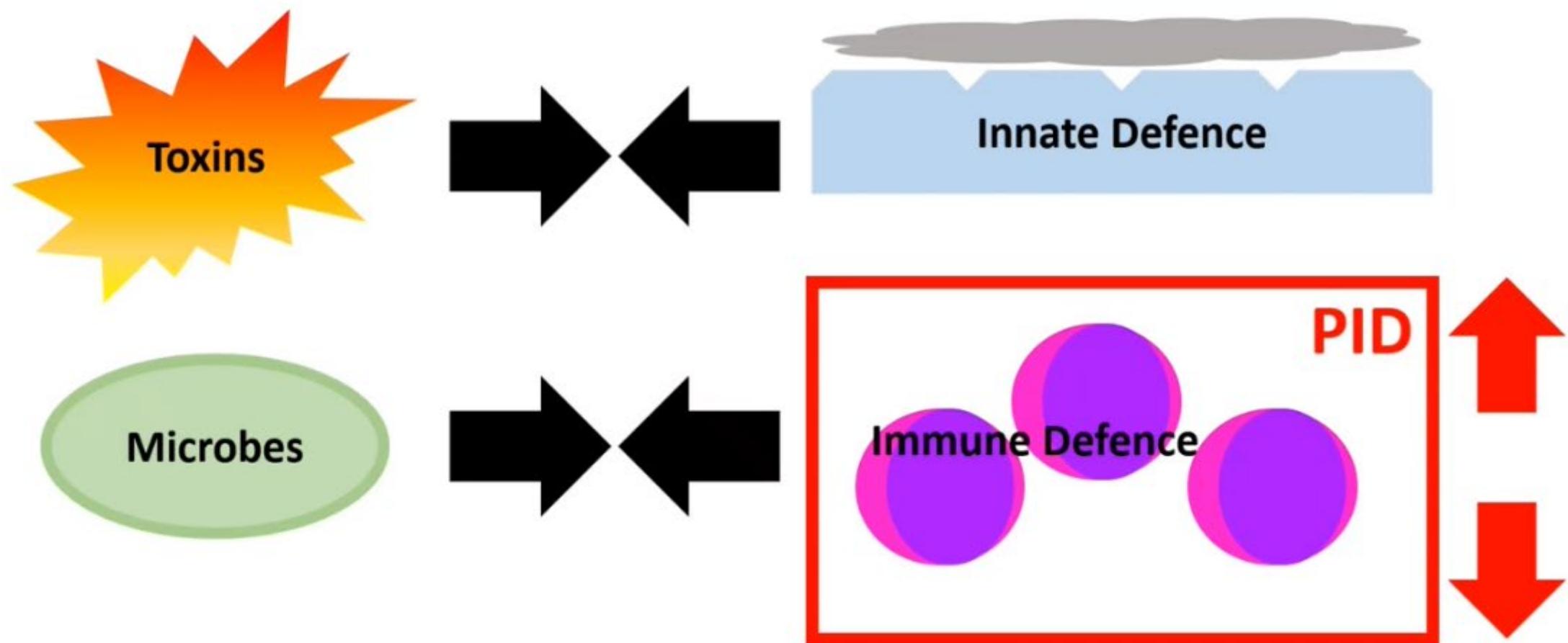
60

24

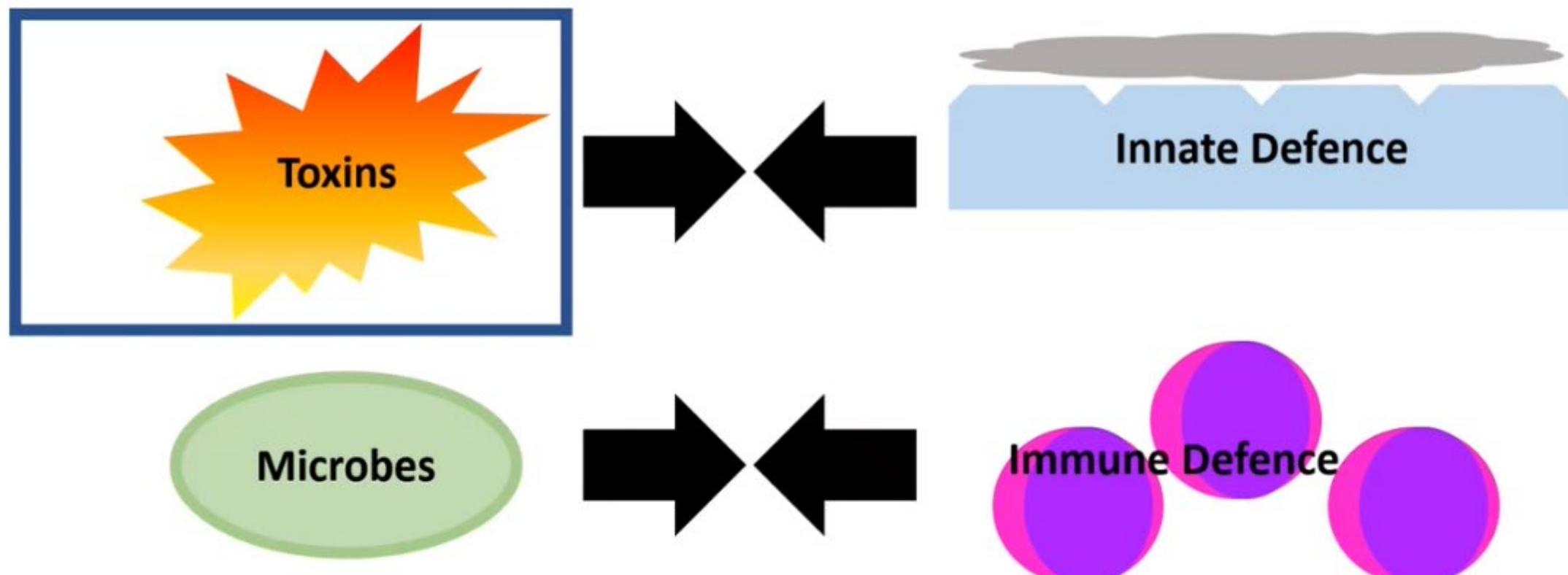
## Why are the lungs affected?

17,280 breaths per day

# Balance



# Balance



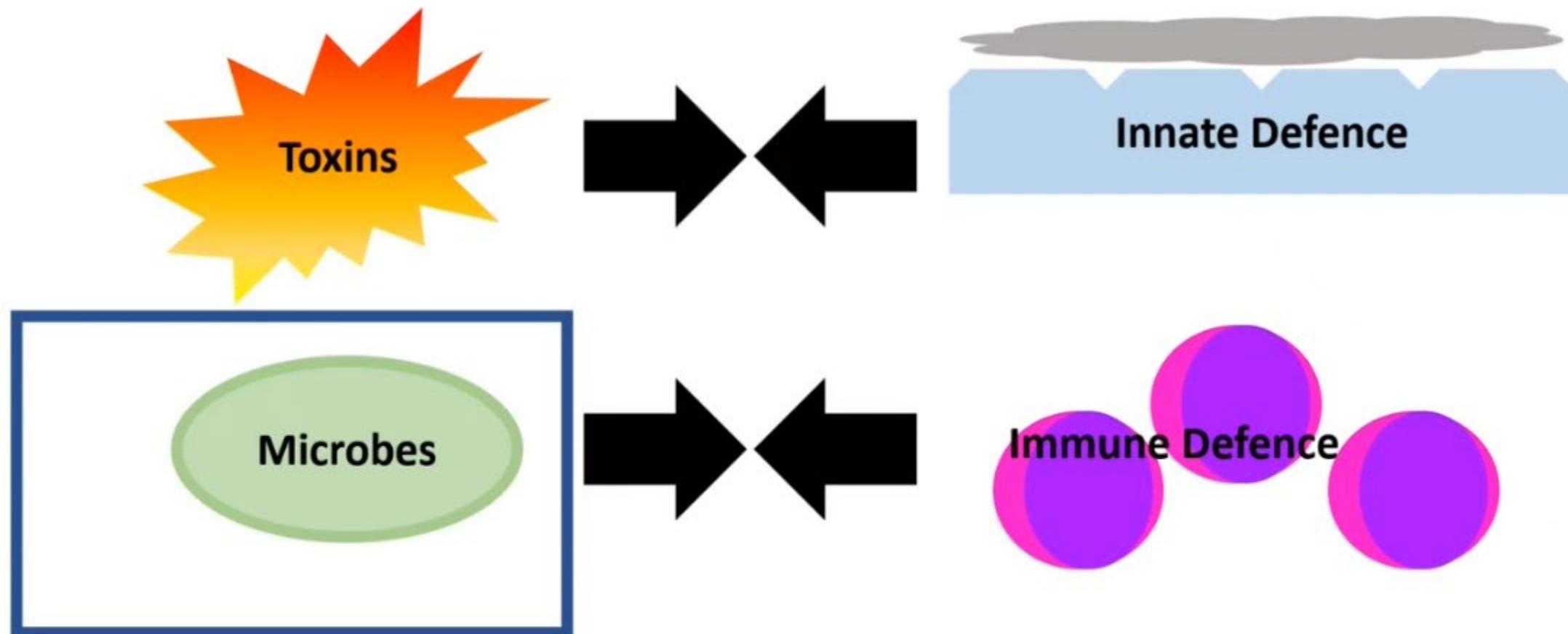
# VAPING

Harm Reduction?  
Too Harmful?



IMAGE CREDIT: <https://www.pennmedicine.org/news/news-releases/2019/august/nicotine-free-e-cigarettes-can-damage-blood-vessels>

# Balance

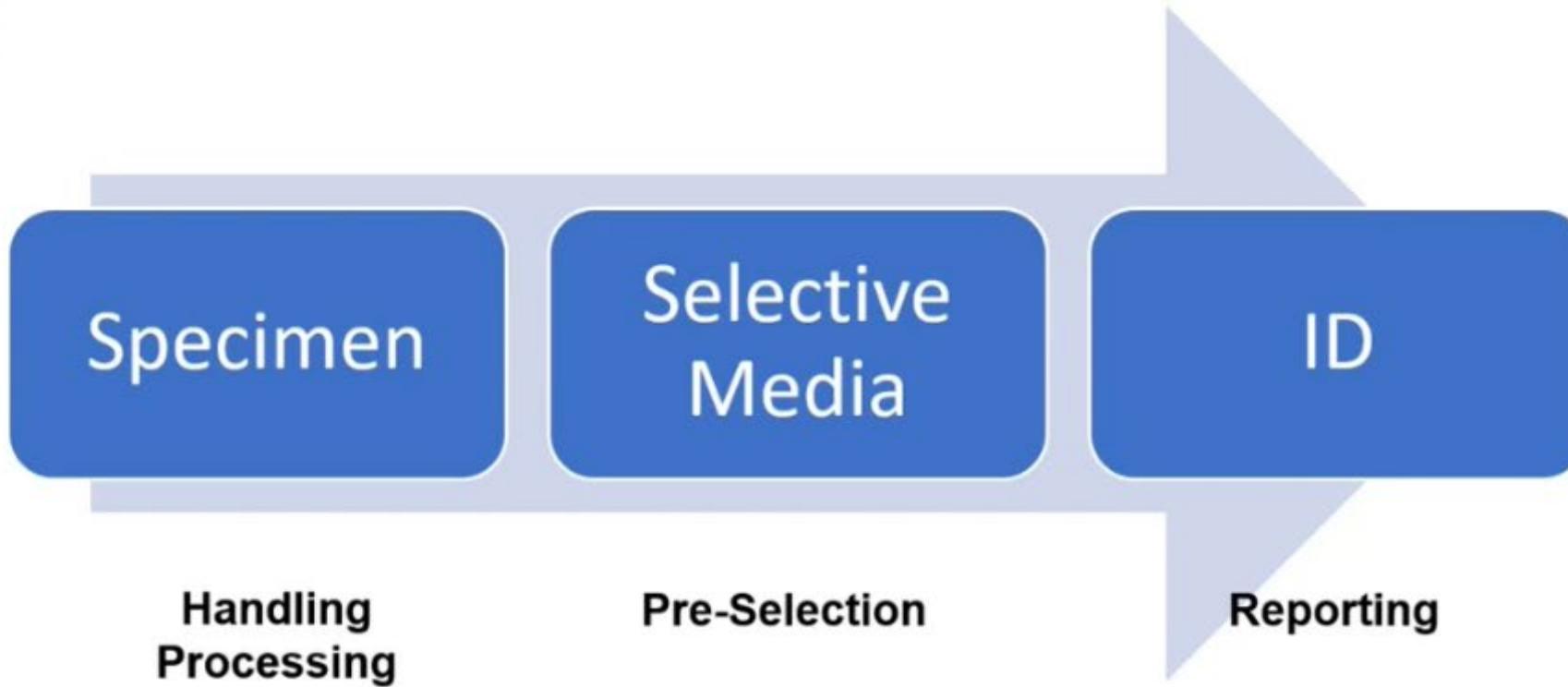


***“The healthy human airway is **sterile**, with several innate immune mechanisms acting in coordination to maintain this sterility. Smoking appears to disrupt these innate immune mechanisms, and as a consequence, microbial pathogens are able to persist in the lower airway in COPD”***

