TOLD

Education in Tuberculosis & Other Lung Diseases

PNEUMONIA IN THE IMMUNOCOMPROMISED

UNIVERSITY OF TURKU

THIJS FEUTH

21ST OF NOV 2024

Affiliations & potential conflicts of interest

University of Turku	Clinical lecturer in pulmonology and allergology
VARHA / Tyks	Specialist in pulmonology and allergology
Dutch Journal of Medicine	Columnist
FILHA	Deputy member of the Council
Lab Quality	Consultant for quality control of spirometry
Sanofi	Advisory Board
Pfizer	Lecture fee
BioMerieux	Consultant
AstraZeneca	Scientific consultant, consultant, Domestic educational event participation
Boehringer Ingelheim	Domestic educational event participation
GSK	Domestic educational event participation
HealthFox Oy	Scientific collaborator (not paid)

What patients are immunocompromised?

Please answer in the chat

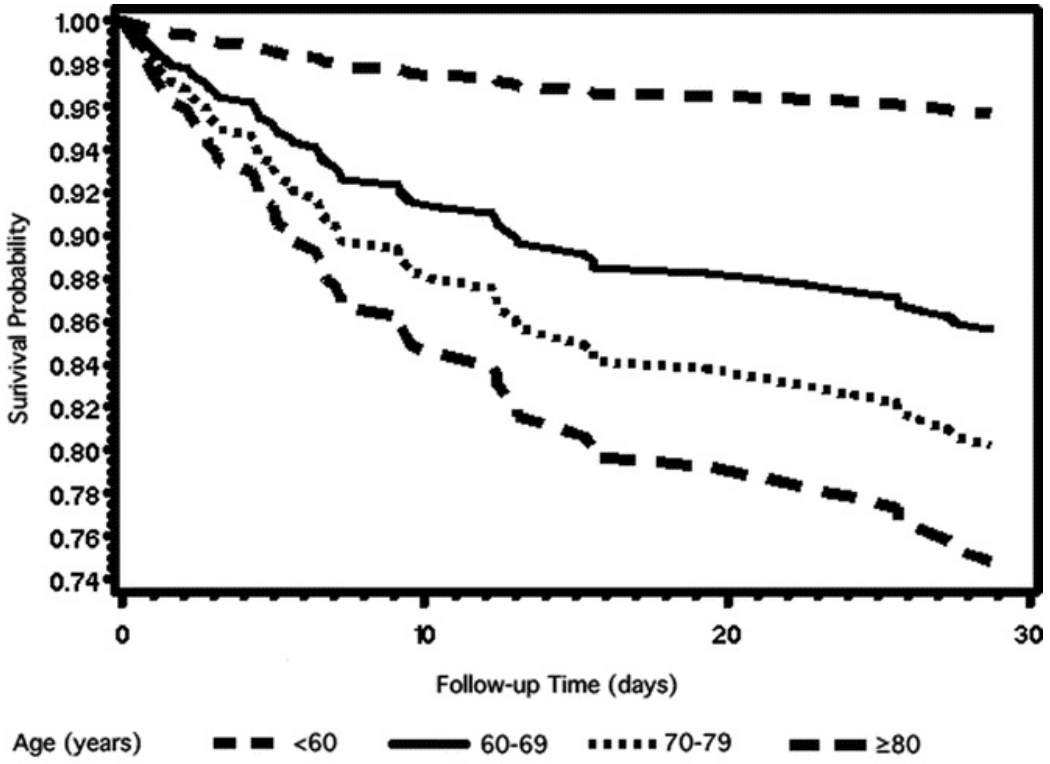
What patients are immunocompromised?

Ramirez et al. Consensus statement; Chest 2020:
We suggest that patients with CAP should be considered to be immunocompromised if they have an underlying disease or medical treatment that alters the immune system to the point that they are at elevated risk of pneumonia not only by common organisms but also by uncommon avirulent or opportunistic organisms

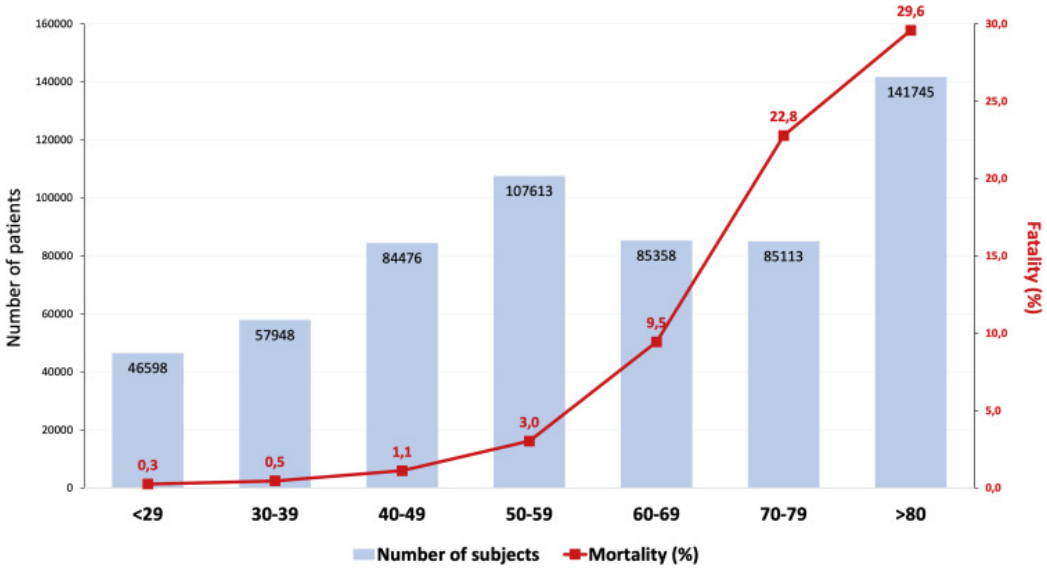
ATS definition; ATS Annals 2023:
Immunocompromised host pneumonia (ICHP) is defined as infectious pneumonia that occurs in an individual with a quantitative or functional host immune defence disorder

How about age?

