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

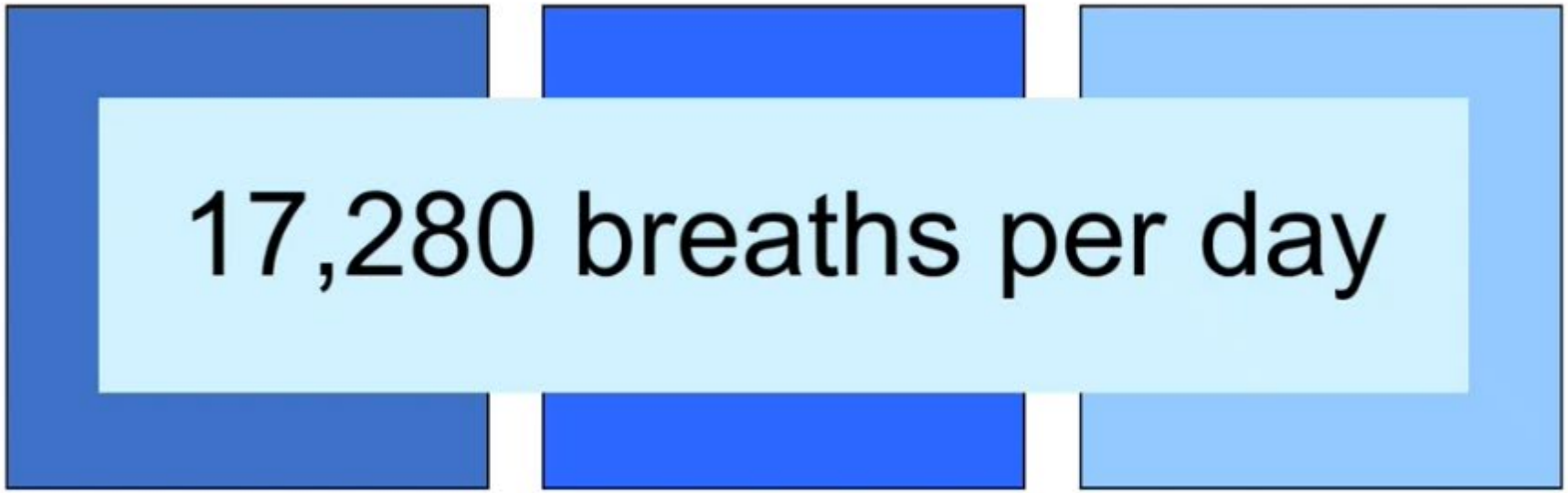
Why are the lungs affected?

12

60

24

Why are the lungs affected?



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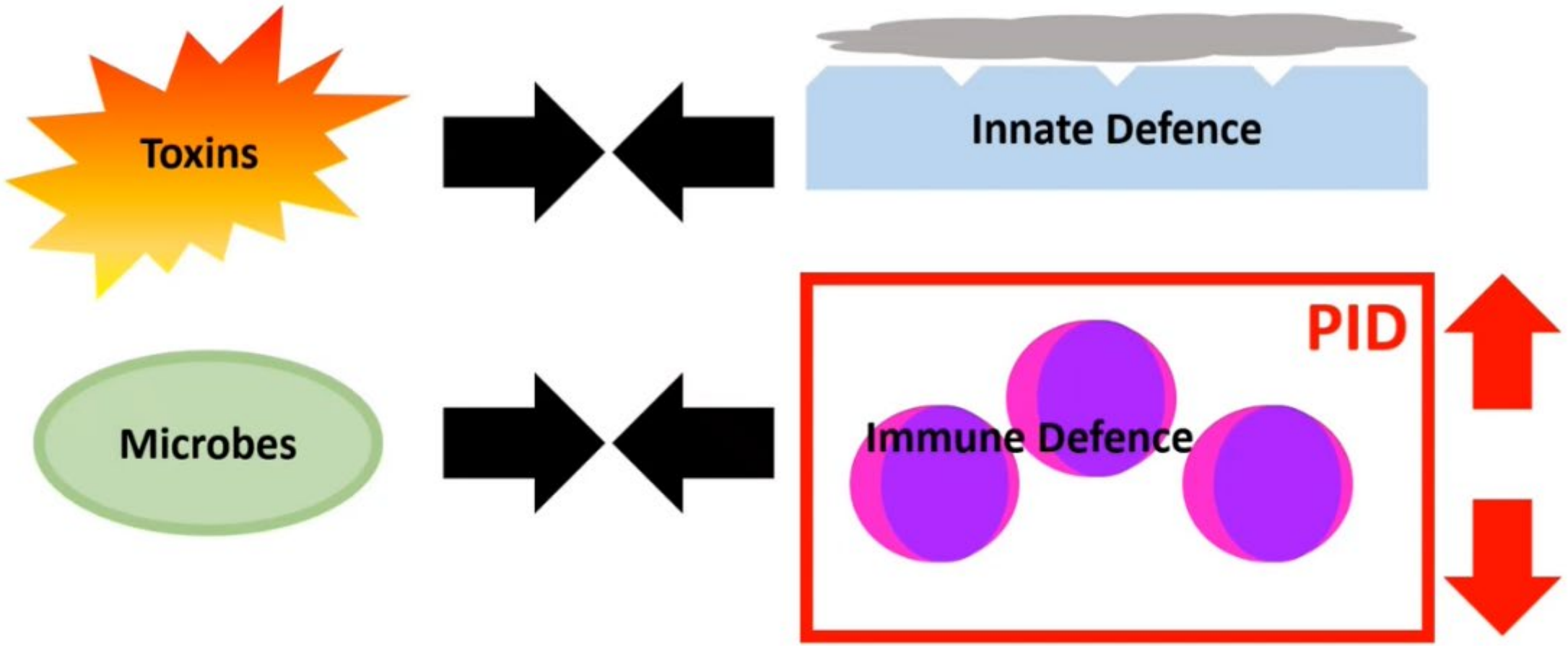

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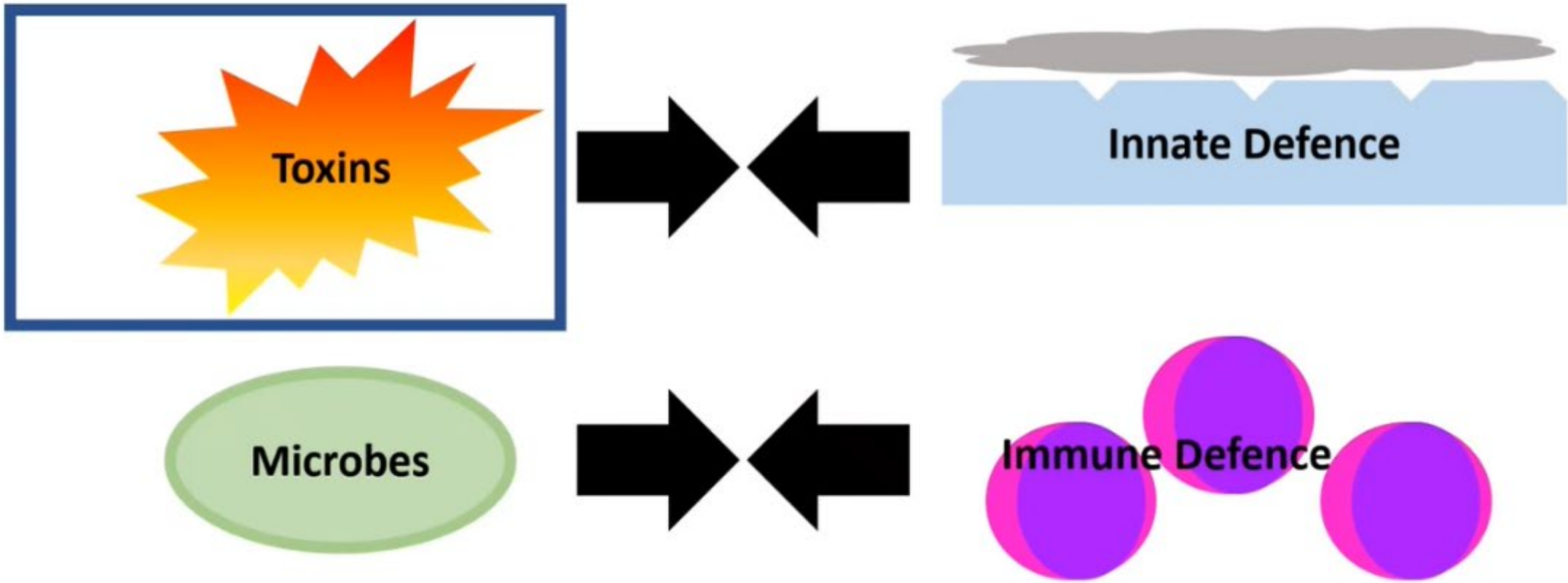


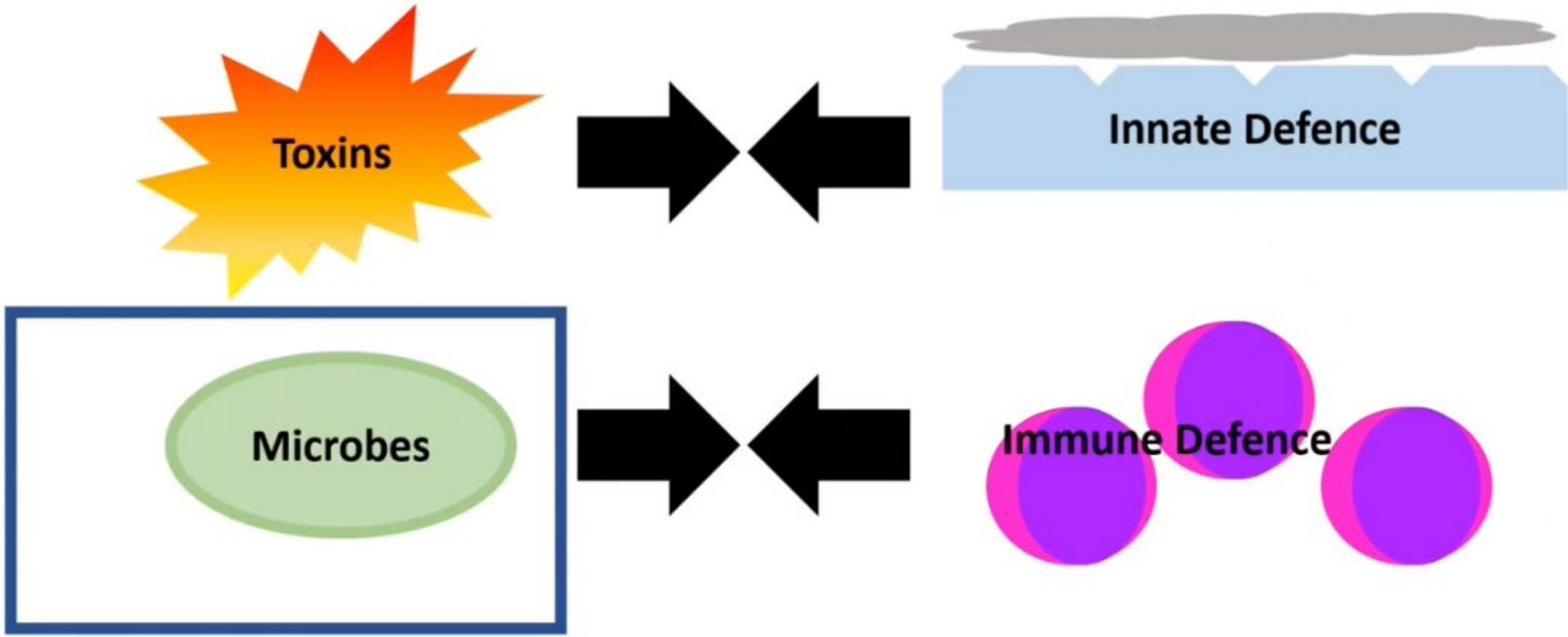
VAPING

Harm Reduction?