**AJRCCM 2006**

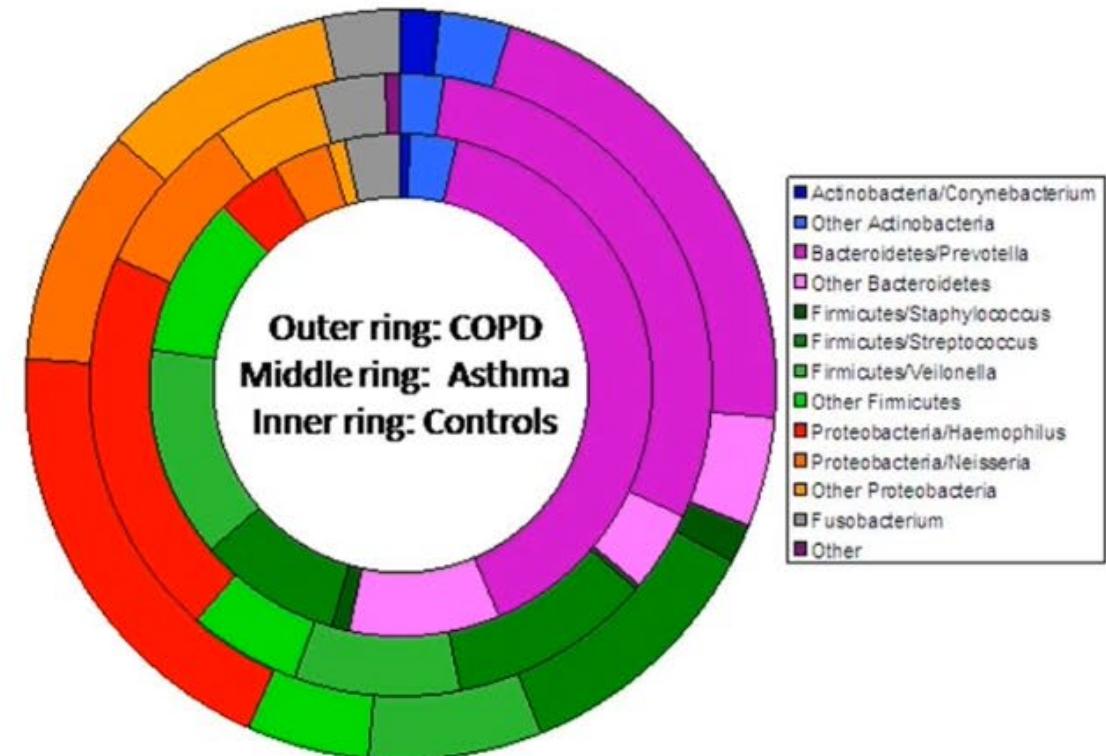
“free from bacteria or other living microorganisms; totally clean”

# Sterile?



“no growth of the potential pathogens we looked for and were capable of detecting”

# A healthy human airway microbiome?



Hilty M et al. Disordered microbial communities in asthmatic airways. *PLoS One*. 2010 Jan 5;5(1):e8578

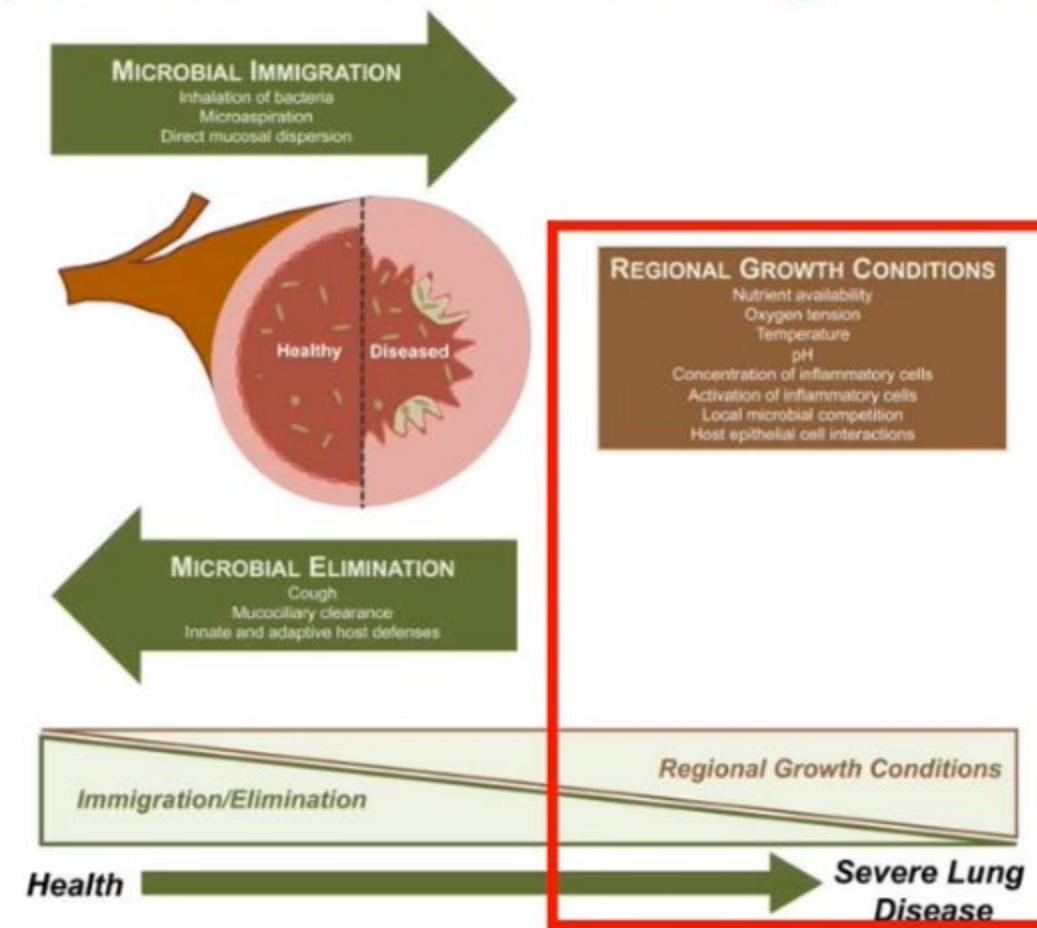
# What is a ‘Microbiome’?

*“the ecological community of commensal, symbiotic and pathogenic micro-organisms that literally share our body space”*

**“The lung microbiome is:**

- Detectable in health
- Altered in disease
- Predictive of outcomes
- Correlated with variations in immunity”

# An Ecosystem Approach to the Lung Microbiome



Dickson RP et al. The role of the microbiome in exacerbations of chronic lung diseases. *Lancet* 2014;384(9944):691-702

## Clinical Implications

Negative sputum culture doesn't mean not bacterial

Positive sputum culture doesn't mean that bug is causative

Respiratory viruses known to be important

FUTURE:

Restoration of 'eubiosis'

## The intersection of Immunology and Pulmonology

People with PAD first present to respiratory clinicians

Immunologists managing PAD encounter respiratory acute and chronic respiratory complications

MDT working

# PID: Diagnostic Delay

Severe  
Persistent  
Unusual  
Recurrent



*15<sup>th</sup> Century, Catalonian; Metropolitan Museum of Art*

## Acute Infections

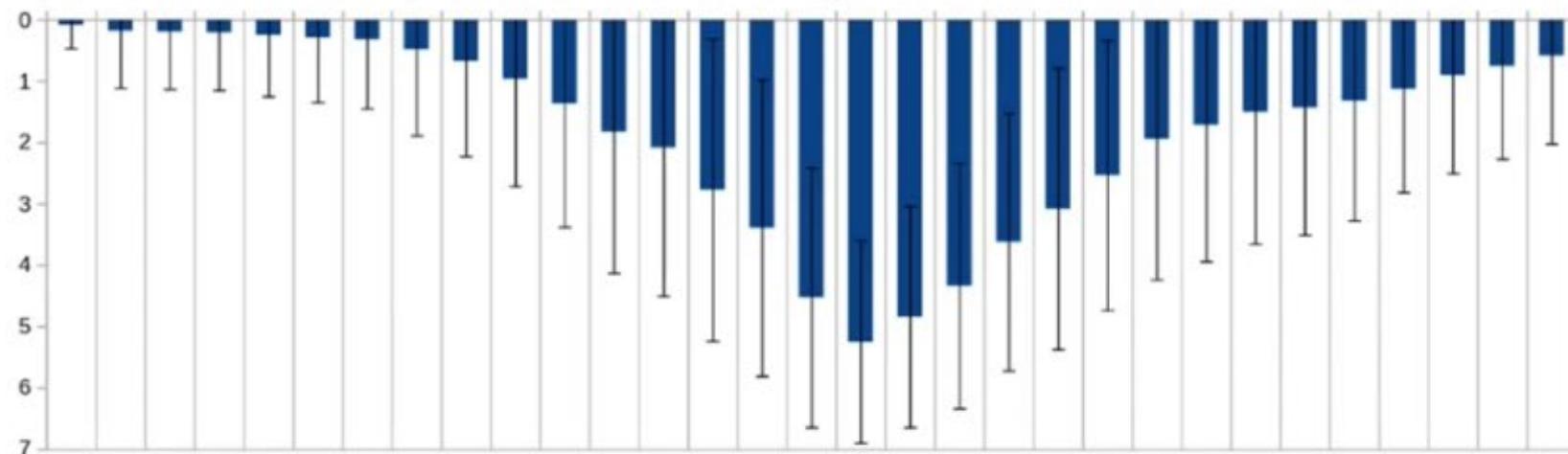
Prior to diagnosis

Whilst on immunoglobulin replacement (IV/SC)

- ▶ Prophylactic antibiotics commonly employed
- ▶ May need longer courses of antimicrobials

# The Biology of Acute Infections

Time (d)	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
URTS (%)	3	4	6	6	6	7	7	7	8	14	22	29	32	45	53	75	84	76	68	53	42	41	34	33	31	31	31	25	18	11	8	
Sore Throat (%)	0	1	1	1	1	1	1	1	3	4	8	14	16	18	22	29	41	45	38	32	28	23	16	11	11	8	7	4	4	3	3	3
Cough (%)	6	7	7	7	8	8	8	11	14	21	29	32	34	44	58	71	87	86	77	64	56	42	36	33	31	29	29	28	24	22	17	
Short of Breath (%)	1	1	1	3	4	4	4	7	7	10	11	15	16	16	25	26	37	43	39	30	28	26	22	18	18	15	14	13	13	11	10	7
Wheeze (%)	0	0	0	0	0	0	0	0	0	4	4	10	12	15	21	28	34	29	24	22	19	12	12	12	8	8	7	6	4	3	3	
White Sputum (%)	0	0	0	0	0	1	1	3	3	5	7	11	11	10	12	17	18	17	20	22	19	19	12	8	7	7	4	4	4	3		
Purulent Sputum (%)	0	1	1	1	1	1	3	4	8	8	15	19	25	37	48	59	66	67	59	43	34	27	15	11	10	8	7	7	4	4	4	
Increased Sputum Volume (%)	0	1	1	1	3	3	3	7	11	12	21	27	33	45	59	74	82	80	73	59	55	47	27	19	17	15	14	11	8	7	7	
OAT (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	100	100	99	99	96	93	75	72	68	64	60	58	56	10	
TSC Mean	0.1	0.2	0.2	0.2	0.2	0.3	0.3	0.5	0.7	1.0	1.4	1.8	2.1	2.8	3.4	4.5	5.3	4.8	4.3	3.6	3.1	2.5	1.9	1.7	1.5	1.4	1.3	1.1	0.9	0.8	0.6	
TSC SD	0.4	0.9	0.9	0.9	1.0	1.1	1.1	1.4	1.5	1.8	2.0	2.3	2.4	2.5	2.4	2.1	1.7	1.8	2.0	2.1	2.3	2.2	2.3	2.2	2.2	2.1	2.0	1.7	1.6	1.5	1.4	