1-yr mortality of critically ill patients with pneumonia by age category (adjusted survival curve). Data from Canada.[1]



COVID-19 patients according to age groups and crude mortality rates. (data from China, NYC, Spain, Italy, UK May 2020)



1. Wendy Sligl et al. *Critical Care Medicine 2010;* 38(11):p 2126-2132.

Clara Bonadad et al. JAMDA 2020. p 915-918.

Pneumonia and age

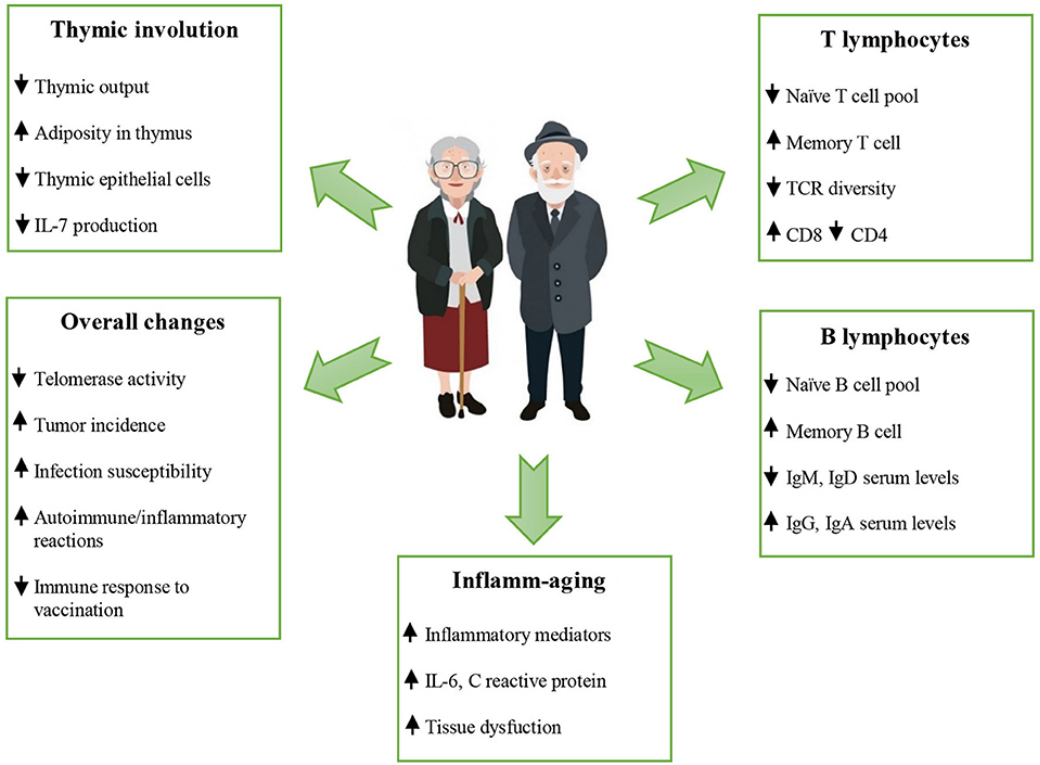
Different dynamics of immunity[1,2]

- 'Inflamm-aging'
- Immune senescence
  - Decreased production of B- and T-cells
  - Lymfocyte function impaired
  - Impaired / shorter protection after vaccination

Pulmonary function decreased with age

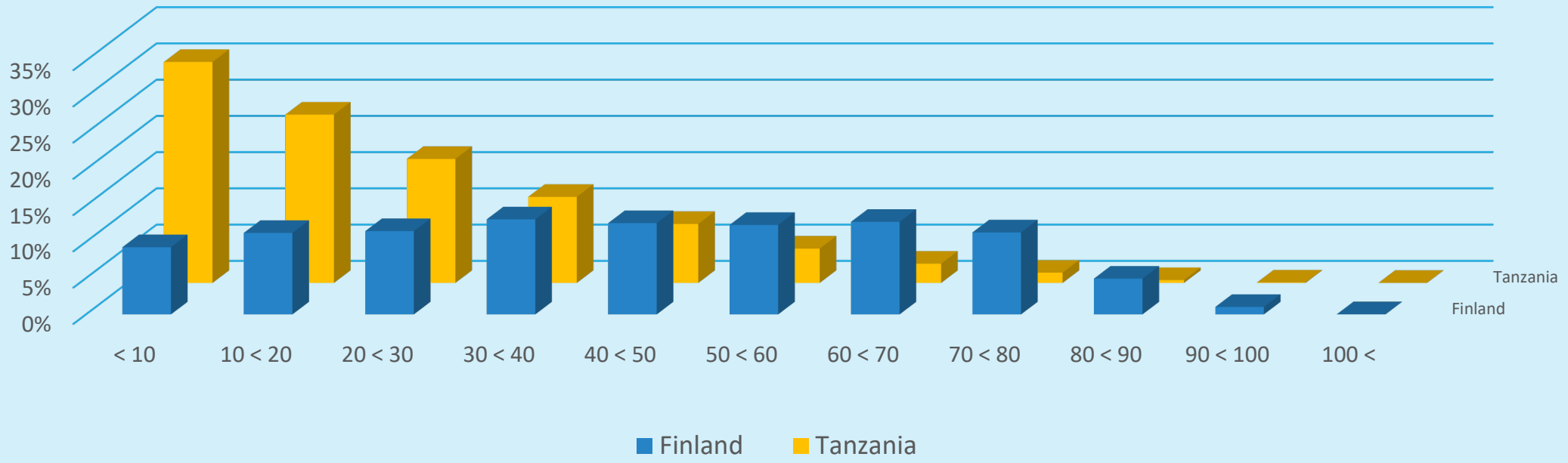
Symptoms not always clear. Only fever and/or delirium, without fever, is not uncommon