Too Harmful?

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

Balance

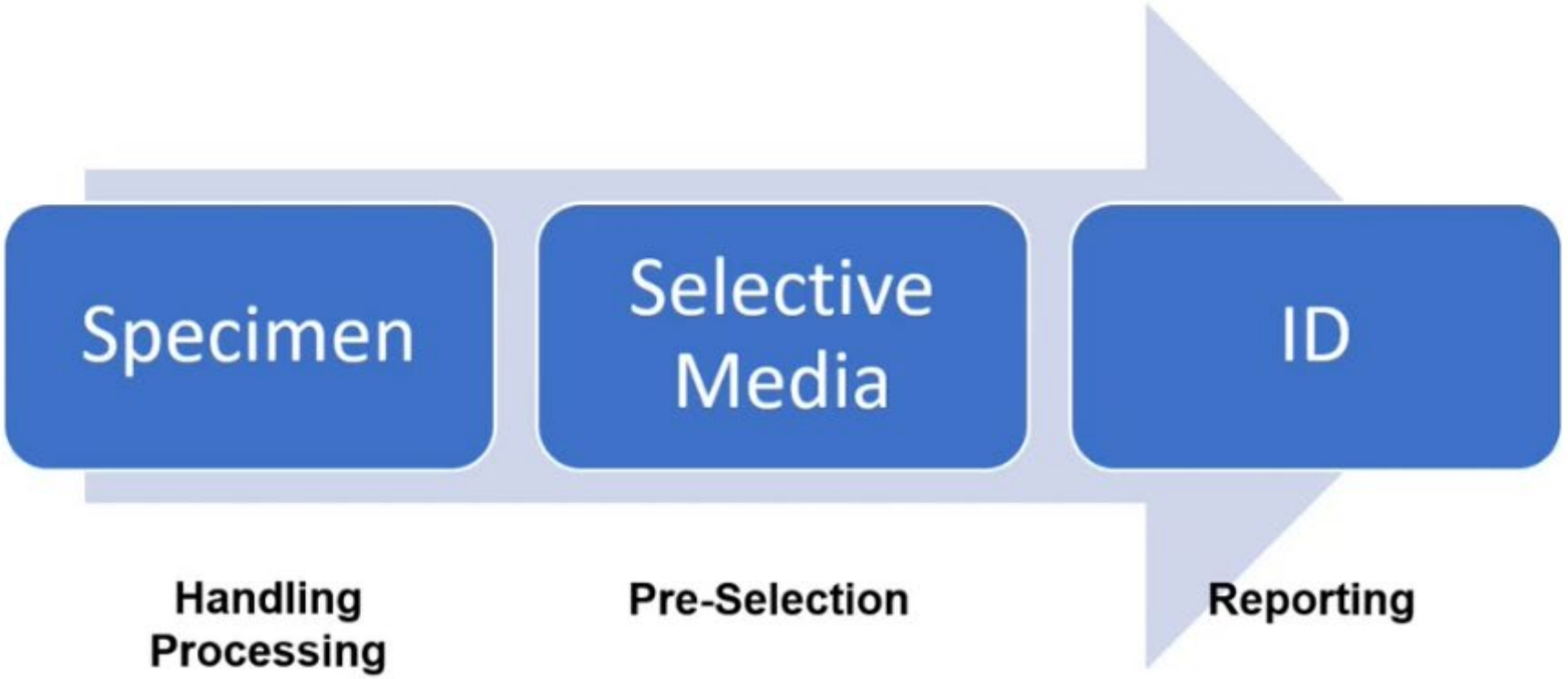


"The healthy human airway is sterile, with several innate immune mechanisms acting in coordination to maintain this sterility. Smoking appears to disrupt these innate immune mechanisms, and as a consequence, microbial pathogens are able to persist in the lower airway in COPD"

***AJRCCM* 2006**

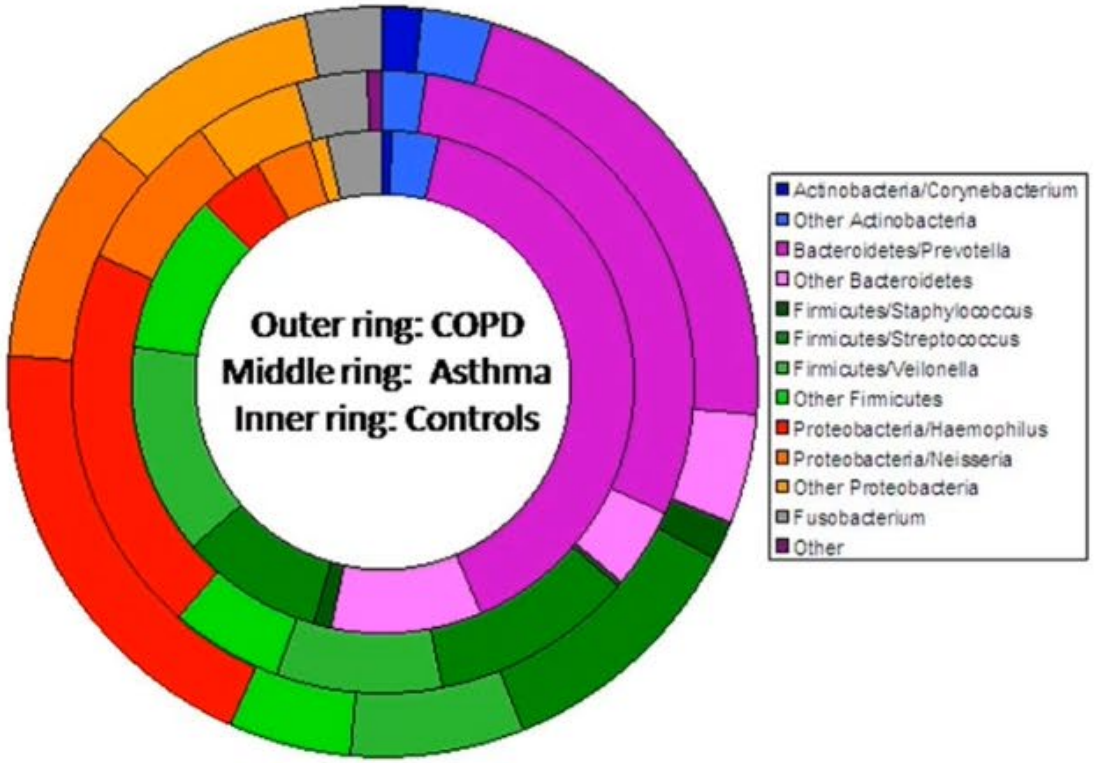
"free from bacteria or other living microorganisms; totally clean"

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"

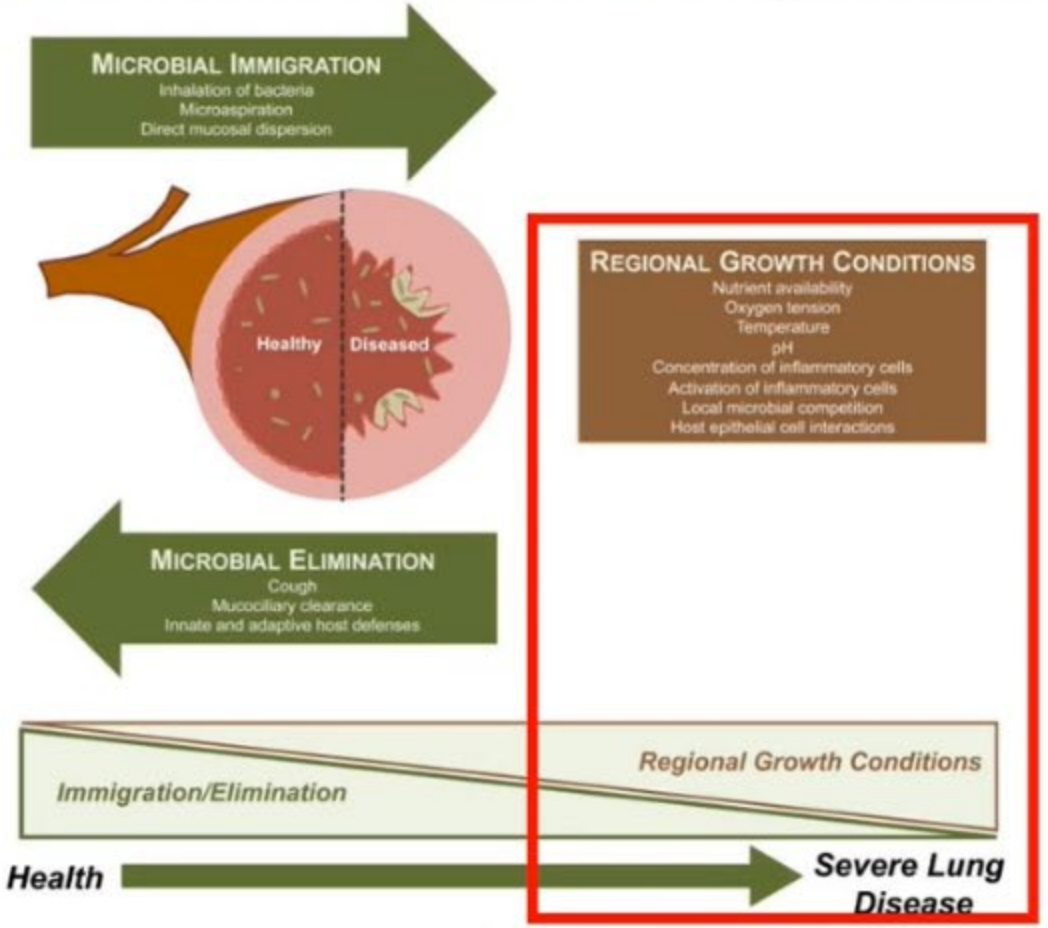
Lederberg J, McCray AT. 'Ome sweet 'omics – a genealogical treasury of words. *Scientist* 2001;15:8