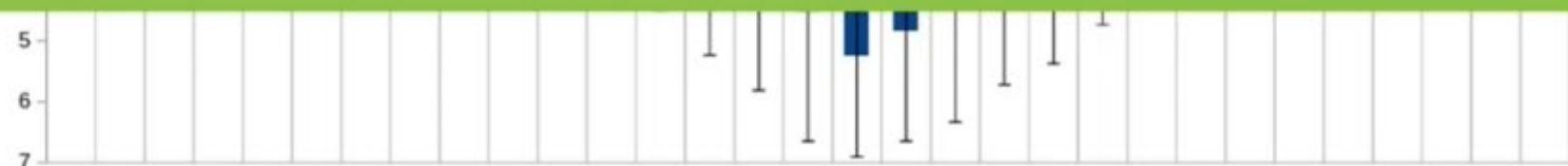


# The Biology of Acute Infections

Time (d)	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
URTS (%)	3	4	6	6	6	7	7	7	8	14	22	29	32	45	53	75	64	76	68	53	42	41	34	33	31	31	31	25	18	11	8
Sore Throat (%)	0	1	1	1	1	1	1	3	4	8	14	16	18	22	29	41	45	38	32	28	23	16	11	11	8	7	4	4	3	3	3
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Short of Breath (%)	1	1	1	3	4	4	4	7	7	10	11	15	16	25	26	37	43	39	30	28	26	22	18	18	15	14	13	13	11	10	7
Wheeze (%)	0	0	0	0	0	0	0	0	0	4	4	10	12	15	21	28	34	29	24	22	19	12	12	12	8	8	7	6	4	3	3
White Sputum (%)	0	0	0	0	0	1	1	3	3	5	7	11	11	10	12	17	18	17	20	22	19	19	12	8	7	7	4	4	4	3	
Purulent Sputum (%)	0	1	1	1	1	1	3	4	8	8	15	19	25	37	48	59	66	67	59	43	34	27	15	11	10	8	7	7	4	4	4
Increased Sputum Volume (%)	0	1	1	1	3	3	3	7	11	12	21	27	33	45	59	74	82	80	73	59	55	47	27	19	17	15	14	11	8	7	7
OAT (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	100	100	100	99	98	97	96	95	94	93	92	91	90	10

Strongest symptomatic predictors for commencing antibiotics were cough, shortness of breath, and purulent sputum.

There was a median delay of 5 days from the onset of symptoms to commencing antibiotics.



## Micro-Organisms at Exacerbations in CVID

A: Viral PCR on nasopharyngeal swabs in 54 respiratory exacerbations in patients with CVID.

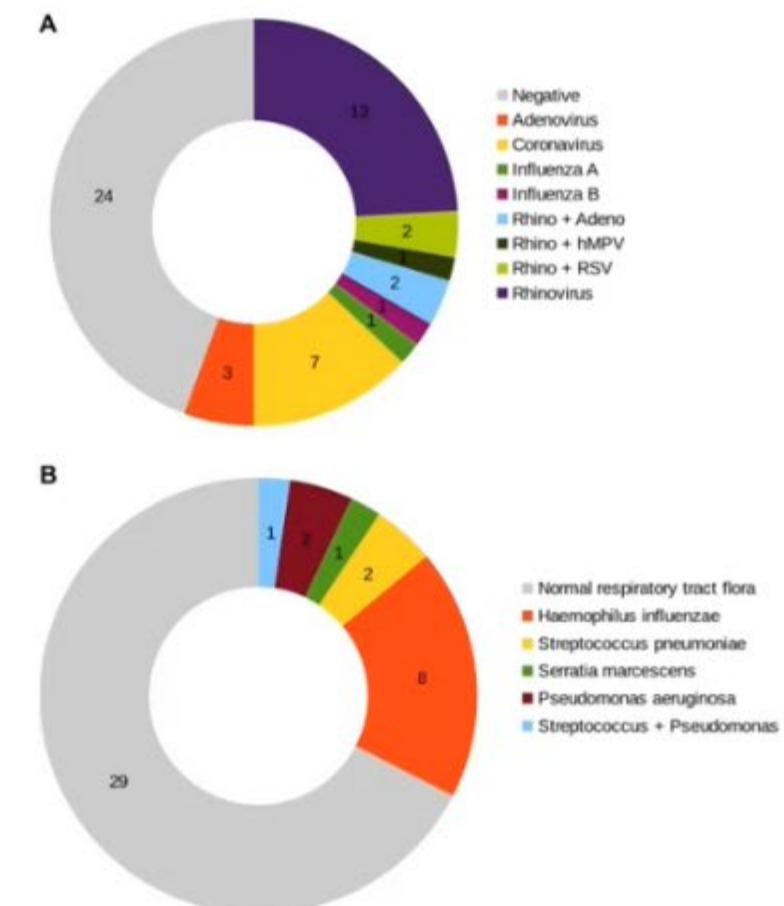
No pathogen (gray) was found in 24 (44%) exacerbations.

**A pathogenic virus was found in 30 (56%).**

Rhinovirus was found in 18 (33%) exacerbations.

B: Bacterial culture on spontaneous sputum in 43 respiratory exacerbations in patients with CVID.

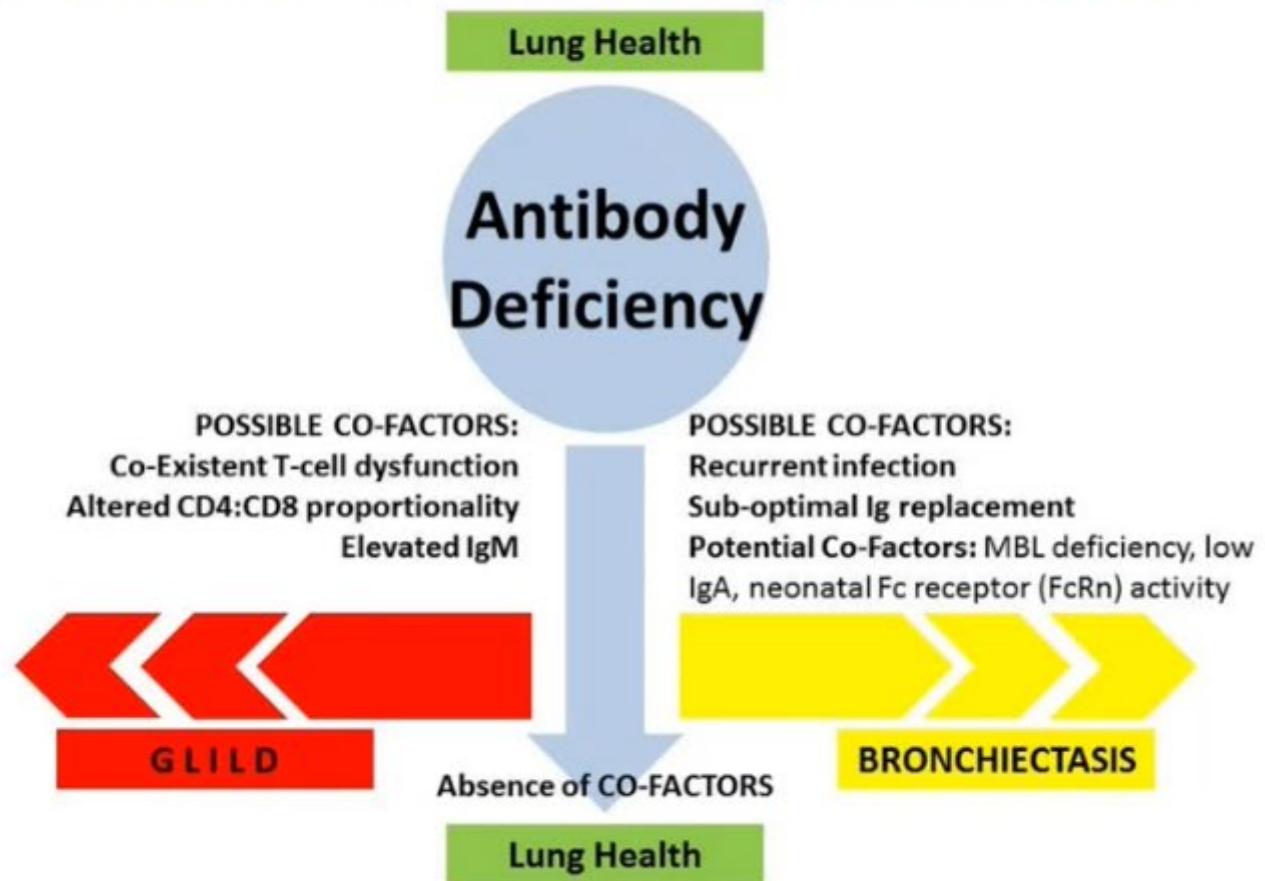
No pathogen (gray) was found in 29 (67%) exacerbations. A pathogenic bacterium was found in 14 (33%) exacerbations.



## Treatment of Acute Infections

- Guided by last microbiology where possible
- Send a sputum prior to therapy
- Longer course (day 14), higher dose (eminence-based medicine)
- Co-Amoxiclav reasonable first choice
  - *Haemophilus influenzae*, *Streptococcus pneumoniae*
- BAL if not resolving
- Think virus / PCP etc if cell-mediated component
- Not the same class as the prophylactic
- Most people stop the prophylactic during acute treatment

# Chronic Lung Disease in PAD Syndromes



# Bronchiectasis

Defined as permanent dilatation of the airway

“Clinically Significant” implies symptoms +/- exacerbations

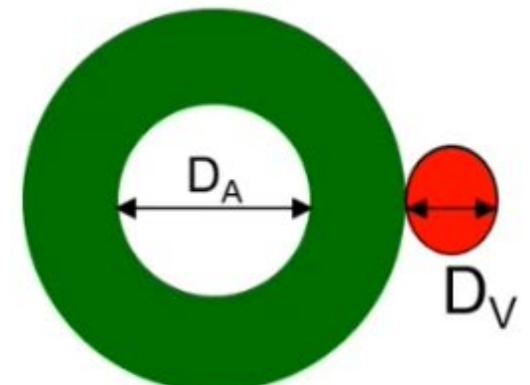
Internal diameter of airway > accompanying vessel ( $D_A > D_V$ ): signet rings