Comorbidities and co-medications



1. Janko Nikolich-Zugich, Nature Immunology 2018:10-19
2. Moskalev et al. Aging and disease 2020;1363-1373.

Populations of Tanzania and Finland



Data from 2023 (World of Data)

Neonatal immunity and respiratory infections

- Specific challenge: birth from a **near-sterile uterus** through a **microbe-rich** environment
- Delivery poses a sudden exposure to thousands of antigens
- Immunity is not 'suppressed', but skewed towards **Th2 inflammation**
- With suboptimal Th1 responses and B-cell differentiation
- **Vulnerable to acute respiratory infections** and diarrhea
- But neonatal immunity is in general very effective in coping with the specific challenge of being newborn

- Disclaimer: immunity of neonates is not my expertise, so please correct me if I'm wrong!

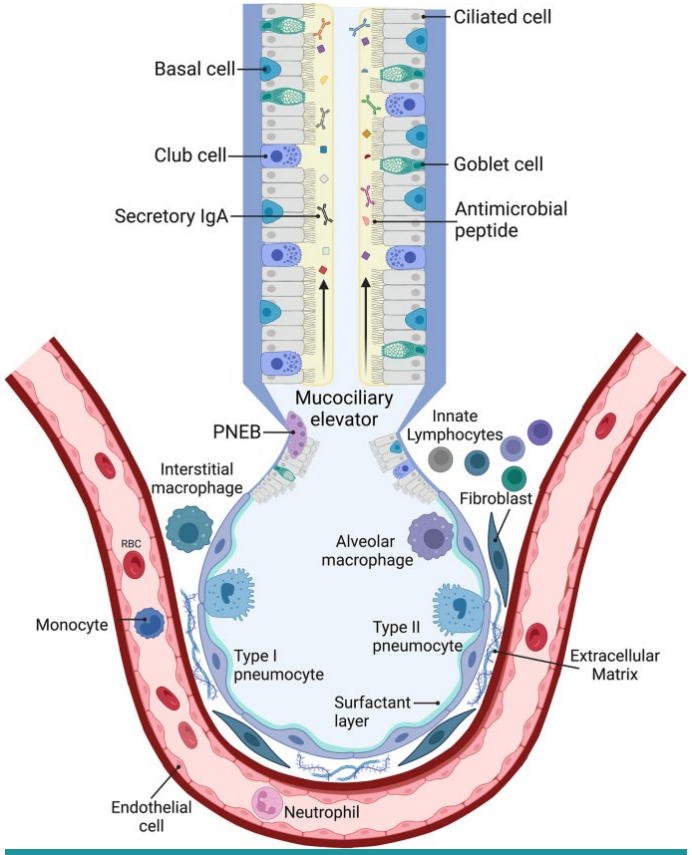
Basha et al. Expert Rev Clin Immunol 2015:1171-1184.
Jack C Yu et al. Front Immunol 2018: 01759,

Pulmonary immunity

Native immunity
- Anatomy
- Epithelium and tight junctions (caludins)
- Microbiome
- Alveolar macrophages and native lymphocytes
- Interleukins, interferons, IgA, lysozyme, surfactant

Humoral immunity
- Specific antibodies / immunoglobulins (produced by plasma cells / effector B cells)

Cell-mediated immunity
- Phagocytes
- Cytotoxic (CD8) T lymphocytes
- CD4 helper T lymphocytes
- Release of cytokines (Th1: IFN-γ; Th2: IL-4, IL-5, IL.13)



Korkmaz & Traber. Pneumonia 2023

Back to the question: Who is immunocompromised?

Age is an important factor in immunity, but elderly are generally not considered to be immunocompromised

Alcoholism is associated with altered immune function and an increased risk of pneumonia, but is also generally not considered as an immunocompromised condition[1,2]

The same goes for several acute viral infections, although they may pose patients at risk for other respiratory infections (pneumococcal pneumonia, fungal infections)[3]

Despite the existing definitions, the term 'immunocompromised' remains unclear, and open for interpretation.

We tend to reserve the term for patients with a specific condition with a well-defined effect on immunity, which often poses them at significant risk for infection with opportunistic pathogens.[4]

1. Simou et al. BMJ Open 2018
2. Andrés de Roux, Chest 2006
3. Peltola et al. CID 2006
4. Torres et al. Thorax 2013

Clinical consequence…

With a severe pneumonia, we should ask ourselves the following question

Why does this person,
under these conditions,
have a severe pneumonia?