"The lung microbiome is:

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

Dickson RP, Cox MJ. Sampling. In: Cox MJ, Ege MJ, von Mutius E (eds). The Lung Microbiome. *ERS Monograph* 2019 pp1-17

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

15th Century, Catalonian; Metropolitan Museum of Art

Acute Infections

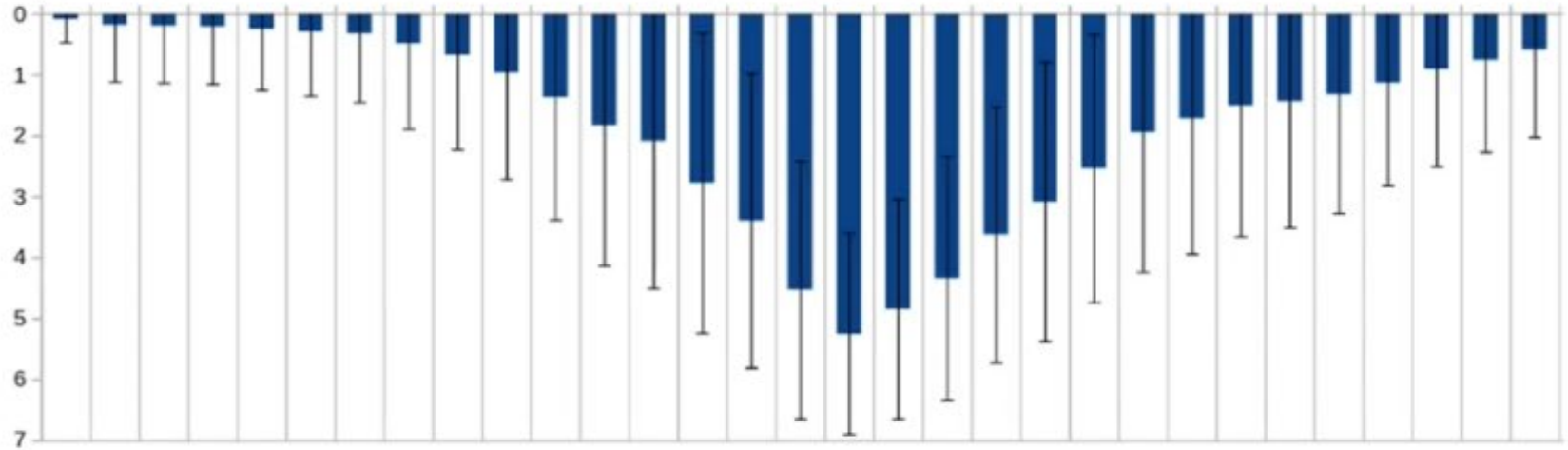
Prior to diagnosis

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	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	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	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



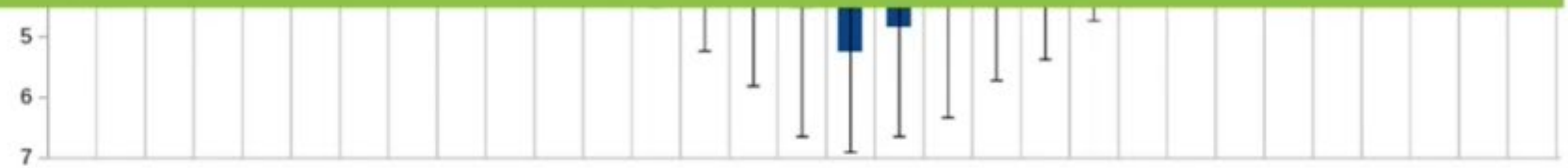
Sperlich J *et al.* *JACI In Practice* 2018;18:159-168

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	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	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	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

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.



Sperlich J *et al.* *JACI In Practice* 2018;18:159-168

Micro-Organisms at Exacerbations in CVID

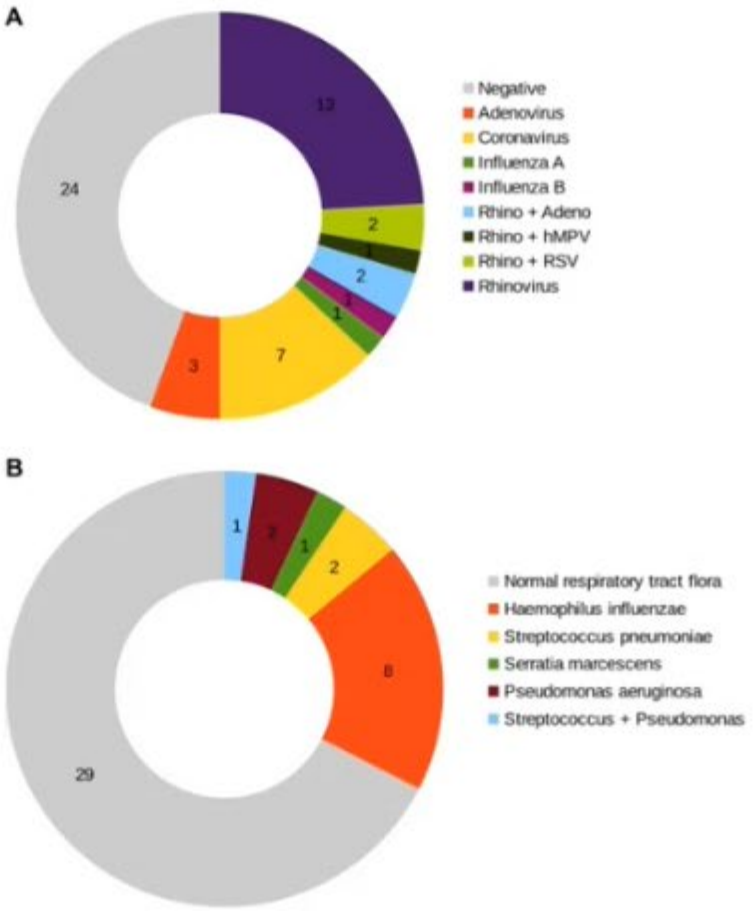
A: Viral PCR on nasopharyngeal swabs in 54 respiratory exacerbations in patients with CVID.

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.