Wall thickening

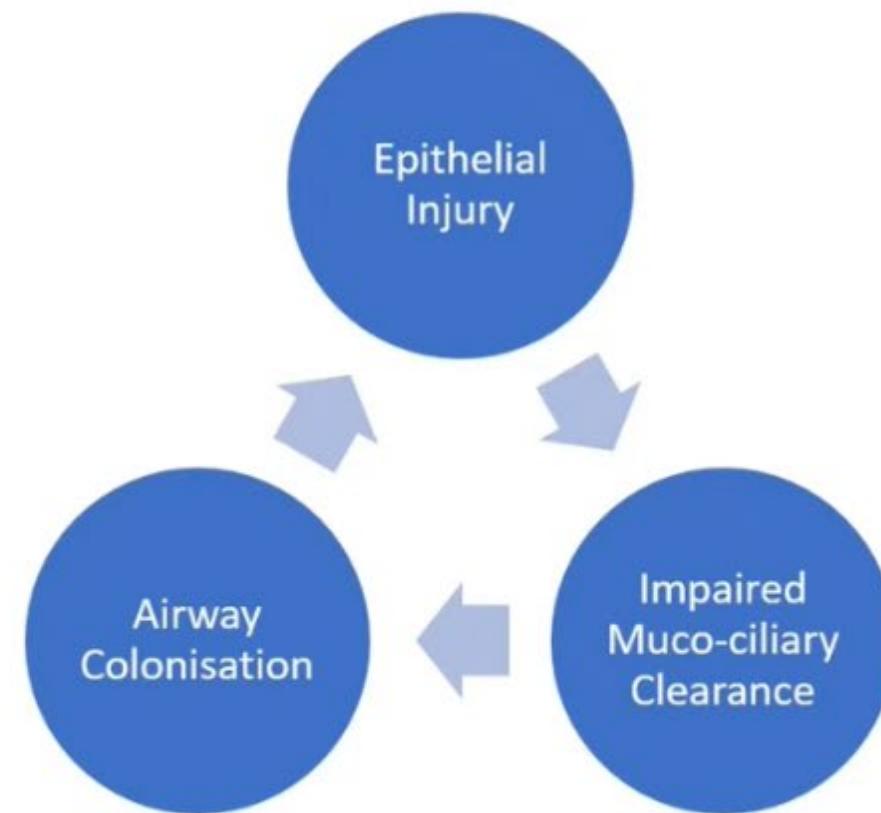
Non-tapering bronchi: tram lines

Mucus plugging

Visible in outer 1cm of lung

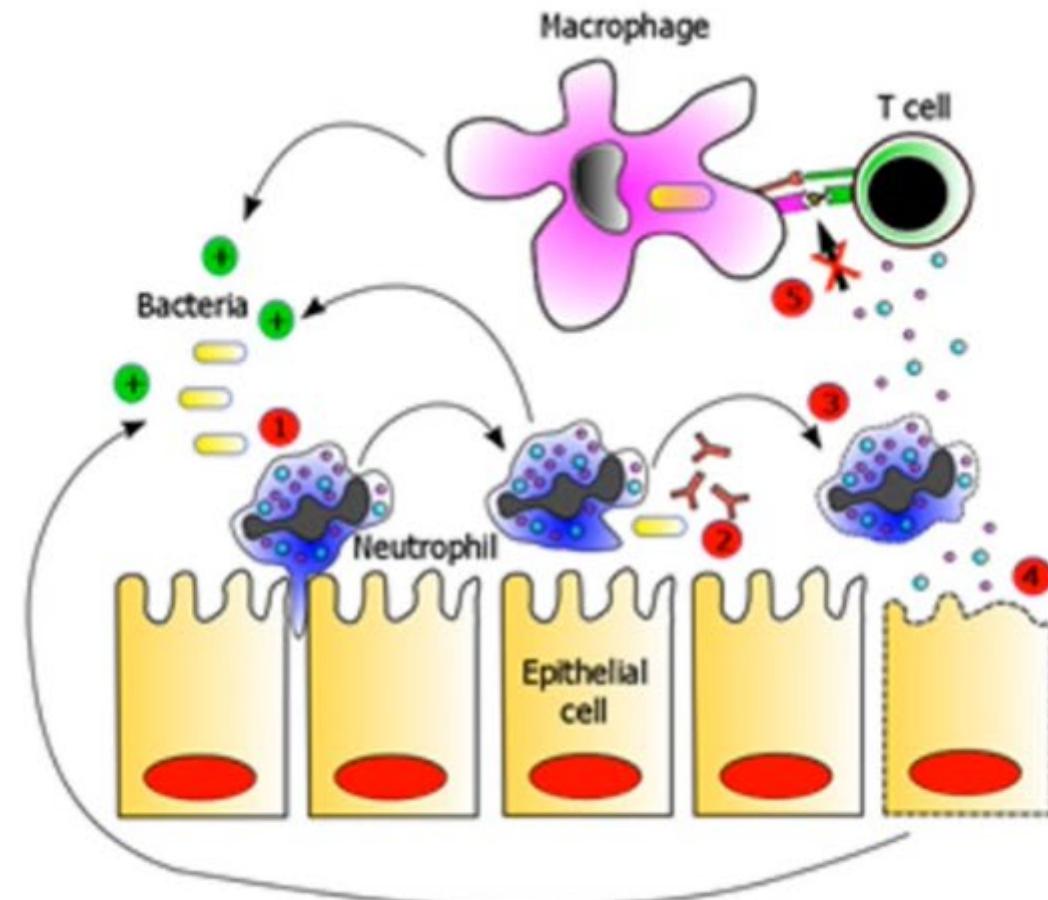


# The Vicious Cycle (Vortex) Hypothesis



## Mechanism of Bronchiectasis in PAD

- 1: Neutrophils recruited to the airway in response to bacteria.
- 2: Inadequate antibody response leads to frustrated phagocytosis.
- 3: Neutrophils release granule contents and die *in situ*, damaging bystander epithelial cells...
- 4: ...impairing the development of acquired immune responses and...
- 5: ...recruiting more neutrophils to perpetuate the pathological cycle.



## Paradox: 'IgA provides airway mucosal defence'

Selective IgA deficiency is less severe than IgG deficiencies

Systemic IgG reduces respiratory infection frequency

*BUT:*

Low systemic IgA a risk for infection on Ig replacement

## Aims of Treatment

Minimise symptoms

Minimise exacerbations

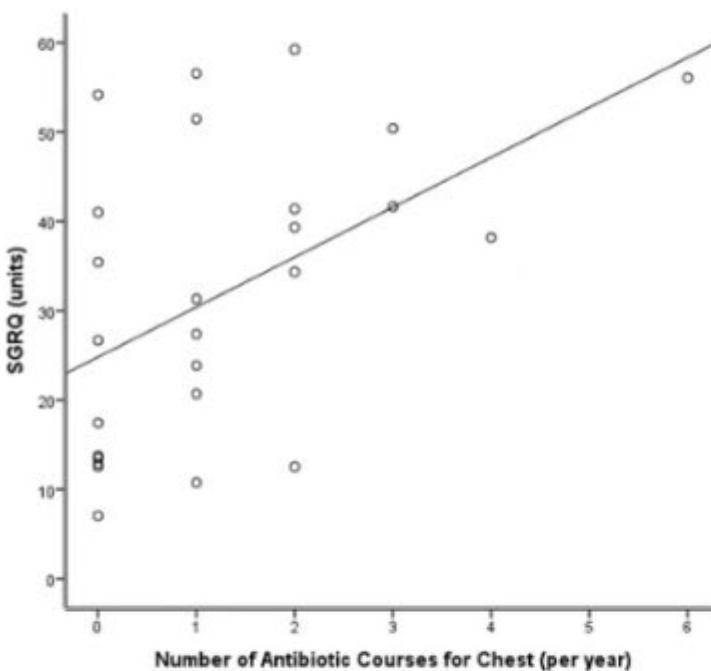
Maximise functional capacity

(thereby improving quality of life)

Maximise lung function

Prevent structural progression

# Effect of Respiratory Infection on Health Status



Respiratory health-status relates to:

- lung function impairment
- Breathlessness
- infection frequency

(but not CT score)

## Aims of Treatment

Minimise symptoms

Minimise exacerbations

Maximise functional capacity

(thereby improving quality of life)

Maximise lung function

Prevent structural progression

**CVID:**

Annual spirometry and gas transfer

5 yearly screening CT

Sputum surveillance

# Microbiome in Bronchiectasis

## ORIGINAL RESEARCH

### A Novel Microbiota Stratification System Predicts Future Exacerbations in Bronchiectasis

Gernot B. Rogers<sup>1</sup>, Nur Masirah M. Zain<sup>2</sup>, Kenneth D. Bruce<sup>3</sup>, Lucy D. Burr<sup>2</sup>, Alice C. Chen<sup>1</sup>, Damian W. Rivett<sup>3</sup>, Michael A. McGuckin<sup>1</sup>, and David J. Senier<sup>1,4\*</sup>

<sup>1</sup>Immunity, Infection, and Inflammation Program, Mater Research Institute, University of Queensland, and Translational Research Institute, Woolloongabba, Queensland, Australia; <sup>2</sup>Institute of Pharmaceutical Science, King's College London, and <sup>3</sup>Division of Ecology and Evolution, Department of Life Sciences, Imperial College London, London, United Kingdom; and <sup>4</sup>Department of Respiratory Medicine, Mater Adult Hospital, South Brisbane, Australia

#### Abstract

**Rationale:** Although airway microbiota composition correlates with clinical measures in non-cystic fibrosis bronchiectasis, these data are unlikely to provide useful prognostic information at the individual patient level. A system enabling microbiota data to be applied clinically would represent a substantial translational advance.

**Objectives:** This study aims to determine whether stratification of patients according to the predominant microbiota can provide improved clinical insight compared with standard diagnostics.

**Methods:** The presence of bacterial respiratory pathogens was assessed in induced sputum from 107 adult patients by culture, quantitative PCR, and, in 96 samples, by ribosomal gene pyrosequencing. Prospective analysis was performed on samples from 42 of these patients. Microbiological data were correlated with concurrent clinical measures and subsequent outcomes.

**Measurements and Main Results:** Microbiota analysis defined three groups: *Pseudomonas aeruginosa* dominated ( $n = 24$ ), *Haemophilus influenzae* dominated ( $n = 34$ ), and other taxa

dominated ( $n = 36$ ). Patients with *P. aeruginosa*- and *H. influenzae*-dominated communities had significantly worse lung function, higher serum levels of C-reactive protein (CRP), and higher sputum levels of IL-8 and IL-16. Predominance of *P. aeruginosa*, followed by *Haemophilus* species, was the best predictor of future exacerbation frequency, with *H. influenzae*-dominated communities having significantly fewer episodes. Detection of *P. aeruginosa* was associated with poor lung function and exacerbation frequency, irrespective of analytical strategy. Quantitative PCR revealed significant correlations between *H. influenzae* load and sputum IL-8, IL-16, and serum CRP. Genus richness was negatively correlated with 24-hour sputum weight, age, serum CRP, sputum IL-1β, and IL-8.

**Conclusion:** Stratification of patients with non-cystic fibrosis bronchiectasis on the basis of predominant bacterial taxa is more clinically informative than either conventional culture or quantitative PCR-based analysis. Further investigation is now required to assess the mechanistic basis of these associations.

**Keywords:** prognostic markers; airway inflammation; microbiome

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\*Joint senior authors.

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Author Contributions G.B.R., N.M.Z., K.D.B., L.D.B., A.C.C., D.W.R., M.A.M., D.J.S. all contributed to the conception, execution, analysis, and reporting of this study, and approved the final version. G.B.R. acts as the guarantor of the manuscript.

Correspondence and requests for reprint should be addressed to Gernot B. Rogers, PhD, Mater Medical Research Institute, Translational Research Institute, 37 Kent Street, Woolloongabba, QLD 4102, Australia. E-mail: gernot@qimr.edu.au

This article has an online supplement, which is accessible from this issue's table of contents online at [www.atsjournals.org](http://www.atsjournals.org).

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DOI: 10.1165/lung.00757.201310-289OC

Internet address: [www.atsjournals.org](http://www.atsjournals.org)

The pathophysiology of non-cystic fibrosis (CF) bronchiectasis is generally considered to be characterized by an airway inflammatory response to chronic

bacterial infection (1). An association between high bacterial load (as determined by culture-based approaches) and systemic inflammation, airway

inflammation, and a greater risk of exacerbations (2) appears to support this hypothesis. However, although *Pseudomonas aeruginosa* infection is

Induced sputum in 96 patients, classified as:

*Pseudomonas* dominated

*Haemophilus* dominated

Other

*Pseudomonas* or *Haemophilus* dominant: -greater airway and systemic inflammation

Genus richness negatively correlated with airway and systemic inflammation

Multiple regression indicated that *Ps. aeruginosa* predominance was the best predictor of exacerbation frequency ( $\beta = 0.501$ ,  $p < 0.001$ ).

Other studies: further dysbiosis at exacerbation (not studies in PAD).