> Exposure / transmission

> Socio-economic conditions / public health

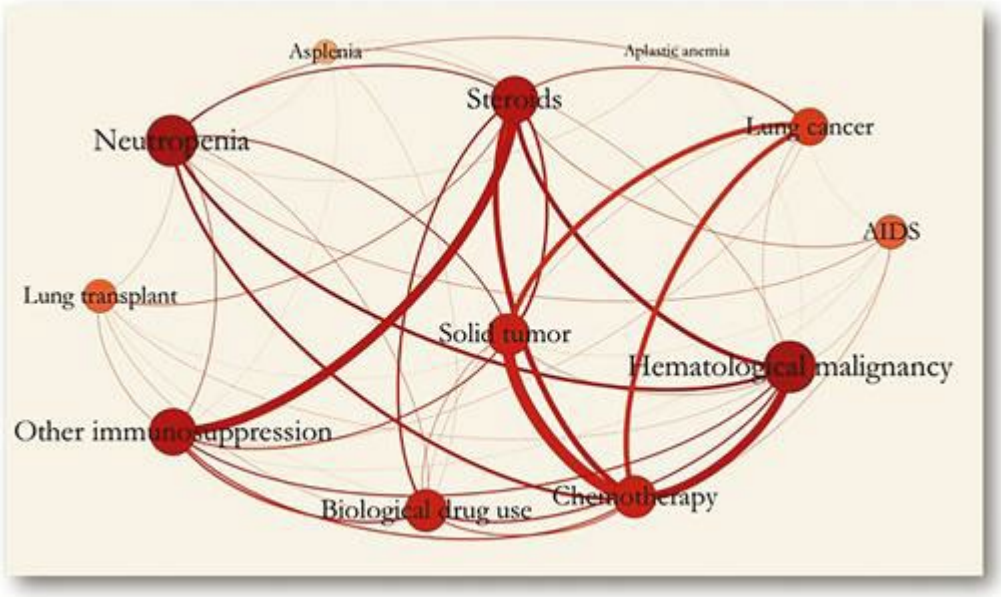
> Individual predisposing factors / comorbidities / medications / immune disorder / vaccinations

Can have consequences for further investigations, treatment, and future prevention

What diseases and drugs pose patients at risk for pneumonia?

Diseases that predispose to pneumonia

- Haemotological malignancies
  - Leukemia, lymphoma, myeloma
- HIV (with CD4 cell count < 200 cell)
- Bronchiectasis
- Cystic fibrosis
- Stem cell transplantation
- Renal failure
- Liver failure
- Solid tumors, especially lung infections
- Common variable immune deficiencies
- …
- Multimorbidity



Di Pasquale CID 2019

Drugs that predispose to pneumonia

Glucocorticosteroids
- >20 mg > 14 vrk
- Cumulative 600 mg

Drugs directed at B- and/or T lymphocytes
- Rituximab (anti-CD20; B-cells)
- Alemtuzumab (anti-CD52; B- & T-cells)

DMARDs

Chemotherapy → neutropenia

Biologicals
- TNF-inhibitors (infliximab)
- Others

Elie Azouley et al. Intensive Care Medicine 2020. 298-314.

Image: ChatGPT

Corticosteroids

High and diffuse penetration → mediates inflammation at a systemic level

- Efficient absorption in the gastrointestinal tract
- Associate with plasma proteins to be distributed through the circulation
- Passes through biological membranes to reach intracellular glucocorticoid receptors

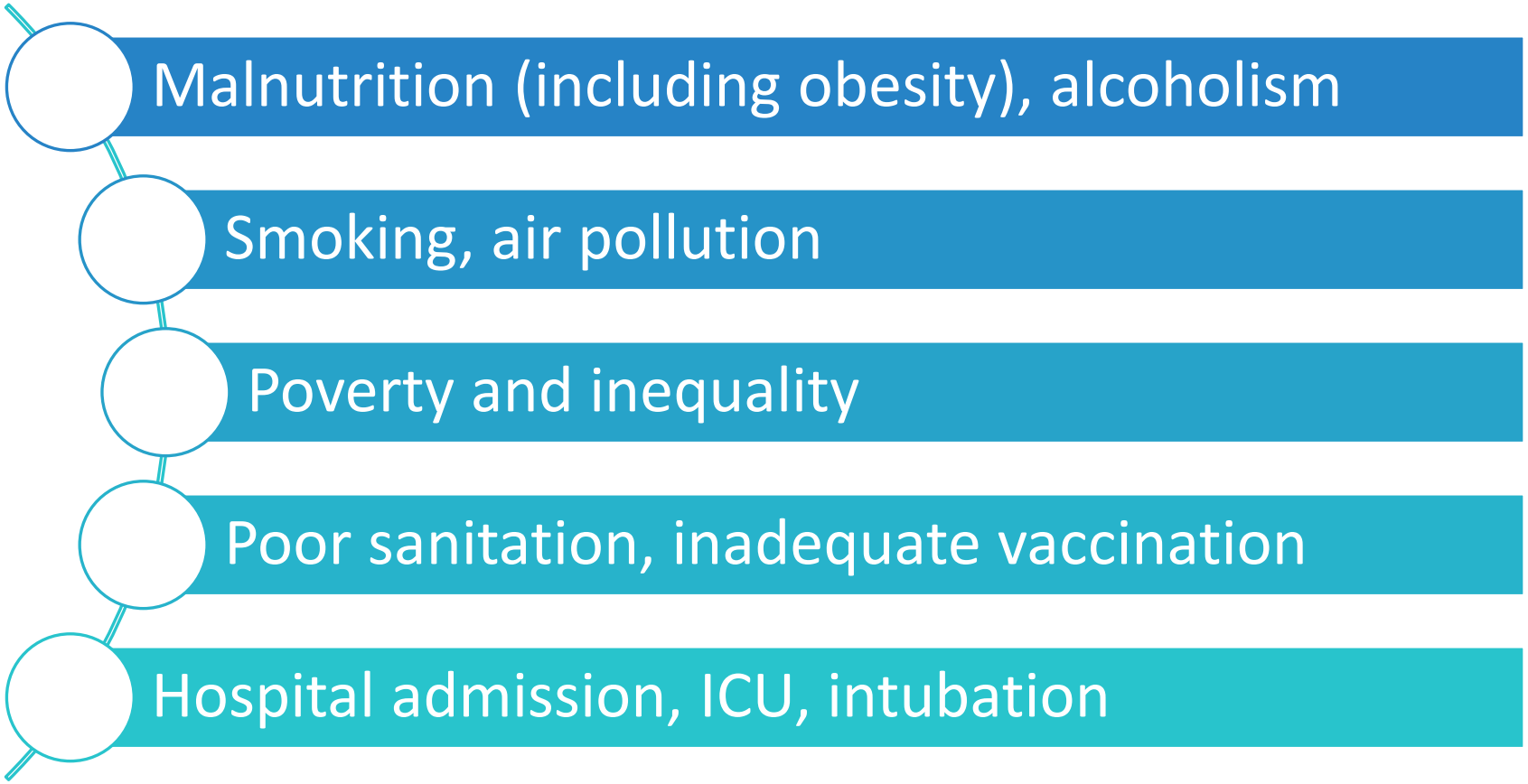
Wide effects comes with the cost of side effects