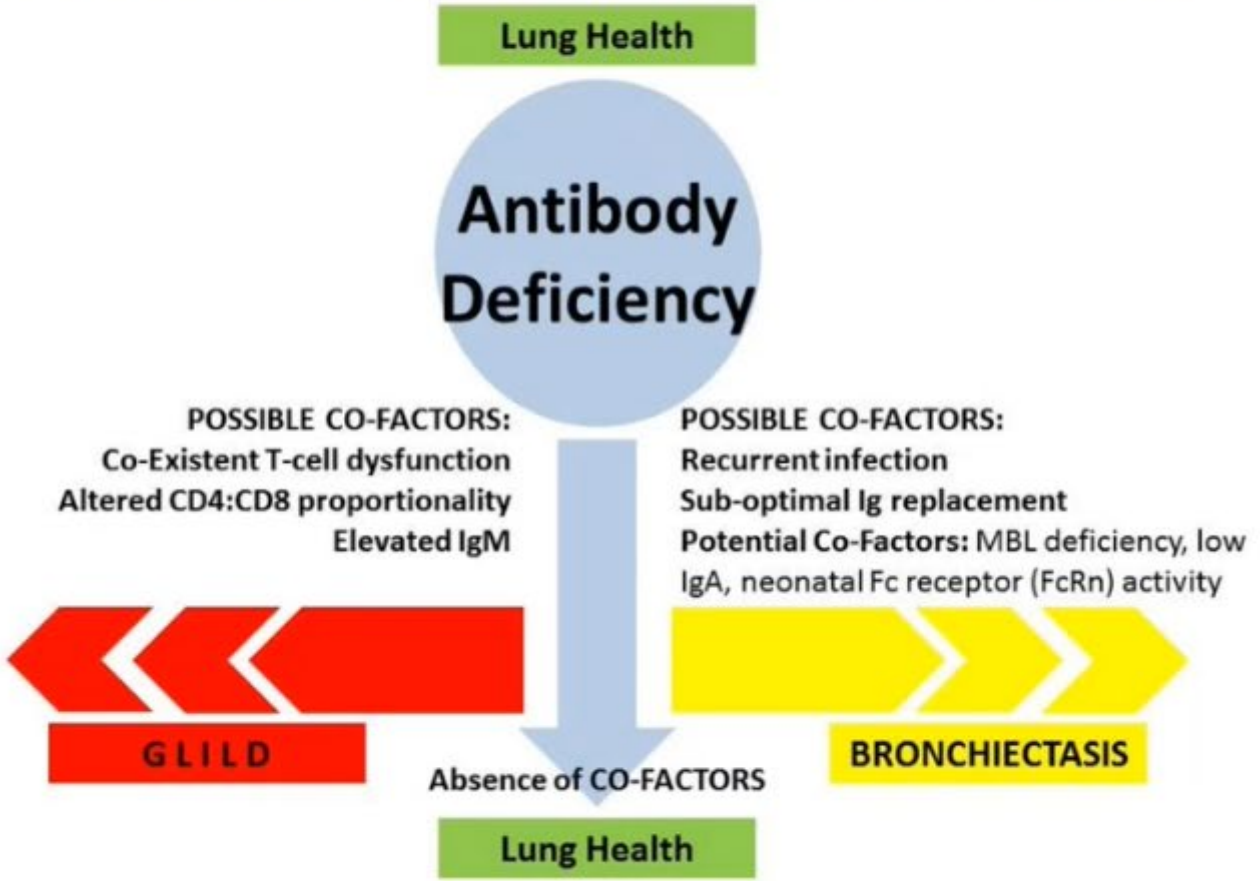


Sperlich J *et al.* *JACI In Practice* 2018;18:159-168

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

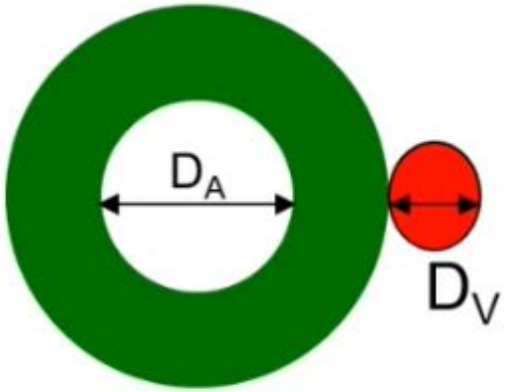
Chronic Lung Disease in PAD Syndromes



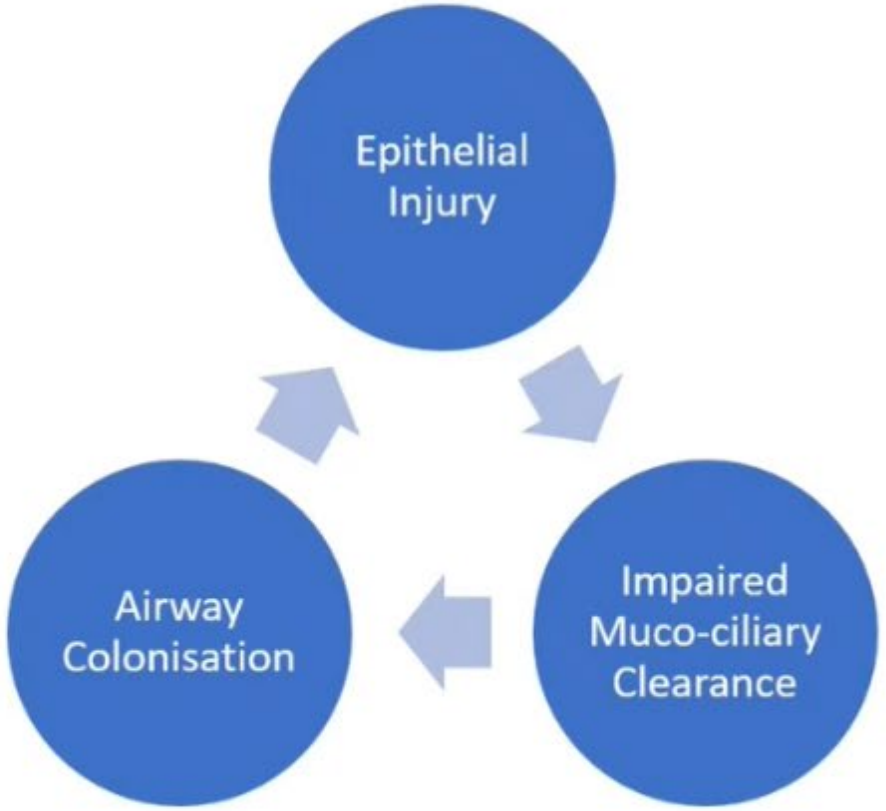
Verma N, Grimbacher B, Hurst JR. *Lancet Respiratory Medicine* 2015;3:651-660

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

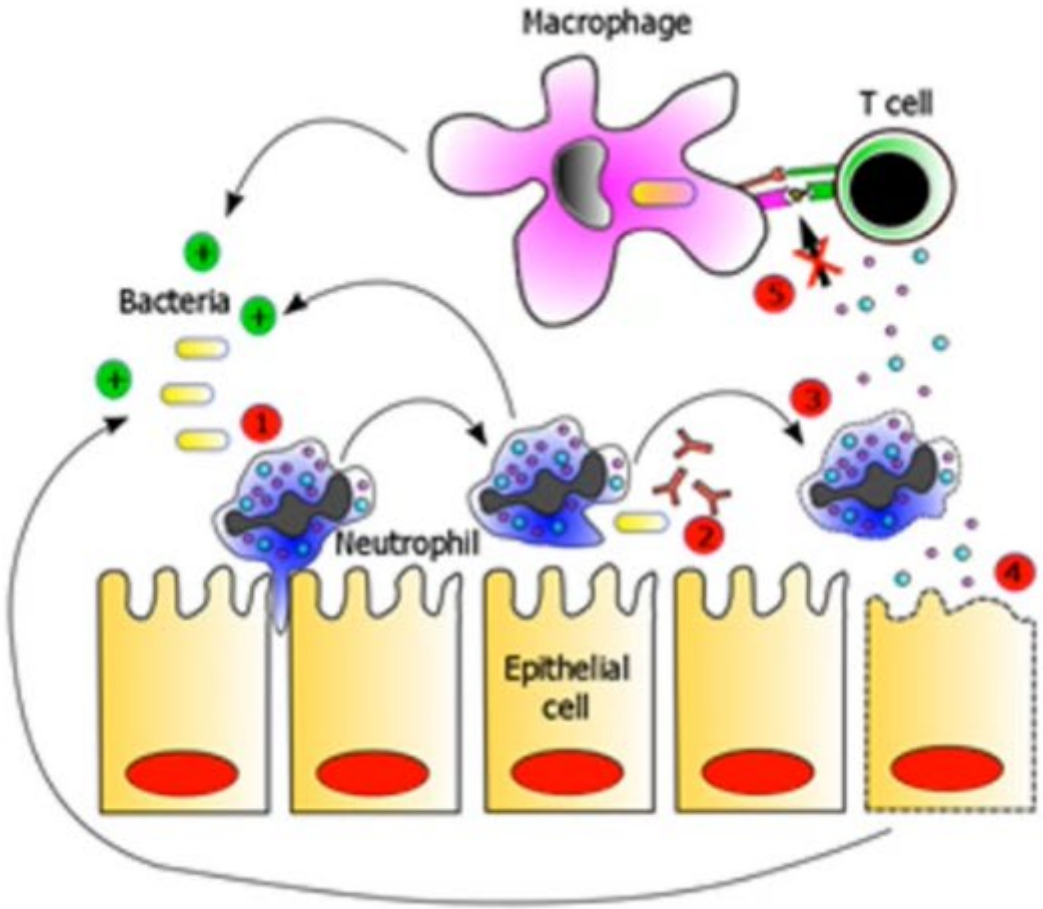
1: Neutrophils recruited to the airway in response to bacteria.

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.



Lowe DM and Hurst JR. *European Respiratory Monograph* 2018;81:153-166

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

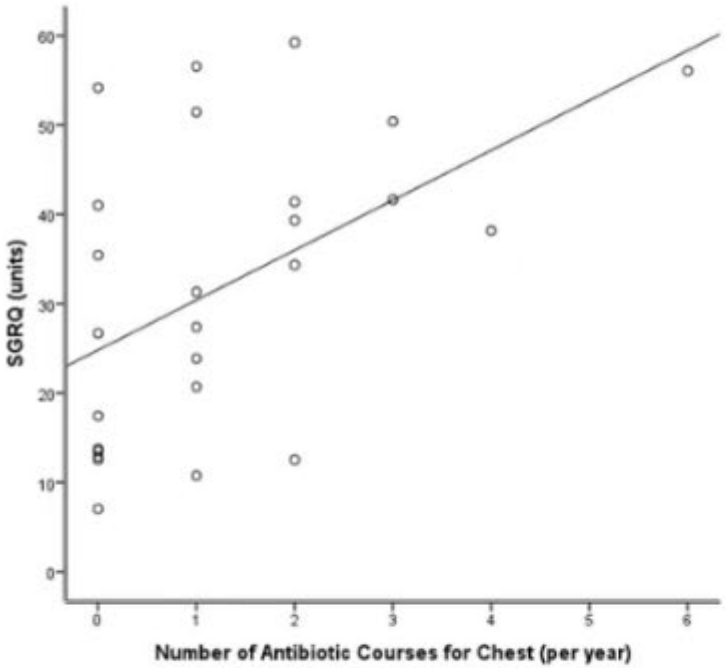
Maximise functional capacity

(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)

Hurst JR *et al*. Activity, Severity and Impact of Respiratory Disease in Primary Antibody Deficiency Syndromes. *J Clin Immunol* 2013

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

Geraint B. Rogers[1], Nur Masirah M. Zain[2], Kenneth D. Bruce[2*], Lucy D. Burr[1], Alice C. Chen[1], Damian W. Rivett[3], Michael A. McGuckin[1], and David J. Serisier[1,4*]

[1]Immunity, Infection, and Inflammation Program, Mater Research Institute, University of Queensland, and Translational Research Institute, Woolloongabba, Queensland, Australia; [2]Institute of Pharmaceutical Science, King's College London, and [3]Division of Ecology and Evolution, Department of Life Sciences, Imperial College London, London, United Kingdom; and [4]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 taxon 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-1β. Predominance of *P. aeruginosa*, followed by *Veillonella* 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* levels and sputum IL-8, IL-1β, and serum CRP. Genus richness was negatively correlated with 24-hour sputum weight, age, serum CRP, sputum IL-1β, and IL-8.

Conclusions: 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

(Received in original form October 1, 2013; accepted in final form December 27, 2013)

*Joint senior authors.

Supported by the Mater Adult Respiratory Research Trust Fund.

Author Contributions: G.B.R., N.M.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 reprints should be addressed to Geraint B. Rogers, Ph.D., Mater Medical Research Institute, Translational Research Institute, 37 Kent Street, Woolloongabba, QLD 4102, Australia. E-mail: geraint.b.rogers@gmail.com

This article has an online supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

Ann Am Thorac Soc Vol 11, No 4, pp 496–503, May 2014

DOI: 10.1513/AnnalsATS.201310-335OC
Internet address: 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

CrossMark

European Respiratory Society guidelines for the management of adult bronchiectasis

Eva Polverino[1], Pieter C. Goeminne[2,3], Melissa J. McDonnell[4,5,6], Stefano Aliberti[7], Sara E. Marshall[8], Michael R. Loebinger[9], Marlene Murris[10], Rafael Cantón[11], Antoni Torres[12], Katerina Dimakou[13], Anthony De Soyza[14,15], Adam T. Hill[16], Charles S. Haworth[17], Montserrat Vendrell[18], Felix C. Ringshausen[19], Dragan Subotic[20], Robert Wilson[3], Jordi Vilaró[21], Bjorn Stallberg[22], Tobias Welte[19], Gernot Rohde[23], Francesco Blasi[7], Stuart Elborn[3,24], Marta Almagro[25], Alan Timothy[26], Thomas Ruddy[27], Thomy Tonia[28], David Rigau[27] and James D. Chalmers[29]

@ERSpublications
The publication of the first ERS guidelines for bronchiectasis http://ow.ly/wQSO30dU3oI

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/10.1183/13993003.00629-2017].