**“Any dominance is bad”?**

# Management of Bronchiectasis

**Treat the cause (IVIG)**

**Targeted physiotherapy**

**Exercise ?PR**

**Attention to Respiratory Exposures: smoking**

**Prompt treatment of infections**

**(?) Antibiotic prophylaxis**

**(?) Bronchodilators**

**(?) Mucolytics**

**Consideration of oxygen / NIV / transplant as appropriate**

**(Not inhaled corticosteroids)**



TASK FORCE REPORT  
ERS GUIDELINES

## European Respiratory Society guidelines for the management of adult bronchiectasis

Eva Polverino<sup>1</sup>, Pieter C. Goeminne<sup>2,3</sup>, Melissa J. McDonnell<sup>4,5,6</sup>,  
Stefano Alberti<sup>7</sup>, Sara E. Marshall<sup>8</sup>, Michael R. Loebinger<sup>9</sup>,  
Marlene Murris<sup>10</sup>, Rafael Cantón<sup>11</sup>, Antoni Torres<sup>12</sup>, Katerina Dimakou<sup>13</sup>,  
Anthony De Soto<sup>14,15</sup>, Adam T. Hill<sup>16</sup>, Charles S. Haworth<sup>17</sup>,  
Montserrat Vendrell<sup>18</sup>, Felix C. Ringshausen<sup>19</sup>, Dragos Subotic<sup>20</sup>,  
Robert Wilson<sup>21</sup>, Jordi Vilard<sup>22</sup>, Björn Stålberg<sup>23</sup>, Tobias Weite<sup>24</sup>,  
Gernot Rohde<sup>25</sup>, Francesco Blasi<sup>26</sup>, Stuart Elborn<sup>2,3</sup>, Marta Almagro<sup>27</sup>,  
Alan Timothy<sup>28</sup>, Thomas Ruddy<sup>29</sup>, Thom Yonan<sup>29</sup>, David Rigau<sup>27</sup> and  
James D. Chalmers<sup>28</sup>

#ERSpublications  
The publication of the first ERS guidelines for bronchiectasis <http://tiny.cc/mey8wq>

Cite this article as: Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017; 50: 1700629 (<https://doi.org/10.1111/ers.13629>).

**ABSTRACT** Bronchiectasis in adults is a chronic disorder associated with poor quality of life and frequent exacerbations in many patients. There have been no previous international guidelines.

The European Respiratory Society guidelines for the management of adult bronchiectasis describe the appropriate investigation and treatment strategies determined by a systematic review of the literature.

A multidisciplinary group representing respiratory medicine, microbiology, physiotherapy, thoracic surgery, primary care, methodology and patients considered the most relevant clinical questions (for both clinicians and patients) related to management of bronchiectasis. Nine key clinical questions were generated and a systematic review was conducted to identify published systematic reviews, randomised clinical trials and observational studies that assessed these questions. We used the GRADE approach to define the quality of the evidence and the level of recommendations. The resulting guideline addresses the investigation of underlying causes of bronchiectasis, treatment of exacerbations, palliative medication, long term antibiotic treatment, anti-inflammatories, mucolytic drugs, bronchodilators, surgical treatment and respiratory physiotherapy.

These recommendations can be used to benchmark quality of care for people with bronchiectasis across Europe and to improve outcomes.

This article has supplementary material available from [erj.ersjournals.com](http://erj.ersjournals.com)

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The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

This document was endorsed by the ERS Executive Committee and by the European Society of Clinical Microbiology and Infectious Disease in August 2017.

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# Macromania

## 3 RCTs of macrolide in bronchiectasis

EMBRACE<sup>1</sup>: azithromycin 500mg x3 week; n=141, 6/12  
**62% exacerbation reduction**

BAT<sup>2</sup>: azithromycin 250mg daily; n=83, 12/12  
**71% exacerbation reduction and improved quality of life**

BLESS<sup>3</sup>: erythromycin 250mg BD; n=117, 48/52  
**43% exacerbation reduction**

PAD..? EMBRACE – exclusion, BAT n=1 CVID, BLESS n=0

**Exclusion of atypical Mycobacteria**

**Deafness and qTC**

**Mechanism?**

**Avoid prophylactic ciprofloxacin**

1. Wong C et al. *Lancet* 2012;380:660-667
2. Altenburg J et al. *JAMA* 2013;309:1251-1259
3. Serisier DJ et al. *JAMA* 2013;309:1260-1267

## Emerging Treatments for Bronchiectasis

Inhaled antibiotics

Anti-virals

Hyper-osmolar agents

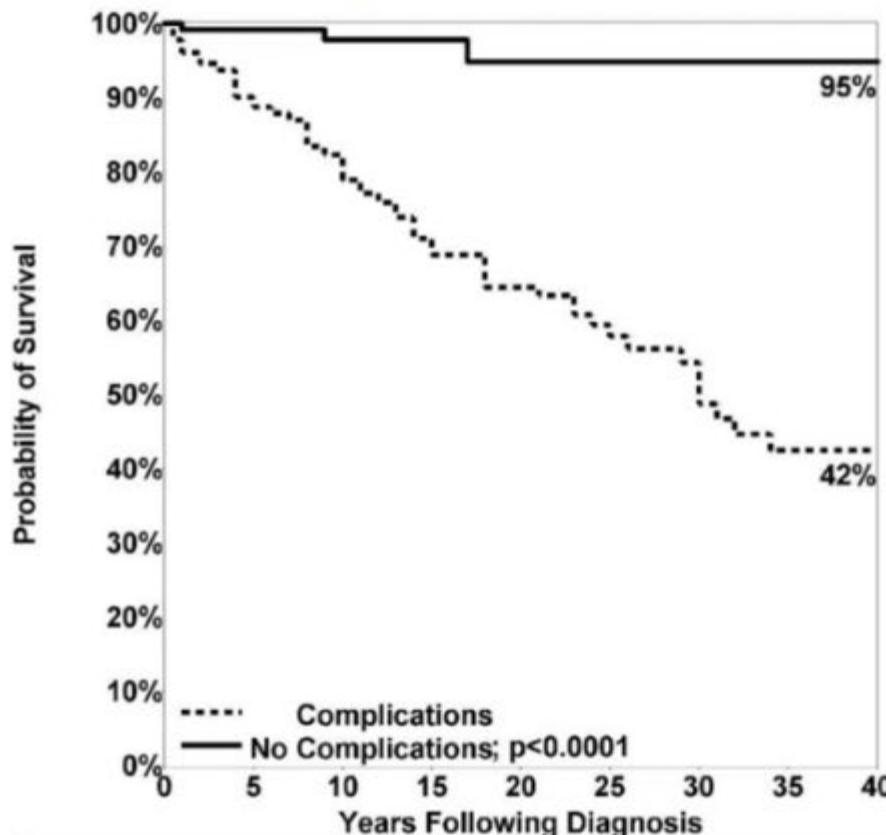
Novel anti-inflammatories (e.g. CXCR2 antagonists)

Mucolytics

Nebulised immunoglobulin

Nasal interventions

## Mortality in CVID



N=473, 40 years

Risk of death 11 times higher for patients with non-infectious complications (HR = 10.95; p<0.0001).

Mortality associated with lymphoma, hepatitis, functional or structural lung impairment, and gastrointestinal disease with or without malabsorption.

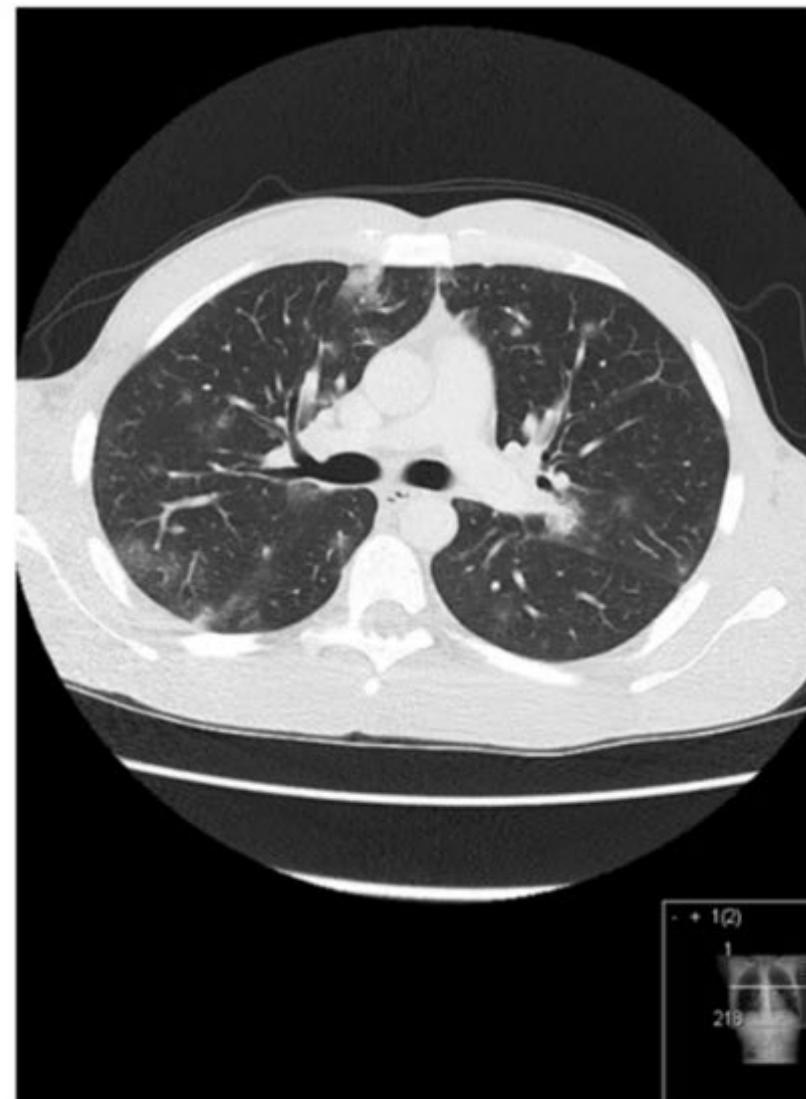
## Case

- 25 year old man presented 2012
- ITP aged 11
- ITP aged 16, given rituximab
- Frequent chest infections
- Hypogammaglobulinaemia 2012
  - criteria met for CVID
- Not breathless, no cough
- Baseline respiratory imaging abnormal



# GLILD

- **10-15% of CVID ‘Granulomatous Variant’**
  - splenomegaly, adenopathy, cytopaenias, GI and Liver disease
- **Lung Involvement**
  - Granulomas and Lymphoproliferation eg LIP, follicular bronchitis and lymphoid hyperplasia (BALT)
- **Associated genetic defects**
  - CTLA-4 / LRBA deficiency



## Aims of Treatment

Reduction of symptoms

Preservation of lung function

# GLILD: ‘eminence’ based medicine

Special Article

**British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders**

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**“GLILD is a distinct clinico-radio-pathological ILD occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded”**



e-GLILDnet  
 European Granulomatous-Lymphocytic Interstitial Lung Disease Network

# Frontiers: Histology

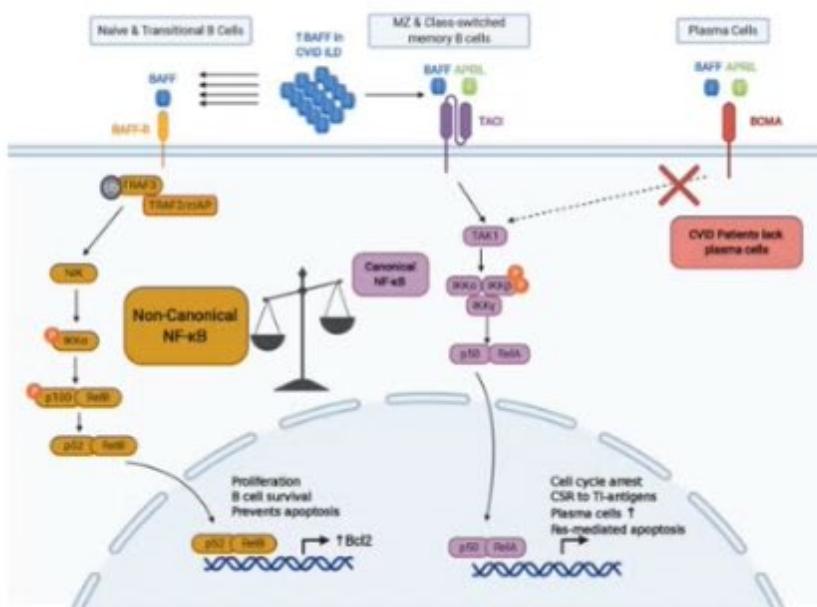
Publication (Ref)	Number of CVID patients with lung biopsies	Granulomata n (%)	Histological findings					Organizing pneumonia	Pulmonary Fibrosis
			Interstitial inflammation	Pulmonary Lymphoid Hyperplasia (Peri)bronchial inflammation	Lymphocytic infiltration	Lymphoid hyperplasia	Fibrosis		
Rao et al. <sup>*</sup> (44)	16	15 (93%)	16 (100%)	16 (100%)	NS	NS	14 (87%)	12 (75%)	6 (37%)
Patel et al. (33)	19	1 (5%)	11 (58%)	7 (37%)	15 (79%)	NS	6 (32%)	8 (42%)	3 (16%)
Maglione et al. (21)	12	3 (25%)	4 (33%)	4 (33%)	2 (17%)	4 (33%)	4 (33%)	4 (33%)	NS
Larsen et al. (47)	34	23 (68%)	12 (35%)	22 (65%)	NS	10 (29%)	25 (71%)	1 (3%)	NS
Verbsky et al.* (61)	34	31/34 (91%)	NS	33/34 (97%)	33/34 (97%)	NS	30/34 (88%)	13/34 (32%)**	NS

Only publications with sufficient histological detail were included; single case histories or small studies (less than 10) are not included. Rao et al. (44) and Patel et al. (33) reported their findings in similar terms, but these varied in other publications. Efforts were made to group similar findings on the basis on similar histological terms in these instances. Where detail for a given finding was not specified (NS), this is also indicated. \*Where the inclusion of previously published cases in a paper could not be completely excluded. \*\* on CT not reported on histology.