Many different effects on immune cells differ per cell type, for example

- Decreased antigen presentation by dendritic cells
- Decreased production of cytokines by cytotoxic T cells
- Increased activation of Natural Killer cells
- Increased apoptosis of eosinophils
- Increased M2 polarization of macrophages

Rowan Hardy et al. Nature Reviews Rheumatology 2020;133-144.

Beyond diseases and drugs



ICHP problems

Symptoms may be blunted

- Sometimes no fever, low level of inflammation
- No clear signs on chest X-ray imaging

Normal and/or opportunistic pathogens

- Including otherwise ‘rare’ infections, such as pneumocystis pneumonia

Differential diagnosis may include non-infectious conditions

- Such as ILD, cryptogenic organizing pneumonia, drug-induced lung disease

May deteriorate rapidly

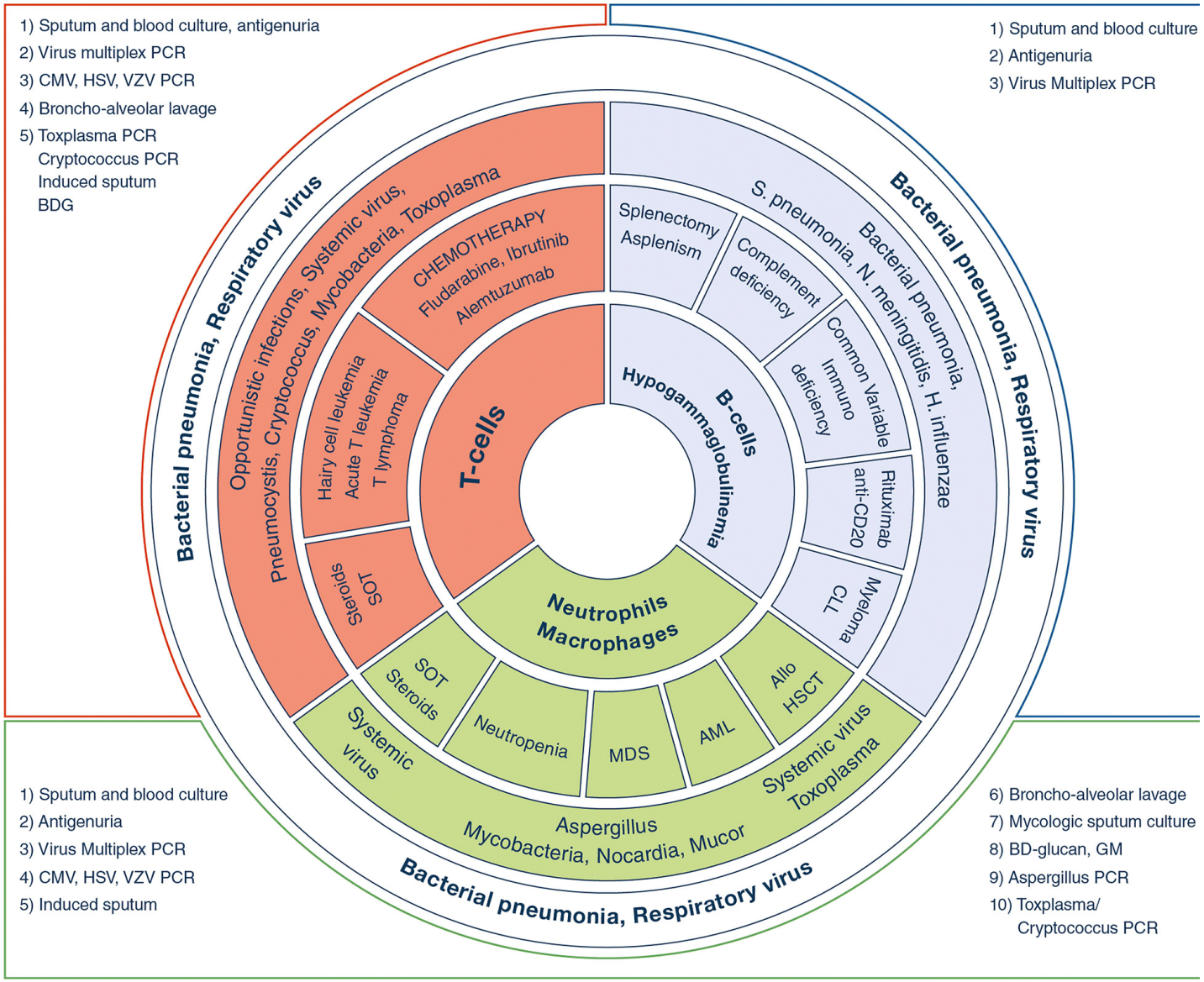
Elie Azouley et al. Intensive Care Medicine 2020. 298-314.
Image: Hotpot.AI