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 answered 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, pathogen eradication, long term antibiotic treatment, anti-inflammatories, mucoactive 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

Received: March 26 2017 | Accepted after revision: July 10 2017

The guideline 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 Diseases in August 2017.

Macromania

3 RCTs of macrolide in bronchiectasis

EMBRACE[1]: azithromycin 500mg x3 week; n=141, 6/12

62% exacerbation reduction

BAT[2]: azithromycin 250mg daily; n=83, 12/12

71% exacerbation reduction and improved quality of life

BLESS[3]: 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

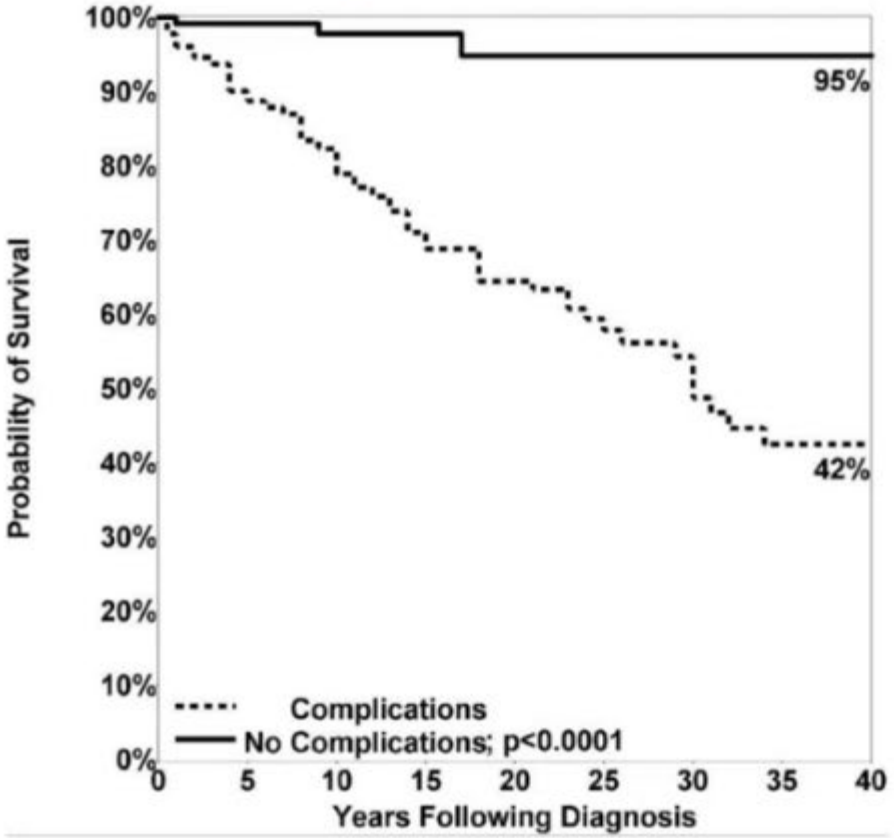
Novel anti-inflammatories (e.g. CXCR2 antagonists)

Mucolytics

Nebulised immunoglobulin

Nasal interventions

Mortality in CVID



N=473, 40 years

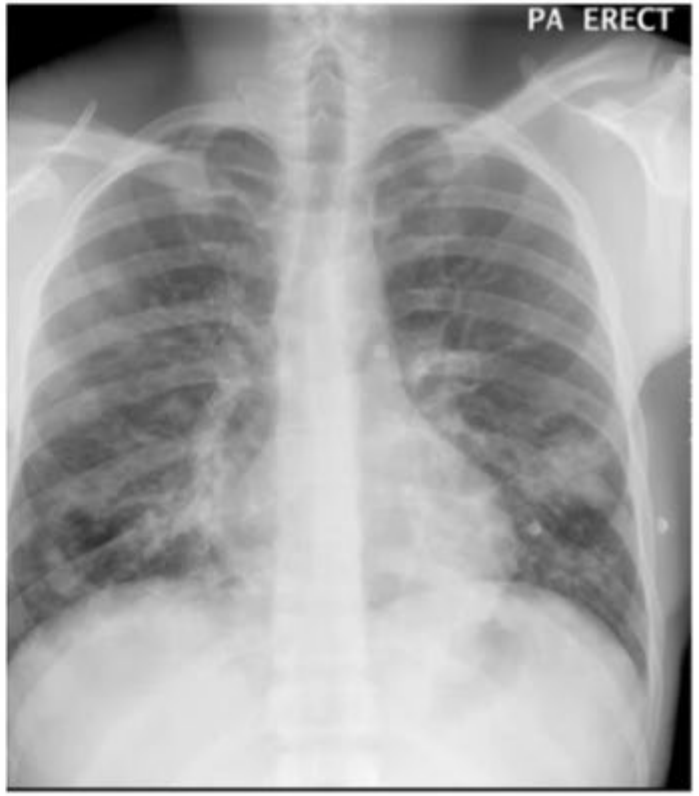
Risk of death 11 times higher for patients with non-infectious complications (HR = 10.95; p<0.0001).

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

Resnick E *et al.* Morbidity and mortality in common variable immune deficiency over 4 decades. *Blood* 2012;**119**:1650-1657

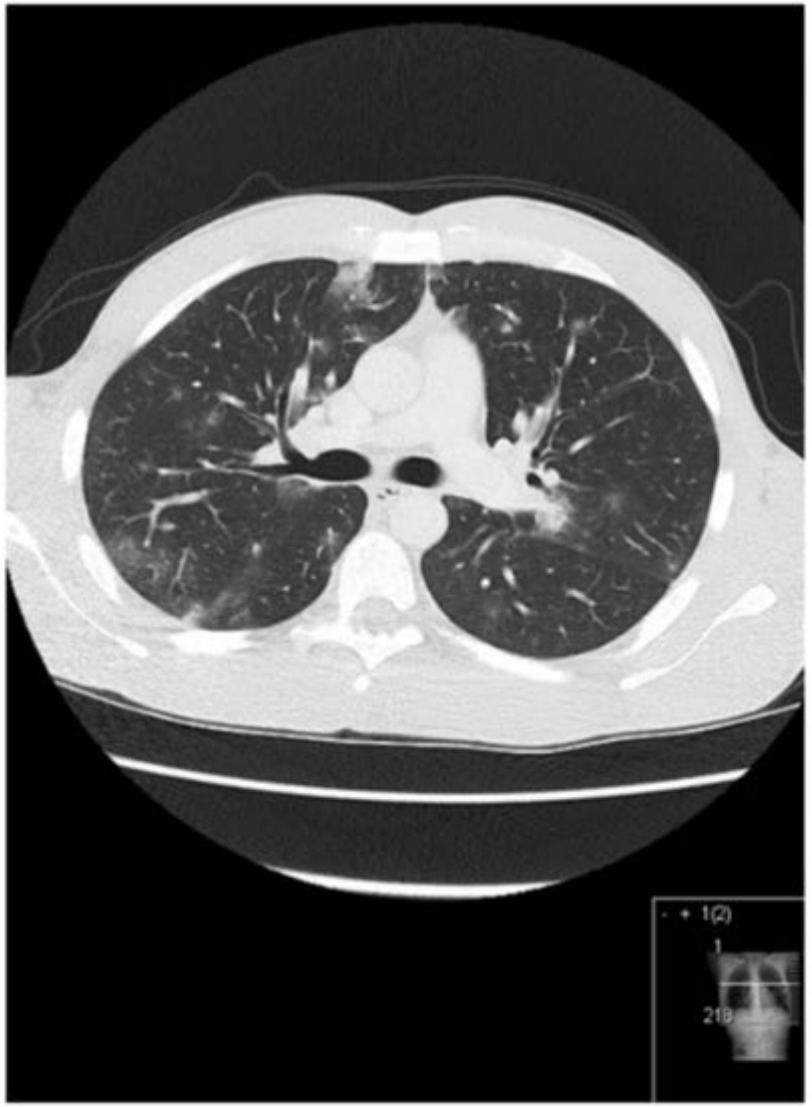
Case

- 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

John R. Hurst, PhD, FRCP[a], Nisha Verma, MRCP[b], David Lowe, MRCP[b], Helen E. Baxendale, MRCP, PhD[c], Stephen Jolles, FRCP, FRCPath, PhD[d], Peter Kelleher, PhD[e], Hilary J. Longhurst, FRCPath[f], Smita Y. Patel, PhD, FRCPath[g], Elisabetta A. Renzoni, PhD[h], Clare R. Sander, PhD, FRCP[i], Gerard R. Avery, FRCR[j], Judith L. Babar, FRCR[k], Matthew S. Buckland, PhD, FRCP[l], Siobhan Burns, FRCPath[m], William Egner, FRCP, FRCPath, PhD[n], Mark M. Gompels, MD[o], Pavels Gordins, FRCPath[p], Jamanda A. Haddock, FRCR[q], Simon P. Hart, PhD, FRCPE[r], Grant R. Hayman, FRCP, FRCPath[s], Richard Herriot, FRCPath[t], Rachel K. Hoyles, PhD, FRCP[u], Asmaud P. Hulsaver, PhD, FRCP, FCRPath[v], Joseph Jacob, MDRes[w], Andrew G. Nicholson, FRCPath[x], Doris M. Read, FRCPath[y], Ravishankar B. Sargur, FRCP, FRCPath[z], Sinisa Savic, PhD[aa], Suranjith L. Seneviratne, FRCP[ab], Michael Sheaff, MD[ac], Prashantha M. Vaitla, FRCPath[ad], Gareth I. Walters, MD[ae], Joanne L. Whitehouse, PhD, FRCP[af], Penny A. Wright, FRCPath[ag], and Alison M. Condliffe, PhD[ah]

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The British Lung Foundation funded this work (grant reference no. PPRG15-7).
Conflicts of interest: J.R. Hurst has received research support from the British Lung Foundation, has received consultancy and lecture fees from AstraZeneca, Boehringer, Chiesi, Orion, GlaxoSmithKline, Pfizer, Novartis, and Takeda; and has received travel support from AstraZeneca and Boehringer. D. Lowe has received consultancy fees and travel support from Biotest and has received research support from University College London Biomedical Research Centre. S. Jolles reports grants, personal fees, nonfinancial support, and other from CSL Behring and Shire; grants, personal fees, and nonfinancial support from Shire and Biotest; grants from Binding Site; grants and personal fees from Swedish Orphan Biovitrum; personal fees and nonfinancial support from Octapharma, and UCB Pharma; personal fees from LFB Group; and nonfinancial support from Bio Products Laboratory Ltd (BPL), outside the submitted work. P. Kelleher 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