Summarises the literature on the histology of CVID-related ILD and factors that may contribute to the inter- and intra-patient variability in the histological patterns.

Need for standardisation of histological assessments and reporting, together with a better understanding of the immunopathogenesis of CVID-related ILD to resolve the apparent heterogeneity of ILD in guide the selection of rational targeted therapies in different patients.

# Frontiers: B Cell Dysregulation



Dysregulated B cell responses, such as those exacerbated by BAFF, promote the progression of ILD in CVID.

This is supported by the adoption of B cell depleting therapy, either alone or in combination with other immunosuppression, as a fundamental component of CVID ILD treatment.

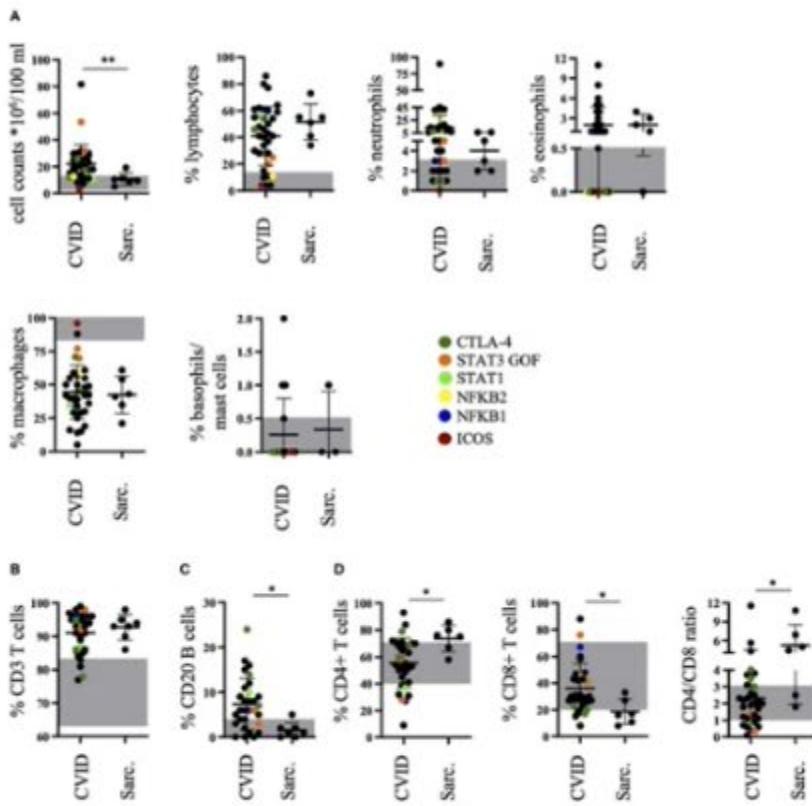
Continued suppression of B cell activation through administration of immunosuppressive antimetabolite agents such as azathioprine or mycophenolate, or potentially through inhibition of BAFF may help maintain CVID ILD in remission.

B cell hyperplasia is a defining aspect of CVID ILD and is perpetuated *via* survival signals mediated by BAFF through BAFF-R.

In addition to B cells, CVID ILD consists of prominent T cell infiltration which appears to also improve with B cell depleting therapy.

The link between B cells and T cells in the CVID lungs remains undefined, and whether depletion of B cells removes a vital antigen-presenting cell, lymphoid structure, source of chemokines, and/or another component required for T cell recruitment and persistence in the lungs is unknown.

# Frontiers: BALF in GLILD



B cells are expanded in BALF of CVID-ILD patients.

This is associated with an expansion of  $T_{FH}$ - and  $T_{PH}$ -like cells and an increase in APRIL potentially supporting B-cell survival and differentiation and proinflammatory cytokines reflecting not only the previously described  $T_H1$  profile seen in CVID patients with secondary immune dysregulation.

Thus, the analysis of BALF might be of diagnostic value not only in the diagnosis of CVID-ILD, but also in the evaluation of the activity of the disease and in determining potential treatment targets confirming the prominent role of B-cell targeted strategies.

# Is optimisation of Ig sufficient?

**CASE REPORT**

Lymphocytic interstitial pneumonia associated with common variable immunodeficiency resolved with intravenous immunoglobulins

N Arish, R Edor, Y Fellig, N Bogot, U Laxer, U Izhar, A Rokach

Respir 2006; 81: 1096–1097. doi: 10.1191/rs.2004.039819

**Abstract**

Lymphocytic interstitial pneumonia (LIP) is a rare form of interstitial lung disease. A few case reports have described an association with common variable immunodeficiency (CVID). Corticosteroids are usually used to treat symptomatic patients but their efficacy has never been studied in a controlled trial. We describe a patient with LIP and CVID who was treated monthly with intravenous immunoglobulins (IVIG) without steroids. The patient improved dramatically. We believe that, in selected cases of LIP and immunodeficiency, IVG given monthly should be considered as the only treatment without adding steroids.

**Introduction**

Lymphocytic interstitial pneumonia (LIP) is by definition a destructive lymphoid infiltrate which occurs most commonly in the alveolar septa but occasionally appears along bronchi and vessels. It may occur in association with a number of conditions including BHD in children, primary immunodeficiency, Sjögren's syndrome, sarcoidosis, grafts and dysplastic nodules, sarcoid, histoplasmosis and lymphangiomyomatosis. Lymphocytic-interstitial pneumonitis occurs in about 10% of adults with this condition and the association of LIP with common variable immunodeficiency (CVID) has been described.<sup>1</sup>

The optimal treatment for LIP is not well established. Most patients are treated with prolonged courses of corticosteroids. We describe a patient who was not treated with steroids.

**CASE REPORT**

A 66 year old woman was admitted to the internal medicine ward for evaluation of worsening dyspnoea, fever, and productive cough. An antibiotic trial with amoxicillin-clavulanic acid and aztreonam given by the family physician did not help. One year before admission the patient developed recurrent episodes of sinusitis, pneumonia and bronchitis. A work-up done by the family physician revealed CVID with low levels of IgA and IgG.

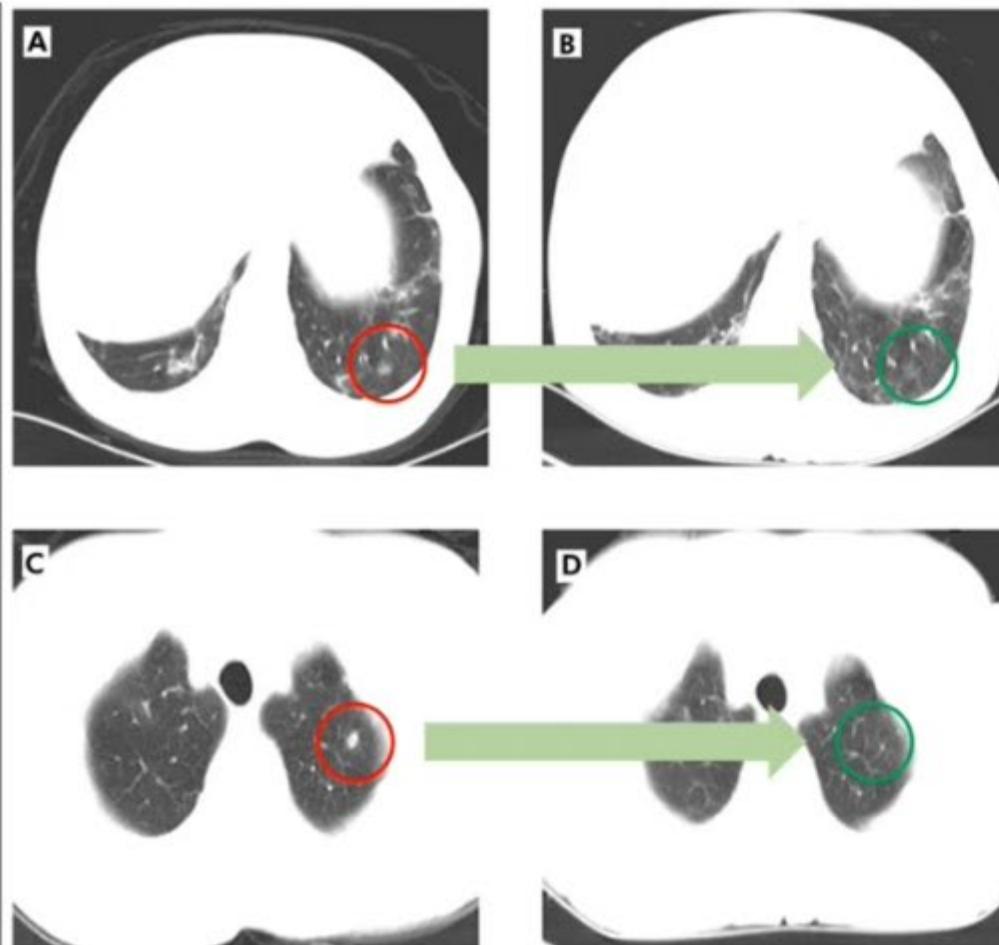
On admission the physical examination was normal with no clinical signs of Sjögren's syndrome or other autoimmune diseases. The sputum was 94% and the sputum were clear. Complete blood count, chemistry panel, liver function tests, and electrolytes were normal. Hemoglobin was 13.5 g/dl, PCV, 4.27 kPa (32 mm Hg), HCO<sub>3</sub>, 22.3 mmol/l, and pH 7.46. Antinuclear antibody, C-ANCA, P-ANCA, and rheumatoid factor were all negative. HIV and EBV serological tests were negative. The level of IgM was less than 42 mg/dl (normal 90–480) and the level of IgG<sub>2</sub> was 86 mg/dl (normal 138–394). The levels of other immunoglobulins were within normal limits.

**DISCUSSION**

We describe a patient suffering from CVID and LIP. Monoclonality in the cell population, which would support a diagnosis of lymphoma, was excluded. The patient was treated with IVIG without steroids.

The optimal treatment for LIP is not well established and there are no controlled trials. However, most patients are treated with prolonged courses of corticosteroids which may control the process or induce remission. Pogos et al<sup>2</sup> described two patients with LIP associated with CVID who were treated with IVIG, both of whom died after severe infections. They

**Abbreviations:** BOOP, bronchiolitis obliterans organizing pneumonia; CVID, common variable immunodeficiency; IVIG, intravenous immunoglobulin; LIP, lymphocytic interstitial pneumonia.



# Is optimisation of Ig sufficient?

1096

**CASE REPORT**

**Lymphocytic interstitial pneumonia associated with common variable immunodeficiency resolved with intravenous immunoglobulins**

N Arish, R Eldor, Y Fellig, N Bogot, U Laxer, U Izhar, A Rokach

*Breath* 2006;45:1096-1097. doi: 10.1136/breath.2004.029819

**Abstract** Lymphocytic interstitial pneumonia (LIP) is a rare form of interstitial lung disease. A few case reports have described an association with common variable immunodeficiency (CVID). Corticosteroids are usually used to treat symptomatic patients, but their efficacy has never been studied in a controlled trial. We describe a patient with LIP and CVID who was successfully treated with intravenous immunoglobulins (IVIG) without steroids. The patient improved dramatically. We believe that, in selected cases of LIP and immunodeficiency, IVIG given monthly should be considered as the only treatment without adding steroids.