Pathogens Di Pasquale et al. GLIMP-tutkimus, CID 2019

	Immunocompromized n = 2626	Immunocompetent n = 596	P-arvo
Streptococcus pneumoniae	8.4%	8.4%	n.s.
Pseudomonas aeruginosa	**5.9%**	**3.7%**	**0,02**
Influenza	4.7%	4.8%	n.s.
Klebsiella pneumoniae	3.7%	3.4%	n.s.
MSSA	3.4%	2.8%	n.s.
MRSA	2.0%	3.2%	n.s.
Pneumocystis jirovecii	**2.2%**	**0.2%**	**<0,001**
Haemophilus influenzae	1.7%	2.5%	n.s.
Legionella	1.7%	0.8%	0.08
Aspergillus fumigatus	**1.3%**	**0.4%**	**0.01**
RSV	**1.0%**	**0.3%**	**0.03**
Mycobacterium tuberculosis	0.8%	0.8%	n.s.
Nontuberculous mycobacteria	**0.8%**	**0.1%**	**0,002**
Nocardia spp	**0.7%**	**0.0%**	**<0,001**
Coronavirus	**0.5%**	**0.1%**	**0.047**
MDR patogens	9.0%	8.8%	n.s.

Pulmonary infections according to type of immunosuppression

Elie Azouley et al. Intensive Care Medicine 2020. 298-314.



Investigations

Radiology

- CT is preferred in ICHP

Blood samples

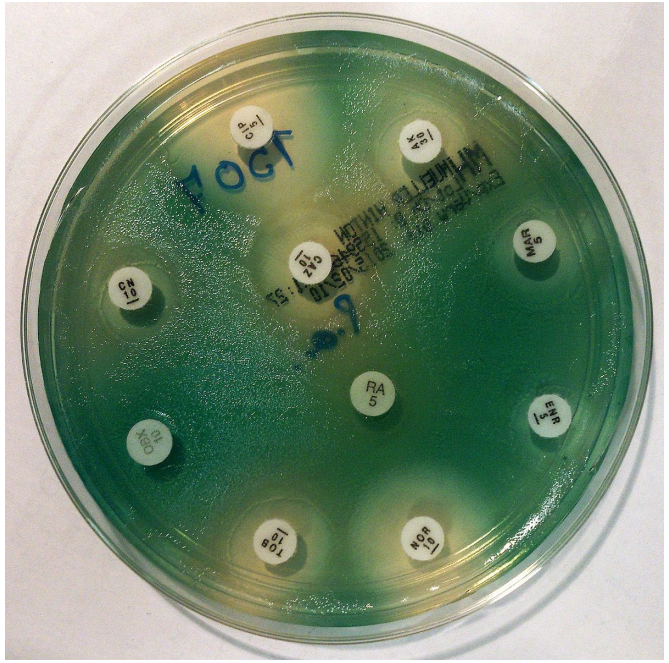
- FBC + differentiation, CRP, PCT, lymphocytes / flow cytometry
- Blood cultures, HIV test
- Serum galactomannan Antigen, Cryptococcus antigen, CMV PCR (in clinical suspicion)
- Plasma levels of immunosuppressive medications

Respiratory tract samples

- Nasopharyngeal swab for viral PCR
- Induced sputum for detection of bacterial / mycobacterial / fungal pathogens
- Bronchoalveolar lavage (BAL)