"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						
			Pulmonary Lymphoid Hyperplasia				Organizing pneumonia	Pulmonary Fibrosis	
			Interstitial inflammation	*(Peri)bronchial inflammation*	*Lymphocytic infiltration*	*Lymphoid hyperplasia*		*Fibrosis*	*Remodeling*
Rao et al.* (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%s	13/34 (32%)**	NS

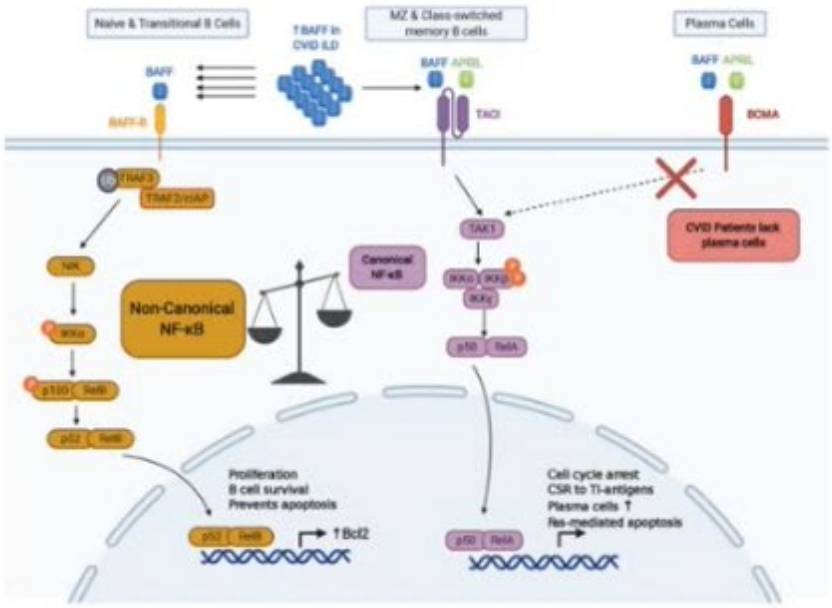
*Only publications with sufficient histological detail were included; single case histories or small studies (less than 10) are not included. Rao et al. (44) and Patel et al. (33) reported their findings in similar terms, but these varied in other publications. Efforts were made to group similar findings 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.

Dhalla F, Lochlainn DJM, Chapel H, Patel SY. Histology of Interstitial Lung Disease in Common Variable Immune Deficiency. Front Immunol. 2020 Nov 20;11:605187. doi: 10.3389/fimmu.2020.605187. PMID: 33329602; PMCID: PMC7718002.

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 depletive 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 mycophenate, or potentially through inhibition of BAFF may help maintain CVID ILD in remission.

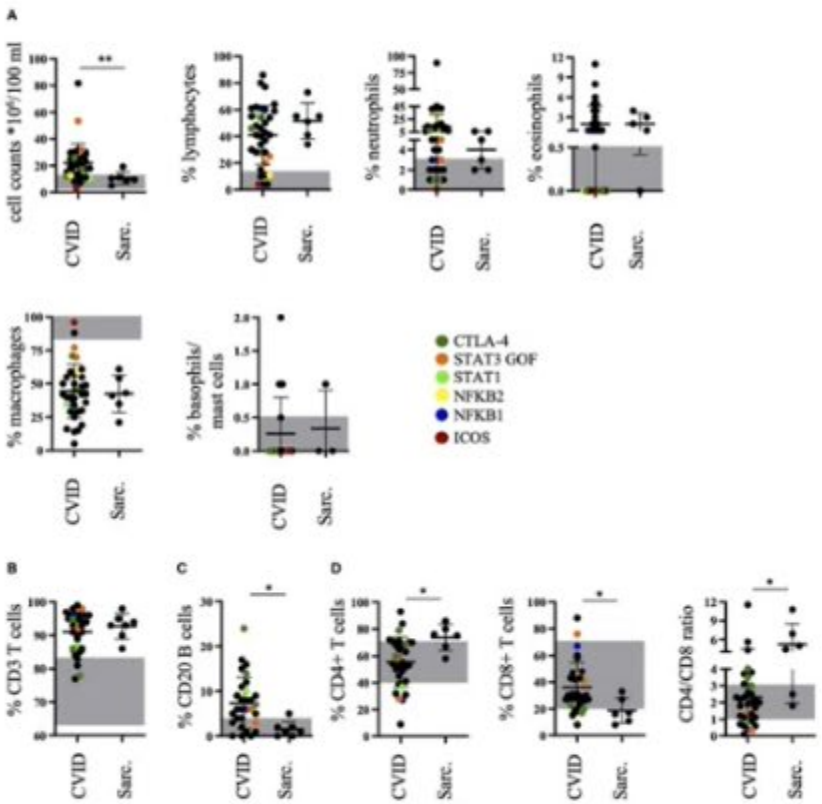
B cell hyperplasia is a defining aspect of CVID ILD and is perpetuated *via* survival signals mediated by BAFF through BAFF-R.

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

Matson EM, Abyazi ML, Bell KA, Hayes KM, Maglione PJ. B Cell Dysregulation in Common Variable Immunodeficiency Interstitial Lung Disease. Front Immunol. 2021 Feb 5;11:622114. doi: 10.3389/fimmu.2020.622114. PMID: 33613556; PMCID: PMC7892472.

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.

Friedmann D, Unger S, Keller B, Rakhmanov M, Goldacker S, Zissel G, Frye BC, Schupp JC, Prasse A, Warnatz K. Bronchoalveolar Lavage Fluid Reflects a T_H1-CD21^{low} B-Cell Interaction in CVID-Related Interstitial Lung Disease. Front Immunol. 2021 Feb 5;11:616832. doi: 10.3389/fimmu.2020.616832. PMID: 33613543; PMCID: PMC7892466.

Is optimisation of Ig sufficient?

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

Thorax 2006;61:1096–1097. doi: 10.1136/thx.2006.059519

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, IVIG given monthly should be considered as the only treatment without adding steroids.

Lymphocytic interstitial pneumonia (LIP) is by definition a reactive lymphoid infiltrate which occurs most commonly in the alveolar septa but eccentrically appears along bronchi and vessels.[1] It may occur in association with a number of conditions including HIV in children, primary immunodeficiency, Sjögren's syndrome, myasthenia gravis, and dysproteinaemic states including hyper- and hypogammaglobulinaemia.[2] Hypogammaglobulinaemia occurs in about 10% of adults with this condition and the association of LIP with common variable immunodeficiency (CVID) has been described.[3]

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 amoxycillin-clavulanic acid and roxithromycin 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_2.

On admission the physical examination was normal with no clinical signs of Sjögren's syndrome or other autoimmune diseases. The saturation was 94% and the lungs were clear. Complete blood count, chemistry panel, liver function tests, and urine analysis were normal. Arterial blood gas analysis on room air revealed Sat_{O_2} 94%, Pa_{O_2} 9.47 kPa (71 mm Hg), Pa_{CO_2} 4.27 kPa (32 mm Hg), HCO_3 22.3 mm Hg, 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 IgA was less than 42 mg/dl (normal 90–430) and the level of IgG_2 was 86 mg/dl (normal 139–554). The levels of other immunoglobulins were within normal limits.

Spirometric parameters were normal and the chest radiograph showed interstitial markings. A computed tomographic (CT) scan of the chest showed axinary pulmonary nodules and ground glass opacities in both lungs (fig 1). Sputum cultures and throat swabs were negative. No acid-fast bacilli were seen. Bone marrow aspiration and biopsy were normal. Flexible bronchoscopy did not reveal endobronchial lesions. The bronchoalveolar lavage (BAL) fluid showed no infection or malignancy; a cell count was not performed. Transbronchial biopsy specimens displayed aggregates of small lymphocytes in the lung parenchyma. A specific diagnosis was not possible.

An open lung biopsy was performed and showed multifocal interstitial lymphoid infiltrates spreading into the alveolar septa and surrounding airways and vessels. The infiltrates were composed of small lymphocytes admixed with plasma cells. The lymphocytes were a mixture of polyclonal B cells (CD20 positive, mainly in nodules) and T cells (CD3 positive, mainly in pulmonary interstitium). Foci of bronchiolitis obliterans organising pneumonia (BOOP) were seen. These findings were consistent with LIP and associated BOOP. Cell rearrangement excluded monoclonality. The mixture of B and T cells combined with the cell rearrangement excluded the diagnosis of lymphoma.

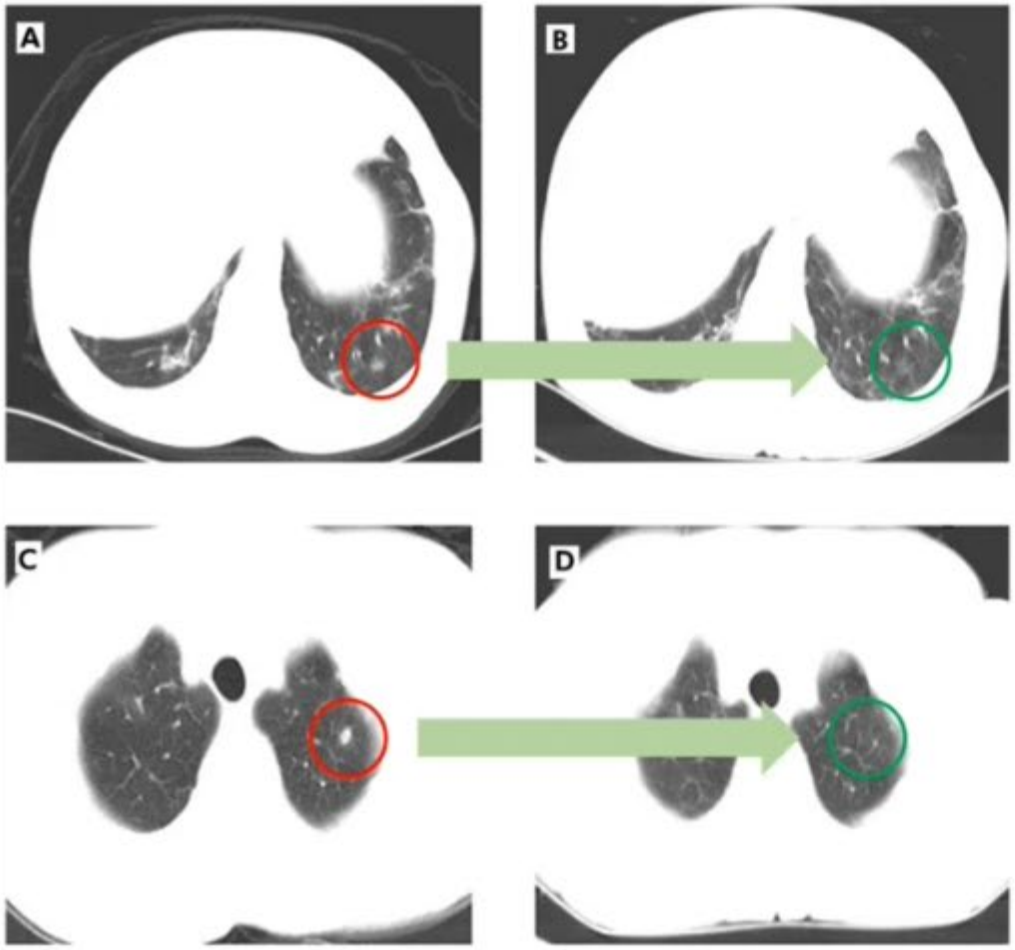
Treatment with corticosteroids was considered but we could not find evidence to support this approach. The risk of severe infections and side effects of steroids made this treatment unfavourable. Treatment was therefore started with IVIG 0.5 mg/kg monthly. Seventeen months after the diagnosis the patient improved dramatically. She had only one episode of pneumonia compared with five episodes during the previous year. The chronic cough and dyspnoea resolved and Pa_{O_2} rose from 9.47 kPa (71 mm Hg) before the diagnosis to 11.87 kPa (89 mm Hg). The A-a gradient fell from 26 mm Hg before the diagnosis to a normal level (7 mm Hg). Pulmonary function tests remained normal and the CT scan showed partial resolution of the findings (fig 1A–D).