**Lymphocytic interstitial pneumonia (LIP)** is a rare form of interstitial lung disease. A few case reports have described an association with common variable immunodeficiency (CVID). Corticosteroids are usually used to treat symptomatic patients, but their efficacy has never been studied in a controlled trial. We describe a patient with LIP and CVID who was successfully treated with intravenous immunoglobulins (IVIG) without steroids. The patient improved dramatically. We believe that, in selected cases of LIP and immunodeficiency, IVIG given monthly should be considered as the only treatment without adding steroids.

**Introduction** Lymphocytic interstitial pneumonia (LIP) is by definition a chronic, slowly developed infection which occurs mainly in the alveolar septa but occasionally appears along bronchi and vessels.<sup>1</sup> It may occur in association with a number of conditions including HIV in children, primary immunodeficiency, Sjögren's syndrome, sarcoidosis, granulomatous diseases,<sup>2</sup> and dysproteinemic states including hyper- and hypogammaglobulinemia.<sup>3</sup> Hypogammaglobulinemia occurs in about 10% of adults with this condition and the association of LIP with common variable immunodeficiency (CVID) has been described.<sup>4</sup>

The optimal treatment for LIP is not well established. Most patients are treated with prolonged courses of corticosteroids. We describe a patient who was not treated with steroids.

**CASE REPORT**

A 56 year old woman was admitted to the internal medicine ward for evaluation of worsening dyspnoea, fever, and productive cough. An antibiotic trial with amoxicillin-clavulanic acid and aztreonam was initiated because her symptoms did not help. One year before admission the patient developed recurrent episodes of asthenia, pneumonia, and bronchitis. A working-dose by the family physician revealed CVID with low levels of IgG and IgM.

**DISCUSSION**

We describe a patient suffering from CVID and LIP. Monoclonal IgG in the cell populations, which would support a diagnosis of lymphoma, was excluded. The patient was treated with IVIG without steroids.

The optimal treatment for LIP is not well established and there are no randomised trials. In most cases, treatments are focused with prolonged courses of corticosteroids which may control the process or induce remission. Rajan *et al* described two patients with LIP associated with CVID who were treated with IVIG, both of whom did after severe infections. They

**Abbreviations:** LIP, lymphocytic interstitial pneumonia; CVID, common variable immunodeficiency; IgG, immunoglobulin G; IgM, immunoglobulin M.

## Development of pulmonary abnormalities in patients with common variable immunodeficiency: associations with clinical and immunologic factors

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**Background:** Patients with common variable immunodeficiency (CVID) have low serum IgG, IgA, and/or IgM levels and recurrent airway infections. Radiologic pulmonary abnormalities and impaired function are common complications. It is unclear to what extent IgG replacement treatment prevents further pulmonary damage and how factors beside infections may contribute to progression of disease.

**Objectives:** To study the development of pulmonary damage and determine how clinical and immunologic factors, such as serum IgG, may contribute to possible changes.

**Methods:** In a retrospective, longitudinal study of 54 patients with CVID already treated with immunoglobulins, we examined changes of lung function and findings on high-resolution computed tomography (HRCT), obtained at 2 time points (the date of the last IgG infusion, function test, and HRCT scan performed before April 2005 [T1] and the date of the measurement performed closest to 5 years earlier [T0], 2 to 2 years apart and expressed patient refills to clinical and immunologic factors such as levels of IgG, tumor necrosis (TNF-α), and mannose-binding lectin (MBL) in serum.

**Results:** Despite a mean (SD) serum IgG level of 7.6 (2.5) g/L for all the patients during the entire study period, lung function decreased from T0 to T1. The combination of a low serum IgA level and serum MBL was associated with the presence of bronchiectasis and lower lung function and with worsening of several HRCT abnormalities from T0 to T1. Increased serum levels of TNF-α were related to deterioration of gas diffusion. A mean serum IgG level less than 5 g/L between T0 and T1 was associated with worsening of linear and/or irregular opacities seen on HRCT.

**Conclusion:** For a period of 4 years, lung function and HRCT deteriorated in CVID patients treated with immunoglobulins.

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## INTRODUCTION

Common variable immunodeficiency (CVID) is a heterogeneous syndrome characterised by failure of B-cell differentiation and defective immunoglobulin production, leading to recurrent bacterial infections, particularly in the respiratory

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n=54  
ON Ig

# First Line Therapy

	Symptoms	Lung Function	Lung Function Trajectory	% agree Rx
✓	Symptomatic	Abnormal	Deteriorating	Consensus: 100%
✓	Asymptomatic	Abnormal	Deteriorating	Consensus: 100%
✓	Symptomatic	Normal	Deteriorating	Consensus: 81%
	Symptomatic	Normal	Stable	no consensus
	Symptomatic	Abnormal	Stable	no consensus
	Asymptomatic	Normal	Deteriorating	no consensus
	Asymptomatic	Abnormal	Stable	no consensus
✗	Asymptomatic	Normal	Stable	Consensus: 6%

# First Line Therapy

- 90% agreed that when treatment was required, first-line should be corticosteroids alone.
- Of these 21 respondents, all but 1 preferred oral prednisone (1 preferred intravenous methylprednisolone).
- Of the 20 using oral prednisone, the minimum dose used was 10 to 20 mg/d, and the maximum 1 to 2 mg/kg/d.
- For a 70-kg subject, the median (IQR) dose was 40 (30-70) mg/d.
- For respondents using prednisone with a second agent, the 2 most commonly used second agents were azathioprine (6 respondents) and mycophenolate (4 respondents).

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<sup>21</sup>The British Lung Foundation funded this work (grant reference no. PR05037). Conflict of interest: J. R. Hurst has received research support from the British Lung Foundation. No financial conflicts of interest have been disclosed.  
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<sup>42</sup>Kellison has received research support from Imperial College Healthcare National Health Service (NHS) Trust, Chelsea & Westminster NHS Foundation Trust, and Royal Brompton & Harefield NHS Trust and has received research

# Assessing Response

Preferred test in 82% of 17 respondents was change in gas transfer ( $DL_{CO}$  and/or  $K_{CO}$ )

- 63% of 19 respondents considered a change of 10-20% significant
- 21% considered a change of 20-30% significant.

## Special Article

### **British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders**

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# Second Line Therapy

**TABLE IV.** Consensus on second-line drug therapy in GLILD

Criteria	No. of respondents	% Agree	% Disagree	Mean $\pm$ SD score*
Which of the following drugs would you consider as second-line therapy in GLILD?				
Consensus				
Azathioprine	21	100	0	0.71 $\pm$ 0.25
Rituximab	21	90	5	0.67 $\pm$ 0.40
Mycophenolate	21	81	5	0.62 $\pm$ 0.44
No consensus				
Abatacept	18	33	28	0.03 $\pm$ 0.50
Anti-TNF agents	17	29	47	-0.12 $\pm$ 0.57
Ciclosporin	16	25	25	0.00 $\pm$ 0.48
Hydroxychloroquine	19	42	32	0.07 $\pm$ 0.56
Methotrexate	17	35	29	0.03 $\pm$ 0.51
Sirolimus	18	28	28	0.03 $\pm$ 0.53
Tacrolimus	18	22	33	-0.08 $\pm$ 0.43

\*See text. Scale of -1 (strongly disagree) to +1 (strongly agree), with more extreme scores and smaller SD indicating greater consensus. Consensus defined as ≥80% agreement/disagreement.

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# Rituximab and Azathioprine

- To target B- and T-cells
- 7 patients
  - Rituximab 375 mg/m<sup>2</sup> weekly for 4/52 then repeat 4-6 monthly
  - Azathioprine / 6MP 1-2mg/kg/d
  - Mycophenolate 1g BD
- 18 months
- 5 had failed high-dose steroid
- Background Ig

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ORIGINAL RESEARCH

## Use of Combination Chemotherapy for Treatment of Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD) in Patients with Common Variable Immunodeficiency (CVID)

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### Abstract

**Purpose.** A subset of patients with common variable immunodeficiency (CVID) develop granulomatous and lymphocytic interstitial lung disease (GLILD), a restrictive lung disease associated with early mortality. The optimal therapy for GLILD is unknown. This study was undertaken to see if

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rituximab and azathioprine (combination chemotherapy) would improve pulmonary function and/or radiographic abnormalities in patients with CVID and GLILD.

**Methods.** A retrospective chart review of patients with CVID and GLILD who were treated with combination chemotherapy was performed. Complete pulmonary function

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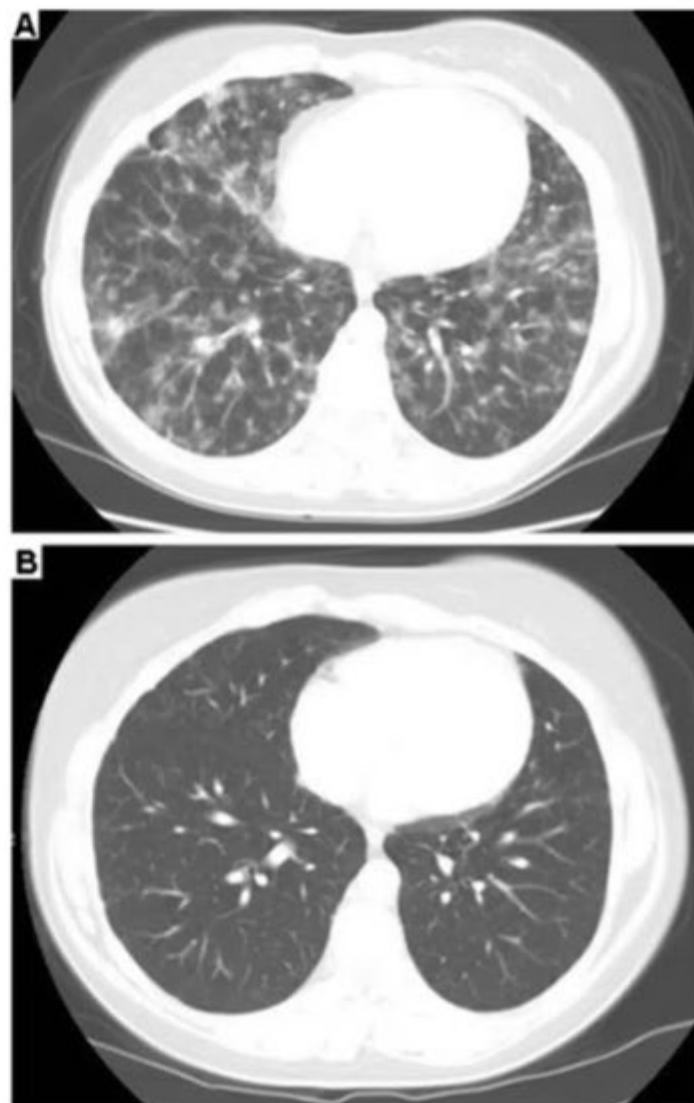
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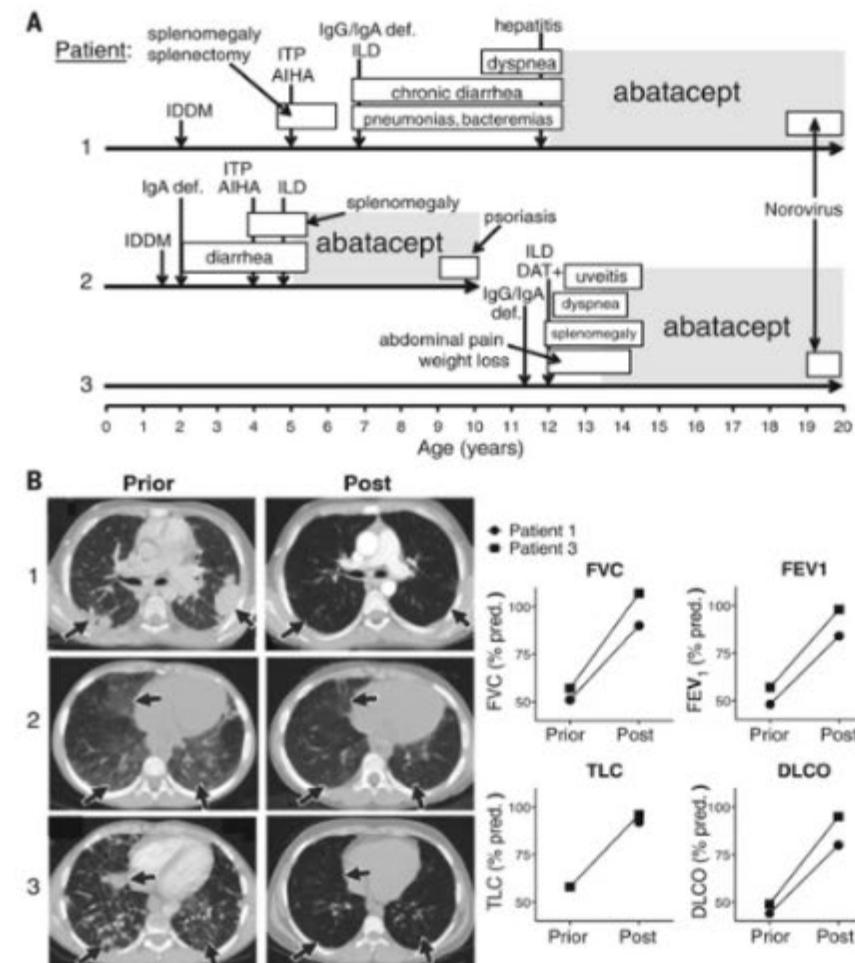
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## Rituximab and Azathioprine