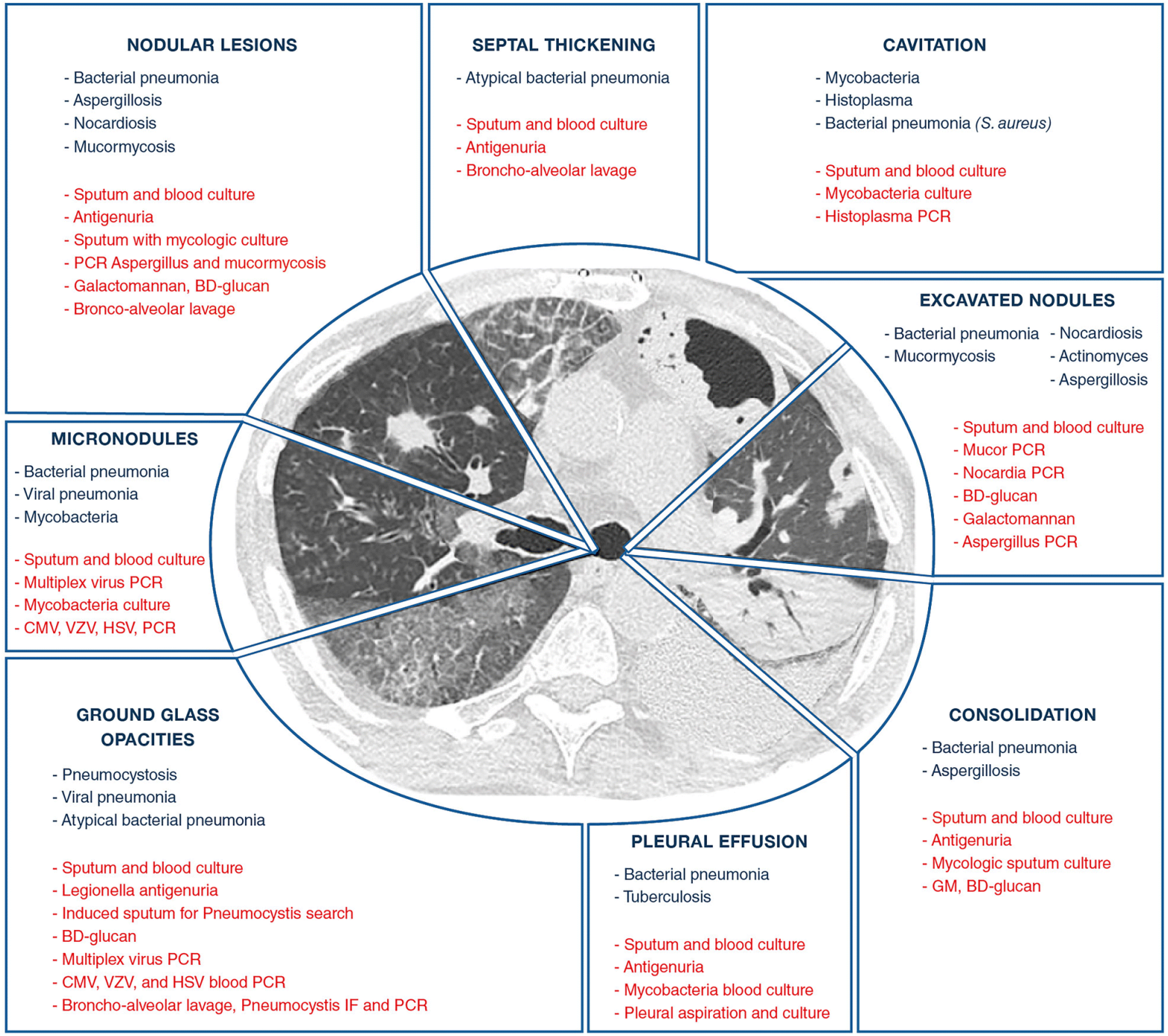
Other samples

- Urine for pneumococcus antigen, legionella, parasite eggs, histoplasma antigen
- Skin lesions: PCR for HSV and HZV; strong associated with viral pneumonia
- Skin lesion for histology and microbiology: viruses, bacteria, mycobacteria, fungi, parasites



Computed Tomography (CT) of the lungs

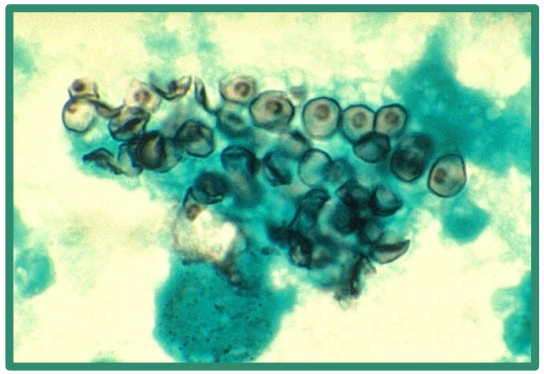
Elie Azouley et al. Intensive Care Medicine 2020. 298-314.