DISCUSSION

We describe a patient suffering from CVID and LIP. Monoclonality 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 controlled trials. However, most patients are treated with prolonged courses of corticosteroids which may control the process or induce remission. Popa *et al*[4] 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 organising pneumonia; CVID, common variable immunodeficiency; IVIG, intravenous immunoglobulins; LIP, lymphocytic interstitial pneumonia



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CASE REPORT

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

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

Stina Gregersen, MD*; Trond Mogens Aaløkken, MD†; Georg Mynarek, MD†; Bærre Fevang, MD‡§; Are Martin Holm, PhD*; Thor Ueland, PhD‡¶; Pål Aukrust, PhD‡§; Johny Kongerud, PhD*; Bjørn Johansen, PhD*; and Stig S. Frøland, PhD‡§

n=54
ON Ig

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European Granulomatous-Lymphocytic Interstitial Lung Disease Network

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 methylprednisone).
- 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).

Special Article

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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.

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Second Line Therapy

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

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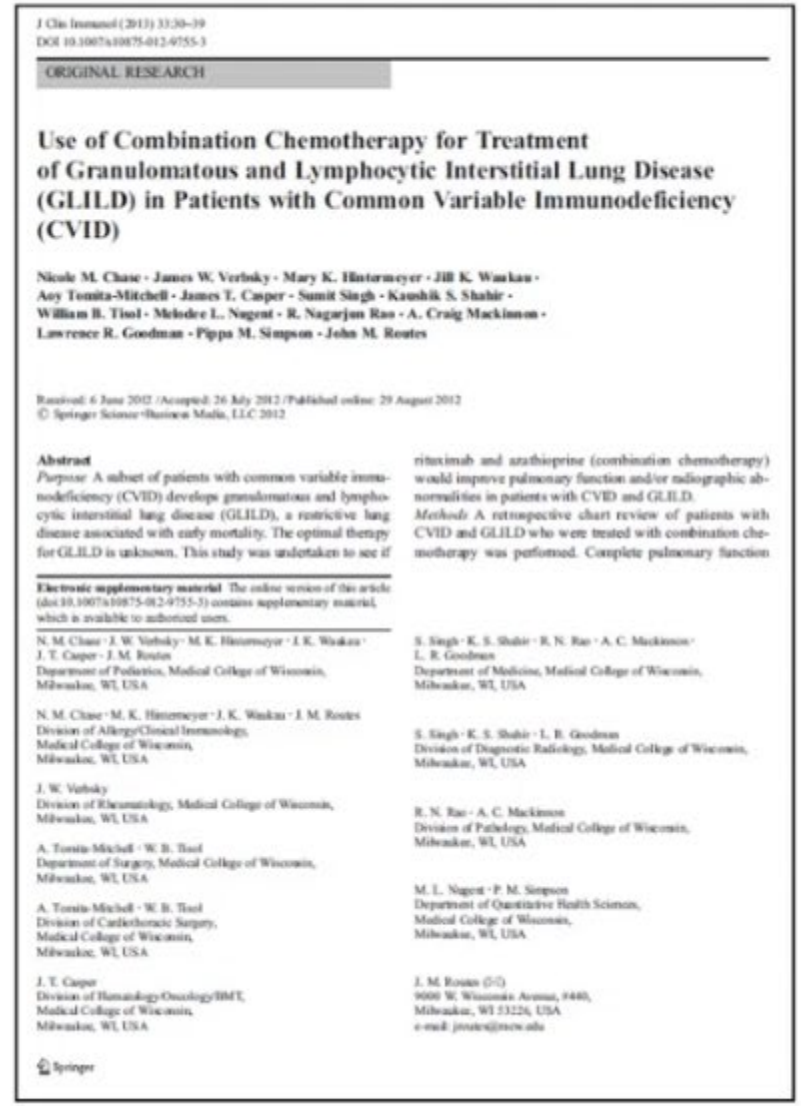
Rituximab and Azathioprine

- To target B- and T-cells
- 7 patients
  - Rituximab 375 mg/m^2 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



J Clin Immunol (2013) 33:30–39
DOI 10.1007/s10875-012-9755-3

ORIGINAL RESEARCH

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

Nicole M. Chase · James W. Verbsky · Mary K. Hintermeyer · Jill K. Waukau · Aoy Tomita-Mitchell · James T. Casper · Sumit Singh · Kaushik S. Shahir · William B. Tisol · Melodee L. Nugent · R. Nagarjun Rao · A. Craig Mackinnon · Lawrence R. Goodman · Pippa M. Simpson · John M. Routes

Received: 6 June 2012 / Accepted: 26 July 2012 / Published online: 29 August 2012

Abstract
Purpose A subset of patients with common variable immunodeficiency (CVID) develops 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 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

Electronic supplementary material The online version of this article (doi:10.1007/s10875-012-9755-3) contains supplementary material, which is available to authorized users.

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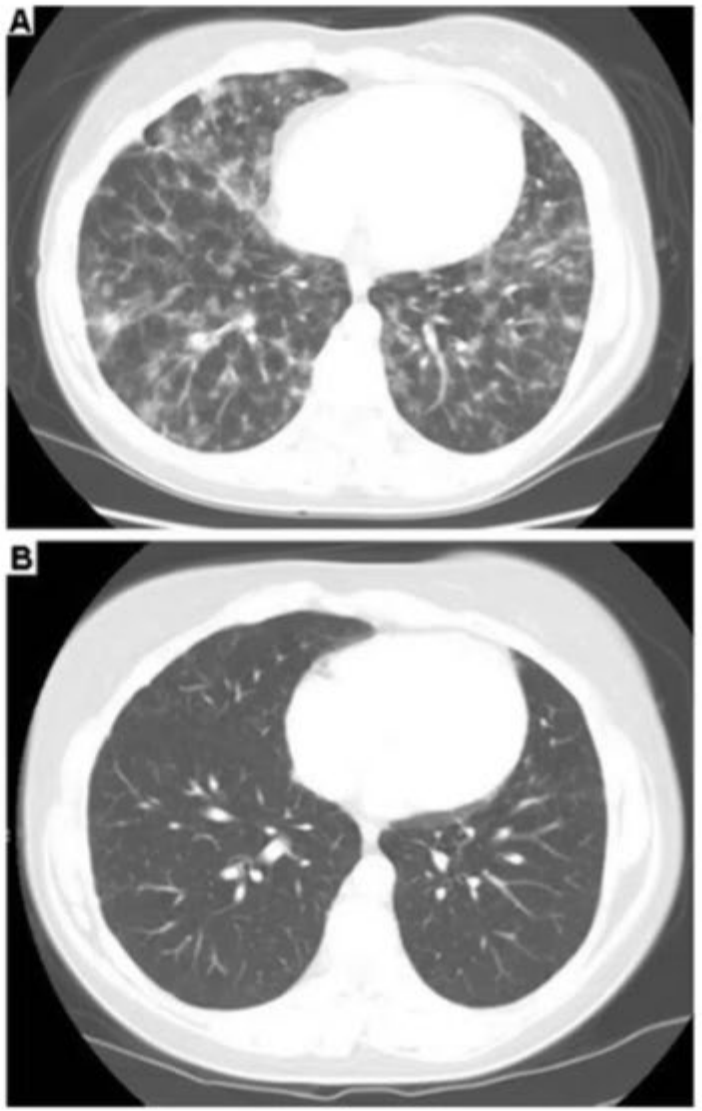
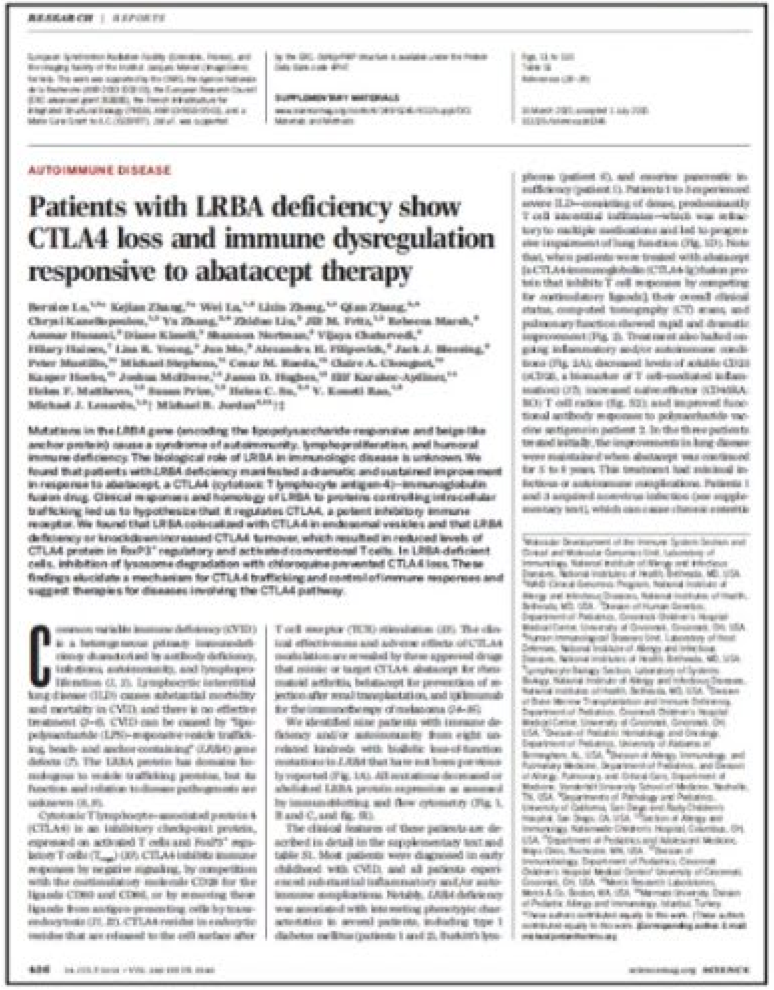
Springer

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_1 and FVC
  - Not all had gas transfer
- Long term outcomes?