- No infection concerns
  - Hepatotoxicity in one
- Improvement in radiology score
  - ?response rate 5/7 (supplementary)
  - More severe restriction
  - Longer standing disease
- Improvement in FEV<sub>1</sub> and FVC
  - Not all had gas transfer
- Long term outcomes?



## GLILD: Targeted Therapy



## (BM) Transplantation

“Mortality was higher, without reaching statistical significance, in patients with...

granulomatous organ involvement (dead vs alive: 86% vs 44%,  $P = 0.09$ )

lung disease before transplantation (dead vs alive: 63% vs 33%,  $P = 0.23$ )”

Immune deficiencies, infection, and systemic immune disorders

## Multicenter experience in hematopoietic stem cell transplantation for serious complications of common variable immunodeficiency

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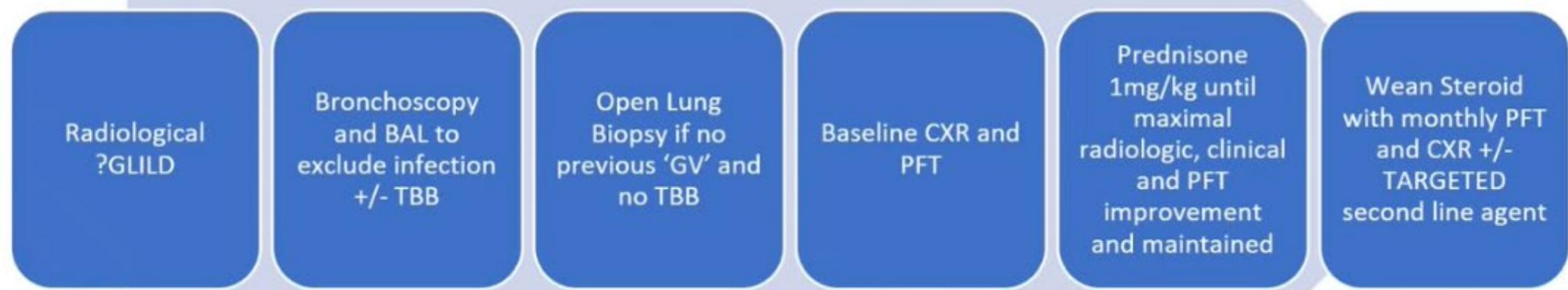
**Background:** Common variable immunodeficiency (CVID) is usually well controlled with immunoglobulin substitution and immunosuppressive drugs. A subgroup of patients has a complicated disease course with high mortality. For those patients, investigation of more invasive, potentially curative

ments, such as allogeneic hematopoietic stem cell transplantation (HSCT), is warranted.

justice. We sought to define the outcome of HSCT for children with EB.

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# GLILD: Local Protocol



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## eGLILD-net will:

- 1. establish a Europe-wide **multi-professional network** of pulmonologists, immunologists, radiologists, pathologists and AHPs, in partnership with patients and including early-career researchers.
- 2. complete a **research prioritisation process**
- 3. establish a **virtual MDT** for case discussion and work towards a prospective database of new cases that will directly improve the care of people living with GLILD, and provide a resource for future research.



## Interstitial lung disease in primary immunodeficiency: towards a brighter future

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**• e-GLILDnet:** The ERS e-GLILDnet CRC is working for better care and research for people affected by GLILD. <http://tiny.cc/meyarw>

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Long disease is a frequent clinical manifestation in people living with primary immunodeficiency diseases, the most prevalent of which are common variable immunodeficiency disorders (CVIDS). CVIDS is primarily characterized by antibody deficiency, but recent definitions and diagnostic criteria recognize a much more complex pattern of immunological defects [1]. CVIDS can be classified into two main disease phenotypes. One group of patients has chronic respiratory disease, including interstitial lung disease, while the other group has a variety of lymphoproliferative, infectious and/or autoimmune complications. The most frequent complication in the lung of CVIDS are acute infections, and secondary chronic complications of infection, such as bronchiectasis. However, up to 15% of patients with CVIDS develop an interstitial lung disease [2]. It follows that bronchiectasis are primarily driven by antibody deficiency, but CVIDS-associated interstitial lung disease is also an important part of a complex immunopathology process [3]. It is estimated that people with CVIDS-ILD often have shortened life expectancy [4], but there is no clear evidence of survival differences between CVIDS-ILD and other forms of ILD [5]. With an EU population of 707 million, we estimate there are up to 50,000 people living with CVIDS in Europe, and thus 4000 with CVIDS-ILD. While people with "induction only" CVIDS can live expect a near normal life expectancy [6], those with systemic immune dysregulation including CVIDS-ILD often have a much more complicated course. CVIDS-ILD increases morbidity and mortality in CVIDS [6], although the outcome is now recognized to be more variable than originally reported [6].

The nomenclature to use for ILD in CVIDS is complex and there is no consensus. The term granulomatous lymphocytic interstitial lung disease (GLILD) is in common use but there need not be a granuloma. Mycobacterium avium complex (MAC) infection is a well-known cause of ILD in CVIDS, and a classic radio-pathological ILD occurring in patients with CVIDS, associated with a lymphocytic infiltrate and/or granulomas in the lung and/or where other conditions have been considered and where positive excluded" [1]. Lung pathology and its radiological correlate in CVIDS-ILD/GLILD are heterogeneous including frequent ground-glass opacities due to lymphocytic interstitial pneumonitis, regarding

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**Background:** Granulomatous–lymphocytic interstitial lung disease (GLILD) is a rare, potentially severe pulmonary complication of common variable immunodeficiency disorders (CVIDS), informative clinical trials and consensus on management are lacking.

**Aims:** The European GLILD network (e-GLILDnet) aims to describe how GLILD is currently managed in clinical practice and to determine the main uncertainties and unmet needs regarding diagnosis, treatment and follow-up.

**Managing Granulomatous–Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders: e-GLILDnet International Clinicians Survey**

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<sup>322</</sup>

### Granulomatous-Lymphocytic Interstitial Lung Disease: an international research prioritisation

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**frontiers**  
in Immunology

**Treatment Strategies for GLILD in Common Variable Immunodeficiency: A Systematic Review**

**OPEN ACCESS**

**Edited by**  
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**Introduction:** Besides recurrent infections, a proportion of patients with Common Variable Immunodeficiency Disorders (CVID) may suffer from immune dysregulation such as granulomatous-lymphocytic interstitial lung disease (GLILD). The optimal treatment of this complication is currently unknown. Experienced-based expert opinions have been produced, but a systematic review of published treatment studies is lacking.

**Objectives:** To summarize and synthesize the published literature on the efficacy of treatments for GLILD in CVID.

**Methods:** We performed a systematic review using the PRISMA guidelines. Papers describing treatment and outcomes in CVID patients with radiographic and/or histological evidence of GLILD were included. Treatment regimens and outcomes of treatment were summarized.

**Results:** 9124 papers were identified and 42, reporting information about 253 patients in total, were included for review. These papers described case series or small, uncontrolled studies of monotherapy with glucocorticoids or other immunosuppressants, rituximab, imiquimod or rituximab plus azathioprine, abatacept, or hematopoietic stem cell transplantation (HSCT). Treatment response rates varied widely. Cross-study comparisons were complicated because different treatment regimens, follow-up

- *We could not draw definitive conclusions regarding optimal treatment for GLILD in CVID from the current literature since quantitative, well-controlled evidence was lacking.*
- *Our findings highlight the need for further research with uniform, objective and quantifiable endpoints.*
- *This should include international registries with standardized data collection including regular pulmonary function tests (with carbon monoxide-diffusion), uniform high-resolution chest CT radiographic scoring, and uniform treatment regimens, to facilitate comparison of treatment outcomes and ultimately randomized clinical trials.*

OVERALL RANK	PATIENT RANK	CLINICIAN RANK	QUESTION
1	1	1	Do corticosteroids or an alternative agent have the best risk-benefit to induce remission in adults with GLILD?
2	2	4	Do corticosteroids or an alternative agent have the best risk-benefit to maintain remission in GLILD?
3	6	2	In newly diagnosed GLILD, is first-line treatment superior to watchful waiting?
4	4	5	Are there specific risk factors in CVID for developing GLILD?
5	3	8	What is the optimal screening approach to detect incident cases of GLILD in people with CVID?
6	9	6	Are there specific pathological endotypes of GLILD with different natural history and treatment responses?
7	13	3	What is the value of a lung biopsy in the work-up of a patient with suspected GLILD?
8	7	11	What is the value of anti-fibrotic drugs such as pirfenidone and nintedanib in treating GLILD?
=9	9	14	Are there specific genetic endotypes of GLILD with different natural history and treatment response?
=9	11	12	Develop a discovery biomarker programme on blood and BAL to assist diagnosis and management of GLILD.
11	4	20	What is the benefit of a higher vs. lower trough immunoglobulin replacement target in GLILD?
12	11	15	What is the value of CT PET in the work-up of a patient with suspected GLILD?
13	8	19	Is GLILD a pathogen driven local manifestation of a systemic immune dysregulation?
=14	15	18	Is immunosuppression for GLILD associated with increased risk of infection?
=14	26	7	What is the value of broncho-alveolar lavage in the work-up of a patient with suspected GLILD?
16	18	16	What is the value of blood or other biomarkers in the work-up of a patient with suspected GLILD?
17	25	10	Do higher or lower dose corticosteroids have the best risk-benefit to induce remission in GLILD?
=18	13	23	What is the role of B cells in the pathogenesis of GLILD?
=18	15	21	Is GLILD an intrinsic dysregulation of the adaptive immune system?
=18	20	16	What is the optimal first line treatment of GLILD in children?
=18	23	13	Which type of lung biopsy has the most favourable risk-benefit?
=18	27	9	What is the value of blood or other biomarkers in assessing disease activity?
23	15	24	What is the value of bone-marrow transplantation in the treatment of GLILD?
=24	18	27	Which epigenetic modifiers contribute to the manifestation of GLILD?
=24	20	25	What is the value of thoracic MRI in the work-up of a patient with suspected GLILD?
=24	23	22	What is the outcome of lung transplantation for GLILD?
27	20	26	Develop a health-status questionnaire to assess burden in GLILD

## Summary: Lung Disease in PAD

- Be alert to the possibility of patients with PID/PAD in respiratory and infection practice: **SPUR**
- Optimise immunoglobulin replacement to minimise infection frequency
- Breakthrough infections are often viral
- Bronchiectasis is the commonest chronic lung manifestation
- Monitor with annual PFTs and 5-yearly(?) CT
- Think GLILD in atypical CVID: investigate and treat
- A multi-professional approach is best

# Thank You

## Comments and Questions

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