Addressing the pathogen

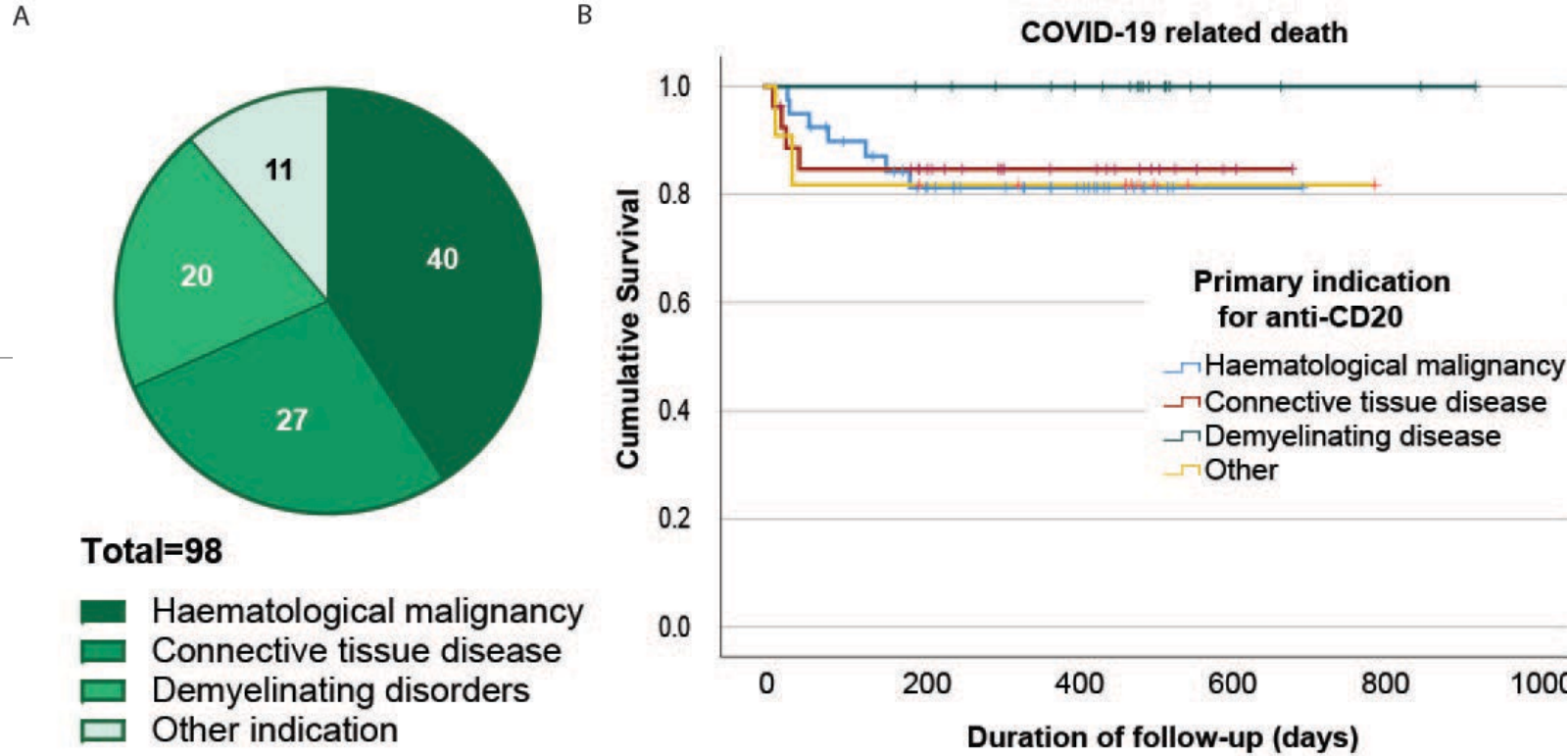
Bronchalveolar lavage

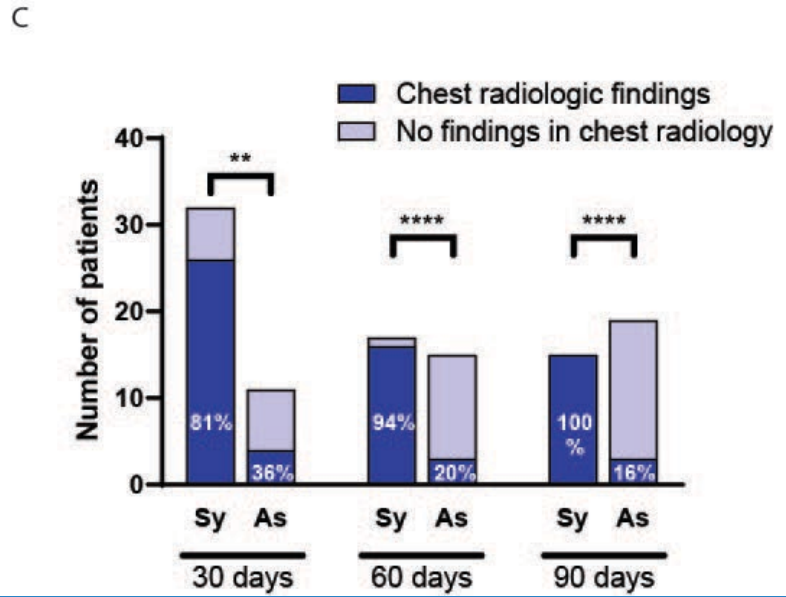
◦ Routine staining and culture	de-escalation of antibiotic therapy
◦ Nocardia culture	
◦ Fungal staining and culture	Can be positive without clinical relevance
◦ Antigen testing / multiplex PCR	
◦ Galactomannan	Aspergillus (can be false pos in β-lactam antibiotics, other fungi)
◦ Aspergillus PCR	Very sensitive, high Negative predictive value
◦ (quantative) CMV-PCR	can be positive due to viral shedding without pneumonia
◦ Cells / differentiation	
◦ Histology	

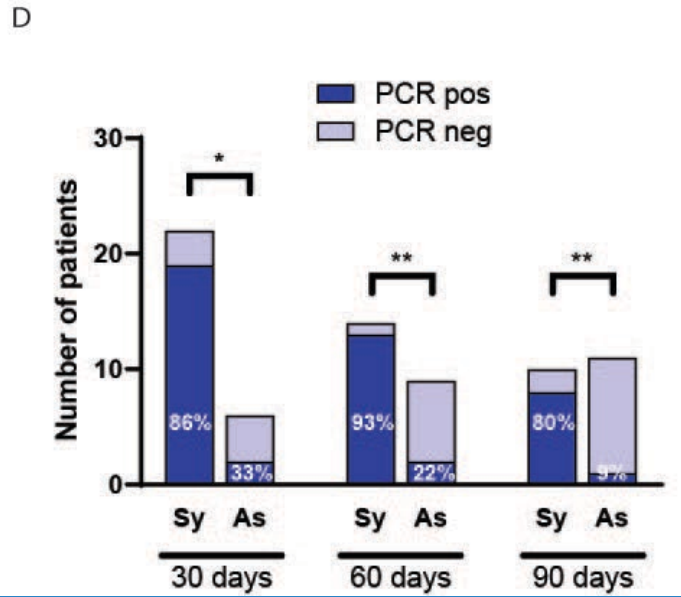


Rituximab and prolonged COVID-19 pneumonia

FEUTH ET AL.
EJCMID 2024







No consensus on definition of

‘immunocompromised’

The prevalence of immune disorders is increasing due to availability of treatment

But treatments are becoming more specific, with less side effects on immunity

Clinical findings in ICHP can be misleading

- Consider TT if available (and accessable)
- Address the pathogen

ICHP with common viral pathogen can be severe and prolonged

Ask yourself: Why does this person, under these conditions, have a severe pneumonia?

Take home

Thank you!

matfeu@utu.fi