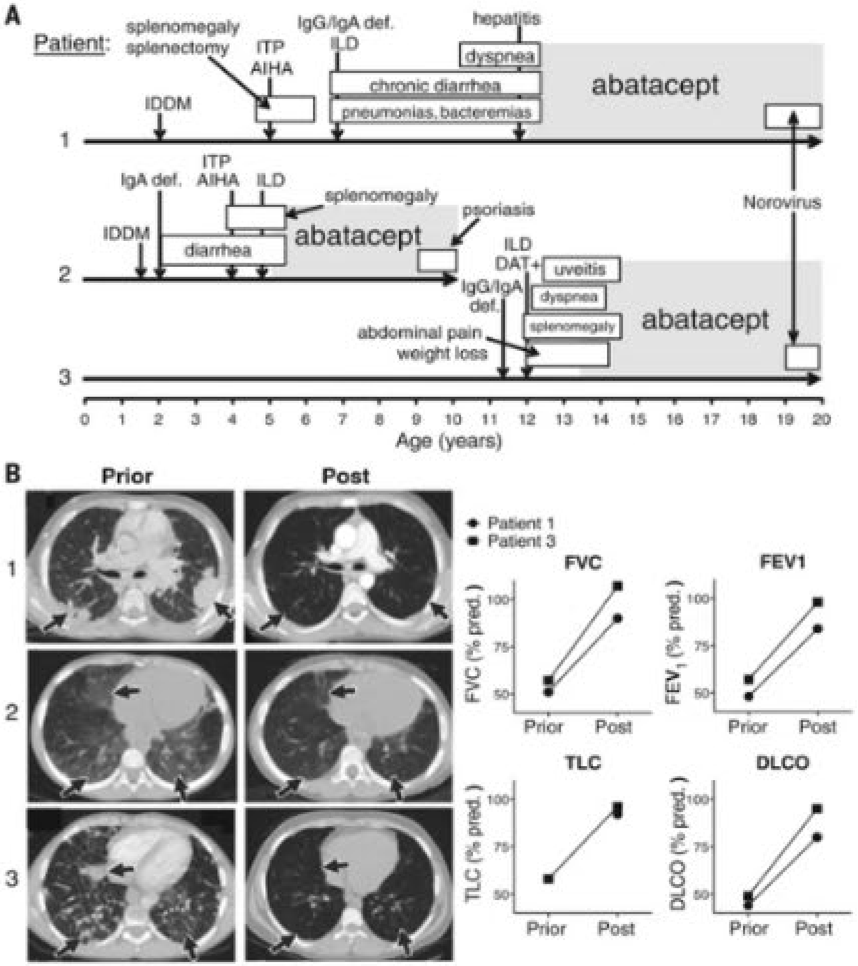


GLILD: Targeted Therapy



AUTOIMMUNE DISEASE

Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy



UCL

(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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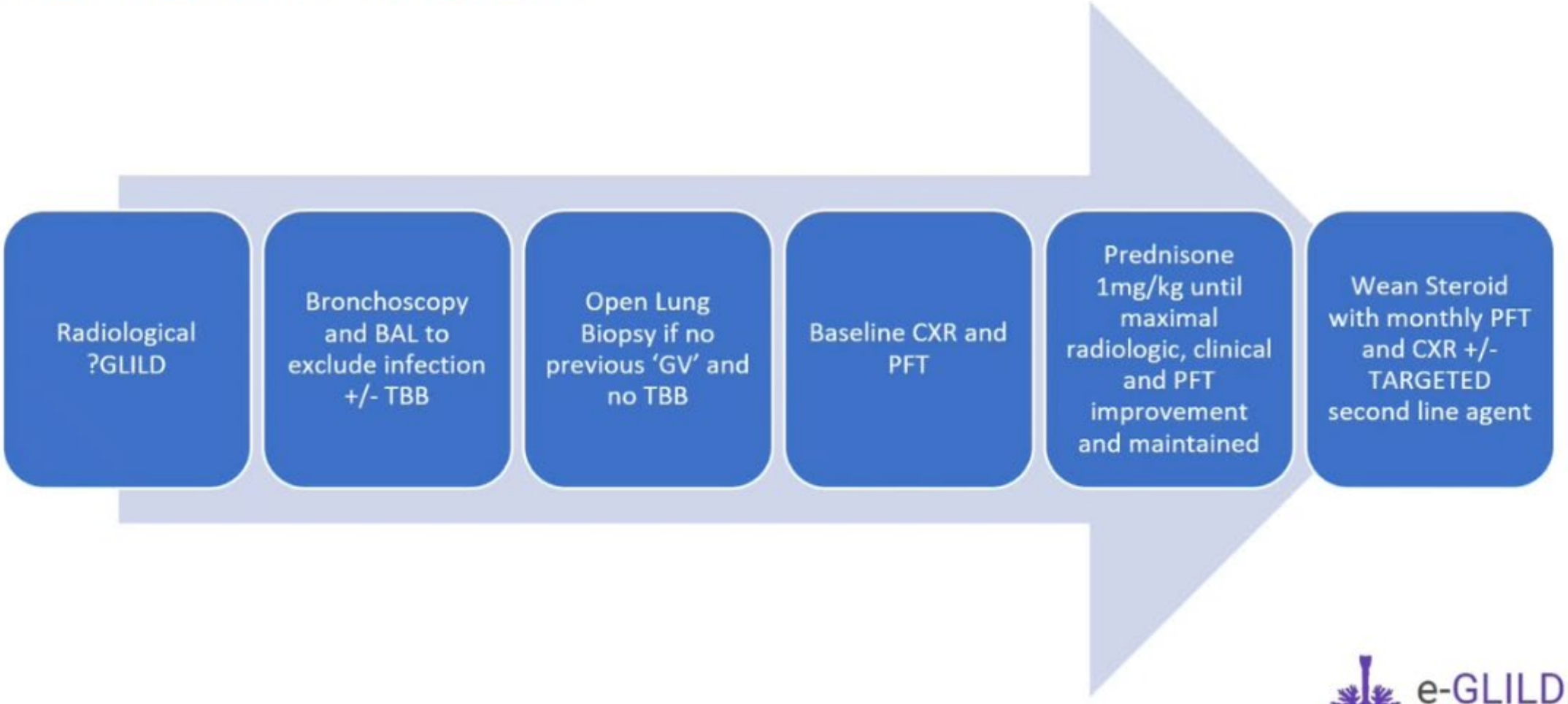
Background: Common variable immunodeficiency (CVID) is usually well controlled with immunoglobulin substitution and immunomodulatory drugs. A subgroup of patients has a complicated disease course with high mortality. For those patients, investigation of more invasive, potentially curative treatments, such as allogeneic hematopoietic stem cell transplantation (HSCT), is warranted.

Objective: We sought to define the outcomes of HSCT for patients with CVID.

GLILD: Local Protocol



e-GLILDnet
European Granulomatous-Lymphocytic Interstitial Lung Disease Network

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

John R. Hurst[1] and Klaus Warnatz[2,3], on behalf of the ERS eGLILDnet Clinical Research Collaboration[4]

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

- *161 responses from adult and paediatric pulmonologists and immunologists from 47 countries.*
- *Most respondents experienced difficulties in establishing the diagnosis of GLILD.*
- *There was little uniformity in diagnostic or therapeutic interventions.*
- *Fewer than 40% of respondents saw a definite need for biopsy.*
- *66% used corticosteroids for remission-induction and 47% for maintenance therapy; azathioprine, rituximab and mycophenolate were the most frequently prescribed steroid-sparing agents.*
- *Pulmonary function tests were the preferred modality for monitoring patients during follow-up.*

e-GLILDnet
European Granulomatous-Lymphocytic Interstitial Lung Disease Network

Granulomatous-Lymphocytic Interstitial Lung Disease: an international research prioritisation

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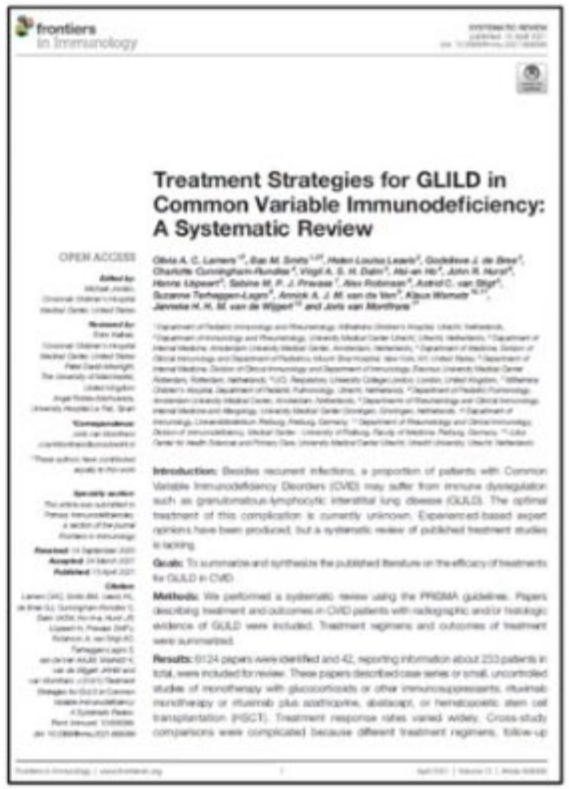

frontiers in Immunology

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

OPEN ACCESS

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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.

Goals: 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 histologic evidence of GLILD were included. Treatment regimens and outcomes of treatment were summarized.

Results: 6124 papers were identified and 42, reporting information about 233 patients in total, were included for review. These papers described case series or small, uncontrolled studies of monotherapy with glucocorticoids or other immunosuppressants, rituximab monotherapy 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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